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TITLE

DOPAMINE AND REWARD:

EFFECTS OF DOPAMINE ANTAGONIST DRUGS

ON OPERANT AND CONSUMMATORY BEHAVIOURS

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A thesis submitted to the CNAA by Gavin Phillips in partial fulfilment of the requirements for the award of the degree of Doctor of Philosophy.

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ABSTRACT

PHILLIPS, G. **Dopamine and reward: Effects of dopamine antagonist drugs on operant and consummatory behaviours.**

The Herrnstein matching law was used to dissociate motoric from motivational drug-induced performance changes. The effects of neuroleptic drugs were compatible with, at low doses, a reduction in reinforcer efficacy, and at higher doses, an additional motor impairment. However, the Herrnstein matching law was found to be prone to artifactual error; in particular, under reinforcement-lean conditions reductions in reinforcer efficacy were time-dependent. These problems compromised the use of the Herrnstein matching law to assess drug-induced performance changes.

Raclopride-induced time-dependent reductions in response rate occurred in the absence of both primary and secondary reinforcement. Within-session decrements in both operant and consummatory behaviour were observed following administration of sulpiride to the anterodorsal striatum, but not following administration of sulpiride to the nucleus accumbens. The implications of this finding are discussed in relation to the internal organisation of behaviour, and Parkinson's disease.

Consumption of sucrose and operant responding maintained by sucrose pellets follows an inverted-U-shaped concentration-intake function. Systemic administration of raclopride shifted the curve to the right. It is argued that this curve shift reflects an impairment in the primary reward process. Effects of intracranial administration of sulpiride on sucrose consumption were restricted to the nucleus accumbens at a low concentration of sucrose, but were also observed within the anterodorsal striatum and basolateral amygdala at higher concentrations. These findings are discussed in relation to the neuroanatomical substrates for the guidance of behaviour by external cues, and for reward processes.

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DOPAMINE AND REWARD: EFFECTS OF DOPAMINE ANTAGONIST DRUGS ON OPERANT AND CONSUMMATORY BEHAVIOURS.

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CHAPTER 1

BRAIN DOPAMINE AND REWARDED BEHAVIOUR

1.1 DOPAMINE

Dopamine (DA) was first detected in the CNS as long ago as the late 1950's (Montagu, 1957), and shortly afterwards localised within cell bodies and nerve terminals (Carlsson *et al.*, 1962). The discovery by Hornykiewicz (1966) that DA was profoundly depleted in the brains of patients suffering from Parkinson's disease (PD) was the first concrete indication that DA functioned as a neurotransmitter in its own right, rather than simply being a precursor to noradrenaline (NA). Subsequent understanding of DA systems has made rapid progress. DA (3,4-dihydroxyphenylethylamine) is synthesised from the amino acid tyrosine, which is widely distributed in brain tissue (Weiner & Molinoff, 1989). Metabolism of tyrosine in the cytosol of catecholaminergic neurons by the enzyme tyrosine hydroxylase yields L-DOPA (3,4-hydroxyphenylalanine). Due to the low capacity of tyrosine hydroxylase and subsaturated concentrations of the cofactor tetrahydrobiopterin, hydroxylation of tyrosine is the rate-limiting step in DA synthesis. L-DOPA is converted to DA by DOPA decarboxylase, and actively taken up by synaptic vesicles. Adrenergic neurons metabolise DA to NA within the synaptic vesicles.

1.1.1 Anatomy of dopamine systems

The most extensively studied DA projections originate in the ventral mesencephalon (Anden *et al.*, 1964), and consist of the projections of the A8, A9 and A10 cell groups (Dahlstrom & Fuxe, 1964). These neurons project forwards via the medial forebrain bundle to diverse telencephalic brain areas (Lindvall & Bjorklund, 1983; Bjorklund &

Lindvall, 1986). The A9 and A10 projection fibres have been traditionally divided into two distinct systems. In brief, the nigrostriatal DA system arises from the A9 group situated in the ventral pars compacta of the substantia nigra (SNc; Fallon *et al.*, 1978), and projects to the dorsal striatum (Anden *et al.*, 1966; Ungerstedt, 1971). Medial aspects of the SNc project to the medial striatum, and lateral aspects innervate the lateral striatum (Beckstead *et al.*, 1979; Domesick *et al.*, 1976; Fallon & Moore, 1978).

The second major DA system is the mesocorticolimbic DA system. This arises from within the A10 cell group, and is situated medial to the SN in the ventral tegmental area of Tsai (VTA). The VTA densely innervates the nucleus accumbens septi (NAS) and olfactory tubercle, in the ventral striatum (Anden et al., 1966; Ungerstedt, 1971), primarily from its medial and lateral portions (Beckstead *et al.*, 1979). In common with the A9-to-striatum medial-lateral topography noted above, medial A10 efferents innervate medial aspects of the NAS, while lateral portions preferentially innervate the lateral NAS (Fallon & Moore, 1978; Lindvall & Stenevi, 1978). Fibres innervating other limbic areas, including the lateral septum, amygdala, and interstitial nucleus of the diagonal band appear to arise exclusively from within the medial VTA (Beckstead *et al.*, 1979; Fuxe, 1965; Lindvall & Stenevi, 1978; Ungerstedt, 1971). The VTA also projects to nuclei of the thalamus (Beckstead, 1976, Beckstead *et al.*, 1979; Herkenham, 1977), to deep layers of the anteromedial prefrontal cortex (Beckstead *et al.*, 1976, 1979; Berger *et al.*, 1976; Fallon & Moore, 1978; Lindvall *et al.*, 1974; Thierry *et al.*, 1973), and throughout the entorhinal cortex (Beckstead, 1976; Lindvall *et al.*, 1974). In addition, while A9 cells may project to multiple sites, A10 cell innervation appears more localised (Fallon, 1981).

However, projections sites of the A9 and A10 cell groups to some extent overlap.

Both groups (medial A9 and A10) innervate the NAS, olfactory tubercle, lateral septum, central and basolateral amygdala, bed nucleus of the stria terminalis, frontocingulate and entorhinal cortices (Beckstead *et al.*, 1979; Carter & Fibiger, 1977; Fallon *et al.*, 1978; Moore & Bloom, 1978; Ungerstedt, 1971). A10 DA cells also project to the entire ventromedial portion of the dorsal striatum, which is the primary projection site of the nigrostriatal DA system (Beckstead *et al.*, 1979; Fallon *et al.*, 1978; Tassin *et al.*, 1976). In addition, both groups also project to contralateral terminal areas (Royce, 1978; Swanson, 1982; Veening *et al.*, 1980). However, A10 cells appear to be specifically colocalised with cholecystokinin (Hokfelt *et al.*, 1980), and medial A9 and A10 cells which project to limbic areas are specifically innervated by an enkephalin-containing system, unlike neurons projecting to other areas (Johnson *et al.*, 1980; Uhl *et al.*, 1979). In short, these DA systems have been collectively termed the mesotelencephalic DA system (Moore & Bloom, 1978).

1.1.2 Dopamine receptor subtypes

The first biochemical effect linked to DA receptors was the in vitro stimulation of cyclic adenosine monophosphate (cAMP) synthesis by DA (Brown and Makman, 1972; Kebabian et al, 1972), Neuroleptic drugs are DA receptor antagonists, and most neuroleptics significantly inhibit cAMP synthesis (Clement-Cormier *et al.*, 1974; Iversen *et al.*, 1976). However, the ergot alkaloids lergotrile and ergotamine are known to be potent DA agonists but do not augment cAMP synthesis (Schmidt and Hill, 1977; Trabucchi *et al.*, 1976). Kebabian and Calne (1979) therefore proposed that DA receptors consist of at least two subtypes, the D1 class linked to adenylate cyclase and cAMP synthesis, and the D2 class which is either uncoupled or exerts an inhibitory

action upon cAMP synthesis (Memo *et al.*, 1985; Stoof and Kebabian, 1981). In addition, D2 receptors appear to exert a direct control over potassium and calcium ion channels on neuronal membranes, and the intracellular effects of D2 receptor activation may be mediated to some extent by inhibition of synthesis of the second messenger inositol-1,4,5-triphosphate (Vallar & Meldolesi, 1989).

Both D1 and D2 receptors may be found throughout DA terminal regions. However, presynaptic autoreceptors present on cell bodies, dendrites and axon terminals (see Muscat, 1987) of DA systems appear to be of the D2 type. Thus, application of DA or DA agonists to the SN suppressed firing of DA cells, an effect which was blocked by administration of sulpiride (a D2 antagonist), but not by SCH-23390 (a D1 antagonist) (Freeman & Woodruff, 1986; Gessa & Mereu, 1984; White & Wang, 1984). Similarly, application of DA agonists to dendrites in the SNr also suppressed firing by DA neurons, and this suppression was ameliorated by antagonists of the D2 type, but not by D1 antagonists (Gessa & Mereu, 1984).

Behavioural studies suggest that D1 and D2 receptors may often be closely linked. D1 receptor blockade reduces locomotor activation induced by a variety of agonists selective for the D2 receptor (Arnt, 1985; Barone *et al.*, 1986; Breese and Mueller, 1985; Christensen *et al.*, 1984a,b; Mailman *et al.*, 1984a,b; Molloy and Waddington, 1984; Shulz *et al.*, 1985). Similarly, unilateral lesion of DA terminal areas leads to rotational behaviour upon resultant asymmetrical activation of DA systems, and D1 receptor blockade reduces or blocks the rotational behaviour induced by amphetamine, or the direct D2 agonist LY-171555 (Arnt and Hyttel, 1984; Barone *et al.*, 1986). Furthermore, the full expression of stereotypic behaviour appears to depend upon concurrent activation of both D1 and D2 receptors (Barone *et al.*, 1986; but see below).

These data have been taken to suggest a synergistic relationship between D1 and D2 receptors; the D1 receptor providing the "tonic" background activation necessary for the expression of the D2 "phasic" component (Barone *et al.*, 1986; Clark & White, 1987). However, other types of D1/D2 receptor interactions have also been described. For example, administration of LY-171555 increases locomotion and chow intake. Although preadministration with SCH-23390 (a D1 antagonist) blocked the effects of LY-17155 on locomotion, it further enhanced intake of chow. Here D1/D2 receptor interactions appeared to be synergistic with regard to locomotion, but antagonistic with respect to feeding behaviour (Muscat *et al.*, 1989). Furthermore, no interaction of D1 and D2 receptors of either variety was found in a conditioned reinforcement procedure (Wolterink *et al.*, 1990).

Activation of D1 or D2 receptors has different effects on reinforced behaviour. Drug self-administration was not supported by the D1 receptor agonist SKF-38393 (Woolverton *et al.*, 1984). In addition, D1 receptors do not appear to be specifically involved in conditioned reinforcement: SKF-38393 did not induce a conditioned place preference (CPP) (Gilbert *et al.*, 1986), and did not enhance manipulandum-specific conditioned responding (Beninger *et al.*, 1989). Conversely, drug self-administration was readily supported by the D2 receptor agonist bromocriptine (Woolverton *et al.*, 1984). Also, the D2 agonist N-0437 did induce a CPP (Gilbert *et al.*, 1986), and administration of LY-171555 markedly enhanced manipulandum- specific conditioned responding (Beninger *et al.*, 1989). By contrast, D1 and D2 receptor antagonists have generally been found to possess similar effects on reinforcement processes, as demonstrated in sham feeding or operant response procedures (Schneider *et al.*, 1986, 1988; Weatherford *et al.*, 1988; Willner *et al.*, 1990a). The reason for this difference in behavioural specificity

between DA agonists and antagonists is not clear (but see Beninger, 1990).

1.1.3 Dopamine and brain circuitry

Behavioural data indicate that the original classification of a nigrostriatal and a mesolimbic DA system (Anden *et al.*, 1966; Ungerstedt, 1971) has much heuristic value. Each would appear to play a critical modulatory role in the functioning of distinct cortico-striato-pallido-thalamic circuitry (Alexander et al., 1986; Alexander & Crutcher, 1990; DeLong, 1990; Swerdlow & Koob, 1987). Although each circuit remains anatomically distinct throughout (DeLong & Georgopoulos, 1981), all take the same general form. Each receives multiple, and specific cortical projections which innervate segregated portions of the striatum (caudate nucleus, putamen or ventral striatum). Input within each circuit becomes progressively integrated in passage through the pallidum and substantia nigra pars reticulata (SNr), and is returned via a specific portion of the thalamus to a single cortical area. In this manner, information from a number of cortical areas may be integrated, and so 'funnelled' back to specific cortical sites. At least five anatomically distinct basal ganglia-thalamocortical circuits have been described: the motor, oc-ulomotor, dorsolateral prefrontal, lateral orbitofrontal, and anterior cingulate or 'limbic' circuit (Alexander *et al.*, 1986).

Of these, the motor circuit is perhaps best understood, and may be most relevant to fundamental behavioural processes. In primates, excitatory glutaminergic input from the primary motor cortex, arcuate premotor area, supplementary motor area and somatosensory cortex converge on the putamen (Jones *et al.*, 1977; Kunzle, 1975, 1977, 1978; Selemon & Goldman-Rakic, 1985). In common with other portions of the striatum, the putamen exhibits a high degree of organisation; neurons related to

representation of the leg are located throughout the dorsolateral region, orofacial characteristics in the ventromedial region, and representation of the arm in an intermediate position (Alexander & DeLong, 1985a; Crutcher & DeLong, 1984a; Kunzle, 1975). Within each leg, arm, and orofacial channel there appears to be further segregation into sub-channels, in which input from each cortical area, though contiguous, remains separate (Alexander +Crutcher, 1990). Movement of individual body parts can be elicited by microstimulation of the putamen (Alexander & DeLong, 1985b), although movement-related neuronal activity appears to be relatively independent of specific patterns of muscular activity (Crutcher & DeLong, 1984b). From the putamen, segregated channels efferent via the globus pallidus to specific nuclei of the thalamus, including the ventrolateral, ventroanterior and centromedian nuclei (Carpenter *et al.*, 1976; Kuo & Carpenter, 1973; Kim *et al.*, 1976; DeVito & Anderson, 1982; Ilinsky *et al.*, 1985). These channels then converge on the supplementary motor area, which possesses direct projections to the spinal cord (Biber *et al.*, 1978; Murray & Coulter, 1981; MacPherson *et al.*, 1982; Palmer *et al.*, 1981).

The modulatory role of the nigrostriatal DA system concerns the GABAergic (gamma-aminobutyric acid) putamen-to-thalamus stage of the motor circuit. This consists of two opposing, parallel pathways that project from the putamen to the internal segment of the globus pallidus (GPi) and SNr, and efferent in a common inhibitory pathway to the thalamus. DA neurons originating in the SNc exert an opposing influence on these putamen output pathways (Hong *et al.*, 1985; Pan *et al.*, 1985; Young *et al.*, 1986), but with the same overall effect on thalamo-cortical activity. The first, an inhibitory GABA/substance P pathway (Albin *et al.*, 1989; Graybiel & Ragsdale, 1983) directly innervates the GPi and SNr, and is under excitatory control by the ascending

nigrostriatal DA pathway. Reduced DA release in the putamen therefore disinhibits the GPi/SNr-to-thalamus pathway, and as this pathway is itself inhibitory, thalamo-cortical activity is decreased. The second, 'indirect' GABAergic output pathway from the putamen appears to be colocalised with enkephalin (Graybiel & Ragsdale, (1983), and passes via the external segment of the globus pallidus (GPe). A further GABergic pathway outputs to the subthalamic nucleus of Luys (STN), before an excitatory glutaminergic pathway completes the circuit and inputs the GPi/SNr output nuclei. Nigrostriatal DA exerts an inhibitory influence on the GABA/enkephalin stage of the indirect pathway, and in effect a reduction in striatal DA again inhibits thalamo-cortical activity.

It is thought that such a mechanism may underly the movement deficits of PD (DeLong, 1990). *N*-methyl-4-phenyl-1,2,3,6-tetra-hydropyridine (MPTP)-induced destruction of SNc DA cells in primates closely models the behavioural characteristics of PD in humans (Bankiewicz *et al.*, 1986; Burns *et al.*, 1983; Kish *et al.*, 1988; Langston *et al.*, 1984). Following treatment with MPTP, neuronal discharge is reduced in the GPe, but tonically enhanced in the the GPi and STN (Filion *et al.*, 1985). Taken together, these data suggest that the behavioural deficits induced by nigrostriatal DA loss arise out of an excessive inhibition of thalamic input to the supplementary motor area. This may be consistent with sensorimotor integration deficits observed following 6-hydroxydopamine (6-OHDA) lesion of the striatum, or ascending nigrostriatal DA input (Marshall et al., 1974, 1980; Marshall, 1976). By contrast, the onset of Huntington's disease is marked by a selective degeneration of the descending GABA/enkephalin pathway (Reiner *et al.*, 1988), manifested in abnormal hyperkinetic choreiform movements. Degeneration of this pathway would disinhibit the GPe

inhibitory input to the STN. Consequent inhibition of the STN excitatory pathway to the GPi/SNr would ameliorate thalamic inhibition, and hence excacerbate input to the supplementary motor area. It has been suggested that dyskinesias of PD associated with maintenance L-DOPA therapy may evolve on similar lines, although in this case as the outcome of excessive dopaminergic inhibition of the GABA/enkephalin descending pathway, rather than its destruction (DeLong, 1990). However, it should be noted that such models do not entirely accord with anatomical data, and are likely to undergo substantial elaboration in the future. For instance, A9 cell innervation of the striatum is not confined to the caudate-putamen; collateral fibres in addition directly input both the GP and STN (Fallon & Moore, 1978; Lindvall & Bjorklund, 1979; Versteeg *et al.*, 1976).

The mesolimbic DA system appears to play an analogous role in the modulation of the anterior cingulate, or 'limbic' thalamo-cortical circuit (Alexander *et al.*, 1986; Swerdlow & Koob, 1987). Again, extensive descending cortical input to the (ventral) striatum is thought to become progressively 'compressed' before returning to a single portion of the cortex. Descending cortical projections originate in the anterior cingulate and posteromedial orbitofrontal cortical areas, and also the temporal pole and both inferior and superior temporal gyri of the temporal lobe (Baleydier & Mauguiere, 1980; Hemphill *et al.*, 1981; Powell & Leman, 1976; Selemon & Goldman-Rakic, 1985; Van Hoesen *et al.*, 1976; Yeterian & VanHoesen, 1978). In addition, the NAS also receives extensive innervation from the hippocampus, amygdala, perirhinal and entorhinal cortices (Heimer & Wilson, 1975; Kelley & Domesick, 1982; Kelley *et al.*, 1982; Krayniak *et al.*, 1981, Nauta, 1961, 1962). From the NAS, inhibitory GABA/enkephalin output pathways innervate the ventral pallidum and VTA (Jones & Mogenson, 1980a;

Mogenson *et al.*, 1983; Swanson, 1976; Swanson & Cowan, 1975; Sugimoto & Mizuno, 1987; Yim & Mogenson, 1980), before connecting with posterior and medial portions of the dorsolateral nucleus of the thalamus (Baleydier & Maugiere, 1980; Heimer *et al.*, 1982; Heimer & Wilson, 1975; Jurgens, 1983; Penney & Young, 1981; Tobias, 1975; Vives & Mogenson, 1985; Vogt *et al.*, 1979). Further neuronal pathways complete the limbic circuit by returning input to the anterior cingulate area.

Mesolimbic DA appears to modulate the limbic circuit from within the NAS, which is seen as a functional interface in modulating the translation of limbic signals into locomotor output (Mogenson *et al.*, 1980; Mogenson, 1987; Mogenson & Yim, 1990). There appears to be extensive anatomical overlap in the NAS between DA inputs from the VTA, and innervation by hippocampal and amygdala areas (Cador *et al.*, 1990). Infusion of the excitatory amino acid N-methyl-D-aspartate (NMDA) to the hippocampus caused an increase in locomotion (Yang & Mogenson, 1987). However, administration of low doses of DA to the NAS, which in saline-treated rats had no effect, reversed the effects of NMDA infused into the hippocampus. Conversely, administration of NMDA to the amygdala produced a dose-dependent reduction in locomotor activity (Yim & Mogenson, 1989). Again however, following administration of a low dose of intra-accumbens DA, which in saline-treated rats had no effect, locomotor activity was restored to normal levels. The amygdala appears to play a crucial role in the acquisition and maintenance of behaviour guided by conditioned reinforcers (Cormier, 1981), via amygdala-to-NAS efferents. Thus, NMDA lesions of the amygdala severely impaired the response to a conditioned reinforcer (Cador *et al.*, 1990), or adaptation of response rate to the removal of conditioned reinforcement (Everitt *et al.*, 1989), but this lesion-induced deficit could be ameliorated by

intra-accumbens injection of amphetamine.

Within the NAS, DA terminals appear to synapse directly with GABA/enkephalin neurons (Onteniente *et al.*, 1987; Pickel *et al.*, 1987). Infusion of DA to the NAS increases locomotor activity (Jones *et al.*, 1981; Pijenberg & Van Rossum, 1973), which may be blocked by administration of GABA within the ventral pallidum, or lesion of this area (Jones *et al.*, 1981; Mogenson & Nielsen, 1983; Pycock & Hornton, 1976; Swerdlow *et al.*, 1984). Alternatively, lesion of the NAS blocks spontaneous locomotion and the locomotor stimulant action of amphetamine (Kelly *et al.*, 1975; Koob *et al.*, 1978). In addition, GABA blockade within the VP by infusion of picrotoxin appears to mimic the locomotor stimulant effects of DA administration to the NAS (Jones & Mogenson, 1981; Mogenson & Neilsen, 1983). Administration of naloxone, an opiate receptor antagonist, to the VP also enhances VP output (Yang & Mogenson, 1989). These data suggest that DA exerts an inhibitory action upon efferent NAS-to-VP GABA/enkephalin neurons, which in turn inhibit VP output. In addition, there appears to exist a functional antagonism between cholecystokinin and DA in the NAS (Mogenson & Yim, 1990). Decreased DA activity at mesolimbic DA terminals within the NAS would in effect reduce VP output to thalamo-cortical regions, and inhibit behavioural correlates of neuronal activity within the limbic system. It has been suggested that such a mechanism may underly the bradykinesia of PD (Carey, 1983; Koob *et al.*, 1984).

1.2 DOPAMINE AND REINFORCEMENT

1.2.1 Motor function and dopamine

In contrast with the putative sensorimotor function of the nigrostriatal DA system (Marshall *et al.*, 1974, 1980; Marshall, 1976), the mesolimbic DA system is usually seen as more closely involved in the modulation of motivational and reinforcement processes (Mogenson *et al.*, 1980). This may entail affective correlates of operationally defined motivational states, or reinforcement processes (Epstein, 1982, Fibiger & Phillips, 1986; Phillips, 1984; Tomkins, 1962). In humans, reported euphoria induced by amphetamine is ameliorated by pretreatment with the DA antagonist pimozide (Gunne *et al.*, 1972).

However, the mesolimbic DA system also appears in some manner involved in fundamental processes of behavioural output. Hence, a recurrent problem in assessing the role of DA in reinforcement processes has been that of discriminating between 'nonspecific' and reinforcement-related effects on behaviour. Lesion of DA terminal fields within the NAS markedly reduces spontaneous locomotion (Carey, 1983; Iversen & Koob; 1977; Koob *et al.*, 1981, 1984; Robbins & Everitt, 1982), and impairs the locomotor stimulant effects of the indirectly acting DA agonist amphetamine. Lesion of DA terminal fields within the NAS enhances locomotion elicited by the direct DA agonist apomorphine (Carey, 1983; Iversen & Koob, 1977; Kelly *et al.*, 1975; Winn & Robbins, 1985), but this is presumed to reflect a lesion-induced compensatory increase in receptor sensitivity. Lesion of the nigrostriatal DA terminals may lead to muscle rigidity (Carey, 1983; Johnels, 1982), one symptom of PD (Schwab, 1972).

The problem of dissociating the motoric and motivational roles of DA is particularly acute in relation to studies involving systemic drug administration, which affects all DA terminal areas indiscriminately. Lever pressing for food is physically more demanding

than the nonoperant consumption of food. Consistent with a motoric interpretation, operant procedures are more sensitive to neuroleptic drug action than consummatory procedures (eg. Rolls *et al.*, 1974). Also, nose-poking for ICSS; a relatively undemanding operant, was less sensitive to the disruptive effects of a neuroleptic than lever pressing for the same stimulation (Ettenberg *et al.*, 1981). Nevertheless, within the matching paradigm (Herrnstein, 1970), it is the low response rate, low reinforcement rate schedules that appear most susceptible to neuroleptic drug administration (see Chapters 2 and 3); the significance of this observation is discussed below (section 1.2.4). Furthermore, a licking response for ICSS was more susceptible to neuroleptic action than a lever pressing response (Wauquier & Niemegeers, 1979). Task-specific susceptibility to neuroleptic challenge has been suggested to reflect the threshold of stimulation necessary to maintain the response (Wauquier & Niemegeers, 1979; Wise, 1982): the higher the threshold, the more susceptible the response to neuroleptic drug action. However, it has also been observed that if availability of reinforcement was made contingent on a specific force of lever pressing, pimozide did not reduce high force responding any more at a lower force requirement (Kirkpatrick & Fowler, 1989). Indeed, haloperidol increased the peak response force, and was suggested to reflect a reduction in motor control (Kirkpatrick & Fowler, 1989).

Studies of drug self-administration provide clear evidence that purely motor accounts of dopamine function are untenable. Destruction of DA terminals within the NAS or DA cell bodies in the VTA impairs the self-administration of cocaine or amphetamine (Lyness *et al.*, 1979; Roberts *et al.*, 1977; Roberts & Koob, 1982), an effect not seen following lesions of the dorsal striatum (Koob *et al.*, 1987) or frontal cortex (Martin-Iverson *et al.*, 1986). These data suggest that the reinforcing effects of stimulant

drugs are mediated by the mesolimbic DA system. Evidence suggests that this system is also involved in opiate reinforcement, as rats will self-administer morphine directly into the VTA (Bozarth & Wise, 1981), or methionine enkephalin into the NAS (Goeders *et al.*, 1984). However, Pettit *et al.*, (1984) trained animals to self-administer cocaine or heroin, each drug being made available on alternate days. 6-OHDA-induced lesions of the NAS initially reduced responding for both drugs, but while self-administration of heroin later recovered, responding for cocaine did not. These data suggest that the reinforcing properties of opiate self-administration may be to some extent independent of mesolimbic DA functioning, although this issue remains to be resolved (see Koob & Goeders, 1989). While a reduction in response rate following an experimental manipulation can not necessarily be taken to imply a reduction in the reinforcing properties of the drug, the generally low response rates for drug self-administration make a reduction in motor functioning less plausible as an explanation of these impairments than in the case of operant responding maintained by conventional reinforcers. In fact, impairment of DA function does not necessarily lead to a reduction in response rate in the self-administration paradigm. Low doses of DA antagonists increased response rates for intravenous injections of amphetamine in a comparable manner to that following substitution of saline for drug (Yokel & Wise, 1975, 1976), and also increased responding for high doses of cocaine (Bergman *et al.*, 1990). Although interpretations of neuroleptic-induced increases in drug-reinforced responding are controversial (see Chapter 7), an increase in responding following neuroleptic administration does at least indicate that a reduction in motor ability cannot explain all of the effects of neuroleptic administration.

1.2.2 Neuroleptic-induced Response decrements

A major characteristic of neuroleptic drug action is the so-called "extinction-like" effect, in which decrements in responding are not immediate, but gradually emerge as the session progresses (eg. Fouriezos and Wise, 1976; Franklin and McCoy, 1979; Wise *et al.*, 1978a,b). This pattern of behaviour is also seen following withdrawal of the reinforcer, hence the term "extinction-like". In studies of drug self-administration, pretreatment with high doses of pimozide caused a temporary increase in responding for cocaine or amphetamine, before responding declined later in the session. Substitution of saline for stimulant drug caused a similar pattern of responding (deWit & Wise, 1977; Yokel & Wise, 1975, 1976): responding increased at first, but declined subsequently. Hence, the effects of neuroleptics on behaviour are in some respects comparable to those of an absence of the reinforcer. Consequently, gradual decrements in responding following neuroleptic treatment have been taken as strong evidence for neuroleptic-induced "anhedonia", i.e. a blockade of the primary reinforcing properties of the stimulus (Wise *et al.*, 1978a). This interpretation was supported by the observation that the comparable response decrement induced by extinction was maintained in pimozide-treated animals when the reinforcer was reinstated (Wise *et al.*, 1978b).

The gradual onset of the response-decrementing effect of neuroleptics can not be explained as the outcome of a gradual penetration of the neuroleptic into the brain. For example, pimozide acheived asymptotic effects on VI performance after 2h (Morley *et al.*, 1984), but response decrements induced by pimozide were observed with a 5h pretreatment time. Similarly, Willner *et al.*, (1987) studied VI performance in rats following pimozide pretreatment. Within-session decrements were observed following a 2h pretreatment, and a very similar pattern emerged after a 4h pretreatment time, in

which effects on performance were again largely confined to later periods of the experimental session. A gradually emergent deficit in motor performance also seems unlikely. In VI performance, within-session decrements are most evident under schedules that engender low response rates (Willner *et al.*, 1987, 1990a), which are presumably less physically demanding. Also, following the observation of a pimozide-induced response decrement in intracranial self-stimulation (ICSS), animals showed spontaneous recovery following a brief time-out period (Fouriezos & Wise, 1976). A similar recovery in responding under pimozide was obtained by presentation of a conditional stimulus (Franklin & McCoy, 1979). If the same (light) stimulus had not been previously paired with reinforcement, then it did not cause responding to recover; this suggests that spontaneous recovery is not caused by the nonspecific activating characteristics of the stimulus. Similarly, again using ICSS as the reinforcer, following the observation of a pimozide-induced response decrement in one task (Skinner box or runway), responding was temporarily reinstated upon subsequent testing in the second task (Gallistel *et al.*, 1982). Picrotoxin (a GABA antagonist) also produced an "extinction-like" decline in operant responding, but spontaneous recovery following transfer to the alleyway did not occur. Picrotoxin-induced response decrements appeared to correlate with onset of seizure (Gallistel *et al.*, 1982).

If the within-session decrements caused by neuroleptic drug administration were functionally equivalent to those engendered by removal of primary reinforcement, then these manipulations ought to be interchangeable (Wise *et al.*, 1978; Wise, 1982). Tombaugh *et al.*, (1980) trained rats to respond on a VI240s schedule for food reinforcement. For the following four experimental sessions, one group was administered pimozide, and a second was placed under extinction. Responding by these groups

declined both within- and across-sessions. Finally, for the remaining two experimental sessions, the conditions were reversed. Responding by rats that had previously experienced extinction conditions continued to decline when placed under the pimozide-reward condition, as observed by Wise *et al.*, (1978). However, rats that had previously been administered pimozide under the food reinforcement schedule showed a striking increase in responding when transferred to the vehicle-extinction condition. Thus, the effects of transfer from conditions of nonreward to conditions of reward-under-pimozide were not symmetrical. Comparable data have been observed by others (Gerber *et al.*, 1981; Gramling *et al.*, 1984; Mason *et al.*, 1980; Willner *et al.*, 1987).

These data suggest that extinction and neuroleptic treatment are not equivalent, and therefore neuroleptic-induced within-session decrements do not reflect a blockade of primary reinforcement processes. However, the logical validity of the transfer test has been disputed (Martin-Iverson *et al.*, 1987). According to these authors, in an operant test, rats may be seen as possessing two expectancies on the basis of past experience. One is the contingency of reinforcement upon responding, and the second is that consumption of the reinforcer has rewarding consequences. In extinction, the former expectancy is contradicted, but the latter necessarily remains intact. Under rewarded, but neuroleptic-treated conditions, the positions are reversed: the reinforcement-response contingency remains intact, but the expectation of the rewarding consequences of consumption may not. That is to say, "Reward omission is **not** simply an attenuation of pleasurable sensation" (Martin-Iverson *et al.*, 1987). Given that within-session performance decrements occur even in avoidance procedures (Hillegaart *et al.*, 1987; Sanger, 1986), the nature of neuroleptic-induced within-session response

decrements remains uncertain.

1.2.3 Dopamine and reward

In the light of these data, neuroleptic-induced response decrements can not be taken as evidence that neuroleptics attenuate reward processes. However, other types of experiment do provide evidence to support this position. As noted above, neuroleptic administration, or lesions of DA systems, affect response rate for the self-administration of stimulant drugs in a manner at least partially compatible with a reduction in reinforcement (see above). ICSS procedures offer comparable data. In order to assess the impact of a selective lesion upon ICSS, the effects of a lesion ipsilateral to the electrode may be compared with those of a contralateral lesion. If the effects of the lesion were not specific to the reinforcing impact of ICSS, then either lesion should impair responding. Alternatively, if the lesion were placed in a site mediating the reinforcing impact of the ICSS, then a lesion ipsilateral to the electrode would have a greater impact on responding than a contralateral lesion. Consistent with a reinforcement interpretation of DA function, ipsilateral lesions of ascending DA fibres severely impaired ICSS of the VTA, but contralateral lesions had no effect (Phillips & Fibiger, 1978; Fibiger *et al.*, 1987). DA metabolism in all major terminal areas has also been shown to be responsive to ICSS of the VTA (Phillips *et al.*, 1987). Whereas DA metabolism in the ipsilateral NAS, striatum and olfactory tubercle was increased by ICSS of the VTA, DA metabolism in the contralateral areas was not (Fibiger *et al.*, 1987; Phillips et al., 1987). These data indicated that increased DA turnover in these areas was not related to motor functioning, but rather, was a specific outcome of the reinforcing effects of VTA stimulation. However, it was noted that similar effects on DA

metabolism occurred when rats were yoked to response-independent stimulation: and yoked-stimulation has previously been demonstrated to be aversive (Steiner *et al.*, 1969). This issue is further discussed in Chapter 7, but suggests the possibility that DA may not subserve primary reinforcement processes.

A number of studies have assessed the role of DA in conditioned reinforcement. Typically, this involves a series of conditioning trials, in which the presentation of a previously neutral stimulus (tone or light) is closely followed by a primary reinforcer, eg. water or food. The acquired reinforcing properties of the stimulus may be assessed by its ability to maintain responding in the absence of the primary reinforcer: a more stringent test is the ability of the conditioned reinforcer to support the acquisition of a new operant (Mackintosh, 1974). To control for nonspecific effects of experimental manipulations on behaviour two levers are normally present, only one of which produces conditioned reinforcement. In order to demonstrate drug effects on conditioned reinforcement, changes in response rate must show significant specificity to the lever obtaining conditioned reinforcement. A number of studies have shown that stimulant administration specifically enhances responding on the lever obtaining conditioned reinforcement (Robbins, 1978; Robbins *et al.*, 1983a,b). In contrast, the direct DA agonist apomorphine was found to increase responding on both levers nonselectively (Robbins *et al.*, 1983b). Consistent with neurochemical data obtained following ICSS of the VTA (see above), direct infusion of amphetamine increased responding maintained by conditioned reinforcement when administered directly to either the NAS or the dorsal striatum (Taylor & Robbins, 1984). It was further shown that lesions of the dorsal striatum did not significantly reduce responding for conditioned reinforcement elicited by amphetamine administration to the NAS (Taylor & Robbins, 1986). This suggests

that these DA terminal areas to some extent possess independent roles in conditioned reinforcement (but see Taylor & Robbins, 1986), which may be consistent with the brain circuitry described above.

A conditioned place preference (CPP) induced by previous association with drug treatment is presumed to reflect the reinforcing properties of that drug. It is well established that pairing of a distinct environment with amphetamine causes a preference for that environment when later tested drug-free (eg. Carr & White, 1986, Carr *et al.*, 1988; Reicher & Holman, 1977; Swerdlow & Koob, 1984). Amphetamine CPP is blocked by neuroleptic pretreatment (haloperidol: Spyraki *et al.*, 1982 ; Mithani *et al.*, 1986; alpha-flupenthixol: Mackey & van der Kooy, 1985; SCH-23390: Leone & Di Chiara, 1987). Moreover, amphetamine CPP appears to be mediated by DA terminals within the NAS, rather than by the DA terminals within the caudate nucleus (Carr & White, 1983, 1986). Again, however, factors other than reward may in principle engender, or impair performance in the CPP procedure, and interpretations of drug effects should be viewed with caution (Carr *et al.*, 1989; Wise, 1989). Nonetheless, these data suggest a role for DA in the acquisition of conditioned reinforcement.

If the effect of DA blockade were simply to impair the reward value of the stimulus, then experience of the degraded reward would be necessary before decrements in responding could be observed. Gray & Wise (1980) trained rats under a VI150s schedule for food reinforcement. Under pimozide, response rate was decreased even before the delivery of the first food pellet. In consequence, Wise (1982) suggested that, in addition to a blunting of the primary rewarding aspects of the stimulus, neuroleptics in addition impair "motivational arousal", i.e. the incentive-motivational impact of conditioned reinforcement, a feature of reinforcing stimuli which is assumed to activate

behavioural output (Bindra, 1974; Killeen, 1982). There is some support for this position. In drug-free rats, an audible tone was paired with food, and later the effects of the tone on lever pressing were examined. Lever pressing was enhanced in the presence of the tone. However, if pimozide was administered prior to the initial pairing of tone and food, then the tone did not enhance lever pressing (Beninger & Phillips, 1981). In an alleyway running procedure following several extinction sessions, availability of reinforcement on a single 'priming' trial leads to a temporary increase in running speed during the subsequent (extinction) session. Neuroleptic administration prior to the temporary availability of reinforcement blocked the priming effect, when tested drug-free on the following day (Horvitz & Ettenberg, 1988; Wiley *et al.*, 1989). Also, responding under extinction was extended following intermittent haloperidol treatment under a continuous reinforcement schedule (Ettenberg & Camp, 1986a,b), a neuroleptic-induced effect analogous to training under conditions of partial reinforcement.

While intact DA functioning is required for incentive-motivational learning to occur, stimulus-stimulus associative learning occurs even when DA functioning is blocked. Defensive burying by rats is an unconditioned response to an aversive stimulus (Pinel & Treit, 1968). If a previously neutral stimulus (eg. a metal prod) is paired with electric shock then this results in prod burying behaviour. This form of prod-s-hock associative learning was not affected by prior neuroleptic treatment, when later tested drug-free (Beninger *et al.*, 1980). Salamone (1986, 1988) studied the effects of haloperidol on the activity and behaviour arising from the presentation of food. Neuroleptic treatment consistently reduced the amount of activity observed, but the rats remained in the proximity of the food dispenser and continued to consume delivered food. Salamone

(1987) has argued that motivated behaviour has both a directional and an activational aspect. Neuroleptic drugs may not affect the former aspect of behaviour, but reduce the quantity (i.e. rate, frequency, duration) of the selected behaviour. This view is consistent with the results of experiments in which neuroleptics impaired response rate, but not the selection of the correct response choice (Bowers *et al.*, 1985; Evenden & Robbins, 1983; Tombaugh *et al.*, 1982; Willner *et al.*, 1990b). According to Salamone (1987, 1988), a deficit in "motivational arousal" should not be seen as incompatible with a deficit in motor functioning, but rather that the motor systems that are impaired by neuroleptic treatment are closely linked to the control of motivation.

In a related conceptualization of the effects of neuroleptics on motivated behaviour, Blackburn *et al.*, (1987, 1989) have emphasised the distinction between preparatory and consummatory behaviours. These authors define preparatory behaviours, such as foraging and hoarding, as responses elicited by incentive stimuli that lead to and facilitate the consummatory response, which should be seen as a separate class of behaviour. In a conditioned feeding procedure, rats were trained to associate a light stimulus with imminent delivery of food (Blackburn *et al.*, 1987). Following

presentation of the conditional stimulus, pinozide increased the latency to approach the food hopper, and the number of entries occurring prior to food delivery. However, upon food delivery, latency to approach the food hopper, and food consumption, were normal. Blackburn *et al.*, (1987, 1989) have consequently emphasised that while DA is involved in preparatory behaviour, DA is not involved in the consummatory response itself.

However, neuroleptics do affect consummatory behaviour. Many studies have demonstrated that neuroleptics decrease food intake and decrease the rate of eating

(Blundell & Latham, 1980). This effect may be accompanied by an increase in meal length, which, it has been suggested, might represent a compensatory response to neuroleptic-induced motor impairment (Blundell & Latham, 1980). However, neuroleptics also impair consummatory behaviour in ways that can not be explained in terms of a motor impairment. In a consummatory procedure, a dilute 0.7% sucrose solution is greatly preferred over plain water. Pimozide or sulpiride decreased preference for sucrose, but at lower doses did not affect the the total volume of sucrose and water consumed (Muscat & Willner, 1989; Towell *et al.*, 1987). A number of other studies assessing consummatory responses to sucrose solutions also indicate that neuroleptic treatment may be analogous to dilution (eg. Geary & Smith, 1985; Xenakis & Sclafani, 1981).

In an operant procedure, in which a range of sucrose concentrations was presented on separate days, the reduction of responding following treatment with pimozide was comparable to the effect of quinine adulteration: the lower the concentration of sucrose, the larger the decrement observed (Bailey *et al.*, 1986). The lowest concentration used in this study was 0.86% sucrose. It was assumed that such a low concentration is barely detectable, and hence "of neutral (anhedonic) value." From this, it was concluded that pimozide cannot have further impaired the reward value of the stimulus, but rather exerted an 'aversive hedonic effect' akin to that of quinine. However, lower concentrations of sucrose remain greatly preferred to water (see above, Towell *et al.*, 1987), and sucrose is detectable by rats down to concentrations as low as 0.0012% (Willner *et al.*, 1990b). Nonetheless, given that in the study of Bailey *et al.*, (1986), response decrements caused by pimozide were concentration-dependent, and pimozide did not affect responding for the highest concentration used (78.7%), these

data weigh against motoric interpretations of neuroleptic drug action.

1.2.4 Quantitative methods for assessing drug effects on reward

1.2.4A Intracranial self-stimulation

Since the discovery of electrical self-stimulation of the brain (Olds & Milner, 1954), ICSS has proved a popular choice of rewarding stimulus. Early studies often employed a single current value in the assessment of experimental manipulations. However, the use of a single current value does not enable the dissociation of drug-induced changes in the reinforcement value of the current stimulus from effects on behavioural output not directly related to reinforcement (see above). Attempts to dissociate reward-related from nonspecific decrements induced by neuroleptic drugs have led to a number of quantitative 'rate-free' methods.

The autotitration-of-threshold method consists of two concurrently available levers (Stein & Ray, 1960; Schaefer & Holtzman, 1979). Responding on one lever results in brain stimulation, but with further responding the programmed value of stimulation progressively declines; responding on the second lever resets stimulation to its original value. In this procedure, the crucial measure of the reward value of the stimulation is not the overall response rate, but the point at which stimulation is reset to maximum. This is said to provide a measure of the lowest (threshold) stimulation value sufficiently rewarding to maintain behaviour, irrespective of the rate of that behaviour. Decreasing the programmed stimulation value increases the threshold at which stimulation is reset to maximum (Zarevics & Setler, 1981). Neuroleptic drugs may also raise this threshold (Shaefer & Michael, 1980, 1985), and in effect raise the stimulation value required to maintain behaviour. Overall response rate on the stimulation lever may be depressed

following neuroleptic treatment, but it should be noted that an increase in the behavioural threshold implies an increase in initiations of reset behaviour relative to the number of responses for stimulation. This has been suggested to reflect an attempt to compensate for the effects of DA blockade (Schaefer & Michael, 1980). However, threshold measures are not absolute in this procedure, but reflect the chosen stimulation parameters; increasing the maximum obtainable stimulation value increases the threshold at which stimulation is reset (Fouriezos & Nawiesnak, 1982). Autotitration may thus be seen as choice behaviour, reflecting the stimulation value currently obtainable relative to stimulation available upon reset (Stellar & Rice, 1989).

A second quantitative method is the rate-frequency curve-shift procedure. Behaviour is rewarded by a train of reinforcing brain stimulation impulses, and the pulse frequency varied from trial to trial within a session. A sigmoidal response-frequency function is typically observed, analogous to a dose-response function. In an alleyway running procedure, increasing runway gradient, or decreasing muscle tone by administration of d-tubocurarine or methocarbamol reduces asymptotic running speed with little consistent effect on the lateral position of the curve (Edmonds & Gallistel, 1974). Conversely, reducing the stimulation current shifts the rate-frequency curve to the right, but has little effect on asymptotic running speed for high pulse frequencies. Hence, drug effects on performance factors should be dissociable from effects on reinforcement. Initial experiments showed that the catecholamine synthesis inhibitor alpha-methyl-para-tyrosine shifted the curve to the right, but also reduced the behavioural asymptote (Edmonds & Gallistel, 1977). However, at low doses pimozide may selectively shift the curve to the right (Franklin, 1978); higher doses in addition reduce the asymptote, and may result in a complete cessation of responding (Gallistel,

1986). Indeed, the limited range over which the curve may be reliably shifted by pimozide, in comparison with a reduction in stimulation value has been the subject of comment (Gallistel & Freyd, 1987). It has been suggested that DA does not directly mediate the reward process, but instead maintains a homeostatic control over neural circuitry operating within a narrow functional range. In this context, apparently modest effects on the lateral position of the curve are said to imply that the neural mechanisms would be operating at an extreme value, and further action at DA receptors could lead to a complete failure of the system (Gallistel & Freyd, 1987). Alternatively, the role of DA in rewarded behaviour may be seen as a gating, or enabling function, such that sufficient DA turnover is necessary for the expression of rewarded behaviour (Miliaressis *et al.*, 1986).

1.2.4B The Herrnstein Matching Law

A related curve-shift procedure, which more commonly involves natural reinforcement, utilises the Herrnstein matching law. Under variable-(VI) or random-(RI) interval schedules, reinforcement is unpredictable, and contingent behaviour is roughly constant over time. Response rate is assumed to increase with reinforcement density, up to a theoretical maximum rate of responding. The relationship between these two variables may be characterised as a negatively accelerated hyperbolic function (Fig.1.1; Catania & Reynolds, 1968), known as Herrnstein's matching law (Herrnstein, 1970) and expressed mathematically as:

$$B = \frac{KR}{(R + Re)}$$ (for derivation, see Chapter 2)

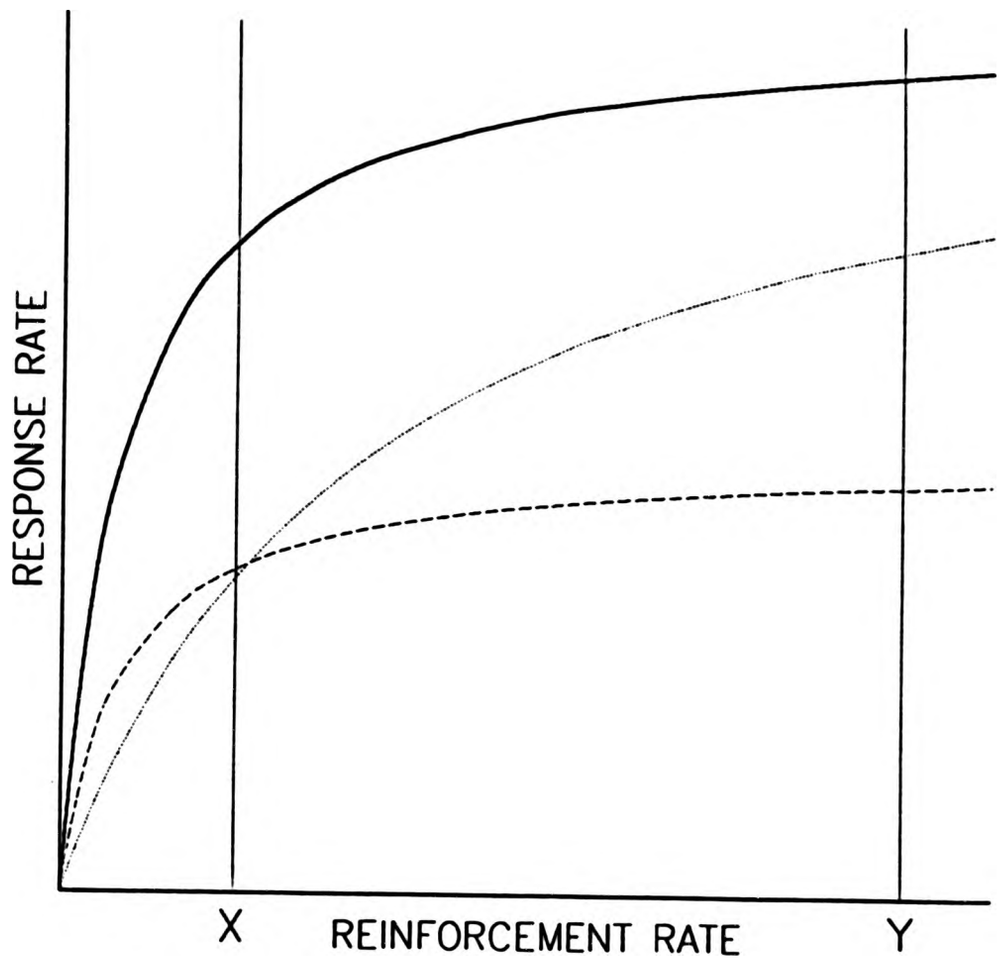


FIG. 1.1. Hypothetical curves for RI performance in control conditions **(full line)** and following treatments that cause motivational **(dotted line)** and motor **(dashed line)** impairments. The former treatment, but not the latter, reduces responding to a proportionately larger extent under reinforcement-lean conditions (*X*) than under reinforcement-rich conditions (*Y*).

In this equation, B is the response rate and R the reinforcement rate; K represents the maximal response rate and Re the reinforcement density that maintains responding at half the asymptotic rate. The constant K has been shown to be selectively affected by motoric manipulations such as increasing the response force requirement, and Re (the lateral position of the rising portion of the curve) by motivational factors such as varying the degree of food deprivation (Bradshaw *et al.*, 1983a,b; Hamilton et al., 1985; Heyman & Monaghan, 1987; McSweeney, 1978; see reviews by de Villiers & Herrnstein, 1976, de Villiers, 1977). Hence, the Herrnstein equation may provide a methodological basis for distinguishing between motoric and motivational explanations of drug-induced performance changes.

In consequence, the matching law has been seen as a potentially useful tool in assessing the functioning of brain dopamine. With few exceptions (eg. cis-flupenthixol, see below), neuroleptic drugs have been found to increase Re, interpretable as a reduction in the efficacy of the reinforcer (Hamilton et al., 1985; Heyman, 1983; Heyman *et al.*, 1986; Willner *et al.*, 1987, 1990a). Effects on Re may or may not be accompanied by a reduction in K, but in common with the ICSS curve-shift procedure effects on K are more likely at higher doses. Neuroleptics tested include pimozide, chlorpromazine, sulpiride and SCH-23390. Cis-flupenthixol however, appears to show only minimal effects on Re at best (Hamilton *et al.*, 1985), and may simply decrease K (Heyman *et al.*, 1986). In addition, there has been some dispute as to the action of pimozide, which has been found by some simply to decrease K (Morley *et al.*, 1984; see Chapter 2 for further discussion). Conversely, amphetamine reduces the value of Re, interpretable as an increase in the value of the operant reinforcer (Heyman, 1983; Heyman & Seiden, 1985; Morley *et al.*, 1985; Willner *et al.*, 1987). Again, effects on K,

when they occur, are less consistent: both reductions (Morley *et al.*, 1985) and increases in K have been reported (Heyman & Seiden, 1985). The matching law appears then to provide a useful tool for dissociating motivational from motoric drug-induced performance changes.

The application of the Herrnstein matching law requires that response data be obtained at a number of reinforcement densities. Results may be speedily achieved by using a multiple schedule (eg. Heyman, 1983), but the disadvantage is that such schedules require a great deal of initial training, and a proportion of animals fail to conform to the hyperbolic curve (Willner *et al.*, 1987, 1990a). An alternative method is to present each schedule separately, and complete experimental manipulations before moving on to the next schedule (eg. Bradshaw *et al.*, 1983a,b). Such a procedure requires less training, but data collection is very much slower. It has been suggested that only two schedules need be employed, since effects on Herrnstein's parameters can be inferred from differential effects under the two densities of reinforcement (Morley *et al.*, 1984, 1985; see also Chapter 2). Initial experiments in this laboratory, using a variant of the 2-schedule inferential procedure in which the two schedules were presented on alternate days, confirmed that pimozide caused performance changes compatible with a decrease in both motivation and motor ability (Willner *et al.*, 1987; 1990a). Importantly, comparable data were also obtained using a 3-schedule method, in which Herrnstein's parameters may be directly computed, and in a multiple schedule procedure in which 5 components were presented in random order (Willner *et al.*, 1990a). However, in these experiments motivational decrements induced by pimozide under the 2-point and 3-point procedures were not constant over time, but were found to increase during the course of the session (Willner *et al.*, 1987, 1990a).

Although consistent data were obtained using the 2-point, 3-point, and 5-component multiple schedules, in a nonrandom multiple schedule procedure, the apparent effects of pimozide on Herrnstein's parameters were crucially determined by the order of component presentation. Under conditions in which reinforcement density (and response rate) increased during the session, pimozide appeared selectively to decrease motor ability. However, if reinforcement density (and response rate) decreased during the course of the session, then pimozide appeared selectively to reduce the motivation to respond (Willner *et al.*, 1987). A resolution of these apparently paradoxical findings was provided by the observation that both of these apparent effects would be expected if the suppressive effect of pimozide increased during the course of the experimental session. Given the well-documented "extinction-like" effects of neuroleptics (see above), these paradoxical changes in Herrnstein's parameters may reflect a gradual decrement in performance as the session progresses. Such decrements would clearly compromise the use of Herrnstein's equation in evaluating neuroleptic drug action. It seemed a matter of some urgency to assess the potential contribution of time-dependency in procedures utilising the Herrnstein method, and this problem formed the starting point for the studies to be described in the present thesis.

CHAPTER 2

THE HERRNSTEIN MATCHING LAW:

DISSOCIATING MOTOR CAPACITY FROM MOTIVATION

2.1 INTRODUCTION

Herrnstein's matching law is based on three assumptions:

1. In a given situation, the total output of all behaviours remains constant.

2. The frequency of each behaviour, relative to the total frequency of all behaviours, arises through the excercise of choice.

3. Choice is determined by the reinforcement rate of each behaviour, relative to the total reinforcement rate for all behaviours.

That the relative frequency of responding matches the relative frequency of obtained reinforcement was first described by Herrnstein (1961). Mathematically, this may be expressed as:

$$\frac{B1}{B1 + Be} = \frac{R1}{R1 + Re} \qquad (1)$$

where B1 and R1 refer to the behaviour and respective reinforcement rate in question, and Be and Re the respective totals of all other, 'extraneous' behaviours and associated reinforcement rates. To predict an operant response rate (Bo) for a given reinforcement rate (Ro), rearranging equation 1 gives:

$$Bo = \frac{(Bo+Be).Ro}{Ro + Re} \qquad (2)$$

Furthermore, if assumption 1 holds, and the total output of all behaviours (Bo + Be) remains constant, one may simplify equation 2, thus:

$$Bo = \frac{K.Ro}{(Ro + Re)} \qquad (3)$$

This is known as Herrnstein's equation, and describes in mathematical form the negatively accelerating hyperbolic relationship between response rate and reinforcement rate. Strictly speaking then, the constant K measures the total output of all behaviours. However, if Re is set at zero, and therefore all behaviour is operant behaviour, it follows that:

$$Bo = \frac{K.Ro}{Ro} \qquad (4)$$

Ro cancels itelf out, and in effect K would measure the maximum response rate, also known as motor capacity. This can be inferred using the Herrnstein matching law by computing the asymptote of the response-reinforcement matching curve, which is taken as an independent measure of the animal's physical ability to respond (see Section 7.2.1 for further discussion).

Conversely, if one sets the reinforcement value of Re at 0.5 relative to the reinforcer value of Ro, then it follows that the relative reinforcer value of Ro must also be 0.5. Substituting these values in equation 3 now gives:

$$Bo = K \times 0.5 \qquad (5)$$

If the operant reinforcement rate (Ro) that would maintain responding (Bo) at half the value of K is computed, it can be seen that this would automatically provide a measure

of the reinforcement efficacy of Ro, relative to all extraneous reinforcement available in the situation, Re. This is because at this point on the curve Ro equals Re. In this manner Re is seen as an independent measure of reinforcer efficacy, and is defined as the reinforcement rate which would theoretically maintain responding at half the value of K. As predicted, the constant K has been shown to be selectively affected by motoric manipulations, and Re by motivational factors (Bradshaw *et al.*, 1983a,b; Hamilton *et al.*, 1985; Heyman & Monaghan, 1987; McSweeney, 1978; see reviews by de Villiers & Herrnstein, 1976; de Villiers, 1977). However, it should be noted that attempts to validate the independence of Herrnstein's parameters have not always met with success; these cases will be discussed in Chapter 7.

The matching procedure appears then to provide a useful method for dissociating motivational from motoric drug-induced performance changes. However, a minimum of three response-reinforcement data points are required to compute Herrnstein's hyperbola. Animals may be trained and tested under one scheduled reinforcement rate at a time (eg. Bradshaw *et al.*, 1983a,b), under three schedules of reinforcement in a 3-day cycle (Willner *et al.*, 1990a), or under a multiple schedule in which several schedule components in the same session (eg. Heyman, 1983; Willner *et al.*, 1987). Unfortunately, all methods are laborious and time-consuming to operate, and are only learned by rats following prolonged training. However, Morley *et al.*, (1984, 1985) have advanced a simplified, inferential method for assessing effects on Herrnstein's parameters. Factors that influence the value of K are thought to be unrelated to the reinforcement value of the stimulus, but are motoric in nature. Hence, changes in K arise through a proportionately comparable change in response rate irrespective of the contingent reinforcement density, changing the asymptote of the curve but leaving the

lateral position of the rising portion unaffected. Conversely, Re is suggested to reflect the reinforcement value of the stimulus, and is measured as the lateral postion of the rising portion of the curve. Hence a change in Re is reflected in a progressively smaller change in response rate relative to baseline as reinforcement density is increased. From this, it has been suggested that it is not essential to derive K and Re in dissociating motoric from motivational influences upon behaviour (Morley *et al.*, 1984, 1985). Instead, data need only be obtained at two distinguishable reinforcement rates to achieve this objective, and changes in response rate relative to baseline computed. Given that motivational and motoric influences upon behaviour each may either increase or decrease following an experimental manipulation, it can be seen that effects on the curve may take one of eight possible forms (described in detail by Bradshaw & Szabadi, 1989). Each may be inferred by comparing changes in response rate occurring at just two reinforcement densities. Experience suggests that animals readily learn to distinguish between two schedules, even when presented on alternate days (Willner *et al.*, 1987, 1990a).

In the present study, the 2-schedule procedure was first validated by reducing the motivation to respond (increasing available feeding time), or increasing the motoric requirements of the task (weighting the lever). These manipulations were predicted to cause, respectively, a selective suppression of reinforcement-lean responding (equivalent to an increase in Re), and a nonselective suppression of responding irrespective of the reinforcement density (equivalent to a reduction in K). Then, a series of pharmacological experiments were carried out to determine the interpretability of data generated by the 2-point method, and also, by implication, of Herrnstein's equation.

2.2 METHODS

Subjects

A total of 64 adult, male Lister Hooded rats (NIMR, Mill Hill) were used. They were maintained on a twelve hour light/dark cycle (light on 08.00h) at a temperature of 21°C. Animals were housed in pairs, and weighed 250-300g at the start. Testing took place between 14.00 and 18.00h. Animals in experiment 2.1 were maintained on 23h food deprivation except as described below; animals in all subsequent experiments were maintained on 21h food deprivation. Water was available at all times in the home cage. Daily sessions continued six days a week.

Apparatus

The experiments were conducted in eight identical operant chambers (Campden Instruments Ltd, London, UK), delivering a 45mg food pellet reinforcer (experiment 2: Larkhall Labs, Charlbury, UK; all other experiments: Campden Instruments Ltd, London, UK). A force of approximately 9g was required to depress the lever. All sessions for a given subject were conducted in the same chamber. An Acorn System 4 microcomputer (Acorn Computers, Cambridge, UK) was used to record lever presses and to control pellet delivery.

Procedure

After a period of training under continuous reinforcement (5 sessions), animals were placed on a training regime under random-interval schedules of reinforcement; sessions were of 30mins duration. Reinforcement was delivered for the first lever press after a predetermined period, which varied randomly between a minimum of 2s and a

maximum of twice the mean interval for that schedule. Each schedule was signalled by a 0.5s 800Hz sinusoidal tone, which sounded at a schedule-specific inter-tone interval (ITI). Two RI schedules were used in each experiment (experiment 2.1, RI7.5s and 240s, ITI's 2s and 64s respectively; experiments 2.2 and 2.3: RI7.5s and 300s, ITI's 2s and 80s respectively). The two schedules were presented on alternate days (ALT-2 procedure); on any one day, each schedule was presented to one half of the subjects. Test sessions commenced following the attainment of asymptotic performance (40 sessions).

Experiments 2.1 and 2.2

Using 16 subjects, the effects of varying the response force requirement were examined by adding weights to the levers; the effects of increasing the initial force requirement (9g) by a factor of 2, 3, 4 and 8 were tested sequentially. Subsequently, the effects of increasing the period of daily food access from 1h to 2, 3 and 4h were also tested sequentially. A minimum of two control days were interposed between successive tests under changed experimental conditions.

Following the reattainment of steady state performance under standard conditions (21h food deprivation, 9g lever weight), the effects of fenfluramine (0.75, 1.5 and 2.25mg/kg) were assessed. A separate group of animals (n=12), were tested under fluoxetine (1.5, 3 and 4.5mg/kg).

Experiment 2.3

A period of at least 2 weeks separated each drug test for any one group. Prior to each test, it was ensured that baselines were stable, i.e. no significant changes in response rate for at least 5 days prior to test start. For one group (n=12), the effects

of sulpiride (20,40 and 80mg/kg) and metergoline (0.5, 1 and 2mg/kg) were assessed. A second group (n=12) was tested under yohimbine (0.5, 1, 2 and 4mg/kg) and clonidine (2.5, 5, 10, 20 and 40ug/kg). Finally, a third group (n=12) was administered scopolamine (6.25, 12.5, 25 and 50ug/kg) and methyl-scopolamine (12.5, 25 and 50ug/kg).

Drugs

Drugs, solutes, pretreatment times and administration routes were:

Clonidine hydrochloride (Sigma, Poole, UK), distilled water, 30mins, i.p.

Fenfluramine hydrochloride (Sigma, Poole, UK), distilled water, 30mins, i.p.

Fluoxetine hydrochloride (Eli Lilly, USA), warm 0.9% saline (60°C approx.), 75mins, i.p.

Metergoline hydrochloride (Farmitalia, Milan, Italy), dissolved in up to two drops of glacial acetic acid (84ul approx.), then made up to volume with distilled water, 30mins, i.p.

SCH-23390 maleate (Schering Corporation, Bloomfield, USA), warm 0.9% saline (60°C approx.), 30mins, s.c. in the scruff of the neck.

(-)Scopolamine bromide (Sigma, Poole, UK), distilled water, 30mins, i.p.

(-)Scopolamine methyl bromide (Sigma, Poole, UK), distilled water, 30mins, i.p.

Sulpiride (Sigma, Poole, UK), dissolved in up to two drops of glacial acetic acid (84ul approx.) then made up to volume with distilled water, 60mins, i.p.

Yohimbine hydrochloride (Sigma, Poole, UK), distilled water, 30mins, s.c. in the scruff of the neck.

All doses were administered in a volume of 1 ml/kg, and respective solutes served

as vehicle treatments. Each dose was administered in ascending order; at each dose level both vehicle and drug were administered before each schedule, in a counterbalanced order across schedules and days. Drug sessions were separated by at least two drug-free days.

Analysis

Response rates for each drug and dose; and proportional changes in response rate relative to respective vehicle scores, were subjected to analyses of variance supplemented where appropriate by tests of simple main effects and planned comparisons.

2.3 RESULTS

Experiment 2.1

The effects upon ALT-2 performance of varying the experimental procedure are shown in Fig. 2.1. Adding weights to the lever decreased responding under both schedules (Fig. 2.1, top right panel: $F(1,13) = 225$, $p < 0.001$), and to a proportionately comparable extent at all levels of response force (Fig. 2.1, bottom right panel: $F(1,13) = 0.03$, N.S.). In contrast, reducing the length of food deprivation greatly decreased responding under reinforcement-lean conditions (Fig. 2.1, top left panel: $F(3,78) = 9.7$, $p < 0.001$), but only the lowest level of deprivation decreased responding under reinforcement-rich conditions ($F(1,78) = 6.5$, $p < 0.05$). It follows that reductions in responding under reinforcement-lean conditions were proportionately larger than those under reinforcement-rich conditions (Fig. 2.1, bottom left panel: $F(1,13) = 25.2$, $p < 0.001$).

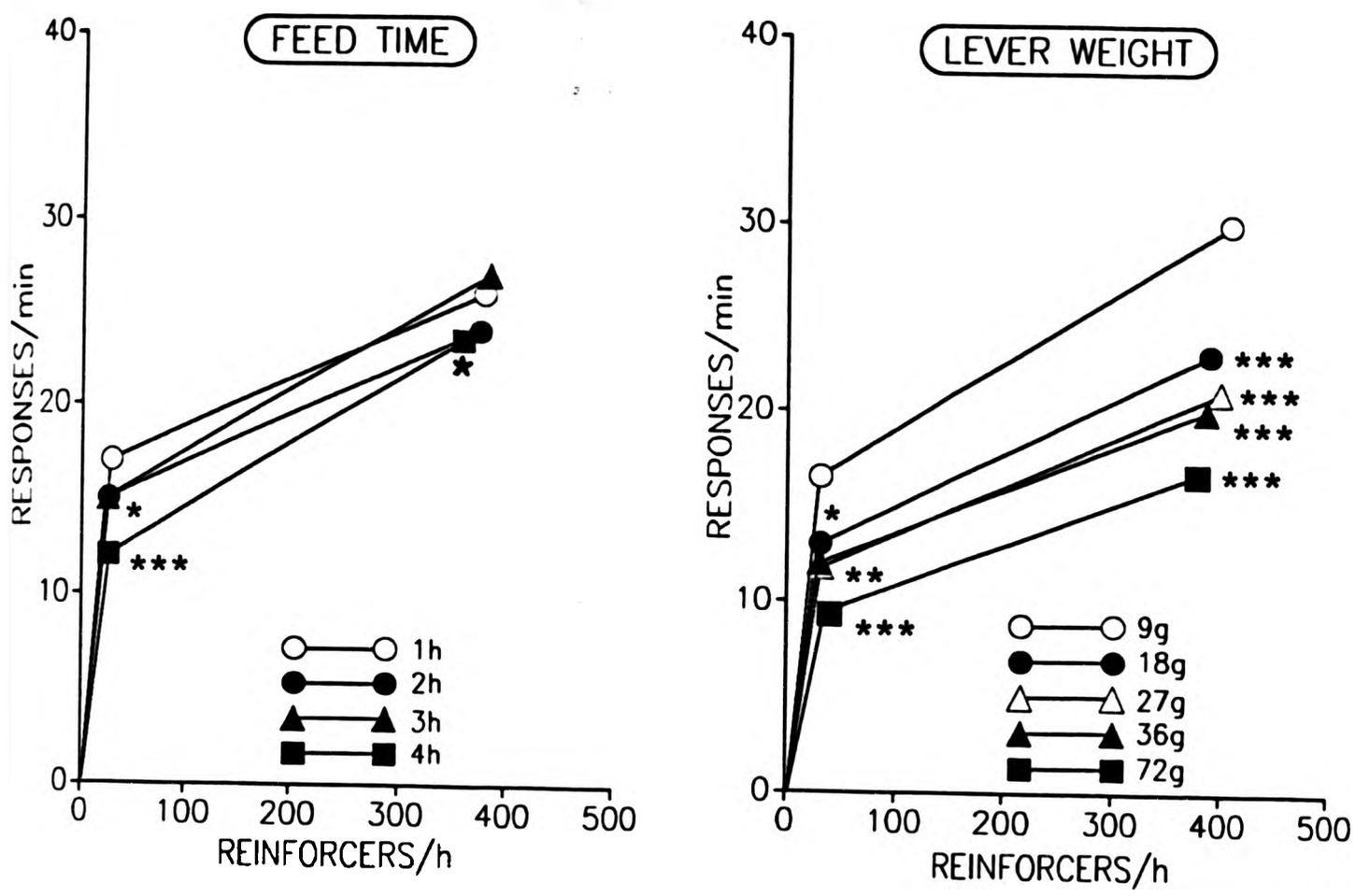
Experiment 2.2

Fenfluramine dose-dependently suppressed responding under both the reinforcement-lean, and reinforcement-rich schedule (Fig. 2.2, top right panel: $F(2,26) = 25.4$, $p < 0.001$). Proportionately, these reductions in response rate under the two schedules were very similar (Fig. 2.2, bottom right panel: $F(1,13) = 2.5$, N.S.). Fluoxetine also suppressed responding under both reinforcement frequencies (Fig. 2.2, top left panel: $F(2,22) = 6.7$, $p < 0.01$). However, in contrast to the nonselective effect of fenfluramine upon response rate, the suppressant effect of fluoxetine was proportionately larger under reinforcement-lean conditions, and reached statistical significance at the highest dose tested (Fig. 2.2, bottom left panel, 4.5mg/kg: $F(1,33) = 4.8$, $p < 0.05$).

Experiment 2.3

Like fluoxetine, the DA D-2 antagonist sulpiride (20 and 40mg/kg) preferentially suppressed responding under reinforcement-lean conditions (see Table 2.I and Fig. 2.3, top left panel, rich vs. lean suppression: $F(1,11) = 8.4$, $p < 0.05$). Only the highest dose (80mg/kg) suppressed responding under the reinforcement-rich schedule ($F1,33) = 62.3$, $p < 0.001$). By contrast, no other drug tested in this experiment showed a preferential effect under reinforcement-lean conditions (Table 2.I); this may clearly be seen when the results are expressed as a proportion of responding under control conditions (Fig. 2.3). Both metergoline and yohimbine exerted a non-monotonic action upon response rate: responding was enhanced at low doses, but suppressed at higher doses. However, while the effects of yohimbine and metergoline were not generally specific to the schedule in operation (yohimbine, rich vs. lean schedule: $F(1,11) = 0.5$, N.S.), metergoline at the

lowest dose tested (0.5mg/kg) preferentially enhanced responding under the reinforcement-rich schedule ($F(1,33) = 10.9$, $p < 0.01$). By contrast, clonidine and scopolamine monotonically suppressed responding, although to a consistently larger extent under the reinforcement-rich schedule (rich vs. lean supression: $F(1,11) = 40.0$, 29.8 respectively, $p < 0.001$). Revealingly, the most striking example of a preferential impact upon reinforcement-rich responding is provided by methyl-scopolamine. Response suppression under reinforcement-rich conditions was never less than 80% and is clearly at, or near floor levels. In this context, it is remarkable that response suppressions under the reinforcement-lean schedule were never more than 9% (rich vs. lean suppression: $F(1,11) = 162$, $p < 0.001$).



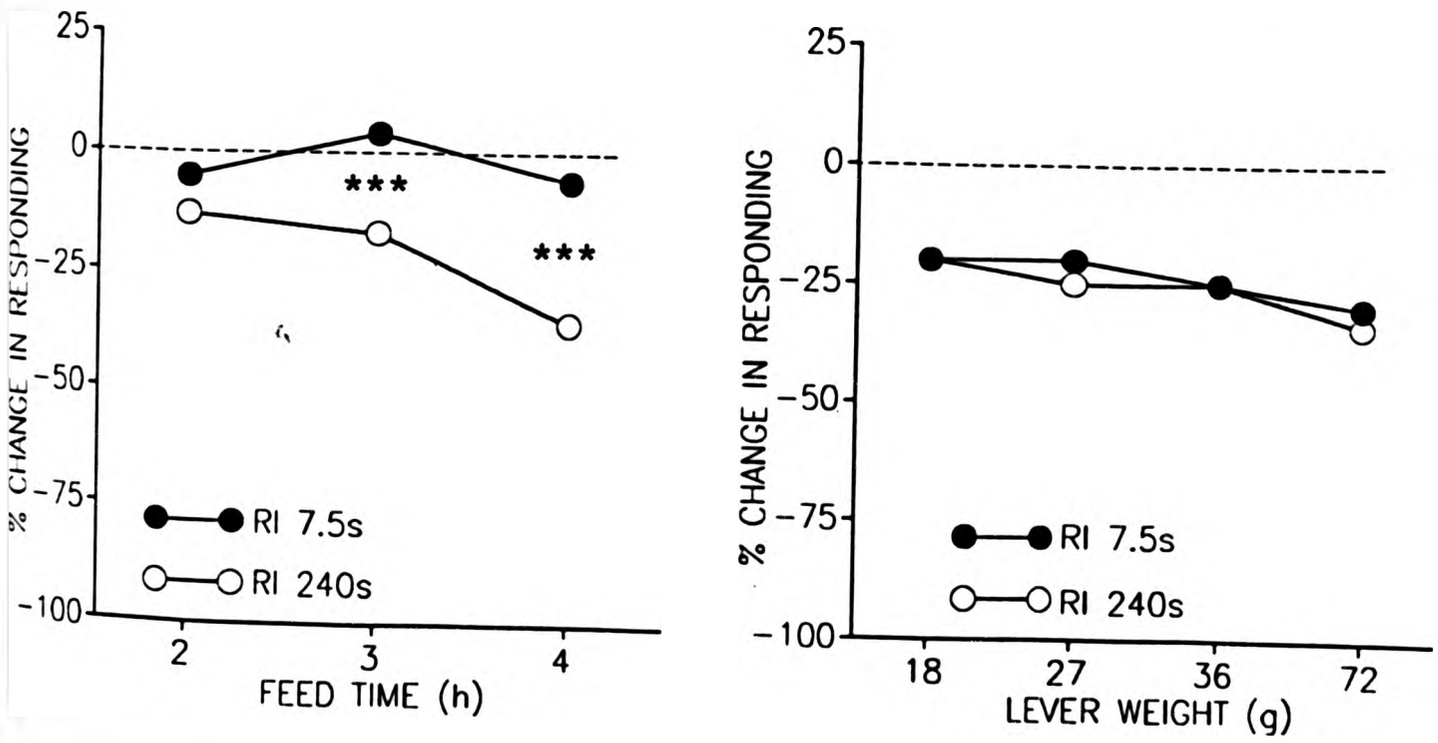


FIG. 2.1. Effects of increasing the period of daily food access (left panel) and increasing the response force requirement (right panel) on performance under the ALT-2 procedure. Upper panels, responses and reinforcements; lower panels, proportional decrease in responding relative to vehicle treatment. Values are means. Stars indicate statistical significance of manipulations: *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$.

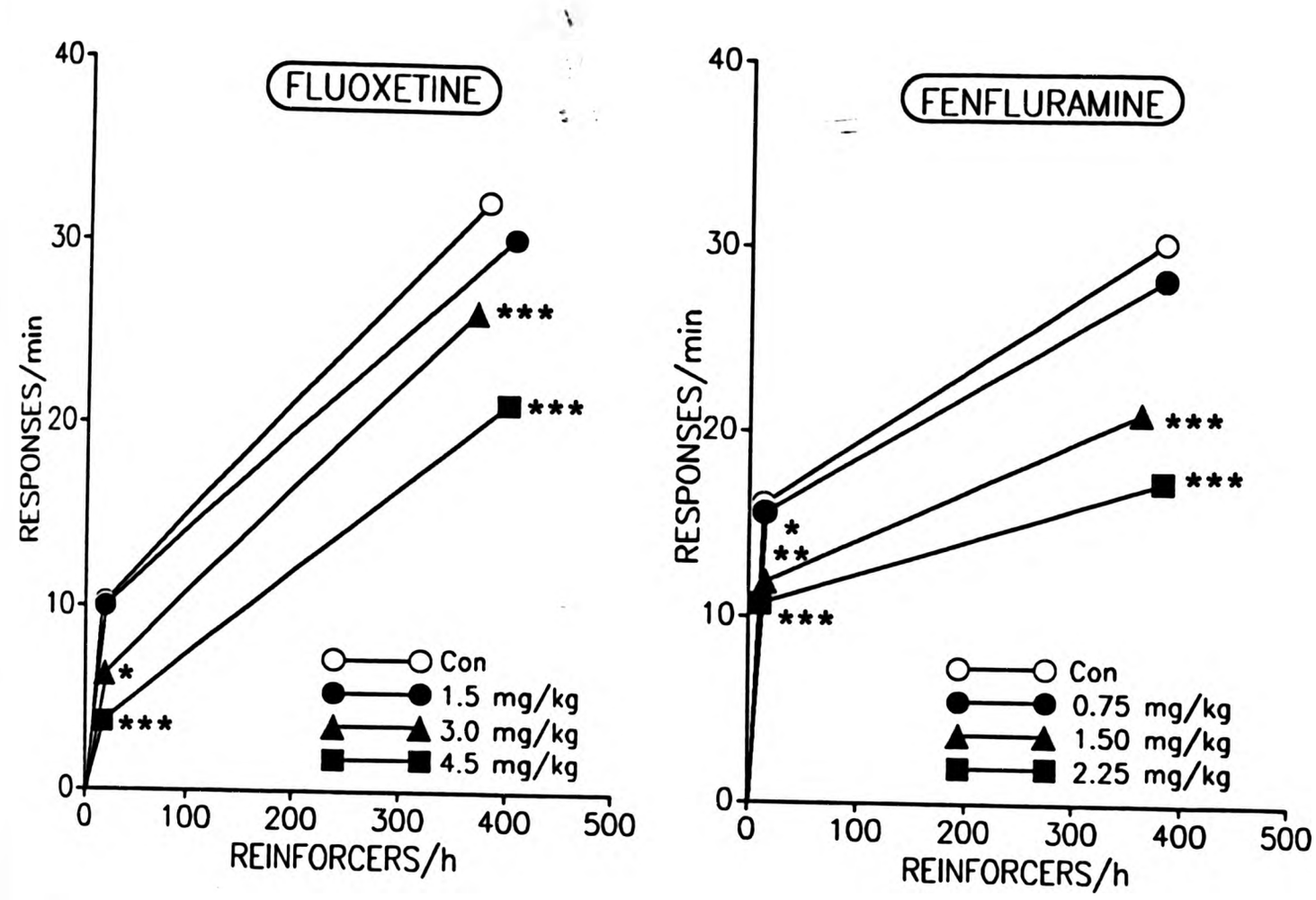
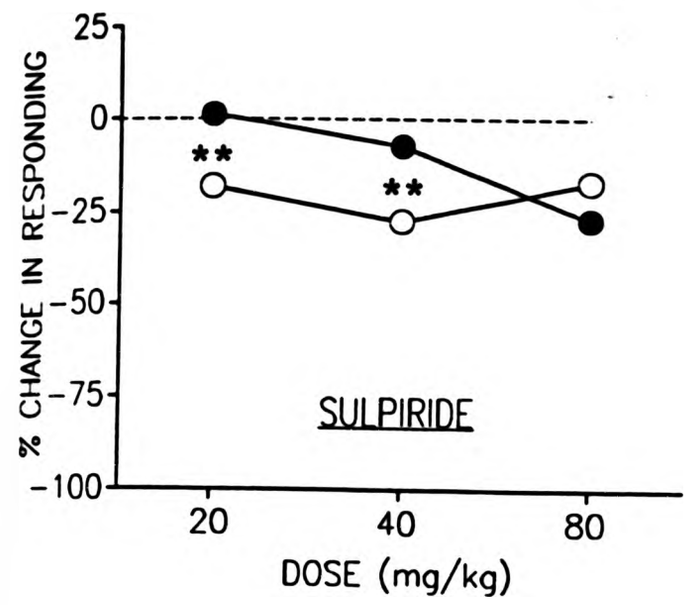
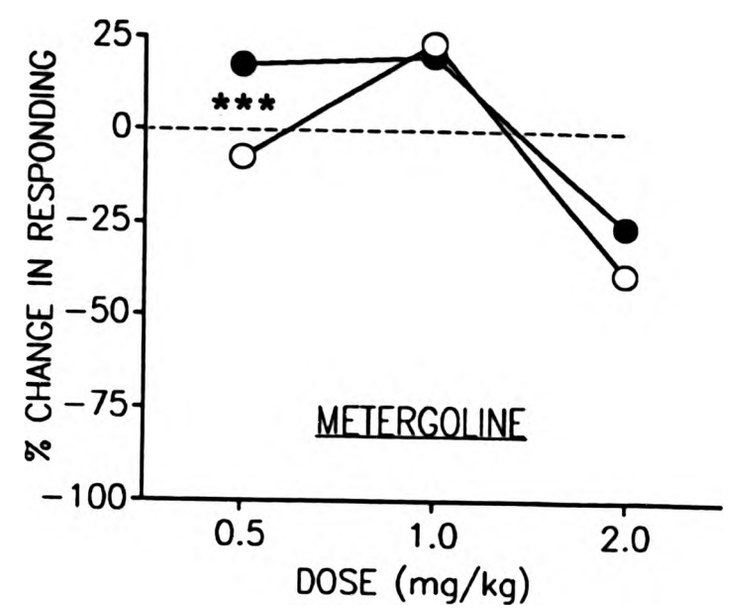
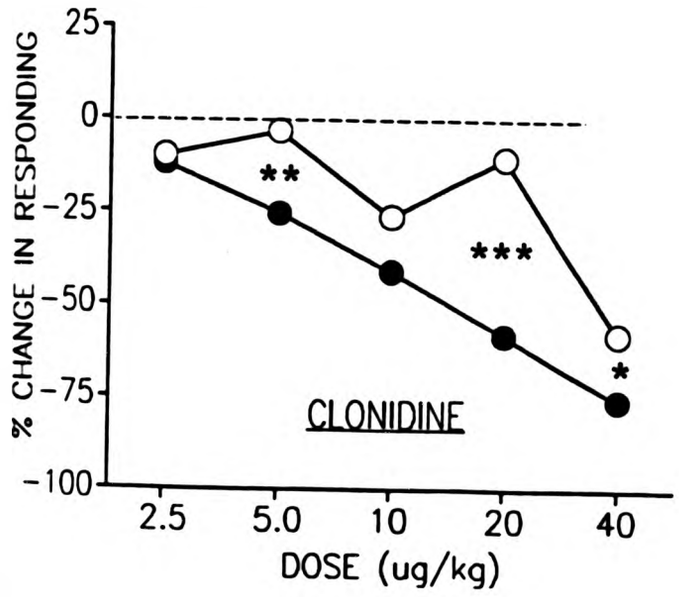
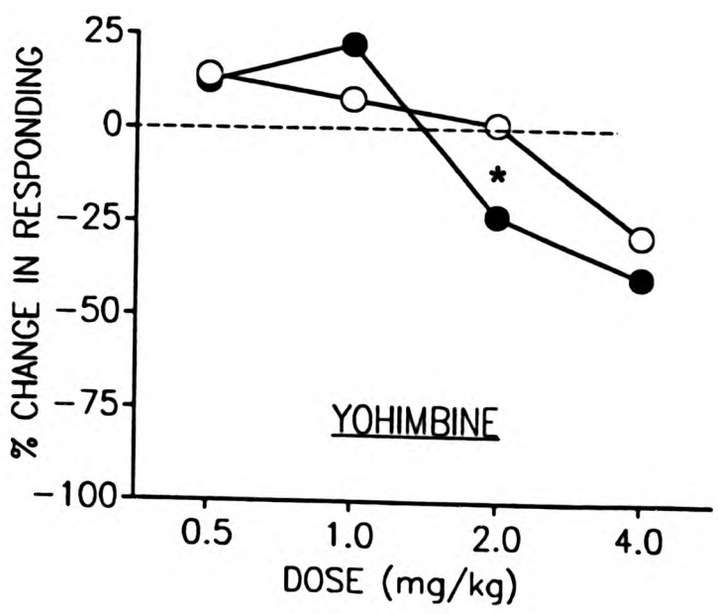


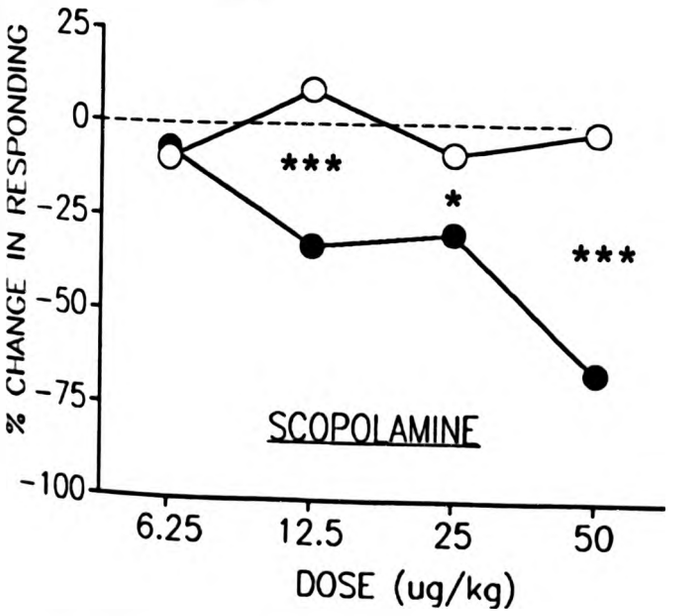
FIG. 2.2. Effects of fluoxetine (left panel) and fenfluramine (right panel) on performance in the ALT-2 procedure. Upper panels, responses and reinforcements; lower panels, proportional decrease in responding relative to vehicle treatment. Values are means. Stars indicate statistical significance of drug effects: *, $p<0.05$; ***, $p<0.001$.











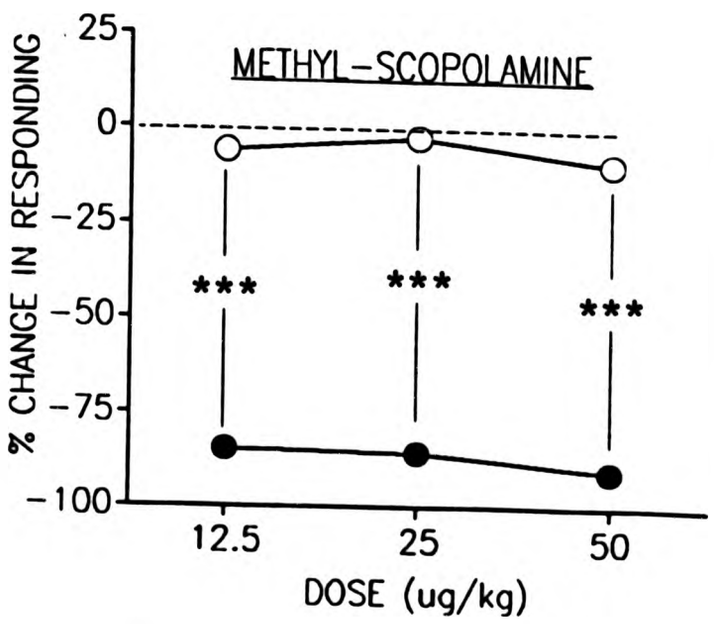


FIG. 23. Drug effects on performance in the ALT-2 procedure, shown as percentage change in responding compared with vehicle treatment. **Filled circles**, RI7.5s; **open circles**, RI300s. Values are means. Stars indicate statistically significant differences of drug effects under the two schedules: *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$.

TABLE 2.I

DRUG EFFECTS ON RESPONSE RATE IN THE ALT-2 PROCEDURE

DRUG	DOSE	RI 7.5s (R/min)[1]	Sig[2]	RI 300s (R/min)	Sig
Sulpiride (mg/kg)	0.0	30.0 (2.3)[3]		12.1 (1.2)	
	20.0	30.3 (2.6)		11.1 (1.5)	
	40.0	27.9 (2.4)		8.5 (0.9)	***
	80.0	21.8 (2.0)	***	10.3 (1.2)	
Yohimbine (mg/kg)	0.0	25.0 (2.5)		11.0 (1.1)	
	0.5	28.1 (3.0)	*	12.3 (0.9)	
	1.0	28.4 (2.4)	*	11.6 (1.0)	
	2.0	18.9 (2.8)	***	10.6 (1.4)	
	4.0	14.6 (2.1)	***	7.0 (0.6)	**
Metergoline (mg/kg)	0.0	28.2 (2.5)		10.0 (2.6)	
	0.5	32.7 (2.5)	**	9.4 (0.9)	
	1.0	34.9 (3.6)	***	12.9 (1.4)	*
	2.0	21.4 (1.8)	***	6.3 (0.7)	*
Clonidine (ug/kg)	0.0	25.9 (1.8)		10.9 (1.2)	
	2.5	22.6 (1.6)	*	9.6 (0.8)	
	5.0	19.6 (1.7)	***	10.8 (1.5)	
	10.0	14.3 (1.7)	***	7.7 (0.8)	*
	20.0	11.6 (0.9)	***	9.4 (0.9)	
	40.0	5.4 (0.7)	***	5.0 (1.1)	***
Scopolamine (ug/kg)	0.00	26.5 (2.6)		9.2 (1.3)	
	6.25	24.9 (2.3)		8.2 (1.1)	
	12.50	17.4 (2.4)	***	9.8 (1.7)	
	25.00	19.8 (4.2)	***	8.7 (1.4)	
	50.00	7.8 (1.8)	***	9.1 (1.4)	
Methyl Scopolamine (ug/kg)	00.0	25.3 (2.5)		11.0 (1.2)	
	12.5	1.6 (0.8)	***	10.3 (1.4)	
	25.0	5.2 (0.1)	***	10.0 (1.2)	
	50.0	2.4 (0.2)	***	9.9 (1.0)	

1. R/min: Responses per minute.

2. Sig: statistical significance of drug-induced changes in response rate, compared with vehicle baseline; *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$.

3. Values are means, and (in brackets) 1 SEM.

2.4 DISCUSSION

2.4.1 Validation of the ALT-2 procedure

Increasing feeding time suppressed responding under the reinforcement-lean schedule to a proportionately larger extent than under reinforcement-rich conditions. By contrast, increasing the force required to depress the lever did not selectively affect responding under reinforcement-lean, or reinforcement-rich conditions, but induced proportionately comparable decrements in both. These findings are as predicted, and accord with those of other workers (Bradshaw *et al.*, 1983a,b; Hamilton *et al.*, 1985; Heyman & Monaghan, 1987; McSweeney, 1978); they suggest that the ALT-2 method robustly discriminates between motivational and motoric influences upon behaviour.

The effects of fluoxetine and fenfluramine further support this proposition. In observational studies of consummatory and postprandial behaviours, fluoxetine appears to enhance satiety (eg. Clifton *et al.*, 1989; Willner *et al.*, 1990c). The effect of fluoxetine in the ALT-2 procedure was similarly comparable to the provision of extra feeding time: responding was preferentially suppressed under reinforcement-lean conditions. Conversely, although its precise mechanisms of anorectic action are less than clear, fenfluramine does not appear to enhance satiety in observational studies (Montgomery & Willner, 1988; Willner *et al.*, 1990c). Consistent with this finding, fenfluramine nonselectively suppressed responding in the ALT-2 procedure under both conditions of reinforcement frequency.

Previous work (conducted while an undergraduate) with the DA antagonists SCH-23390 (a D-1 receptor antagonist) and sulpiride (a D-2 receptor antagonist) provides further support for the validity of the ALT-2 procedure (see Willner *et al.*, 1990a), as do the effects of sulpiride in the present ALT-2 study. At low-to-moderate

doses, both drugs selectively suppressed responding under reinforcement-lean conditions, suggestive of a reduction in the motivation to respond (SCH-23390: Fig. 2.4, right panels; sulpiride: Fig. 2.5, right panels, and Fig. 2.3, top left panel). Again, ALT-2 data are in agreement with those of other procedures (eg. Fouriezos & Wise, 1976; Fouriezos *et al.*, 1978; Liebman, 1983; Spyraki *et al.*, 1982; Towell *et al.*, 1987). This selective motivational impairment was maintained over a wider dose range by sulpiride than SCH-23390 (sulpiride: 20-40mg/kg; SCH-23390: 6.5ug/kg only). At higher doses both drugs also markedly suppressed responding under high response rate, reinforcement-rich conditions, suggestive of an impairment in the ability to respond (sulpiride: 80mg/kg; SCH-23390: 13ug/kg).

The ALT-2 data accord with a more sophisticated variant of the Herrnstein method: the ALT-3 procedure. This procedure differs from the ALT-2 method in using three different schedules rather than two, which allows curve fitting to the Herrnstein equation. This is not impossible under the ALT-2 condition (Willner *et al.*, 1987), but is of doubtful validity since the method provides no estimate of goodness of fit. Curve fitting to ALT-3 data does provide a goodness-of-fit estimate, which justifies deriving the parameters Re and K. The effects of both SCH-23390 and sulpiride on responding in the ALT-3 procedure were comparable with those noted for the ALT-2 procedure (SCH-23390: Fig. 2.4, left panels; sulpiride: Fig. 2.5, left panels). At lower doses, both drugs selectively suppressed responding under relatively reinforcement-lean conditions, consistent with an increase in the parameter Re (Fig. 2.6), and at 13ug/kg SCH- 23390 also suppressed responding under the reinforcement-rich schedule (Willner *et al.*, 1990a), which corresponds to a reduction in the motor parameter K (Fig. 2.6, left panel). Overall, the effects of D-1 and D-2 antagonists are very comparable in both the ALT-2

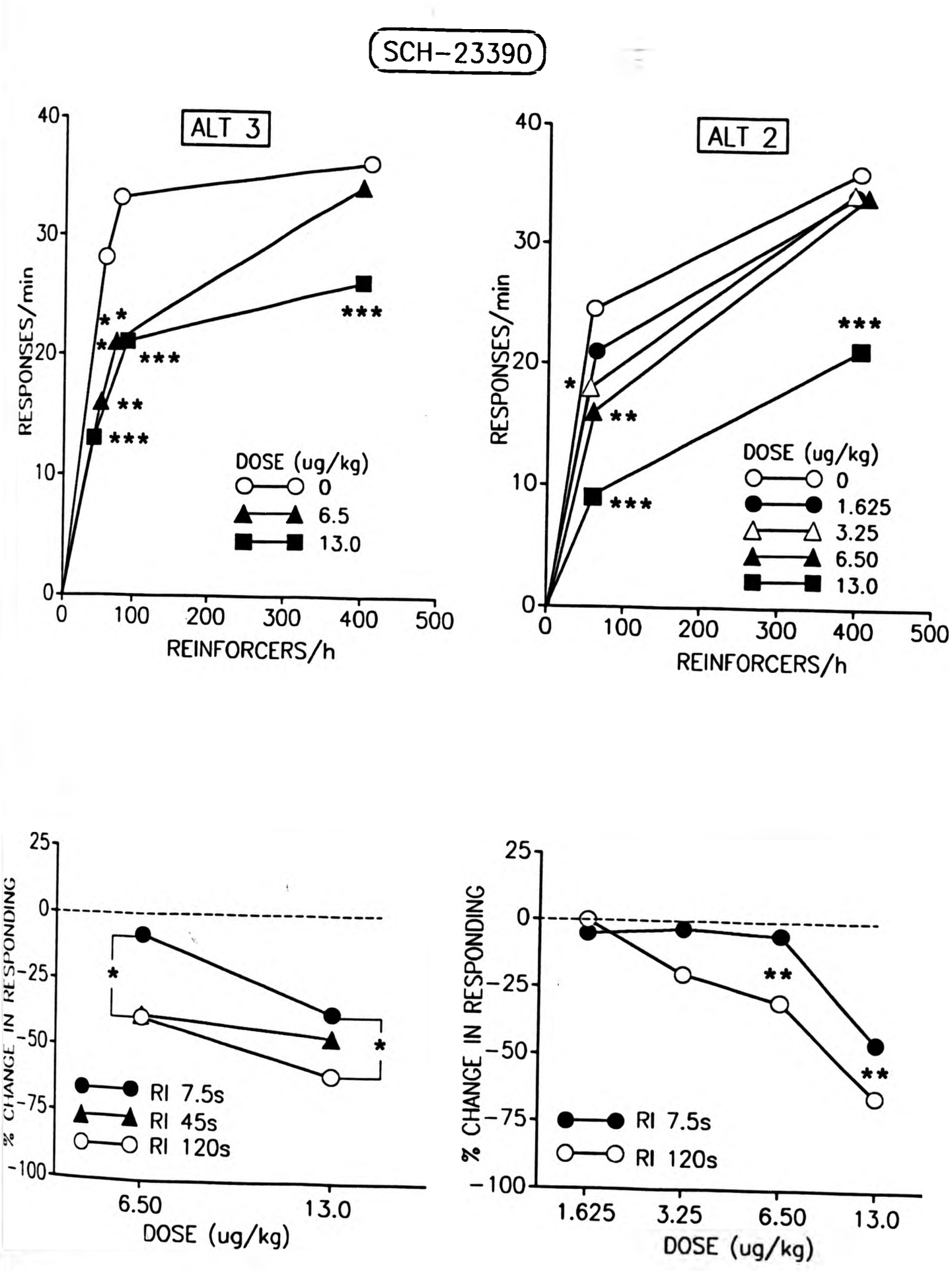


FIG. 24. Effects of SCH-23390 on RI performance: **left panels**, 3 schedules presented in a 3-day cycle (ALT-3); **right panels**, 2 schedules presented in a 2-day cycle (ALT-2). **Upper panels**, responses and reinforcements; **lower panels**, proportional decrease in responding relative to vehicle treatment. Values are means. Stars indicate statistical significance of drug effects: *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$. Redrawn from Willner *et al.*, 1990a.

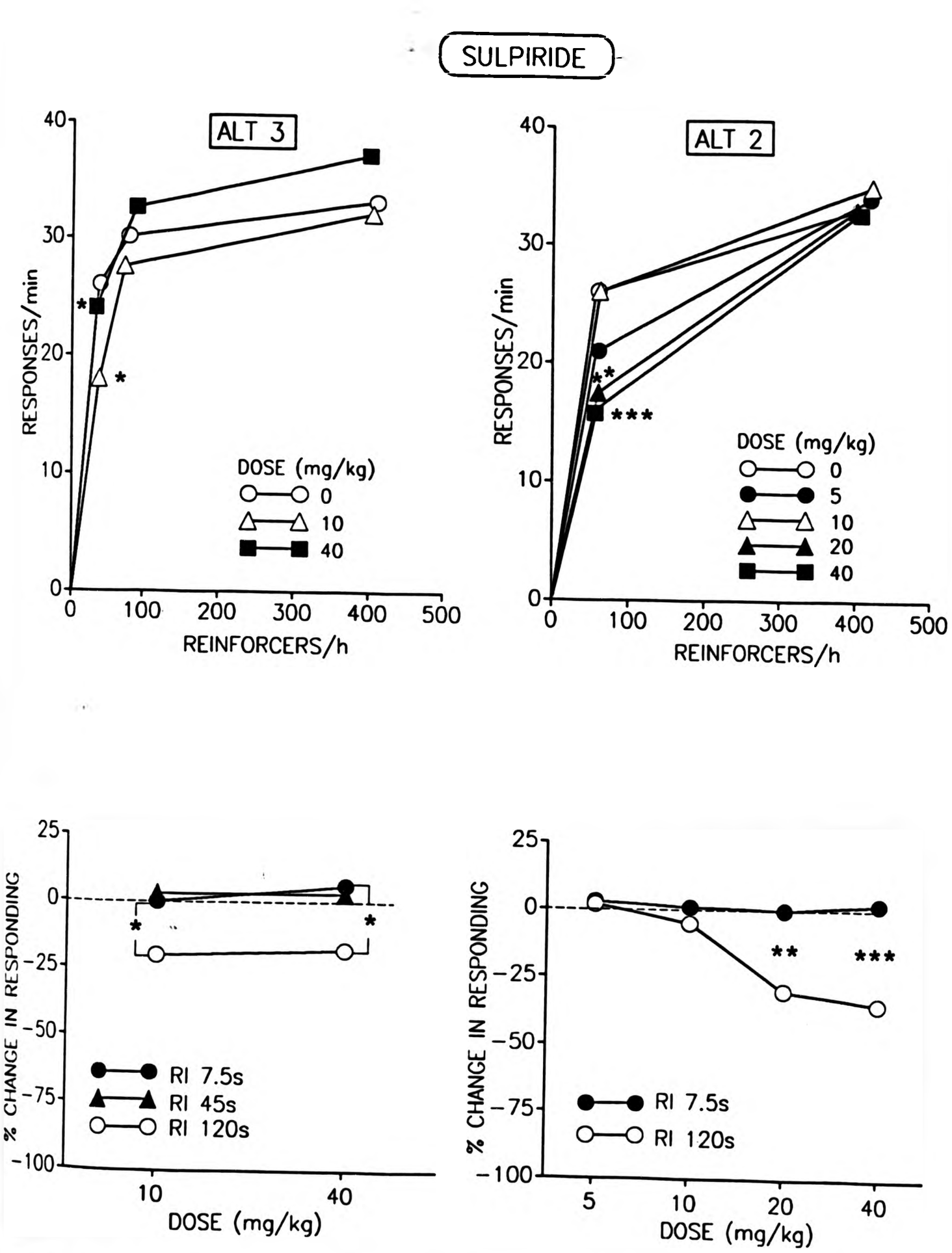


FIG. 2.5. Effects of sulpiride on RI performance: **left panels**, 3 schedules presented in a 3-day cycle (ALT-3); **right panels**, 2 schedules presented in a 2-day cycle (ALT-2). **Upper panels**, responses and reinforcements; **lower panels**, proportional decrease in responding relative to vehicle treatment. Values are means. Stars indicate statistical significance of drug effects: *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$. Redrawn from Willner *et al.*, 1990a.

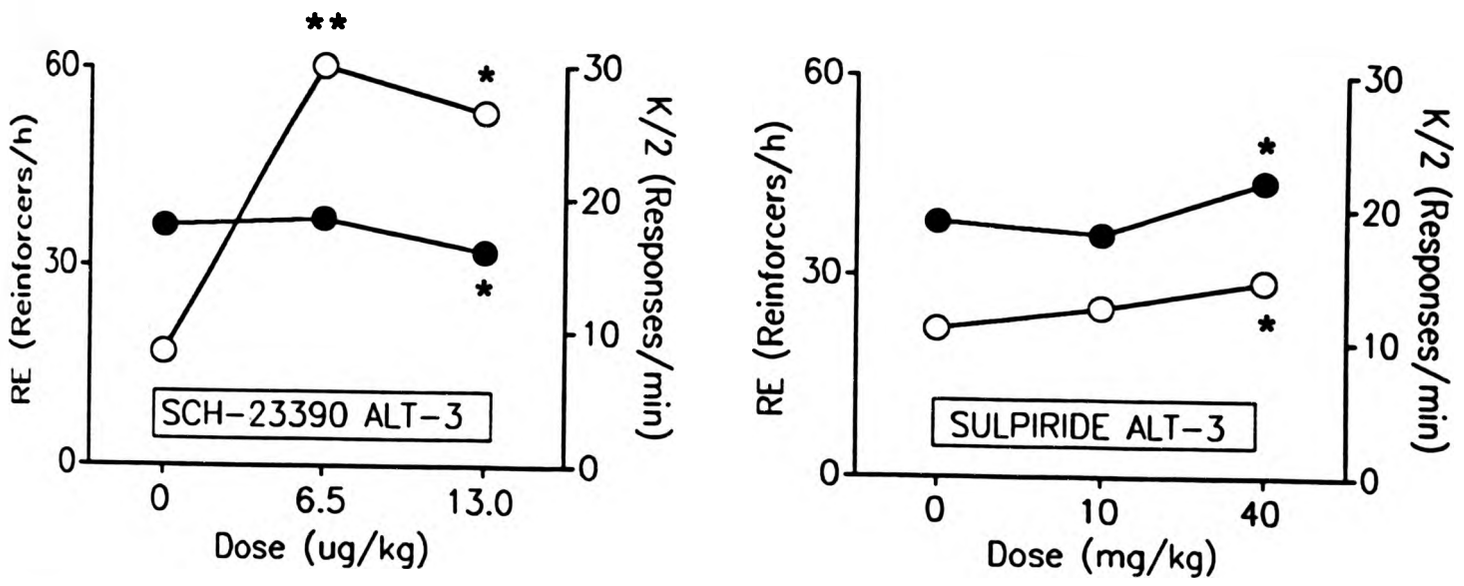


FIG. 2.6. Matching law parameters for SCH-23390 **(left panel)** and sulpiride **(right panel)**, calculated from data derived from the ALT-3 procedures. **White circles**, Re; **black circles**, K. Values are means. Stars indicate statistical significance of drug effects: *, $p<0.05$; **, $p<0.01$. Redrawn from Willner *et al.*, 1990a.

and the ALT-3 procedures, in common with their demonstrably similar profile in other procedures, such as sham feeding (Schneider *et al.*, 1986, 1988; Weatherford *et al.*, 1988).

2.4.2 Artifacts and the Herrnstein methodology

Although the ALT-2 procedure appears a useful tool in the assessment of neuroleptic drug effects, a number of potential artifacts may limit its utility in the interpretation of other data. At 0.5mg/kg, the 5-HT antagonist metergoline selectively enhanced responding under the reinforcement-rich schedule. Matching analysis of 2-schedule performance (Morley *et al.*, 1984, 1985) indicates that this pattern of results represents an increase in motor capacity (increase in K), coupled with a reduction in the motivation to respond (increase in Re). However, 1mg/kg metergoline nonspecifically enhanced responding under both schedules, which must be seen as a selective increase in K (see below). This seems an unlikely state of affairs. Responding for solid operant pellets under a FR40s schedule may also be enhanced by metergoline (Rech & Commissaris, 1982), but at 1mg/kg responding under continuous reinforcement for a liquid reinforcer was suppressed (unpublished observations). The hyperphagic effect of the 5-HT1A agonist 8-OH-DPAT has been suggested to involve nonspecific behavioural arousal (Montgomery *et al.*, 1988, 1989), and the ALT-2 data provided by metergoline might be seen in this context.

Clonidine, an alpha-adrenergic receptor agonist monotonically suppressed responding, and to a proportionately larger extent under the reinforcement-rich schedule at 3 of the 5 doses tested (2.5-40ug/kg). According to the inferential Herrnstein procedure (Morley *et al.*, 1984, 1985), this may be interpreted as a reduction in motor

ability (decreased K), together with an increase in the motivation to respond (decreased Re). The former effect may be consistent with the well documented sedative action of clonidine (eg. Florio *et al.*, 1975; Velley *et al.*, 1981). However, the apparent increase in motivation using low doses of clonidine (presumably acting at presynaptic alpha-2 receptors) is difficult to reconcile with other data. Reinforcing effects of clonidine have been attributed only to high, postsynaptic (alpha-1 receptor stimulating) doses (Asin & Wirschafter, 1985; Shearman *et al.*, 1981). In a consummatory preference test, doses of clonidine tested in the ALT-2 procedure reduced the preference for a palatable sucrose solution (Towell, Muscat and Willner, unpublished observations). In other matching procedures, depletion of brain noradrenaline leads to a reduction in the motivation to respond (Morley *et al.*, 1987, 1988). Overall, these discrepant results do not inspire confidence in the matching interpretation of the effects of clonidine.

Yohimbine, an alpha-adrenergic antagonist, enhanced responding at low doses (0.5-1mg/kg) but suppressed responding at higher doses (1,2mg/kg). Expressed relative to baseline, changes in response rate were not specific to the reinforcement density in operation. According to an inferential matching analysis (Morley *et al.*, 1984, 1985), these data represent an increase in the capacity to respond at low doses (increase in K), and a reduction in the capacity to respond at higher doses (reduction in K). The implications of these data for the Herrnstein methodology are discussed in Chapter 7.

The effects of scopolamine, an acetylcholine muscarinic receptor antagonist, were somewhat similar to those of clonidine, although dose-dependent supressions in responding were even more specific to the reinforcement-rich schedule. This would suggest a reduction in the ability to respond, together with a marked increase in motivation. However, a selective suppression of responding under the reinforcement-rich

schedule was shown to an even more striking degree by methyl-scopolamine, a derivative of scopolamine which possesses only minimal central efficacy. Methyl-scopolamine did not simply reduce response rates under reinforcement-rich conditions to a proportionately larger extent than under reinforcement-lean conditions, but also in absolute terms (see Fig.2.3). This is clearly in violation of the Herrnstein matching law. Observation of animals suggested a difficulty of ingestion of solid operant pellets, and the effects of scopolamine in the ALT- 2 procedure may simply be the result of dry mouth. Indeed, while both scopolamine and methyl-scopolamine have previously been found to suppress responding for food reward, only scopolamine also reduced responding for water reward (Adams, 1977). In the present instance it would seem especially clear that data provided by a matching analysis can be very misleading.

2.4.3 Time-dependency in the matching paradigm

The effects of DA antagonists appear to be more readily interpretable than those of most of the other agents studied in these experiments. However, with DA antagonists there is a further, and serious problem: the effects of the drugs are time-dependent. This phenomenon, which is well established in other contexts (Ettenberg *et al.*, 1979; Fouriezos & Wise, 1976; Franklin & McCoy, 1979; Gray & Wise, 1980; Hillegaart *et al.*, 1987; Sanger, 1986; Tombaugh *et al.*, 1980; Wise *et al.*, 1978a,b; Willner *et al.*, 1987, 1989, 1990a; see also Section 1.2.2), was first encountered within the matching paradigm using pimozide, a mixed D-1/D-2 antagonist. In the ALT-3 procedure, reductions in both reinforcer efficacy (increased Re) and motor capacity (decreased K) were detected. However, whereas effects on K were constant across time, the effects of pimozide, and also of SCH-23390, on Re were not immediate, but increased during the

course of a session (Fig. 2.7; Willner *et al.*, 1990a). In the ALT-2 procedure, pimozide and SCH-23390 both produced this time-dependent effect: the selective suppression of reinforcement-lean responding increased during the course of the session (Willner *et al.*, 1987, 1990a).

By contrast, other workers, using a superficially similar 2-schedule procedure found pimozide induced only a selective motor impairment (Morley *et al.*, 1984). Methodological differences are revealing. Whereas the former study, and all ALT-2 procedures in the present chapter utilised a fixed time period of schedule operation (30 minutes), the latter did not. Each session terminated either after 49 reinforcers had been obtained or after 60 minutes, whichever occurred sooner. As the two VI schedules in operation were VI10s and VI100s, performance under the reinforcement-rich schedule would have terminated after approximately 8 minutes, while performance under the reinforcement-lean schedule terminated only after a full hour. Given steady-state behaviour under both vehicle and drug, this might be acceptable. However, behaviour following neuroleptic administration is not stable (see Willner *et al.*, 1987, 1990a; and Ch.3).

The phenomenon of time-dependency in the action of neuroleptic drugs severely limits the usefulness of single schedule methods (such as the present ALT-2 and ALT-3 procedures, and the 2-VI procedure of Morley *et al.*, 1984) as a vehicle for behavioural analysis of neuroleptic drug action. However, these data also raise a more serious problem: if time-dependency is also apparent in multiple-schedule procedures, then this would undermine the entire basis for using the matching paradigm to study this class of drugs. In fact, Willner *et al.*, (1987) noted an apparently progressive action of pimozide in a multiple random-interval schedule, in which reinforcement density either

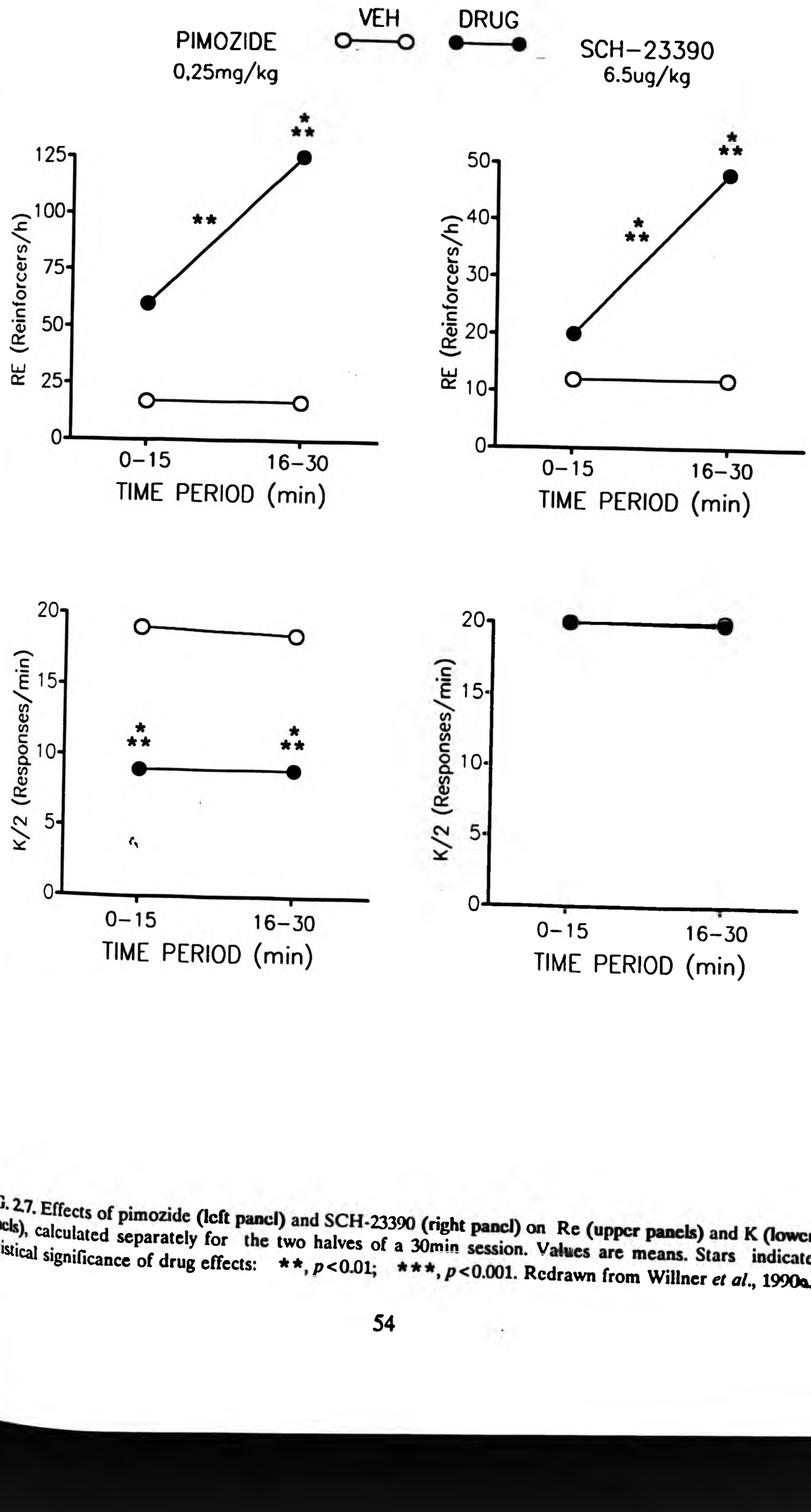


FIG. 2.7. Effects of pimozide (left panel) and SCH-23390 (right panel) on Re (upper panels) and K (lower panels), calculated separately for the two halves of a 30min session. Values are means. Stars indicate statistical significance of drug effects: **, $p<0.01$; ***, $p<0.001$. Redrawn from Willner *et al.*, 1990a.

increased, or decreased during the session. In the increasing reinforcement density schedule pimozide selectively decreased K, but with decreasing reinforcement density only an increase in Re was observed. These effects were hypothesised to be the spurious outcome of a progressive onset of the effects of pimozide. Potential artifacts, including satiety, fatigue, loss of reinforcement secondary to motor incapacitation, or a gradual penetration of the blood-brain barrier were excluded (see Willner *et al.*, 1987). If implementations of Herrnstein's matching law using multiple schedules are to be of use in assessing neuroleptic action, drug effects must be constant over time. A new multiple schedule procedure was therefore devised in order to discriminate between schedule-dependent and time-dependent effects of DA receptor blockade. This procedure is described in the following chapter.

CHAPTER 3

NEUROLEPTIC DRUG ACTION UPON MULTIPLE SCHEDULE PERFORMANCE

3.1 INTRODUCTION

Gradual onset is a well-described feature of neuroleptic drug action, which has been observed in a variety of appetitively motivated operant procedures (Fouriezos & Wise, 1976; Franklin & McCoy, 1979; Gray & Wise, 1980; Tombaugh *et al.*, 1980; Wise *et al.*, 1978a,b; Willner *et al.*, 1989, 1990a), in addition to both aversively motivated, and unconditioned behaviours (Ettenberg *et al.*, 1979; Hillegaart *et al.*, 1987; Sanger, 1986). However, the possibility that time-dependency may intrude into the matching paradigm has serious implications. As described in Chapter 2, the analysis of data from single RI schedules using Herrnstein's equation suggests that time-dependent effects of DA antagonists may influence the calculated parameter values. This analysis was applied to data collected either from two different random-interval (RI) schedules administered on alternate days, or from three schedules administered in a 3-day cycle. Pimozide both decreased the value of K calculated from these data and increased the value of Re. However, whereas the effect on K was constant throughout the session, the effect on Re increased with time (Willner *et al.*, 1987, 1990a). Very similar data were obtained using the selective D1 and D2 receptor antagonists SCH-23390 and sulpiride, except that at lower doses, both these drugs appeared to cause selective, but still time-dependent, increases in Re (Willner *et al.*, 1990a). It seems clear that the so-called "extinction-like" effect of DA antagonists can influence the values calculated for the parameters of the matching law, at least in single-RI schedules.

The use of Herrnstein's matching law to analyse performance in multiple

schedules assumes steady-state behaviour. However, Willner *et al* (1987), using a 5-component multiple RI schedule, found that pimozide appeared to induce either selective motoric, or selective motivational effects, depending upon the order of presentation of the five components. Using an ascending sequence of reinforcement densities, pimozide reduced K without affecting Re, while using a descending sequence of reinforcement densities pimozide increased Re without affecting the value of K. In both cases, these effects are equivalent to a gradual increase in the suppressant effect of pimozide during the course of the session. If the inconsistencies observed by Willner *et al* (1987) were the result of time-dependency in the effects of pimozide, then the calculation of matching law parameters and their use as an explanatory device, would not be appropriate.

The purpose of experiment 3.1 was to establish whether this time-dependent action of DA antagonists does in fact influence the parameters calculated from data collected in multiple schedules. In order to distinguish effects of time from those of component presentation order, two schedules were devised in which both ascending and descending sequences of reinforcement density were presented in different parts of the session. The effects on performance in these schedules of the selective D1 receptor antagonist SCH-23390 (Iorio *et al.*, 1983) were then examined. SCH-23390 appears to decrease rewarded performance in a manner similar to other less selective DA receptor antagonists (Nakajima, 1985; Nakajima & McKenzie, 1986; Beninger *et al.*, 1987), and both time-dependent (Beninger *et al.*, 1987) and schedule-dependent (Nakajima, 1985) effects of this compound have been reported. The effects of SCH-23390 in this experiment were clearly time-dependent.

A second study (experiment 3.2) was then carried out using the same schedules to

evaluate the hypothesis that the effects of pimozide in multiple-RI schedules are also contaminated by time-dependency; the effects of amphetamine were also studied. In experiment 3.3 performance under increased deprivation time, and under free food access were assessed, for comparison with pharmacological manipulations. As the data in experiment 3.1 provided clear evidence of time-dependent drug effects, it was no longer appropriate to use the matching equation to analyze the data. Accordingly, in experiments 3.2 and 3.3 the equation was utilised solely as an initial inclusion criterion to identify animals whose performance successfully discriminated between the different reinforcement density components of the multiple schedule.

It was also of concern in these experiments to examine a further potential potential source of error in the matching law - the assumed monotonicity of the response-reinforcement function. Some years ago, Guttman (1953) demonstrated that rather than increasing monotonically, the response rate for increasing sucrose concentration followed a stable, inverted U-shaped function. Even at the highest sucrose concentration (32%), the quantity of obtainable reinforcement was well below a level that might conceivably be satiating (maximum sucrose obtainable =0.4g). As the assumption that response rates increase monotonically with reward value is central to the use of the matching function in the study of reward mechanisms, it seemed of importance to examine matching performance using very sweet reinforcement. Accordingly, a further experiment was carried out in this paradigm using 95% sucrose pellets as the reinforcer (experiment 3.4).

3.2 METHODS

Subjects

Subjects were adult male Lister hooded rats (NIMR, Mill Hill), 32 in experiment 3.1, and 64 in experiments 3.2 - 3.4. Animals weighed 275-325g at the start of experiments, and were maintained on a 12h light/dark cycle (light on 08.00h) at a constant temperature of 22°C. With the exception of experiment 3.3 (see below), food access was restricted to 1h daily (17.00- 19.00h), although water was freely available in the home cage. Experiments were run between 14.00 and 17.00h six days a week, and each animal was run at the same time each day.

Apparatus

The experiments were conducted in eight identical operant chambers, delivering a 45mg food pellet reinforcer (Campden Instruments, London), either of the standard type (containing 10% sucrose; energy content = 3.660kcal/g) in experiments 3.1, 3.2 and 3.3, or very sweet (containing 95% sucrose; energy content = 3.766kcal/g) in experiment 3.4. A force of approximately 9g was required to depress the lever. All sessions for a given subject were conducted in the same chamber. An Acorn System 4 microcomputer (Acorn Computers, Cambridge) was used to record lever presses and to control pellet delivery.

Procedure

Animals were trained under continuous reinforcement (CRF), and after 5 sessions they were split into two matched groups and allocated to one of two 5-component multiple random-interval RI schedules. Each 32.5min session began with a 300s warm-up

period using CRF, followed by a 30s timeout, during which the house light was switched off and lever presses had no programmed consequences. Subsequently, a series of five 300s RI components were presented, each separated by a 30s timeout. Within each RI component, a series of intervals were randomly generated, which varied between a minimum of 2s and a maximum of twice the interval defining the component; reinforcement was delivered for the first response within each interval (Zeiler, 1977). These components consisted of three RI schedules (RI 7.5s, RI 45s, and RI 120s) arranged in one of two counterbalanced orders: rich-to-lean-to-rich (RLR) with the components presented in the order RI 7.5s, RI 45s, RI 120s, RI 45s, RI 7.5s; and lean-to-rich-to-lean (LRL) with the components presented in the order RI 120s, RI 45s, RI 7.5s, RI 45s, RI 120s. The schedule in operation was signalled by an 800Hz, 0.5s tone, which sounded at intervals of 2s (rich), 12s (medium) or 32s (lean). Training to asymptotic performance required 60 sessions.

Experiment 3.1

Following attainment of asymptotic multiple schedule performance, animals were administered SCH-23390 (0 and 6.5ug/kg) over two consecutive test sessions. One week later, the experiment was repeated using 13ug/kg SCH-23390.

Experiment 3.2

After 60 sessions of training on the two multiple schedules each group of animals (RLR or LRL) was divided into two matched subgroups (n=16), one of which was tested under pimozide (0 and 0.25mg/kg), the other under amphetamine (0 and 0.5mg/kg). The pimozide group was subsequently retested at a lower dose (0 vs

0.125mg/kg).

Experiment 3.3

The effect of varying the level of food deprivation was examined in the same subjects. All animals were allowed free access to food, until performance stabilized at the free feeding body weight (15 sessions). Subsequently, all animals were returned to the original conditions of 1h food access following daily sessions. This period of food access was then omitted for two days (ie, on those days, food was only available in the operant chamber).

Experiment 3.4

Following restabilization on 1h post-session food access (10 sessions), sweet pellets were delivered in the operant chambers. When performance under sweet reinforcement was stable (10 sessions), the groups were divided as in experiment 3.2, and the subgroups (n=16) tested under pimozide (0 and 0.125mg/kg) or amphetamine (0 and 0.5mg/kg). At the end of each run the number of pellets that remained unconsumed in the food tray was recorded.

Drugs

SCH-23390 maleate (R-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine-7-ol maleate, Schering Corp, New Jersey, USA) was dissolved in warm 0.9% saline (40°C approx.); d-amphetamine sulphate (Smith, Kline and French, Welwyn Garden City, UK) in distilled water; and pimozide hydrochloride (Janssen, Wantage, UK) in a minimum quantity of glacial acetic acid (84ul approx.) before being

made up to volume with distilled water. Respective solvents were used as vehicle, and injections were s.c. (SCH-23390), or i.p. (pimozide and amphetamine), in a volume of 1ml/kg. Pretreatment times were 2h (pimozide), or 30mins (SCH-23390 and amphetamine), and injections were administered in a counterbalanced order across animals and test sessions. Test sessions were separated by at least three drug- free days.

Analysis

Herrnsteins matching equation [B=KR/(R+Re), where B=response rate; R=reinforcement density; K and Re are constants] was used to identify animals showing an adequate discrimination between the different reinforcement density components of the multiple schedule. The method of Wetherington & Lucas (1980) was used to fit a hyperbolic curve to the data, and to derive the parameters K (the asymptote) and Re (the reinforcement density maintaining half-maximal responding). Animals were selected for testing on the basis of a greater than 75% fit to the hyperbolic curve for at least 3 consecutive sessions prior to testing, calculated using all 5 data points. Matching law parameters were also derived separately for each half of the session (components 1-3 and 3-5). In every case, the mean fit was better than 90%: the data are illustrated for experiment 3.1 in Table 3.I.

TABLE 3.I

PROPORTION OF VARIANCE (%) ACCOUNTED FOR BY HERRNSTEIN'S EQUATION[1]

Treatment	Schedule	Overall	First 3	Last 3
Vehicle	RLR	95.7 (1.6)[2]	90.9 (2.4)	96.2 (1.6)
	LRL	98.6 (0.8)	97.6 (0.6)	95.0 (1.3)
6.5 ug/kg	RLR	95.4 (1.0)	93.3 (1.8)	96.3 (1.2)
	LRL	95.4 (1.5)	91.0 (5.0)	96.4 (1.4)
Vehicle	RLR	94.9 (1.9)	91.5 (2.1)	93.1 (4.3)
	LRL	97.5 (0.7)	95.6 (1.5)	91.0 (1.9)
13 ug/kg	RLR	96.6 (1.0)	90.9 (3.7)	95.5 (1.0)
	LRL	97.4 (0.8)	96.3 (1.8)	96.8 (1.1)

1. Values are shown separately for overall performance and for the first three and last three components of each schedule

2. Values are means, and (in brackets) 1SEM.

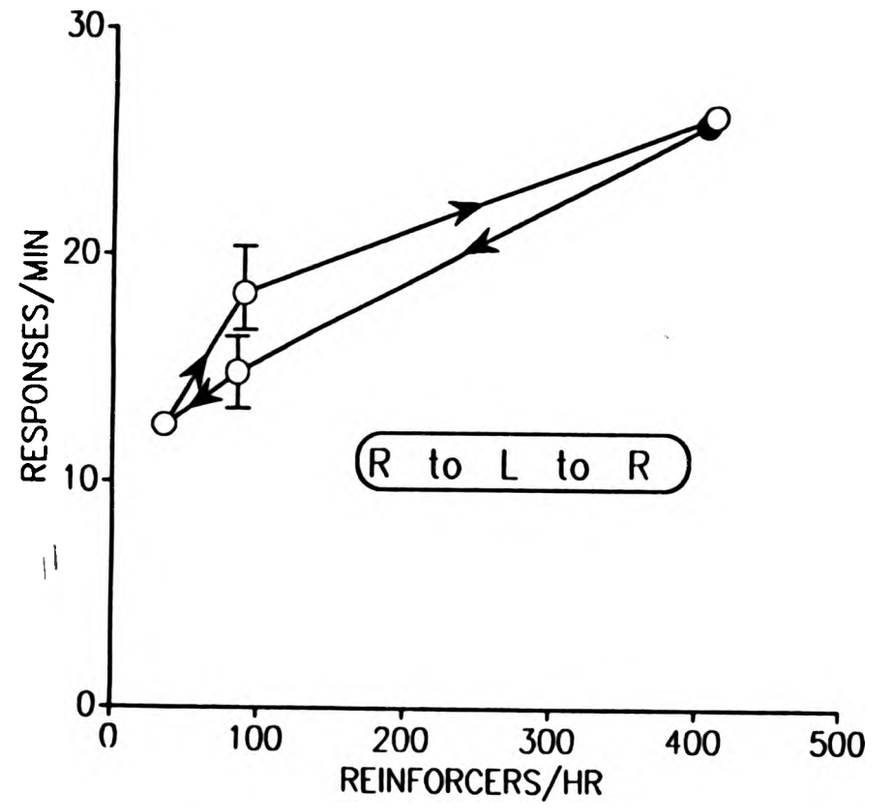
In order to achieve the equal numbers in each group needed by our analysis of variance software, when RLR and LRL groups differed in the number of animals meeting the acceptance criterion, subjects were deleted randomly from the more successful group (maximum deletion = 3). Following this adjustment, the numbers meeting the acceptance criterion were: experiment 3.1, SCH-23390 groups 14/16; experiment 3.2, pimozide groups 13/16, amphetamine groups 13/16; experiment 3.3, free feeding 23/32, food deprivation 27/32; experiment 3.4, pimozide groups 11/16, amphetamine groups 7/16.

In the light of of these unequal numbers, the data were analyzed separately for each group, using 3-way analysis of variance (schedule, component, dose). Two-way analysis (schedule, component) was used for each part of experiment 3.3. Further analyses were carried out on the proportional change in response rates, relative to scores under vehicle treatment (experiments 3.1 and 3.2), 1h post-session food access (experiment 3.3), or standard reinforcement (experiment 3.4). Where appropriate, analysis of variance was supplemented by tests of simple main effects and planned comparisons.

3.3 RESULTS

3.3.1 Performance on the RLR and LRL schedules

Performance on the two multiple schedules was markedly asymmetrical (Fig. 3.1). In both cases, response rates in the first and last component were similar. However, in both schedules, reponding in the medium reinforcement rate component was higher in the L-M-R portion of the schedule than in the R-M-L portion (RLR: $F(1,208) = 9.4$, $p<0.01$; LRL: $F(1,208) = 17.1$, $p<0.001$).



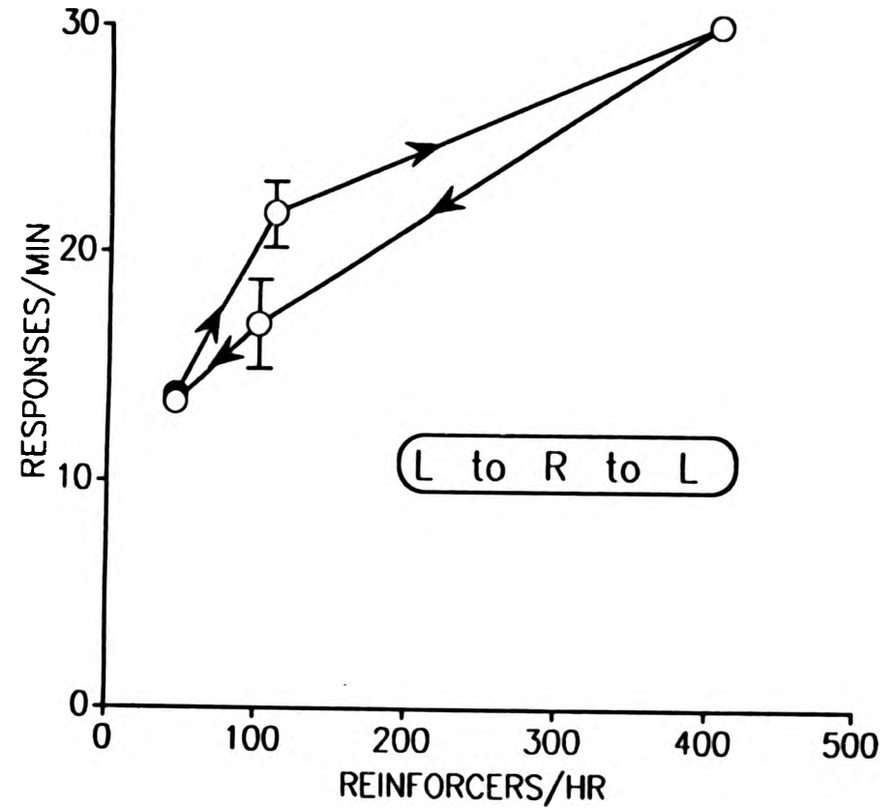
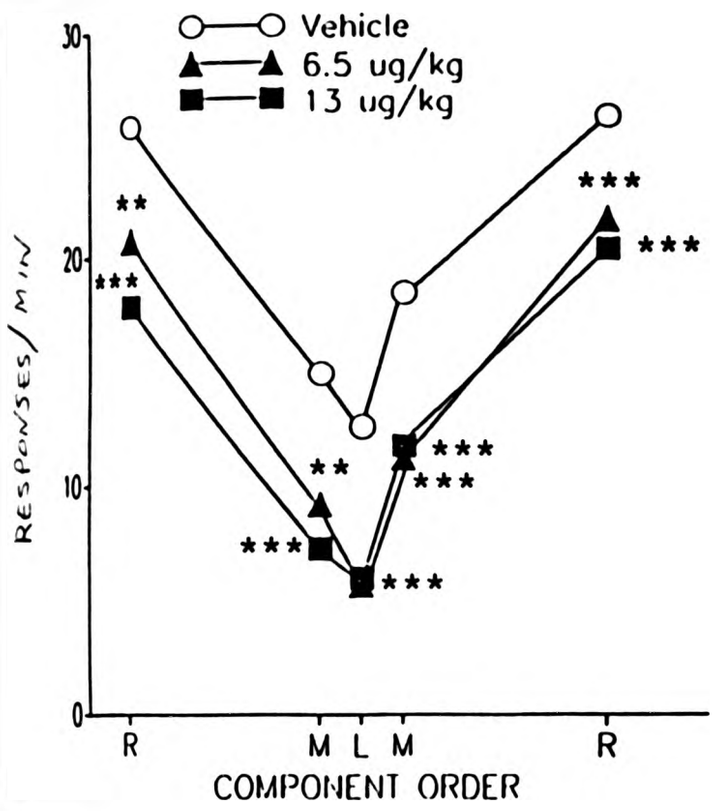


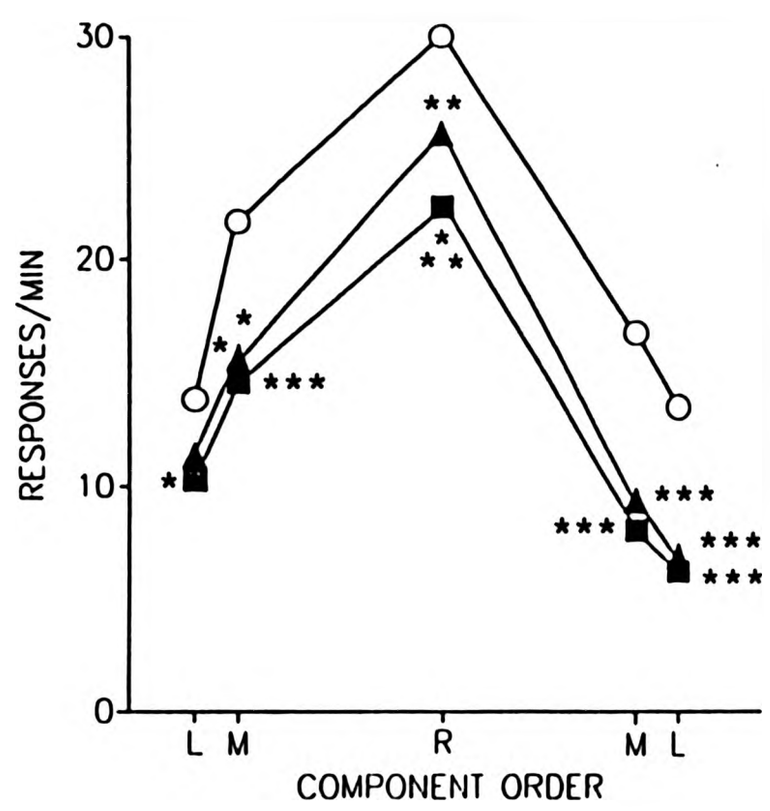
FIG. 3.1. Responding on the RLR (left) and LRL (right) schedules after vehicle pre-treatment (mean of two vehicle sessions). Standard errors are shown for the intermediate reinforcement density component. The arrows show the order of component presentation. Initial component shown as black circle.

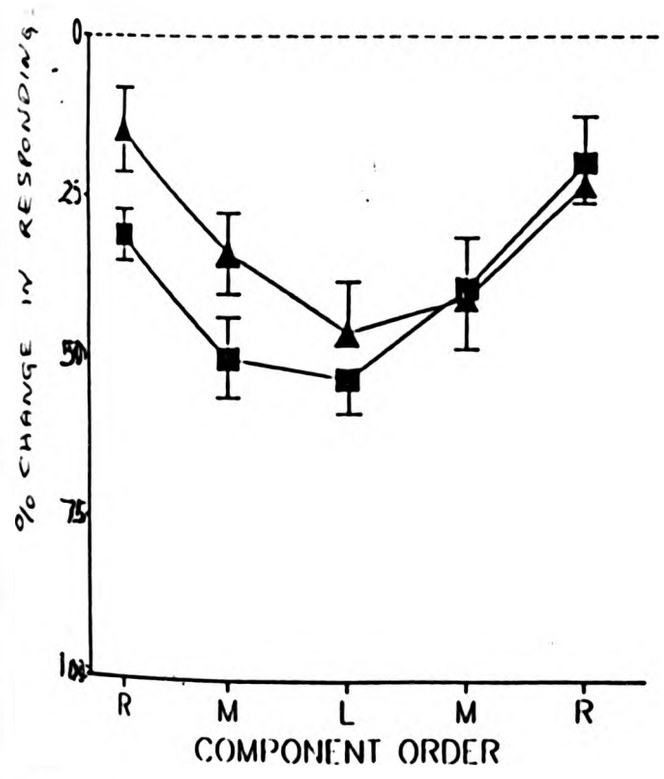
3.3.2 Effects of SCH-23390

Both doses of SCH-23390 significantly reduced response rates in all components of both schedules, with the single exception of the first component of the LRL schedule at the lower dose (Fig. 3.2). In the RLR schedule, SCH-23390 caused similar proportional reductions in responding in the first and last rich component (6.5 ug/kg: $F(1,208) = 1.9$, N.S.; 13 ug/kg: $F(1,208) = 3.4$, N.S.). However, at both doses of SCH-23390, the suppression of performance was substantially greater in the middle lean component than in either rich component (minimum $F(1,208) = 13.6$, $p<0.001$). A greater suppression of responding in the lean component was also obtained in the second portion of the LRL schedule (R-M-L) ($F(1,208) = 17.3, 23.0$, $p<0.001$). However, in this schedule, SCH-23390 had relatively little effect on the initial components, and as a result, the differences between the initial and final lean components were substantial ($F(1,208) = 17.4, 23.0$, $p<0.001$).

These patterns of changes are reflected in the parameters estimated by fitting Herrnstein's equation to the two halves of the schedules. Under vehicle conditions, there were no significant differences between the two schedules, or between the earlier and later portions within a schedule, in the values estimated either for the asymptote (K) or for the the curvature (Re), (maximum $F(1,52) = 2.8$, N.S.). However, SCH-23390 produced different patterns of effects in the two schedules. In the RLR schedule, SCH-23390 had no significant effect on K ($F(1,26) = 0.9$, N.S.), but dose-dependently increased Re ($F(1,26) = 18.7$, $p<0.001$), these effects being of a similar size in the two parts of the session (Fig.3.3). By contrast, in the early part of the LRL schedule, SCH-23390 had no effect on Re ($F(1,52) = 0.1$, N.S.), but dose-dependently decreased K ($F(1,52) = 9.2$, $p<0.01$), while in the later part of LRL schedule, SCH-23390







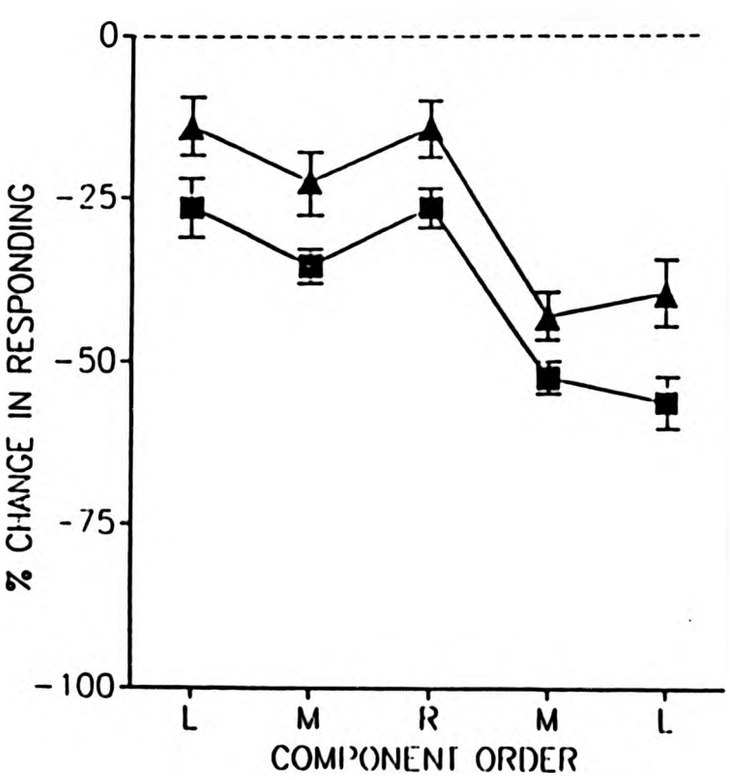
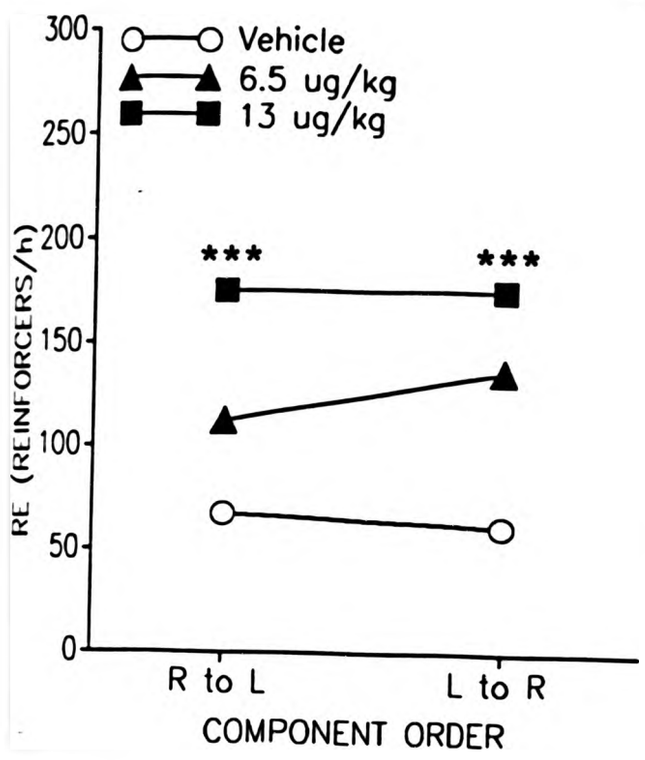
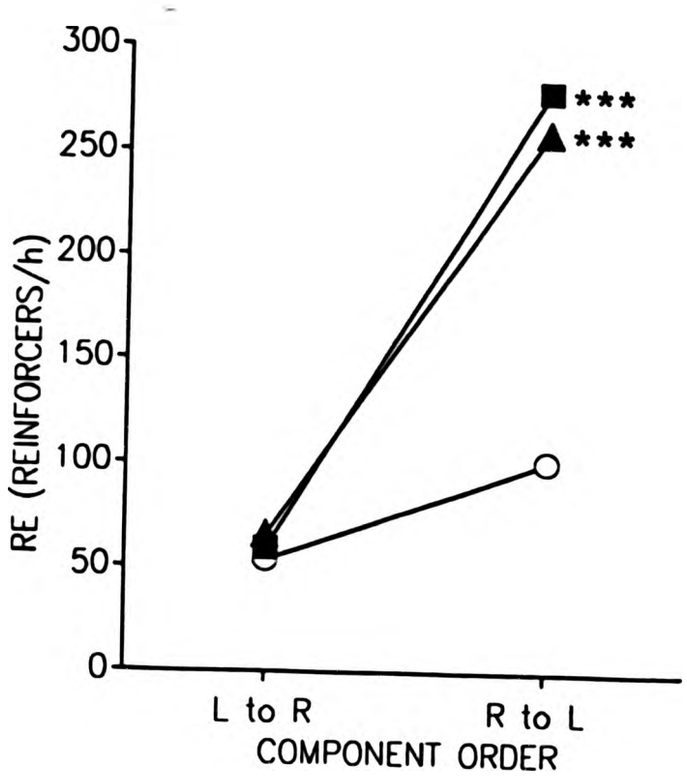
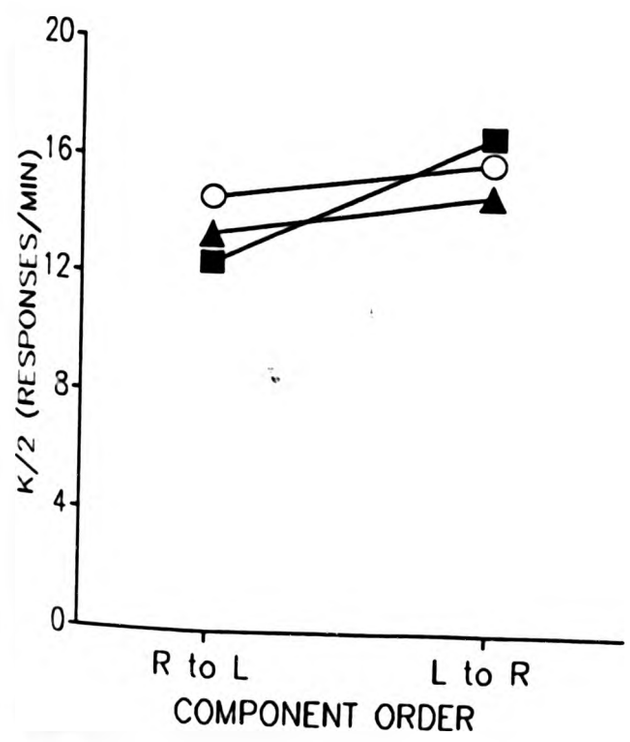


FIG. 3.2. The upper panels show reponse rates after SCH-23390 treatment in the RLR (left) and LRL (right) schedules. The horizontal axis has been distorted so that the L-M-R portion of each figure represents the approximate reinforcement density under lean (L), medium (M) and rich (R) conditions. Values are means. Stars indicate statistical significance of drug effects; *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$. The lower panels show the effects of SCH-23390 expressed as proportional reductions from scores obtained under vehicle treatment (mean and standard error).







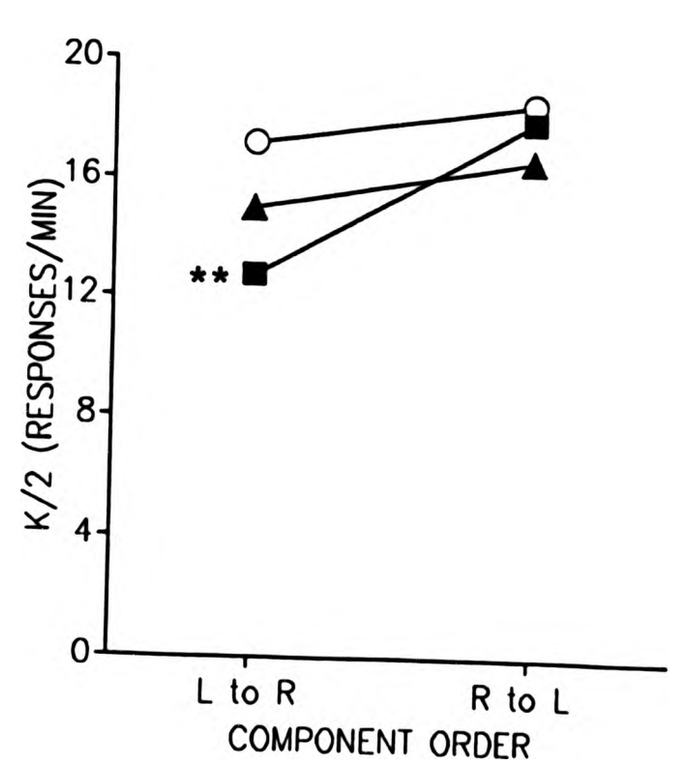


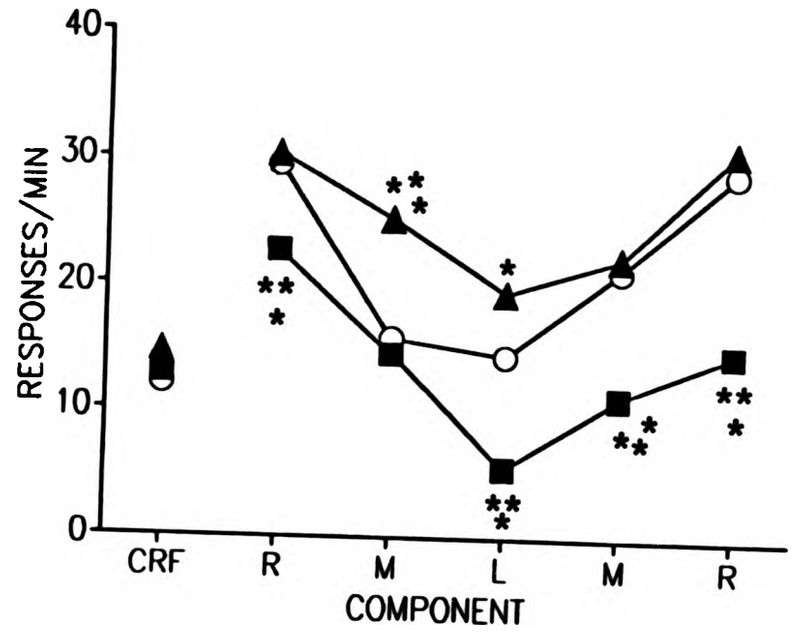
FIG. 3.3. Parameters of Herrnstein's equation: top, Re, bottom, K/2. Parameters have been estimated separately for the early (first three components) and late (last three components) of the RLR (left) and LRL (right) schedules. Values are means. Stars indicate statistical significance of drug effects; **, $p<0.01$; ***, $p<0.001$.

increased Re ($F(1,52) = 41.6, p<0.001$) without affecting K ($F(1,52) = 1.3$, N.S.). The effects of SCH-23390 were significantly smaller under LRL than under RLR conditions in the early part of the session ($F(1,52) = 4.7, p<0.05$), but significantly greater in the later part of the session ($F(1,52) = 9.3, p<0.01$).

3.3.3 Effects of pimozide and amphetamine

Pimozide (0.25mg/kg) significantly reduced response rates within the majority of components ($F(1,14) = 103, p<0.001$). However, as in the case of SCH-23390, responding within initial components was relatively normal (see Fig. 3.4), by comparison with severe impairment of the terminal component (RLR schedule: $F(1,240)=15.2$, $p<0.001$; LRL schedule: $F(1,240)=11.7, p<0.001$). The subsequently administered dose of 0.125mg/kg caused a similar, but smaller response impairment ($F(1,48)=43.4$, $p<0.001$, results not shown). Time-dependency in the effects of pimozide is most clearly revealed in the significant linear trend ($F(1,96)=67.0, p<0.001$) obtained when the results are expressed as proportional changes relative to vehicle treatment (Fig. 3.5A). This representation of the data also shows that in the terminal component, the effect of pimozide was significantly greater under conditions of lean reinforcement ($F(1,72)=8.0, p<0.01$).

Conversely, amphetamine enhanced response rates ($F(1,24)=23.3, p<0.001$). However, this effect was absent in reinforcement-rich components (Maximum $F(1,144)=3.6$, N.S: see Fig. 3.4). As in the case of pimozide, response rate changes within initial lean components were relatively unaffected by amphetamine, in comparison with the effect in terminal lean components. This time-dependency may be most clearly seen when the results are expressed as a percentage of baseline (Fig. 3.5A:



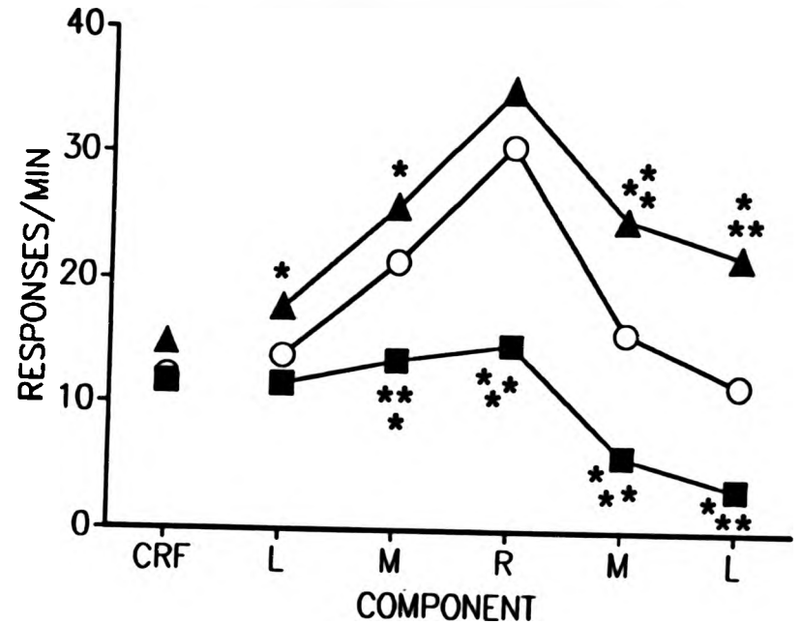


FIG. 3.4. Effects on multiple-schedule RI responding of 0.5mg/kg amphetamine (filled triangles), vehicle (open circles), or 0.25mg/kg pimozide (filled squares). The schedule components were presented in the order shown on the horizontal axis. CRF, continuous reinforcement; R (rich), RI 7.5s; M (medium), RI 45s; L (lean), RI 120s. Values are means. Stars indicate statistical significance of drug effects; *, $p<0.05$; ***, $p<0.001$.

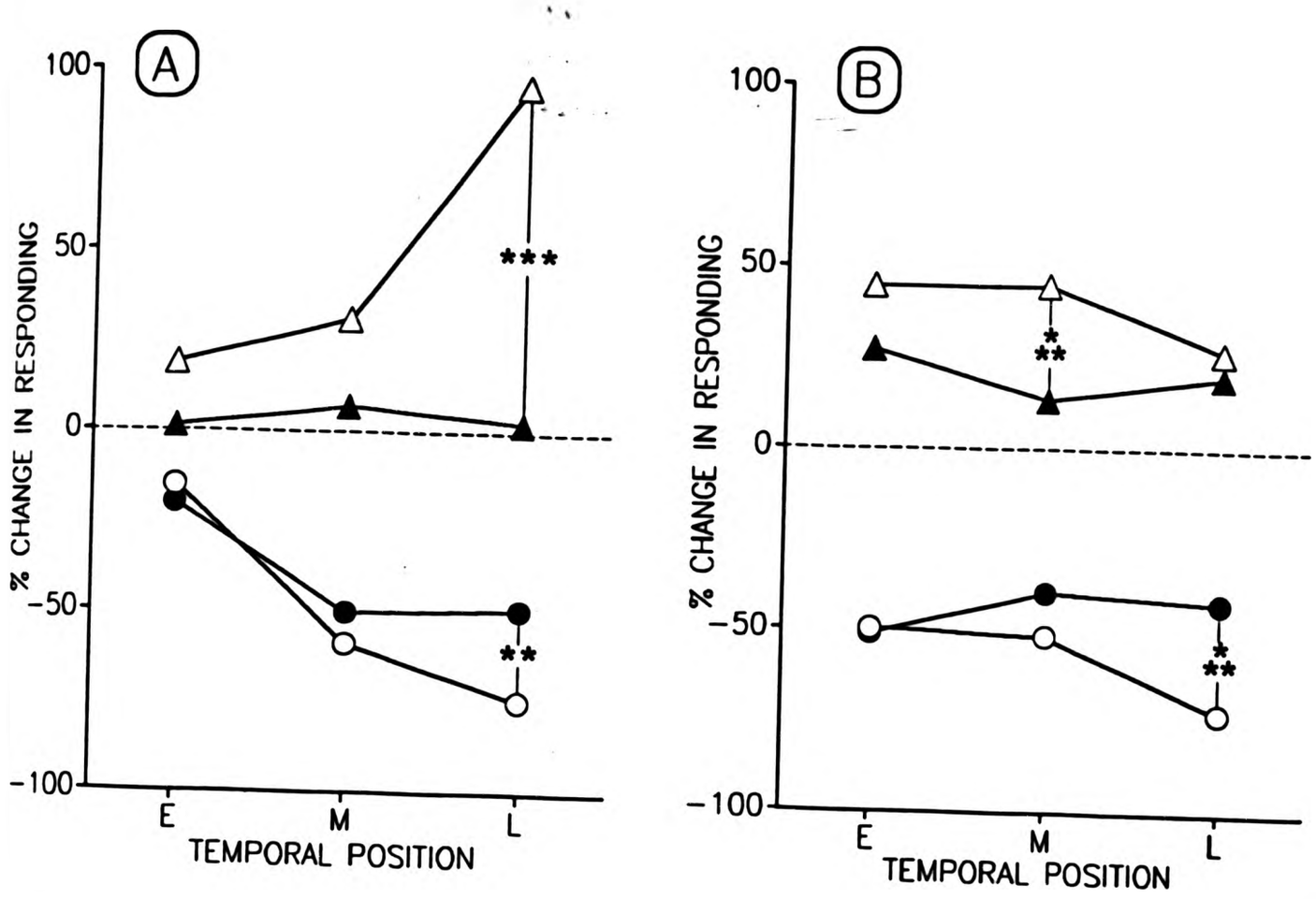
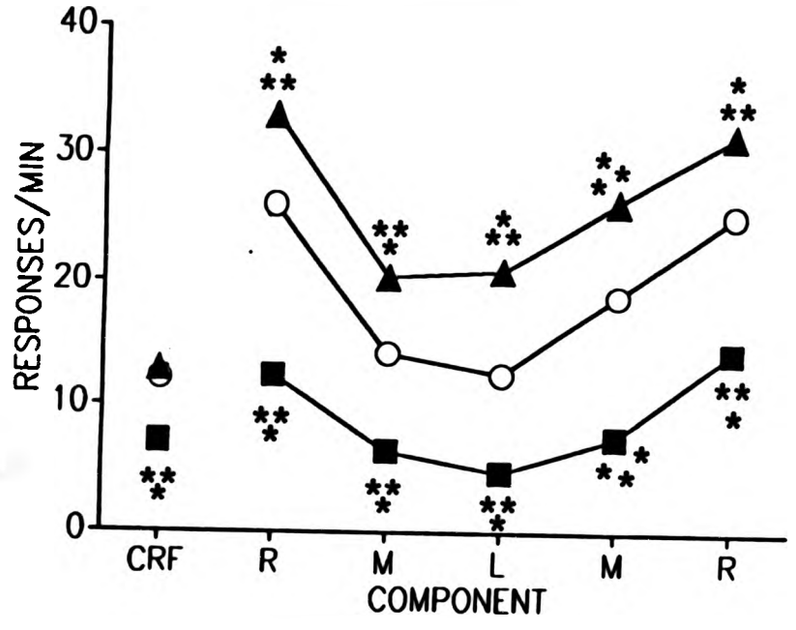


FIG. 3.5. Proportional changes in responding relative to control conditions (21 hrs deprivaton, 85% body weight, vehicle treatment). **Open symbols** show effects under reinforcement-lean conditions (RI 120s), **filled symbols** show effects under reinforcement-rich conditions (RI 7.5s). **A (left panel): triangles**, amphetamine (0.5mg/kg); **circles**: pimozide (0.25mg/kg). **B (right panel): triangles**, 72h deprivation; **circles**, 100% body weight. Temporal position: **E**, early (first component); **M**, middle (third component); **L**, late (fifth and final component). Values are means. Stars indicate statistical significance of drug effects; *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$.



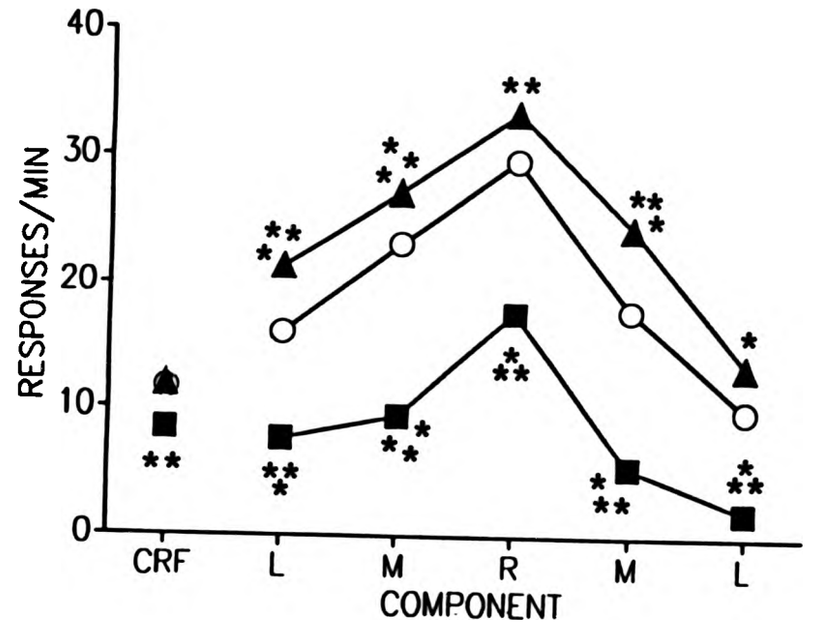


FIG. 3.6. Effects on multiple-schedule RI response rate of increasing deprivation time to 72 hrs (filled triangles) or increasing body weight to 100% free feeding weight (filled squares), from 21 hrs deprivation, corresponding to 85% free feeding weight (open circles). The schedule components were presented in the order shown on the horizontal axis. CRF, continuous reinforcement; R (rich), RI 7.5s; M (medium), RI 45s; L (lean), RI 120s. Values are means. Stars indicate statistical significance of drug effects; *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$.

terminal lean vs. initial lean: $F(1,48)=6.2$, $p<0.05$).

3.3.4 Effects of deprivation conditions

Increasing body weight reduced responding ($F(1,30)=397$, $p<0.001$). In contrast to the gradual performance decrement observed with pimozide, the effect of increased body weight was apparent throughout the session, including the initial CRF warm-up component (Fig. 3.6). The lack of time dependence in the effect of increased body weight is shown by the absence of a significant linear trend in the proportional change in responding (Fig. 3.5B: $F(1,88)= 3.3$, N.S.). However, like pimozide, increasing body weight did cause a proportionally greater suppression of responding in reinforcement-lean components (Fig. 3.5B): response rates were reduced by 44.2%, 56.5%, and 57.9% in rich, medium, and lean reinforcement density components respectively (averaging across all occurences of each component).

Conversely, increasing deprivation time caused large increases in responding (Fig. 3.6: $F(2,92)=71$, $p<0.001$), which again were immediately apparent at the onset of the multiple schedule, and declined slightly as the session progressed (linear trend,$F(1,104)=4.6$, $p<0.05$). As with increased body weight the effects of increasing food deprivation were more apparent under reinforcement-lean conditions (Fig. 3.5B).

3.3.5 Performance maintained by 95% sucrose reinforcement

The introduction of sweet reinforcement caused a substantial decrement in performance, which showed no recovery following prolonged training (10 sessions) (Fig. 3.7; pimozide group: $F(1,20)=195$, $p<0.001$; amphetamine group: $F(1,12)=147$, $p<0.001$). With the exception of the initial lean RI components of the LRL schedule,

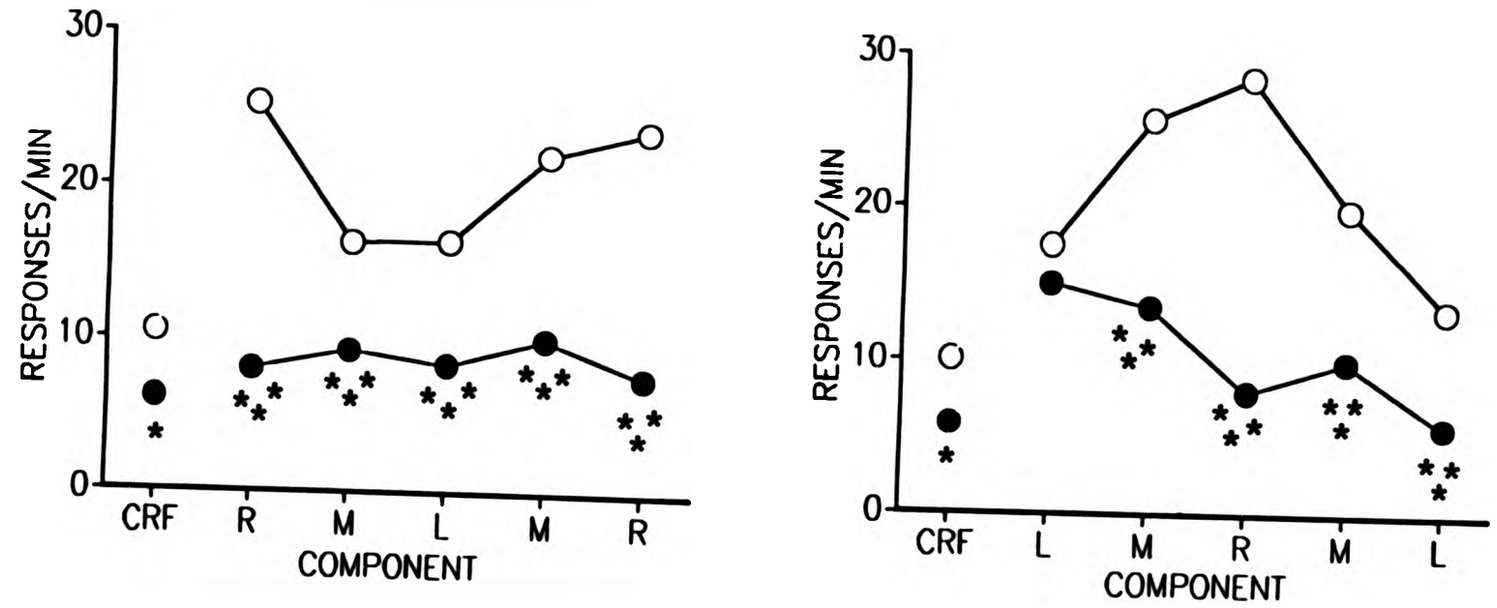


FIG. 3.7. Effects on multiple-schedule RI responding of standard, 10% sucrose pellets (open circles) and very sweet, 95% sucrose pellets (filled circles). The schedule components were presented in the order shown on the horizontal axis. CRF, continuous reinforcement; R (rich), RI 7.5s; M (medium), RI 45s; L (lean), RI 120s. Values are means. Stars indicate statistical significance of drug effects; *, $p<0.05$; ***, $p<0.001$.

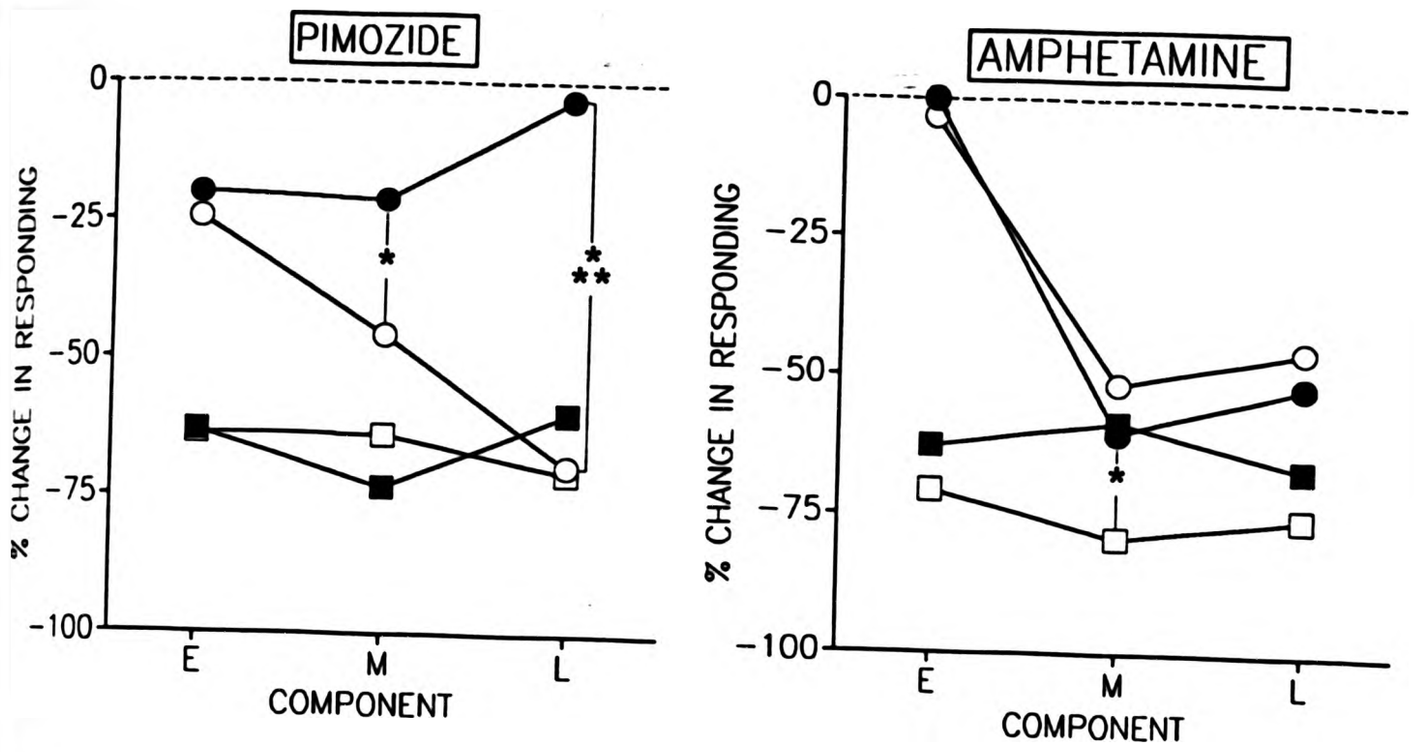


FIG. 3.8. Proportional changes in responding for very sweet 95% sucrose pellets, relative to standard 10% sucrose pellets. **Left panel:** 0.125mg/kg pimozide; **right panel:** 0.5mg/kg amphetamine. **Open symbols:** vehicle; **filled symbols:** drug. **Squares:** reinforcement-rich condition (RI7.5s); **circles:** reinforcement-lean condition (RI 120s). Temporal position: **E**, early (first component); **M**, middle (third component); **L**, late (fifth and final component). Values are means. Stars indicate statistical significance of drug effects; *, $p<0.05$; ***, $p<0.001$.

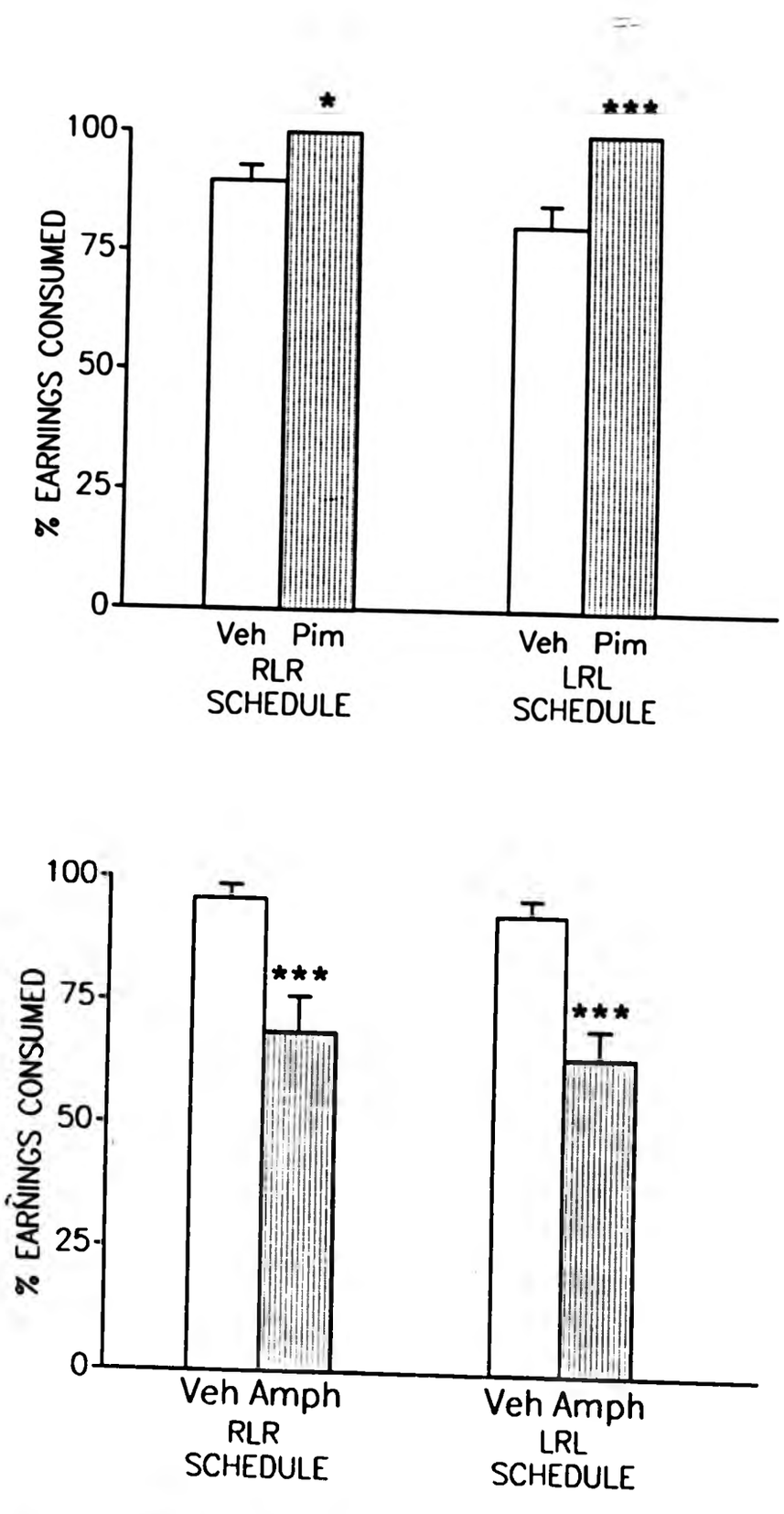


FIG. 3.9. Proportion of earned 95% sucrose pellets consumed. **Upper panel:** pimozide, 0.125mg/kg; **lower panel:** amphetamine, 0.5mg/kg. Values are means. Stars indicate statistical significance of drug effects; *, $p<0.05$; ***, $p<0.001$.

response rates were roughly constant throughout the session; there was no evidence of conventional response-reinforcer matching. In contrast to the complete consumption of standard reinforcement typically observed, approximately 10% of sweet pellets remained in the operant chambers at schedule termination. This was so for both groups later administered with pimozide or amphetamine, and remained the case throughout the experiment.

Within reinforcement-lean components administration of pimozide actually enhanced responding, and in effect blocked decrements caused by very sweet reward (Fig. 3.8, left panel). Even more surprisingly pimozide also reinstated the typical consumption of all earned reinforcement (Fig. 3.9; $F(1,20)=25.4$, $p<0.001$). Amphetamine did not significantly affect responding for sweet reinforcment (Fig. 3.8, right panel: $F(1,12)=1.4$, N.S.), but did further reduce consumption of earned reward (Fig. 3.9: $F(1,12)=47.0$, $p<0.001$).

3.4 DISCUSSION

3.4.1 The RLR and LRL schedules

The two novel schedules devised for the purposes of this study were readily learned by most subjects. The asymmetrical performance in the medium reinforcement-density component was not unexpected. A number of previous studies have reported that response rates in specific components of a multiple schedule depend not only upon the reinforcement density programmed in that component, but also on the temporal environment of reinforcement densities in other components. These asymmetries have been assumed to represent contrast effects, and there has been discussion of the nature of the interaction (Herrnstein, 1970; MacLean & White, 1983; Pliskoff *et al.*, 1968;

Reynolds, 1961; Williams & Wixted, 1986).

Several forms of the matching equation have been devised that take account of contrast effects (Herrnstein, 1970; McLean & White, 1983; Williams & Wixted, 1986). These versions of the equation were not used to analyze the present data, because, despite the marked behavioural asymmetries, similar parameter estimates were obtained (after vehicle treatment) from the early and late portion of the schedules. This comes about because the hypothetical point (Re,K/2), which defines the shape of the hyperbolic matching curve (Willner *et al.*, 1987), falls very close to the actual data obtained under the reinforcement lean schedule, which is outside the region of behavioural asymmetry. However, a different choice of schedule values, that shifted the asymmetrical region to the left, would presumably lead to discrepancies in the calculated parameter values. This suggests that comparison of parameter values between different implementations of the matching procedure (eg. between multiple and single schedules) would only be appropriate if contrast effects were taken fully into account. In general, it will only be valid to compare parameter values if they are derived from experiments using the same procedure.

The decrease in the parameter K in the first half of the LRL schedule, following SCH-23390 illustrates how misleading the use of Herrnstein's equation to analyse and interpret these data may be. K is the value calculated for the asymptote of the matching curve, and supposedly represents the theoretical maximum response rate (Herrnstein, 1970; de Villiers & Herrnstein, 1976). However, it is barely credible that the maximum possible rate of responding could be dependent on the order of presentation of the schedule components, and a motor deficit that lifts during the second half of the session is equally implausible.

3.4.2 Time dependency

In the LRL schedule, the effects of SCH-23390 and pimozide were clearly time-dependent, as predicted from the "extinction-like" effects reported for DA antagonists in single RI schedules (Willner *et al.*, 1987; 1990a). In the RLR schedule, however, the effects were schedule dependent: reinforcement rich components were relatively resistant to SCH-23390, compared with the 50% suppression of responding on the central reinforcement-lean component. Comparing across the two schedules, we see a constant, relatively small, suppression of reinforcement-rich responding, and a time-dependent increase in suppression of reinforcement-lean responding. The rate-increasing effect of amphetamine under conditions of lean reinforcement was also time dependent. With hindsight, this effect was also apparent, though unremarked, in an earlier study of the effect of amphetamine in single RI schedules (Willner *et al.*, 1987, Fig.7).

The gradual onset of the effect of pimozide and SCH-23390 is not itself surprising, since there is a substantial literature describing time dependent effects of DA antagonists, in VI and RI operant schedules and in a host of other paradigms: indeed, a gradual onset of the response decrementing effect seems to be a general principle in the action of this class of drugs (see Sections 1.2.2, and 3.1). However, the demonstration of this effect in multiple schedule performance has serious implications for the use of Herrnstein's matching law to analyse multiple schedule performance. The majority of studies using this paradigm (see Sections 1.2.4B, 2.4.3 and 3.1) have not been designed in a manner that enables a rigorous assessment of the potential contribution of time-dependency. However, a matching law analysis can only be valid if the influence of time-dependency is rigorously excluded. Attractive as the matching paradigm may

seem as a tool for the experimental analysis of the role of dopamine in motivated behaviour, it is suggested that it is in fact ill suited to this purpose.

These findings have clear implications for the future use of the matching paradigm in pharmacological studies. Firstly, interpretation of matching data will necessarily be problematic when drug effects are time dependent. Time dependent effects in this paradigm have so far only been described for DA antagonists (Willner *et al.*, 1987; 1990a), but there is little reason to suppose that these drugs are unique in this respect (see Sanger, 1989, 1990). Secondly, therefore, studies must be designed in such a way that time-dependency may be identified or its influence excluded. In multiple schedules, time-dependency may be identified by varying the order of schedule presentation (as in the present study). In sequential single schedule procedures, the influence of time-dependency may be minimised by sampling behaviour over equivalent time periods in different schedules; procedures in which the duration of the experimental session increases as reinforcement density decreases (eg. Morley *et al.*, 1984) should be avoided.

3.4.3 Schedule dependency

In contrast to the effects of pimozide, SCH-23390 and amphetamine, the effects of manipulating drive level were relatively free of time dependence: following food deprivation, large increases in responding were apparent from the start of the multiple schedule, and large decreases in responding were apparent throughout the session following a period of free feed. In both cases, however, these effects were more apparent under reinforcement-lean conditions. Parameters of the matching equation were not calculated in this study, for the reasons outlined above. However, as Morley *et al* (1984, 1985) have pointed out, it follows from the matching law that changes in

motivational state should exert a greater effect on performance under reinforcement-lean conditions, as, indeed, was observed. It is important to note that it is not necesary to calculate the parameters of the matching law in order to make these deductions.

As noted above, the effects of pimozide, SCH-23390 and amphetamine on responding for standard reinforcement only became apparent as the session progressed. However, at the end of the session, where the greatest drug effects were seen, all drugs affected reinforcement-lean responding more than reinforcement-rich responding; in the case of amphetamine, the effect on reinforcement-rich responding was minimal. Effects of SCH-23390 were very similar to those of pimozide. If it is accepted that proportionately greater effects on reinforcement-lean responding denote changes in the motivational characteristics of the task (Morley *et al.*, 1984, 1985), then these effects of DA antagonist and amphetamine are consistent with changes of a motivational kind, over and above any motor effects that the drugs may also be exerting. The same conclusion has been previously drawn from studies using single RI schedules in the matching paradigm (Willner *et al.*, 1987, 1990a).

This conclusion is, of course, consistent with data derived from many other behavioural paradigms (see Section 1.2.2, and Section 1.3). However, within the matching paradigm it has not previously been possible to distinguish between different sources of motivational impairment. It is clear from the present data that the effects of pimozide (and also SCH-23390) are distinct from those of a decrease in drive level, since while both effects are schedule dependent, the former show time dependency and the latter do not. Rather, DA antagonists may act to impair the processing of information about the reinforcer (see reviews by Wise, 1982; Ettenberg, 1989; see also

following Chapters).

3.4.4 Reinforcer Dependency

Matching theory (see Herrnstein, 1970; de Villiers & Herrnstein, 1976) assumes that substituting very sweet reward for standard, moderately sweet reinforcement should enhance responding. In fact responding declined. It is possible that this may have been due to the onset of satiety as approximately 10% of earned reward was not consumed. However, this seems an unlikely explanation, given that the response decrement was present during the initial 5 minute CRF component. Furthermore, 10% and 95% sucrose pellets had an almost identical caloric content. As discussed further in chapters 4 and 5, it is clear that satiation is by no means a necessary condition for response decrements.

In marked contrast to the suppression of responding reinforced by standard (10%) pellets, pimozide substantially enhanced responding for very sweet (95%) pellets in reinforcement-lean components, and also reinstated the complete consumption of earned reward typical of bland reinforcement. This effect of pimozide is inconsistent with the literature, which uniformly reports that DA antagonists suppress performance (see Chapter 1). Given that the underconsumption of sweet rewards is associated with an increase in preference for them (Young, 1949; Young & Greene, 1953), the paradoxical effects of pimozide may be interpreted as at least consistent with a reduction in the reward value of sucrose. This paradox is examined in detail in later chapters.

Amphetamine further reduced consumption of earned reward, and failed to increase low rates of responding for sweet reinforcement. While consistent with the effects of

pimozide, this departure from rate dependency has few precedents (see Branch, 1983). Although under certain circumstances the consequences of responding (e.g. food versus electric shock presentation) can override baseline rates as the main determinant of amphetamine effects (McKearney, 1974), more often they do not (see Kelleher & Morse, 1968). However, it would appear that the intensity of reinforcing stimulation can determine the effects of amphetamine, regardless of the response rate. Branch (1983) has pointed out that, while being a useful empirical generalisation, the principle of rate dependency in the effects of psychomotor stimulants itself requires explanation. The observation that amphetamine enhanced low response rates maintained by lean scheduling of a standard reinforcer (Fig. 3.4) but failed to enhance lower response rates maintained by a very sweet reinforcer (Figs. 3.7, 3.8) suggests that the density of reinforcement, as determined jointly by its temporal distribution and physical characteristics may provide a more powerful organising principle.

CHAPTER 4

REWARD-DEPENDENT SUPPRESSION OR FACILITATION OF OPERANT BEHAVIOUR BY RACLOPRIDE

4.1 INTRODUCTION

It was demonstrated in Chapter 3 that while neuroleptic drugs have usually been found to suppress rewarded behaviour (eg. Janssen *et al.*, 1965; Seeman, 1980), when very sweet reinforcement was used, pimozide facilitated rewarded performance. The experiments reported in the present Chapter confirm and extend these observations, using raclopride, a highly selective antagonist of dopamine (DA) D-2 receptors (de Paulis *et al.*, 1986) that readily pentrates into the rat brain (Kohler *et al.*, 1985).

Behavioural studies to assess the mechanism by which very sweet rewards suppress response rate were also carried out. These involved examination of the time course of responding under continuous reinforcement, variation of food deprivation conditions to evaluate the potential contribution of satiation, and studying performance under extinction conditions, to evaluate the possibility of aversive effects.

Finally, the effects of raclopride were examined after prolonged extinction, in the presence and absence of cues previously associated with reward.

4.2 METHODS

Subjects

Subjects were adult male, Lister hooded rats (NIMR, Mill Hill, London), 64 in experiment 4.1 and 96 in experiment 4.2. The animals were housed in pairs; body weight (275-325g) was maintained at 85% free feeding weight by restricting food access to 60min at the end of daily experimental sessions. Water was freely available in the home cage. Animals were maintained on a 12h light/dark cycle (08.00-20.00h light), at a temperature of 22°C. All experiments were carried out between 12.00 and 15.00h, sessions continuing 7 days per week.

Apparatus

Experiments were conducted in eight identical operant chambers (Campden Instruments Ltd, London), each delivering a 45mg food pellet reinforcer. A mean force of 9g was required to depress the lever. Three types of reinforcement were used: 1% sucrose pellets, standard 10% sucrose reinforcement, or very sweet tasting 95% sucrose pellets (Campden Instruments Ltd, London). The calorific values of the three types of pellet were: 1%, 0.044kc/g; 10%, 3.66kc/g; 95%, 3.766kc/g.

An Acorn System 4 microcomputer (Acorn Computers, Cambridge) was used to record lever presses and to control pellet delivery. Lever presses by each animal were recorded as totals, and in three 5min time bins; designated bins 1, 2, and 3.

Drug

Raclopride tartrate (S(-)-3,5-dichloro-N-(1-ethyl-2-pyrrolidinyl) methyl-6-methoxysalicylamide L(+)-tartrate) (Astra, Sodertalje, Sweden), weighed as the

salt, was dissolved in double distilled water, which also served as vehicle. Fresh stock was prepared immediately prior to need, and protected from light as a precautionary measure when not in use. Injections were i.p. in a volume of 1ml/kg, and were administered 15min prior to testing. With the exception of extinction sessions 9-12 (see below), test days were separated by at least two drug-free sessions, and treatments were counterbalanced across animals and test days.

Experiment 4.1

During each 15min run, the houselight was illuminated, and a 0.5s 800Hz sinusoidal tone sounded at 1s intervals. Reinforcer delivery was signalled by a tray light of 0.5s duration, and noise from pellet delivery mechanisms. Animals were trained under CRF, using standard, 10% sucrose reinforcement. Following the attainment of asymptotic performance (20 sessions) the 64 animals were divided into two matched groups of 32. One group continued to obtain 10% sucrose reinforcement; the second group from session 21 onwards received 95% sucrose reinforcement. Each batch of eight animals contained four animals receiving 10% sucrose reinforcement, and four receiving 95% sucrose reinforcement. The two groups were matched in such a manner as to ensure that each operant chamber contained either 10% sucrose, or 95% sucrose reinforcement throughout each daily session. Animals receiving 95% sucrose reinforcement achieved new levels of asymptotic performance after 5 sessions. In these animals, unconsumed pellets were consistently found in the operant chamber hoppers at the end of the run. To ensure this reflected stable performance, training continued for a further 10 sessions before experiments began. Animals continued to leave earned reward at stable levels.

The effects of raclopride were then examined. For each dose administered, animals

received both raclopride (50,100,200ug/kg) and vehicle injection. No residual drug effect on responding was observable 24h after drug administration.

During three subsequent consecutive daily sessions, each operant chamber was opened at 5, 10, or 15min after run initiation, counterbalanced across sessions. During each daily session, the three time intervals were also counterbalanced across runs. The number of pellets present was recorded together with related response rates for each 5min bin. The number of pellets left during the second and third bins were calculated by subtracting from the number found in the previous bin. In order to ensure the validity of these data, separate comparison was also made with binned responses and total pellet accumulations found in the session immediately prior to the above three sessions.

After recording stable response rates for primary reinforcement, all pellets were removed from the operant chambers and extinction was initiated. Extinction was defined as three consecutive sessions across which total response rates showed no significant differences. Both groups satisfied this criterion after eight sessions. During extinction sessions 9-12, animals responded under 4 conditions - with or without the cues originally signalling reinforcement, and under raclopride (100ug/kg) or vehicle. Cues were defined as tray and houselights, tone, and functioning pellet delivery mechanisms. The two groups previously in receipt of 10% or 95% sucrose reinforcement were each divided into 4 matched subgroups on the basis of their performance during extinction session 8. Because each subgroup was matched, the order of presentation of the four conditions during a session was in effect randomised both within and across runs. This was achieved through individual control over operant chambers. For session 9 of extinction, each of the subgroups was assigned to one of the four experimental

conditions; for the remaining 3 days required for each animal to experience all four conditions, subgroups were reallocated in counterbalanced order to each of the remaining conditions. No significant differences were found between the two groups which had previously received 10% or 95% sucrose. In consequence their data were pooled and reanalysed for the four experimental conditions.

Finally, all cues were reinstated for extinction session 13. On the basis of these data the two groups were each divided into two matched subgroups. On the day immediately following session 13, reinforcement was again made available. Subgroups within 10% and 95% sucrose groups responded either with or without the cues originally signalling reinforcement.

Experiment 4.2

Subjects were first trained to lever press on CRF, using standard 10% sucrose pellets, as in experiment 4.1. Following attainment of asymptotic performance (15 sessions) using standard 10% sucrose reinforcement, the 96 animals were divided into three matched groups of 32. Two groups received reinforcers of the type described previously (10%, 95% sucrose); the third group received 1% sucrose pellets. New levels of stable performance were obtained after a further 10 sessions. All animals then received three doses of raclopride (50,100,200ug/kg) and vehicle, both treatments being administered at each dose level. After the final raclopride treatment, all animals were permitted ad libitum access to chow. Following reattainment of 100% body weight, animals were allowed sufficient operant experience to achieve new levels of asymptotic performance (10 sessions). The animals were then administered drug or vehicle at each of two doses of raclopride (50,100ug/kg).

Analysis

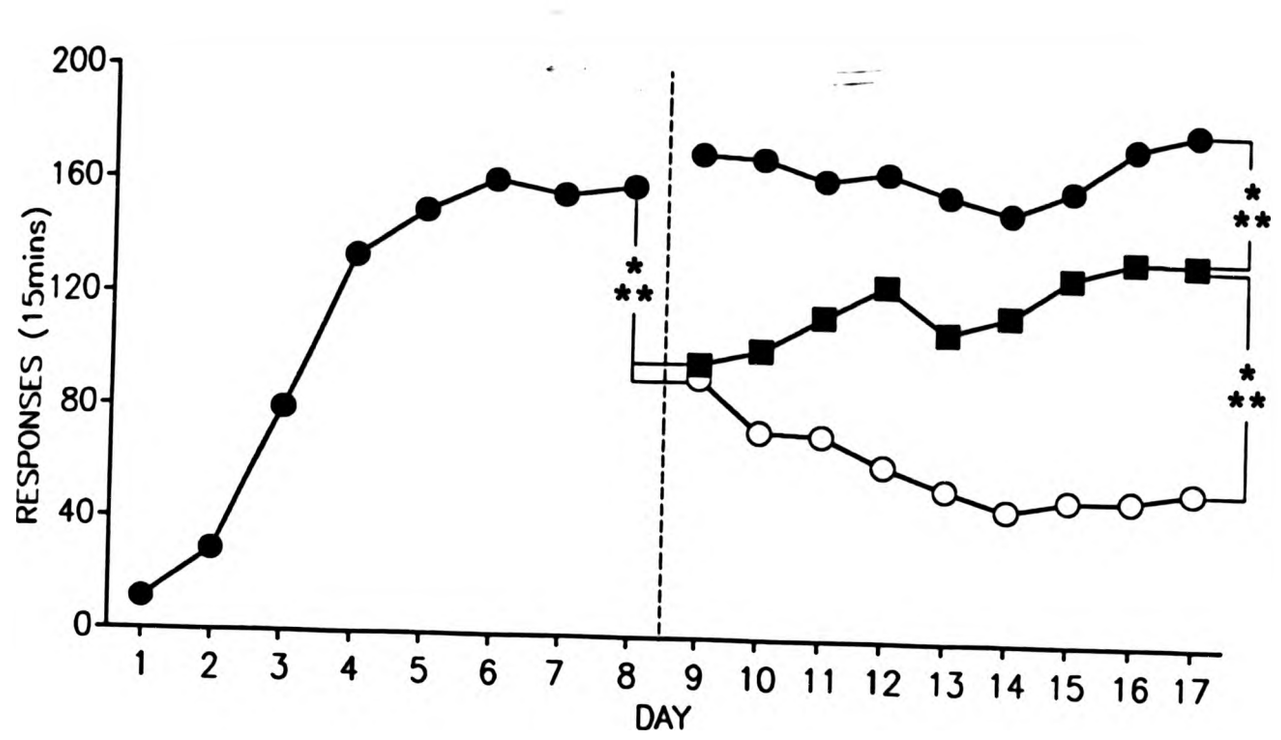
Data were subjected to analysis of variance, supplemented where appropriate by tests of simple main effects and planned comparisons.

4.3 RESULTS

4.3.1 Overall Effects of Raclopride

The effects of varying the concentration of the sucrose reinforcer are shown in Figure 4.1 (data taken from experiment 4.2). On the first day of exposure to 1% or 95% sucrose pellets (day 9 of training, following 8 days of exposure to standard 10% sucrose), response rates of both groups fell by approximately 40% (Fig.4.1, top panel; 1% vs. 10%: $F(1, 93) = 105$, $p < 0.001$; 10% vs. 95%: $F(1, 93) = 91.5$, $p < 0.001$). Subsequently, responding for 95% sucrose increased (day 9 vs. day 17: $F(1, 1488) = 35.4$, $p < 0.001$), but remained at a consistently lower rate than for 10% sucrose (day 17: 95% vs. 10% sucrose, $F(1, 93) = 35.5$, $p < 0.001$). Baseline response rates for 95% sucrose reinforcement were also significantly lower than for 10% sucrose throughout experiment 4.1 (Fig.4.2, top, left panel, 10% vs. 95% sucrose: $F(1, 93) = 66.6$, $p < 0.001$). Responding for 1% sucrose declined gradually (day 9 vs. day 17: $F(1, 1488) = 35.5$, $p < 0.001$), but eventually stabilised at around 30% of the response rate for 10% sucrose (day 17, 1% vs. 10% sucrose: $F(1, 93) = 268$, $p < 0.001$).

Following the introduction of 1% or 95% sucrose pellets reductions in response rates were immediately apparent (Fig.4.2, bottom panel, first 5min: 1% vs. 10% sucrose, $F(1, 93) = 20.2$, $p < 0.001$; 95% vs. 10% sucrose, $F(1, 93) = 54.9$, $p < 0.001$). The further decline in responding for 1% sucrose pellets was attributable primarily to changes



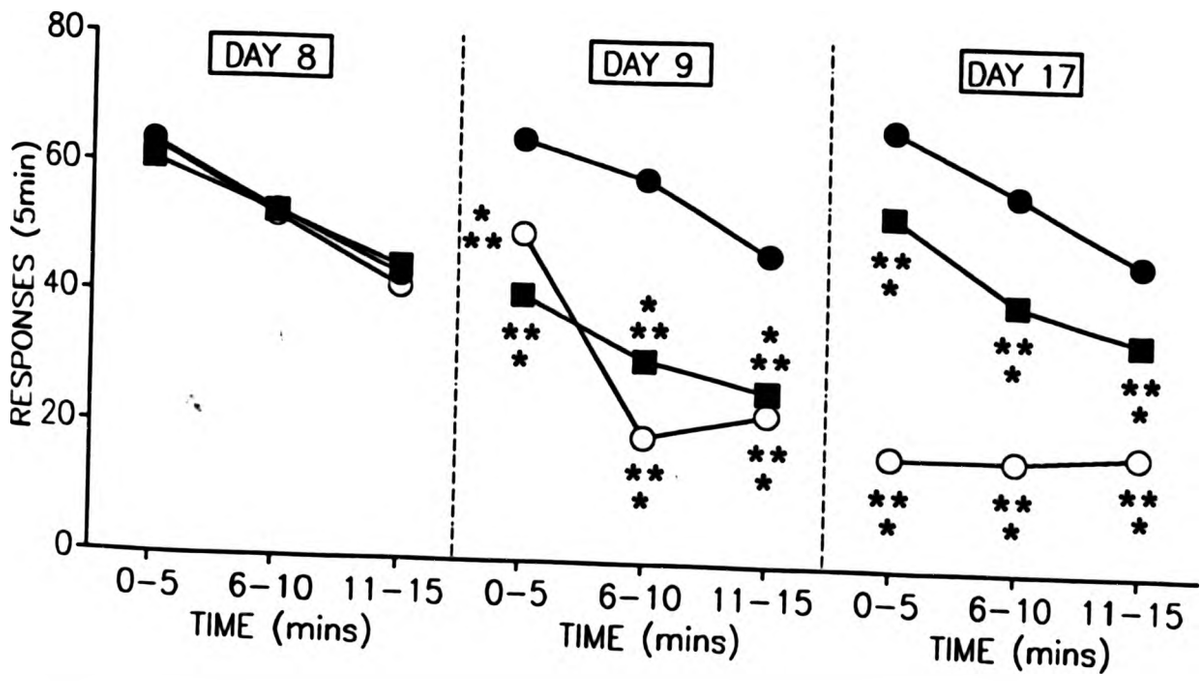
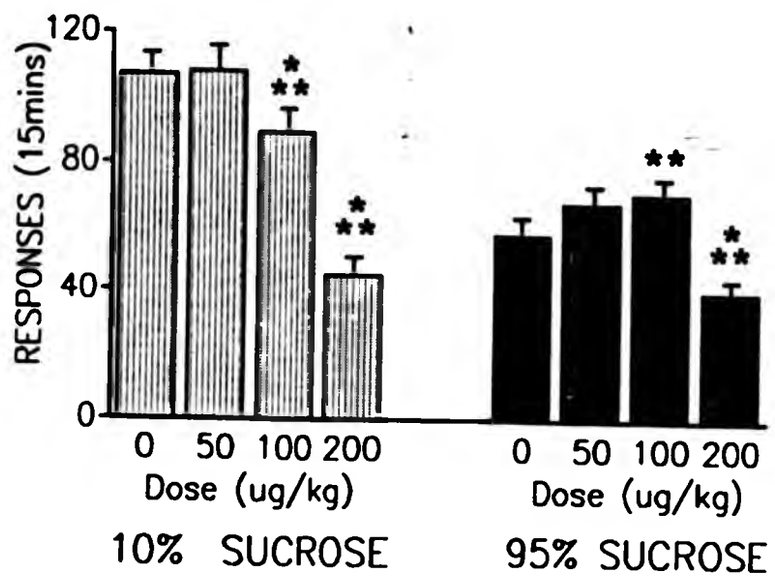
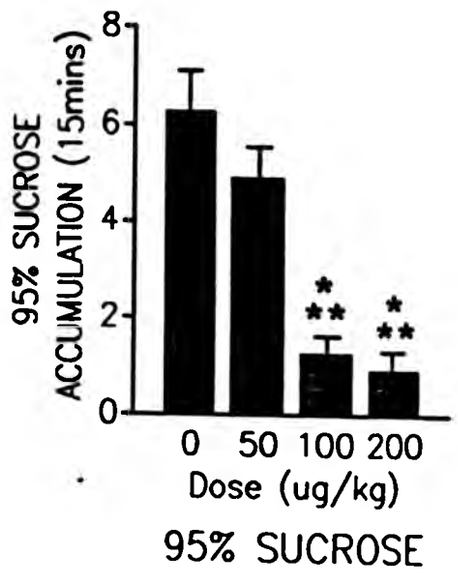
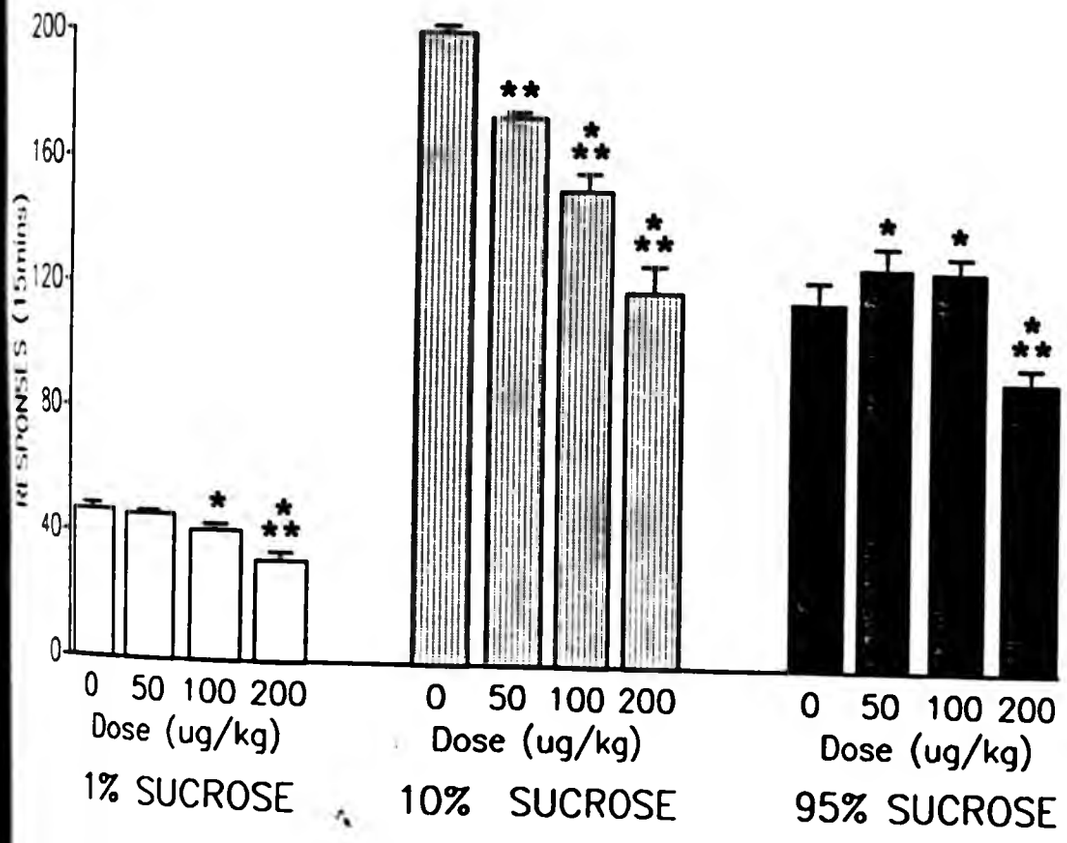
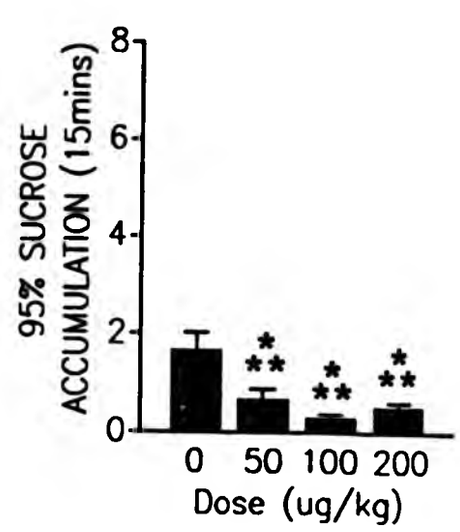


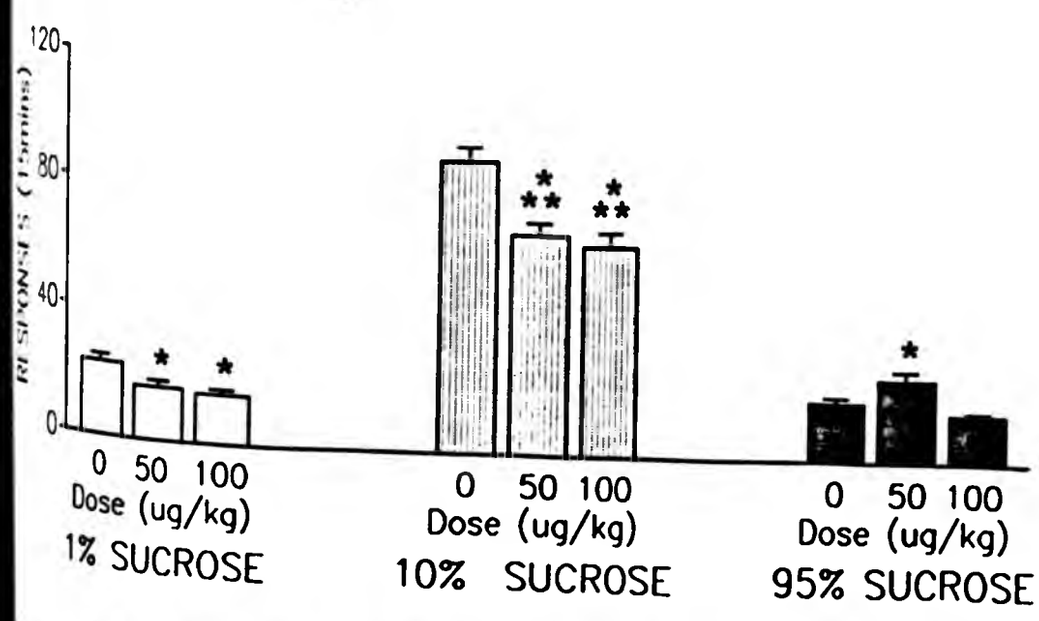
Fig.4.1 Acquisition of CRF responding. **Top panel:** total responses per 15min session. Days 1-8: initial training using standard 10% sucrose pellets. From day 9 onwards animals were divided into three matched groups: **open circles**, 1% sucrose pellets; **filled circles**, 10% sucrose pellets; **filled squares**, 95% sucrose pellets. **Bottom panel:** within-session responding during selected days, in 5min time bins. ***, $p<0.001$ relative to 10% sucrose.











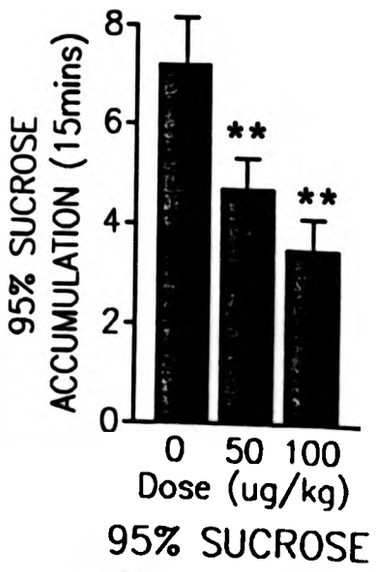


FIG. 4.2. Effects of raclopride upon operant performance for 45mg sucrose pellets, under 15 minutes of continuous reinforcement. **Top and middle panels:** 18h food deprived; **bottom panels:** ad libitum food access. **Left panels:** total responses for 1%, 10% or 95% sucrose pellets; **right panels:** corresponding uneaten 95% sucrose pellets. Values are means. Stars show significance of drug effects relative to vehicle: *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$.

occurring during the first 5min of the session (day 9 vs. day 17, first 5min: $F(1,186)=303$, $p<0.001$). By contrast, the suppressive effect of 95% sucrose was constant across the 15min experimental session, both on day 9 and day 17 (Fig.4.2, bottom panel).

In experiment 4.1, raclopride suppressed responding for 10% sucrose, but facilitated responding for 95% sucrose (reinforcer x dose interaction: $F(2,124)= 16.9$, $p<0.001$; see Fig.4.2, top panel). At 100ug/kg, both these effects were statistically significant (10% sucrose suppression: $F(1,62)=14.0$, $p<0.001$; 95% sucrose facilitation: $F(1,62)= 7.2$, $p<0.01$). However, 200ug/kg raclopride reduced responding in both groups, although to a larger extent for 10% sucrose: response rates by the two groups were indistinguishable at this dose ($F(1,62)= 0.2$, N.S.).

Similarly, in experiment 4.2, administration of 100ug/kg raclopride suppressed responding maintained by 1% or 10% sucrose (1% sucrose group: $F(1,279)= 4.3$, $p<0.05$) but simultaneously enhanced responding for 95% sucrose ($F(1,279)= 5.6$, $p<0.05$). Although 200ug/kg suppressed responding in all groups, the effect was proportionately smaller in the 95% sucrose group: 32%, 31%, and 16% for 1%, 10%, and 95% sucrose groups respectively (1% vs. 95%: $F(1,93)= 5.4$, $p<0.05$; 10% vs. 95%: $F(1,93)= 5.2$, $p<0.05$).

Ad libitum food access reduced responding by all groups ($F(2,93)= 373$, $p<0.001$), although the bitonic nature of the function remained intact (Fig.4.2, bottom panel). At 50ug/kg, raclopride again reduced responding for 1% and 10% sucrose (1% sucrose: $F(1,93)= 8.9$, $p<0.01$), but increased responding for 95% sucrose (Fig.4.2, bottom panel; $F(1,93)= 5.6$, $p<0.05$). 100ug/kg raclopride, which increased responding for 95% sucrose when animals were food deprived (see above), caused a small, nonsignificant decrease in response rate under conditions of ad libitum food access. However, response

rates for 95% sucrose were again more resistant to suppression than the lower sucrose concentrations; proportional decrements were 37%, 31%, and 17% for 1%, 10% and 95% sucrose respectively (1% vs. 95%: $F(1,93) = 7.7$, $p<0.01$; 10% vs. 95%: $F91,93) = 4.3$, $p<0.05$). Under these ad libitum access conditions, baseline response rates for 1% and 95% sucrose were indistinguishable ($F(1,93) = 0.1$, N.S.).

Enhancements of responding for 95% sucrose are even more striking than might at first appear. Animals responding for 1% and 10% sucrose reward consumed all reinforcement obtained. However, a small proportion of earned 95% sucrose reward was not consumed. Raclopride consistently reduced the accumulation of 95% sucrose pellets under both food deprived and ad libitum access conditions (food deprived: experiment 4.1, $F(1,31) = 45.2$, $p<0.001$; experiment 4.2, $F(3,93) = 8.4$, $p<0.01$; ad libitum access: $F(1,31) = 18.0$, $p<0.001$). This was so even at doses which also increased responding and the consequent numbers of reinforcers earned (see Fig.4.2, right panels).

4.3.2 Within-session Effects of Raclopride

Effects of raclopride are further illustrated by within-session data (Fig.4.3). 50ug/kg raclopride reduced responding for 10% sucrose, but increased responding for 95% sucrose during the first 5min. At 100ug/kg, responding for 10% sucrose declined even further. Nonetheless, animals responding for 95% sucrose were either unaffected (Bin 1: $F(1,62) = 1.9$, N.S.) or again demonstrated increases in responding (Bin 2: $F(1,62) = 7.6$, $p<0.01$). The lowest dose used (50ug/kg) did increase responding for 10% sucrose, but this only occurred late in the session during bin 3 ($F(1,62) = 15.5$, $p<0.001$). Late responding for 10% sucrose was unchanged at 100ug/kg, but severely suppressed at 200ug/kg ($F(1,62) = 27.0$, $p<0.001$). Although late responding for 95%

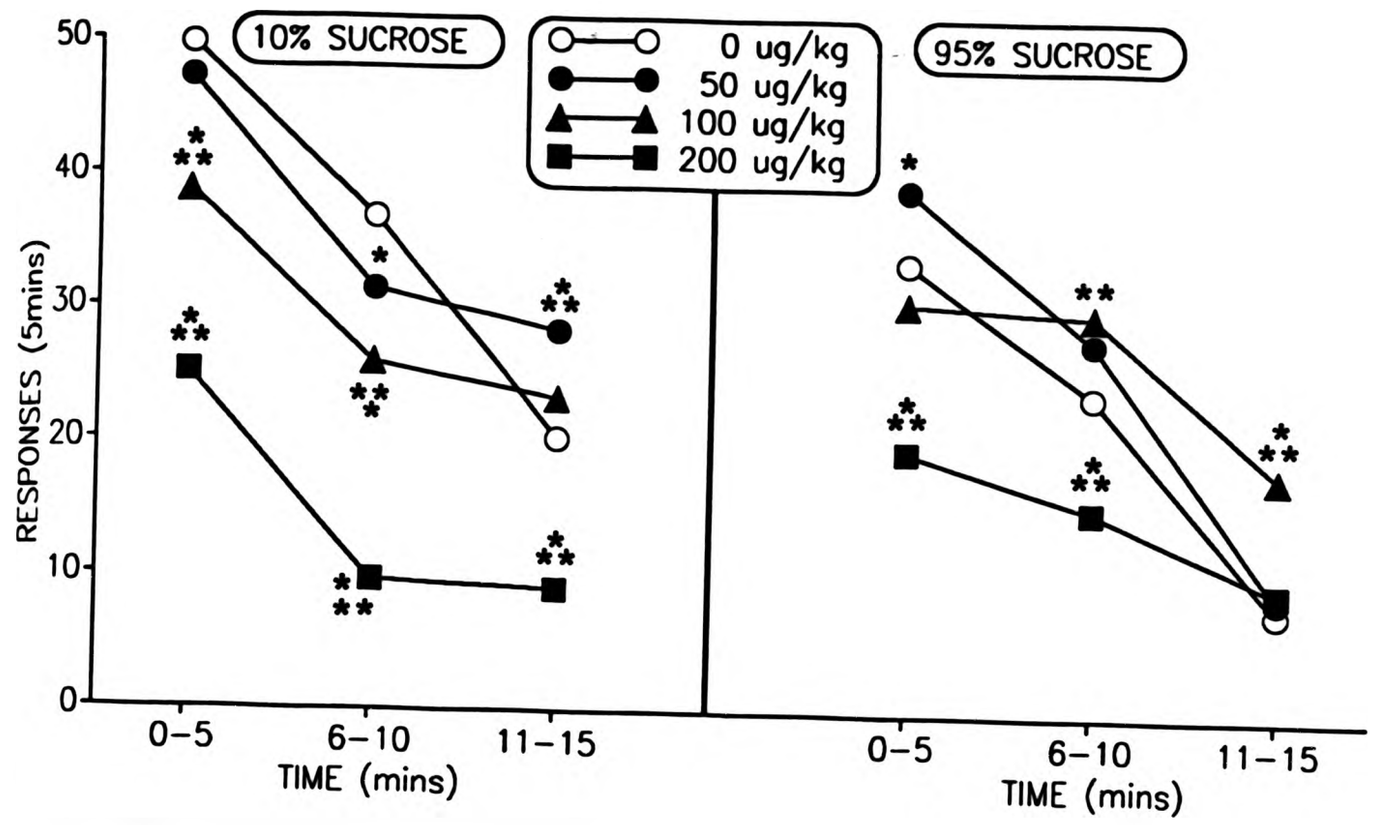


FIG. 4.3. Within-session effects of raclopride upon response rates for 45mg sucrose pellets, under a total of 15 minutes of continuous reinforcement. Values are means. Stars show significance of drug effects relative to vehicle: *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$.

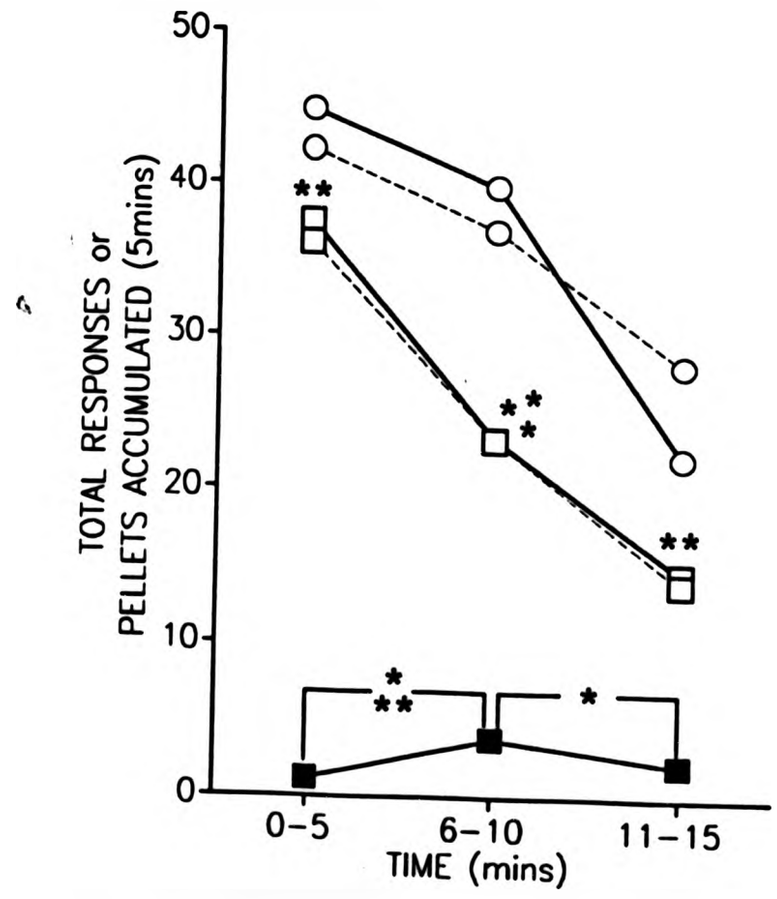


FIG. 4.4. Within-session CRF responding maintained by 45mg sucrose pellets, under a total of 15 minutes of continuous reinforcement. **Circles**, 10% sucrose pellets; **squares**, 95% sucrose pellets. **Open symbols**, responses; **filled symbol**, accumulated 95% sucrose pellets. **Solid lines**, responses corresponding to accumulations; **dotted lines**, responses on day prior to observation of accumulations. Values are means. *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$.

sucrose was unaffected at 50ug/kg, 100ug/kg also increased bin 3 response rates for 95% sucrose ($F(1, 62) = 21.4, p < 0.001$). At 200ug/kg, in contrast with marked response supression for 10% sucrose noted above, response rates for 95% sucrose merely returned to vehicle levels. Hence, late responding for 10% sucrose appeared to show greater sensitivity to both facilitatory and suppressive effects of raclopride.

It should be noted that baseline response decrements across time for 10% and 95% sucrose followed an essentially parallel course (Fig.4.4): response rates for 95% sucrose reinforcement were at a consistently lower level than response rates for 10% sucrose, even during bin 1 ($F(1,62) = 34.2, p < 0.001$). Similar numbers of pellets remained uneaten during bins 1 and 3 ($F(1,62) = 2.24$, N.S.), most pellets being discovered during bin 2 (see Fig.4.4). Despite the low number of uneaten 95% sucrose pellets, the majority of animals contributed to these means: 22/32 animals left at least one pellet during bin 1, 27/32 during bin 2 and 21/32 during bin 3. By contrast, no uneaten 10% sucrose pellets were detected at any time (first 5min. bin: $X^2 = 33.5, p < 0.001$). Opening the chambers to assess the time-course of pellet accumulation did not adversely affect response patterns across time (10% sucrose: $F(1,62) = 0.01$, N.S.; 95% sucrose: $F(1,62) = 0.3$, N.S.), nor did it affect the number of 95% sucrose pellets found in the chambers at the end of the run (previous day, 9.0 +/-1.1; test day, 7.0 +/-0.8; $F(1,31) = 2.0$, N.S.).

4.3.3 Extinction and reacquisition

Prior to extinction, response rates for 95% sucrose were significantly lower than those for 10% sucrose (terminal reinforcement session: $F(1, 62) = 45.0, p < 0.001$). During extinction session 1, animals previously receiving 10% sucrose reinforcement

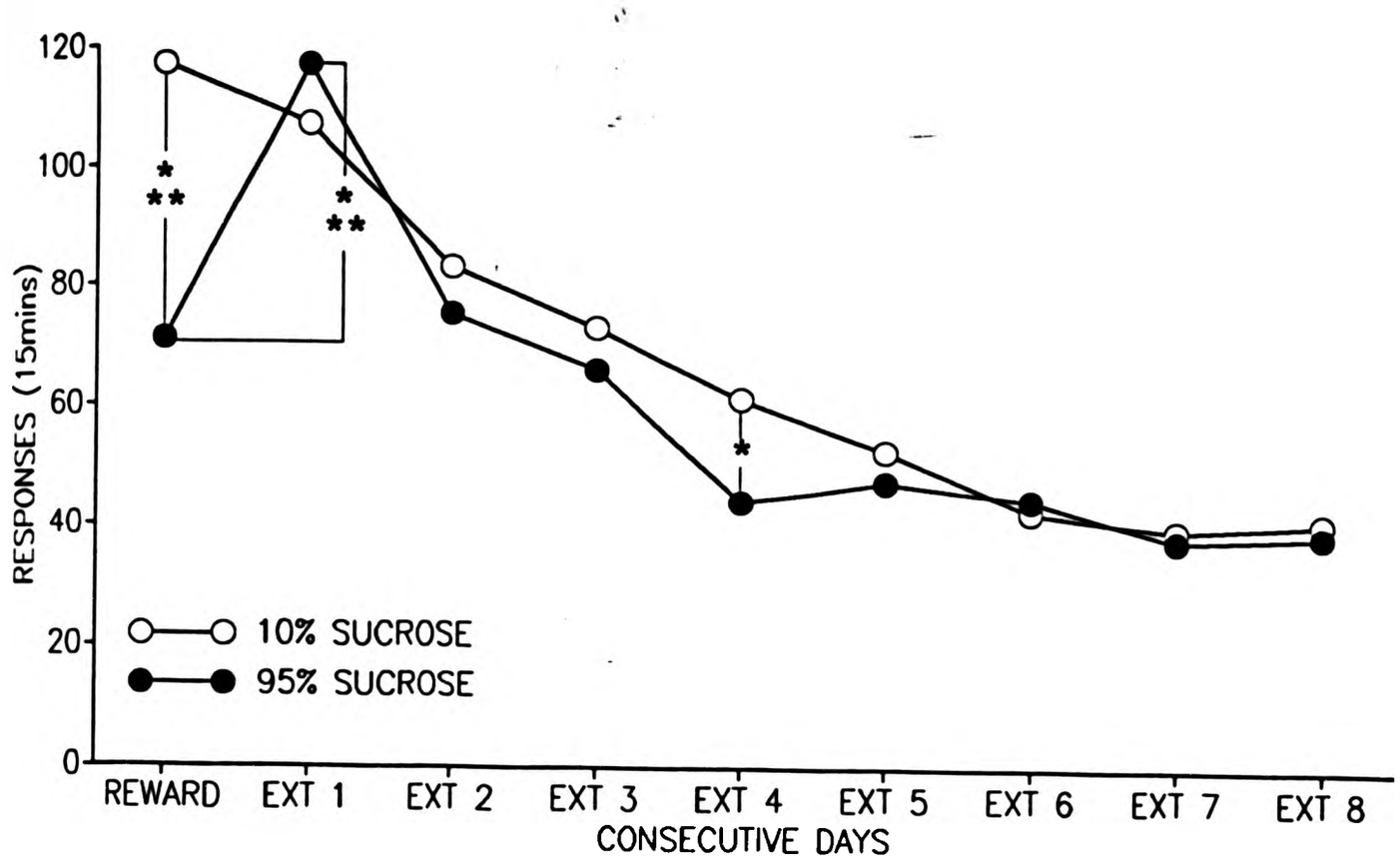


FIG. 4.5. Effects of 45mg sucrose pellet concentration upon response rate following withdrawal of reinforcement. **Reward**, final day of pellet availability under 15 minutes continuous reinforcement; **Ext** 1,2,.., consecutive days of extinction. Values are means. *, $p<0.05$; ***, $p<0.001$.

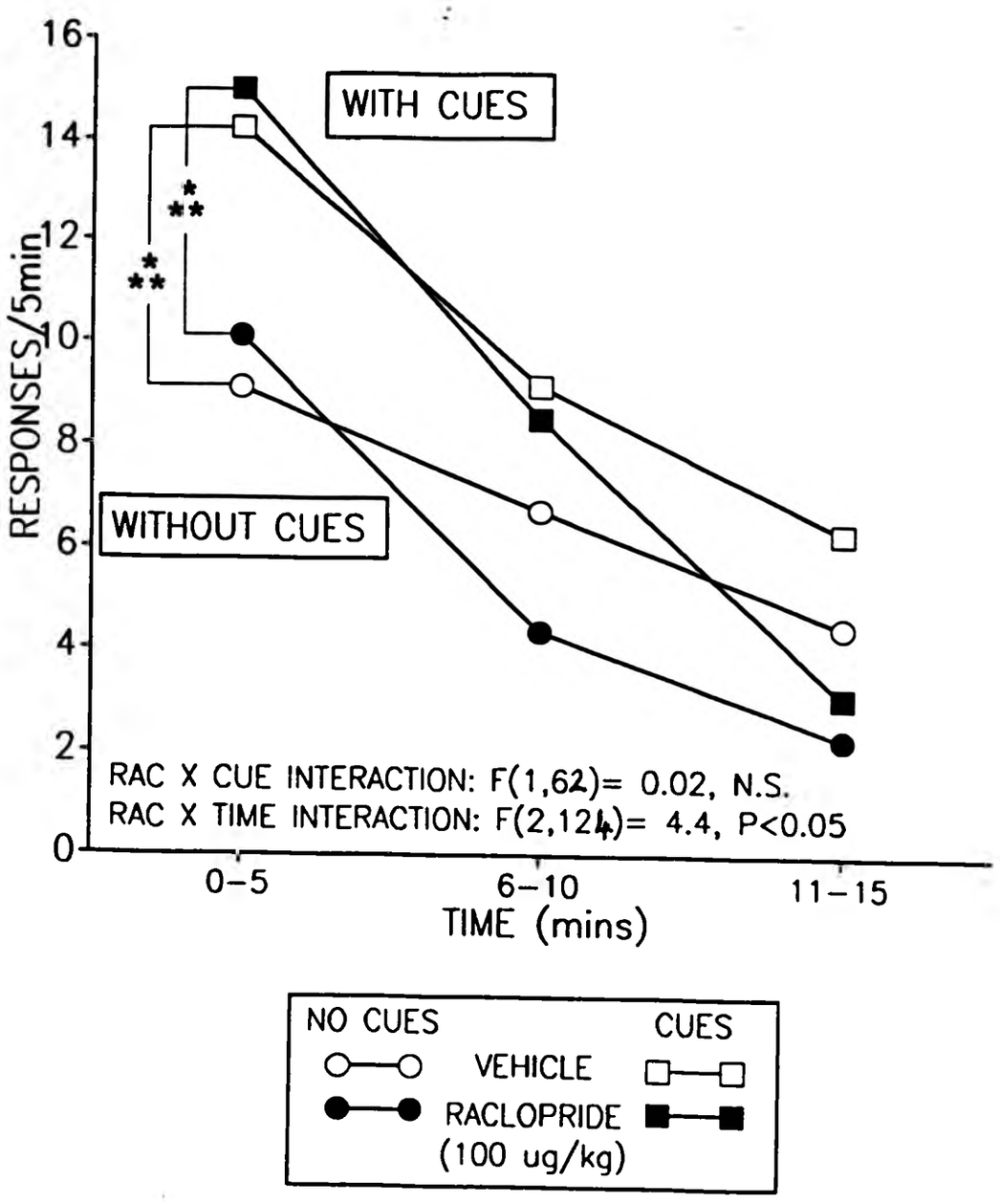


FIG. 4.6. Within-session effects of raclopride upon response rate during 15 minutes of extinction. Values are means. ***, $p<0.001$.

exhibited a slight decline in response rate (Fig.4.5: $F(1,496) = 3.1$, N.S.). However, animals previously in receipt of 95% sucrose demonstrated large increases in response rates ($F(1,496) = 66.8$, $p<0.001$). During subsequent extinction sessions, the 95% sucrose group tended to respond at lower rates than the 10% sucrose group; this effect reached statistical significance in session 4 ($F(1,496) = 6.2$, $p<0.05$).

Following stabilisation of extinction responding (linear trend, response rate under control conditions over extinction days 9-12: $F(1,60)=3.1$, N.S.), removal of cues previously associated with reward caused an immediate decrease in responding (Fig.4.6, bin 1: $F(1,62)=13.8$, $p<0.001$), although the efficacy of cues declined as the session progressed (cue x time interaction: $F(2,124)=4.4$, $p<0.05$), and the effects were not significant during later periods of the session (bins 2 and 3: $F(1,62)=3.1$, 1.8 respectively, N.S.). By contrast, raclopride had no immediate effect (bin 1: $F(1,62)=0.9$, N.S.), but suppressed responding during later periods of the session, when the effects of cues were no longer significant (bin 3: $F(1,62)=8.5$, $p<0.01$; raclopride x time interaction: $F(2,124)=4.4$, $p<0.05$). Hence, the effects of cues were largest early in the session, but the effects of raclopride were largest late in the session.

Upon reinstatement of primary reinforcement, the presence of reward-associated cues immediately enhanced reacquisition of responding for 10% and 95% sucrose (bin 1: 10% sucrose group, mean responses with or without cues: 41.6, 34.3 respectively, $F(1,30) = 6.4$, $p<0.05$; 95% sucrose group, mean responses with or without cues: 26.3, 19.5 respectively, $F(1,30) = 5.7$, $p<0.05$), although effects were less striking in later portions of the session (results not shown). However, cues enhanced reacquisition to a similar extent in both groups (sucrose x cue interaction: $F(1,30) = 3.1$, N.S.).

4.4 DISCUSSION

4.4.1 Effects of reinforcer sweetness on operant performance

Responding for 1%, 10%, or 95% sucrose reinforcement took the form of an inverted U-shape, maximal response rates occurring for 10% sucrose reinforcement. This was the case under both food deprived and ad libitum access conditions, although animals responded at a generally lower rate in the latter case. Operant performance is commonly assumed to be a monotonic function, in which response rate rises to an asymptote with increasing reinforcement (cf. Herrnstein, 1970). The inverted U-shaped function demonstrated in the present study (and also, though less obviously in Chapter 3) therefore requires some consideration.

It is possible that the descending limb of the sweetness-performance function could simply reflect the onset of an aversive component to very sweet reinforcement. However, withdrawal of 10% sucrose led to a gradual decline in responding during extinction, whereas anticipation of 95% sucrose reinforcement led to a striking increase in response rate. This effect is typically observed following the withdrawal of a high-incentive reward (Ferster & Skinner, 1957; Keller & Schoenfield, 1950; Thompson *et al.*, 1963), and suggests that 95% sucrose is not less rewarding than 10% sucrose reinforcement. In a similar study, also using CRF, Guttman (1953) examined operant responding for sucrose solutions varying in concentration up to 32% sucrose. A minute reinforcer volume of only 0.005ml was obtainable, giving a maximum intake of only 1.25ml. As in the present study, responding across concentrations took the form of a stable inverted U-shaped function, with relatively low response rates for the 32% solution, but responding during extinction was in fact highest for animals trained using 32% sucrose. Similar effects have been demonstrated using ICSS. Thus, Hodos & Valenstein (1962) demonstrated an

inverted U-shaped function relating response rate to stimulation intensity. When animals were given a choice between two intensities of stimulation, they displayed a clear preference, in both the hypothalamus and septum, for descending limb stimulation intensities, over ascending limb or even apical response rate intensities. In short, there appears to be no evidence that very sweet reinforcers are less rewarding in the rat.

The descending limb of the concentration-intake function, contingent upon intense rewards, which in the present study were also calorie-loaded, could alternativley result from the onset of postingestional satiation: a small proportion of uneaten 95% sucrose reinforcers did accumulate during the experimental sessions. However, this seems a most unlikely explanation, given that the 10% and 95% sucrose pellets had an almost identical calorie content. The effects of postingestional satiation have been described as gradual, slow-to-act and long lasting (Morgan, 1974). However, the observed pattern of reward accumulation did not suggest such a process. As much reinforcement accumulated within the first 5 minutes of the session as during the final five minutes. Satiation showing rapid onset also occurs using saccharin (Hsaio & Tuntland, 1971; Mook *et al.*, 1980, 1981), and therefore does not appear to depend upon postingestional consequences. Such effects appear to be of central origin (Rolls *et al.*, 1986, 1989; Wilcove, 1973). It should also be noted that response rates for 95% sucrose were significantly lower than those for 10% sucrose even during the first 5 minutes, and maintained a parallel course throughout the session. Finally, the inverted U-shaped function was present independently of the degree of food deprivation (see Fig.4.2).

It is concluded that neither aversion nor post-ingestional satiety can explain the suppression of responding by very sweet rewards during 15min of reinforcer availability. the rapid onset of response suppression by 95% sucrose pellets suggests the involvement

primarily of orosensory factors.

4.4.2 Reward-dependent effects of raclopride

When animals were food deprived, low-to-moderate doses of raclopride (50 or 100ug/kg) reduced responding for 1% or 10% sucrose, but actually facilitated both responding for, and consumption of, 95% sucrose reward. Even in non-deprived animals a very similar picture emerged: raclopride again decreased responding for 1% and 10% sucrose, but (at 50ug/kg) simultaneously increased responding for, and consumption of 95% sucrose reinforcement. Effects of raclopride are further illustrated by within-session data. For the first 10 minutes of the 15 minute sessions, 50ug/kg raclopride increased responding for 95% sucrose, but reduced responding for 10% sucrose reinforcement. However, during the final 5 minutes raclopride increased responding for the 10% sucrose reward, but no longer affected responding for 95% sucrose.

The effects of raclopride on sucrose consumption may be modelled empirically as a rightward shift in a bell-shaped response-reward function (see Fig.4.7). Higher doses which decreased responding at all concentrations did so in a reinforcer-dependent manner: decrements were largest for 1% sucrose, and smallest for 95% sucrose. It is conceivable that raclopride could impair the perception of sweetness. However, experiments in this laboratory have demonstrated that pimozide had no effect upon either the threshold of sweetness perception, or the just-noticeable sweetness difference (Willner *et al.*, 1990a). Therefore, the effect of neuroleptics appears to be a reduction in reactivity to sweetness, rather than in the perception of sweetness at a sensory level. The conclusion that neuroleptics reduced reactivity to rewards is consistent with a number of earlier studies (see Sections 1.2.3 and 7.3).

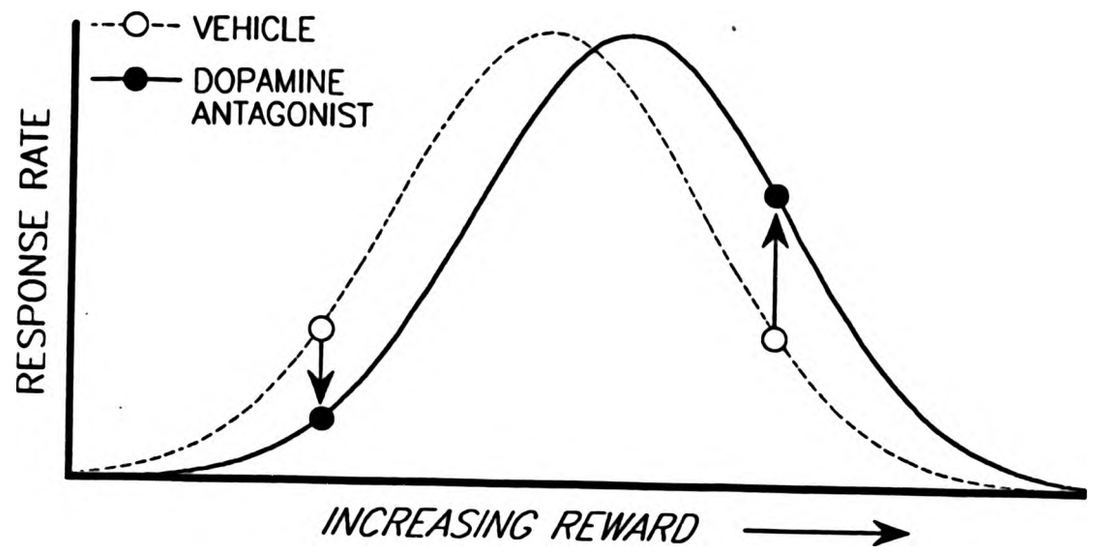


FIG. 4.7. Empirical model of neuroleptic drug action upon an inverted U-shaped response-reward function. Arrows indicate direction of neuroleptic-induced change in behaviour.

4.4.3 Reward-independent effects of raclopride

Performance in reinforcement-lean schedules, in which long chains of behaviour are presumed to be under the control of secondary motivational cues, is typically impaired by neuroleptics in a time-dependent manner: responding typically declines during the course of the experimental session (see Section 1.2.2; see also Willner *et al.*, 1987, 1990a). In the present study, it was observed that during a period of stable responding under extinction conditions, the removal of reinforcement-associated cues caused an immediate decrease in responding, but the efficacy of cues in maintaining behaviour declined as the session progressed. Conversely, raclopride had no initial effect but in a time-dependent manner reduced responding only during later portions of the session. As this portion of the study was carried out following prolonged extinction, these data can not easily be explained by neuroleptic effects on reward. As such, they appear to be distinct from the interactions with sweetness described above. Others have described neuroleptic-induced response decrements during extinction (Phillips & Fibiger, 1990), and in non-rewarded or aversive paradigms (Hillegaart *et al.*, 1987; Sanger, 1986; see Section 1.2.2). Together, these findings suggest that the term "extinction-like", which is frequently used to describe neuroleptic-induced within-session response decrements may be inappropriate.

In conclusion, two effects of raclopride have been described. One, a sucrose concentration-dependent supression or facilitation of rewarded responding is compatible with a decreased reactivity to sweet rewards. The second, a within-session response decrement, is not compatible with a reward-blunting effect. As it is difficult to construct a conceptual integration of these two effects, it may be that they represent two independent actions. This hypothesis is addressed in Chapter 6.

CHAPTER 5

REWARD-DEPENDENT SUPPRESSION OR FACILITATION OF CONSUMMATORY BEHAVIOUR BY RACLOPRIDE

5.1 INTRODUCTION

In the previous chapter, continuously reinforced responding for 1%, 10% or 95% sucrose pellets was shown to follow an inverted-U-shaped function with increasing sucrose concentration: response rate was highest for 10% sucrose pellets. Raclopride reduced responding for 1% and 10% sucrose pellets, but increased responding for 95% sucrose reward. Hence, the directions in which raclopride changed responding depended on the concentration of sucrose reward.

Here, assessment is made of the effects of raclopride upon the nonoperant consumption of sucrose solutions. Further behavioural studies have been carried out to assess the mechanism by which very sweet rewards suppress behaviour. These included examination of the time course by which raclopride enhances intake of very sweet solutions, to evaluate the potential contribution of satiation. The effect of providing a choice of sucrose concentration has also been examined, in order to evaluate the possibility of aversive effects of very sweet solutions. Finally, the effect of raclopride upon intake of an aversive quinine solution was examined, to assess the specificity of the effects of raclopride on intake of sweet solutions.

5.2 METHODS

Subjects

The subjects of these experiments were adult male Lister hooded rats (NIMR, Mill Hill, London). Body weight (275-325g) was maintained at 85% of free feeding weight by restricting food access (SDS, Witham, UK) to 60min at 18.00-19.00h each day. Animals were maintained on a 12h light/dark cycle (light on 08.00h), at a temperature of 22°C. Subjects were housed singly in white polypropylene cages (26 x 19 x 38cm; NKP Cages Ltd, Dartford, UK), containing a 3cm layer of sawdust (SDS, Witham, UK). Sessions were run in the home cage and were conducted at 16.00h. At least one day intervened between successive tests. Water was removed at 19.00h on the day preceeding behavioural tests, but was otherwise freely available.

Materials

With the exception of experiment 5.2, fluid consumption was assessed using 250ml white polythene bottles with 2" ball tipped stainless steel tubes and close-fitting bungs (NKP Cages Ltd, Dartford, UK). For experiment 5.2, 50ml vertically mounted transparent tubes were used, adapted from 'Bird Fountains' (Mars GB Ltd, UK) by the attachment of millimetre scales. 5" ball tipped stainless steel tubes were attached, bent to a 45° angle (NKP Cages Ltd, Dartford, UK). Sucrose was of commercial grade; quinine hydrochloride was obtained from Sigma Chemical Co, St. Louis, USA. Raclopride tartrate (Astra, Lakemedel, Sweden), weighed as the salt, was dissolved in double distilled water, which also served as vehicle. Fresh stock was prepared immediately prior to need, and protected from light as a precautionary measure when not in actual use. Injections were i.p. in a volume of 1ml/kg, and were administered

15min prior to testing. Pharmacological test sessions were separated by at least three drug-free days.

Experiment 5.1

24 animals were randomly assigned to one of three groups of eight. During initial training, each animal was presented with two preweighed bottles, one containing sucrose, the other water. The first group received 0.7% sucrose, the second 7% sucrose, and the third 34% sucrose; concentrations were weight/volume. Bottle positions (sucrose to left or right) were counterbalanced across animals and sessions. Bottles were reweighed at 5 minute intervals for the first 15 minutes, and again at the end of the one-hour exposure. Stable baselines were obtained after ten sessions. For the four test sessions following, animals received raclopride (100, 200, 400ug/kg) and vehicle in a counterbalanced design.

All animals were then presented with a concurrent choice of the three sucrose concentrations. As before, bottles were reweighed every 5 minutes for the first 15 minutes, and finally at the end of the one-hour session. The position of each concentration (left, middle or right) was counterbalanced across animals and sessions. After four training sessions in this procedure, the animals received three test sessions in which raclopride (200, 400ug/kg) and vehicle were administered in a counterbalanced design.

Experiment 5.2

During initial familiarisation (3 one-hour sessions), animals (n = 16) were presented with three containers; during this period one contained water and the other two were

empty. The position of the water container (left, middle or right) was counterbalanced across animals and sessions. In this manner initial preference for the maintenance water bottle position was eliminated. Then, for three days only, subjects were presented for one hour with a concurrent choice of the three concentrations of sucrose used in experiment 5.1, their positions being counterbalanced across animals and sessions. Fluid intakes were recorded at 5, 10, 15 and 60 minutes as in experiment 5.1. On the first test day, 4 animals were administered raclopride (150ug/kg), while the rest received vehicle. The 4 animals receiving drug on each of the following two test days were extracted from the vehicle group of the previous test day. Animals that had received raclopride were excluded on subsequent tests.

Experiment 5.3

For four sessions, animals (n=21) were initially familiarised with the procedure by the presentation of a single water bottle for one hour. From session 5 onwards, animals were randomly allocated to three groups of seven. On each day the three groups received either quinine (0.001%), water or sucrose (0.7%). Each group continued to receive all three solutions in the order indicated, over a three-day cycle. In this manner the presentation of solutions was counterbalanced across both groups and days. Following initial training (6 cycles), animals were administered raclopride (150ug/kg) and vehicle in a counterbalanced order under each condition (quinine, water or sucrose).

Analysis

Data from experiments 5.1 and 5.3 were subjected to analysis of variance,

supplemented where appropriate by tests of simple main effects and planned comparisons. Due to unequal sample sizes, data from experiment 5.2 were analyzed using the t test.

5.3 RESULTS

5.3.1 Effect of choice upon sucrose intake

When presented with a single concentration of sucrose and only water as an alternative, baseline intake was highest for 7% sucrose (Fig. 5.1, top left panel), compared with equivalent but substantially lower intakes of 0.7% and 34% sucrose (0.7% or 34% vs. 7%: $F(1,42) = 278, 294$ respectively, $p < 0.001$). Water intake was relatively high when 34% sucrose was available (0.7% or 7% sucrose vs. 34% sucrose: $F(1,42) = 36.1, 43.9$ respectively, $p < 0.001$). Differences in intake between 7% and 34% sucrose were present during the first 5 minutes, and did not increase in subsequent time bins (Fig. 5.1, bottom left panel; first 5min: $F(1,105) = 42.4$, $p < 0.001$). In contrast to the effects observed in the 2-bottle test, when presented with a concurrent choice of all three sucrose concentrations (Fig. 5.1, top right panel), intake was highest for 34% sucrose (0.7% or 7% vs. 34%: $F(1,46) = 37.9, 29.5$ respectively, $p < 0.001$). This was so even during the first 5 minutes (Fig. 5.1, bottom right panel; $F(1,46) = 19.4$, $p < 0.001$).

5.3.2 Overall effects of raclopride

In sucrose-experienced animals, whether presented with water and a single concentration of sucrose (2-bottle test) or all three concentrations concurrently (3-bottle test), raclopride reduced intake of 0.7% sucrose solution but enhanced intake of 34% sucrose (Fig. 5.2; raclopride x sucrose interactions: two bottle test, $F(6, 63) = 14.1$,

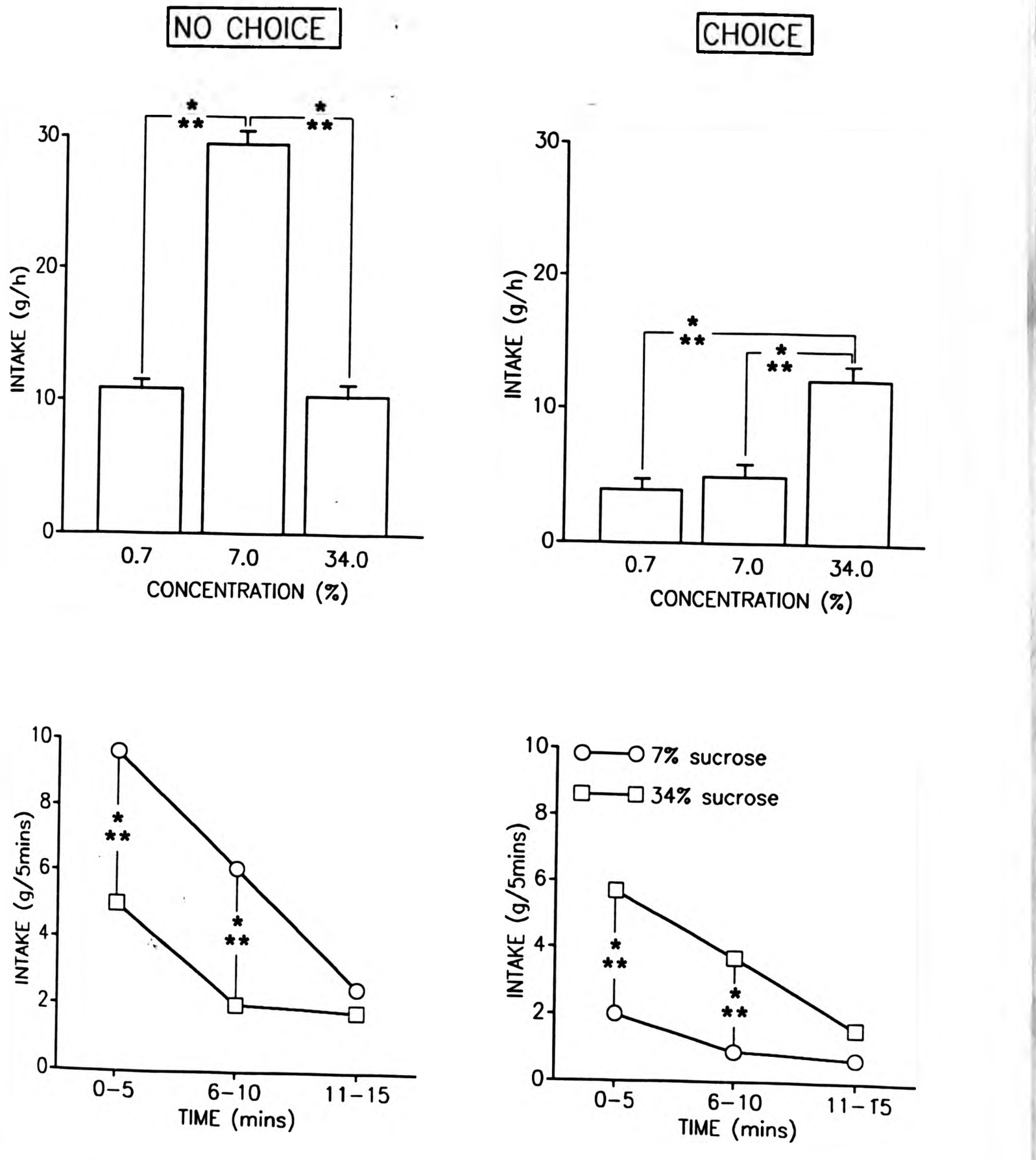


FIG. 5.1. Effects of presentation condition upon intake of sucrose. **Left panel:** separate presentation of 0.7%, 7% or 34% sucrose; **right panel:** concurrent presentation of all three sucrose concentrations. **Top panel:** intakes over 1h; **bottom panel:** intake of 7% and 34% sucrose for the first 15mins, in 5min bins. **Top panel:** values are means +1 SEM; bottom panel excludes SEMs. Stars indicate statistical significance of drug effects; ***, $p<0.001$.

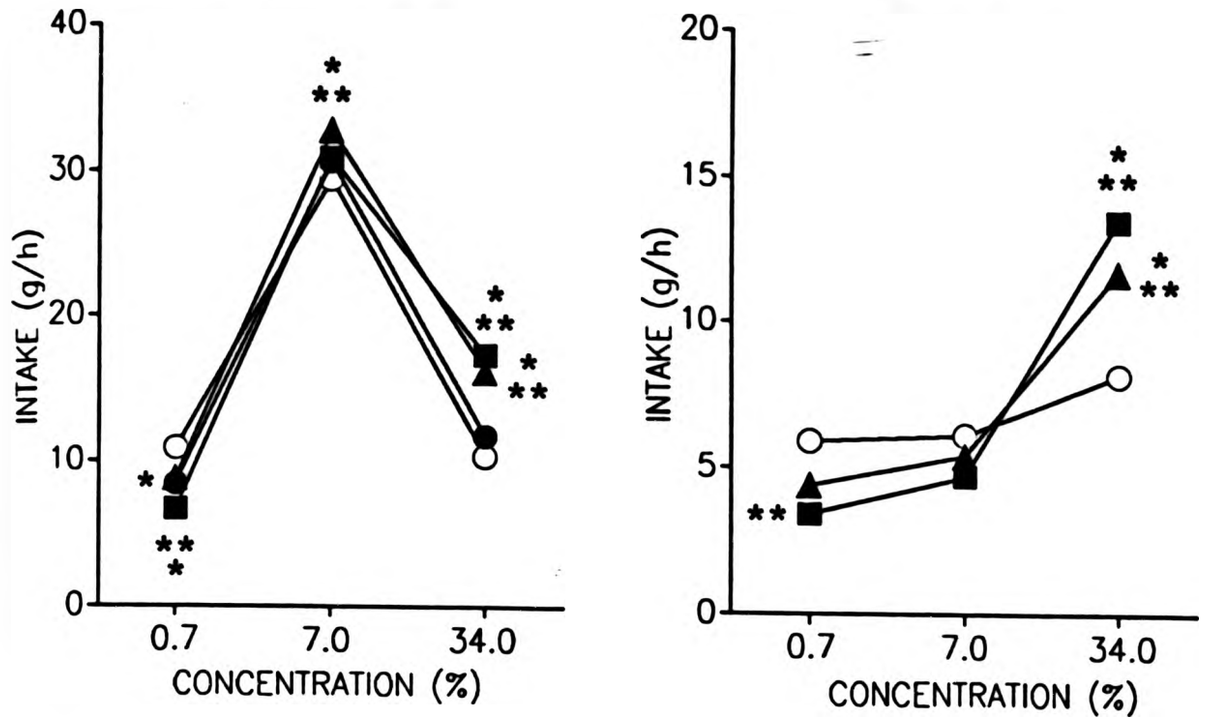


FIG. 5.2. Effects of raclopride upon 1h sucrose intake. **Left panel:** separate presentation of 0.7%, 7% or 34% sucrose; **right panel:** concurrent presentation of all three sucrose concentrations. Vehicle, **open circles;** 100ug/kg raclopride, **filled circles;** 200ug/kg, **filled triangles;** 400ug/kg, **filled squares.** Values are means. Stars indicate statistical significance of drug effects; *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$.

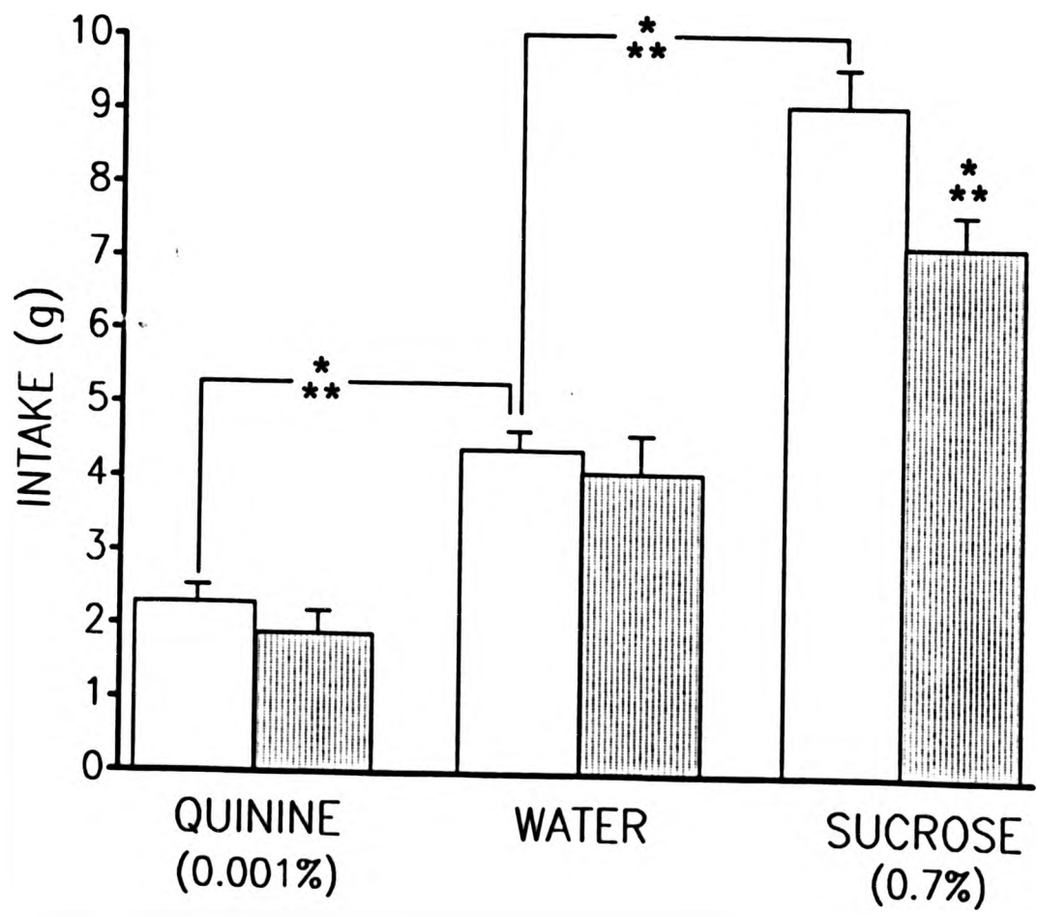


FIG. 5.3. Effects of raclopride upon separately presented quinine (0.001%), water or sucrose (0.7%) solutions, each provided for 1h. Values are means +1SEM. Stars indicate statistical significance of comparisons; ***, $p<0.001$. Open bars: vehicle; hatched bars: 150µg/kg raclopride.

$p<0.001$; three-bottle test, $F(4,46) = 13.8$, $p<0.001$). Raclopride also reduced intake of water when available as an alternative to 34% sucrose ($F(3,63) = 13.0$, $p<0.001$).

In contrast with the complex effects of raclopride on the intake of sweet solutions, intake of a 0.001% quinine solution was unaffected by 150ug/kg raclopride (Fig. 5.3; $F(1,60) = 1.2$, N.S.), as was water intake ($F(1,60) = 0.6$, N.S.). Nonetheless, 150ug/kg raclopride significantly reduced intake of 0.7% sucrose in the same animals ($F(1,60) = 16.0$, $p<0.001$), consistent with the results obtained in the 2-bottle and 3-bottle tests.

5.3.3 Within-session effects of raclopride

In sucrose-experienced animals, effects of raclopride were apparent during the first 5min of testing. Thus, in the first 5 minutes of the 2-bottle test 200ug/kg raclopride significantly decreased intake of 0.7% sucrose ($F(1,63) = 4.3$, $p<0.05$), and also decreased 7% sucrose intake ($F(1,63) = 4.4$, $p<.05$), but increased intake of 34% sucrose (Fig. 5.4; top panel; 34% sucrose: $F(1,63) = 4.1$, $p<0.05$). At this dose, increases in intake of 7% sucrose occurred in the third 5min of the session; however, such increases never occurred at any dose for 0.7% sucrose. At the highest dose used (400ug/kg), animals drinking the intermediate 7% sucrose concentration showed both an immediate decrease in intake ($F(1,63) = 28.9$, $p<0.001$), and a later increase (after 15min: $F(1,63) = 36.7$, $p<0.001$). Water intake was unaffected in the 0.7% and 7% groups, but was reduced throughout the session in the 34% group ($F(3,63) = 10.6$, $p<0.001$, results not shown).

A similar pattern of changes emerged in the three-bottle test, in sucrose-experienced animals (Fig. 5.4, bottom panel). Raclopride decreased consumption of 0.7% sucrose ($F(2,69) = 5.0$, $p<0.05$) concurrently with an enhanced intake of 34% sucrose

($F(2, 69) = 24.5$, $p < 0.001$), and these changes were apparent within 5min of the start of the session.

However, on day 1 of exposure to the three-bottle test, intake of 34% sucrose by naive animals was not at first affected by raclopride (Fig. 5.5, $t(14) = 1.7$, N.S.). In contrast to subsequent time bins and later test days, during this initial period there was no significant difference in intake of the three concentrations (bin 1: 0.7%, 1.1ml; 7%, 1.1ml; 34%, 1.6ml; largest diffference: $t(11) = 1.0$, N.S.). However, in the same session raclopride did increase consumption of 34% sucrose during the third (final) 5min bin ($t(14) = 6.4$, $p < 0.001$). This effect was brought forward 5min on day 2 ($t(10) = 4.8$, $p < 0.001$), and again to the first 5min on day 3 ($t(6) = 8.0$, $p < 0.001$). Unlike the gradually emergent effect of raclopride on consumption of 34% sucrose, the reduction of intake of 0.7% sucrose was apparent within the first 5min of day 1 ($t(14) = 3.5$, $p < 0.01$).

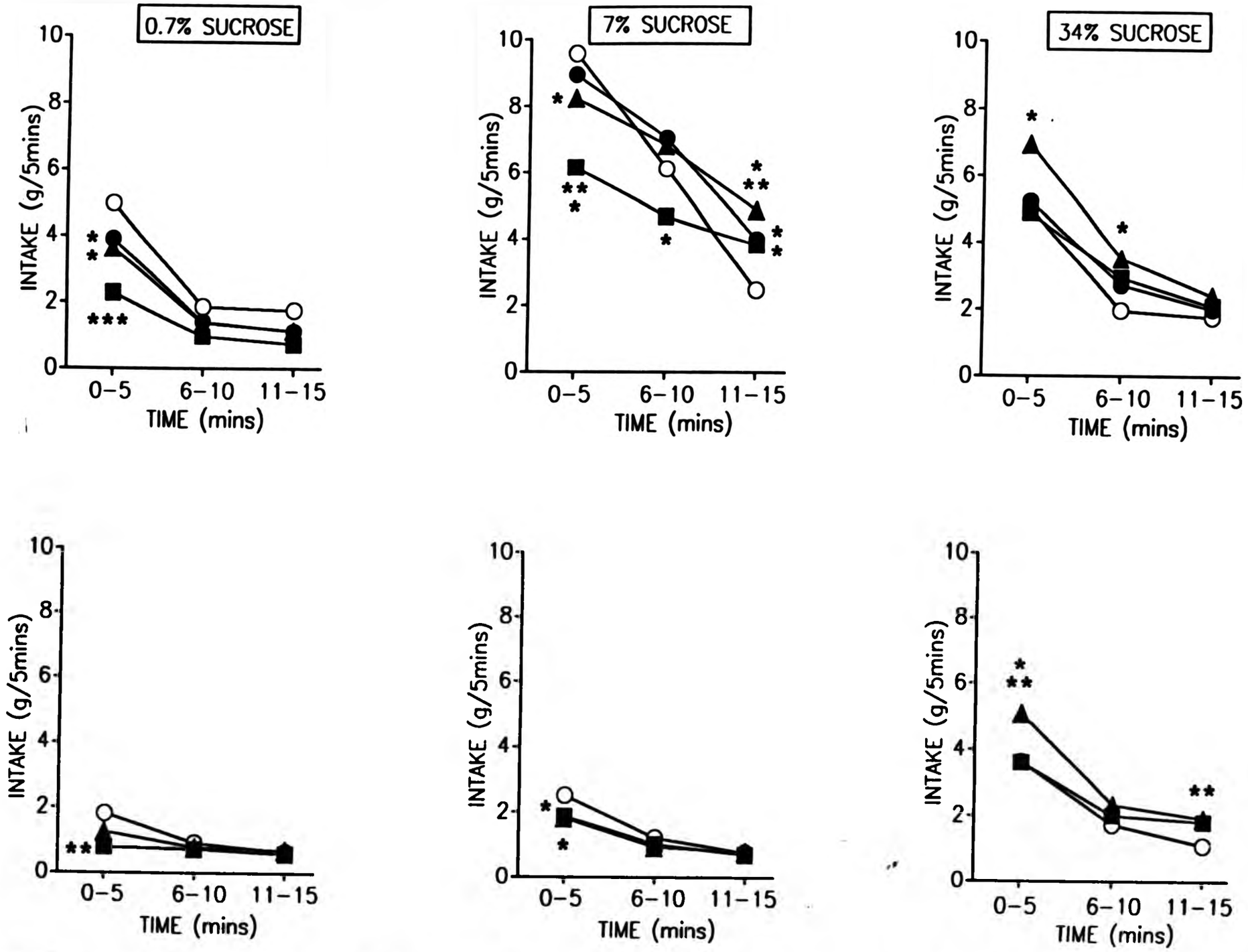


FIG. 5.4. Effects of raclopride upon sucrose intake over the first 15mins of a 1h session, presented in 5min time bins. **Left panel:** 0.7% sucrose; **middle panel:** 7% sucrose; **right panel:** 34% sucrose. **Top panel:** separate presentation of each concentration; **bottom panel:** concurrent presentation of all three sucrose concentrations. Vehicle, **open circles**; 100ug/kg raclopride, **filled circles**; 200ug/kg, **filled triangles**; 400ug/kg, **filled squares**. Values are means. Stars indicate statistical significance of drug effects; *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$.

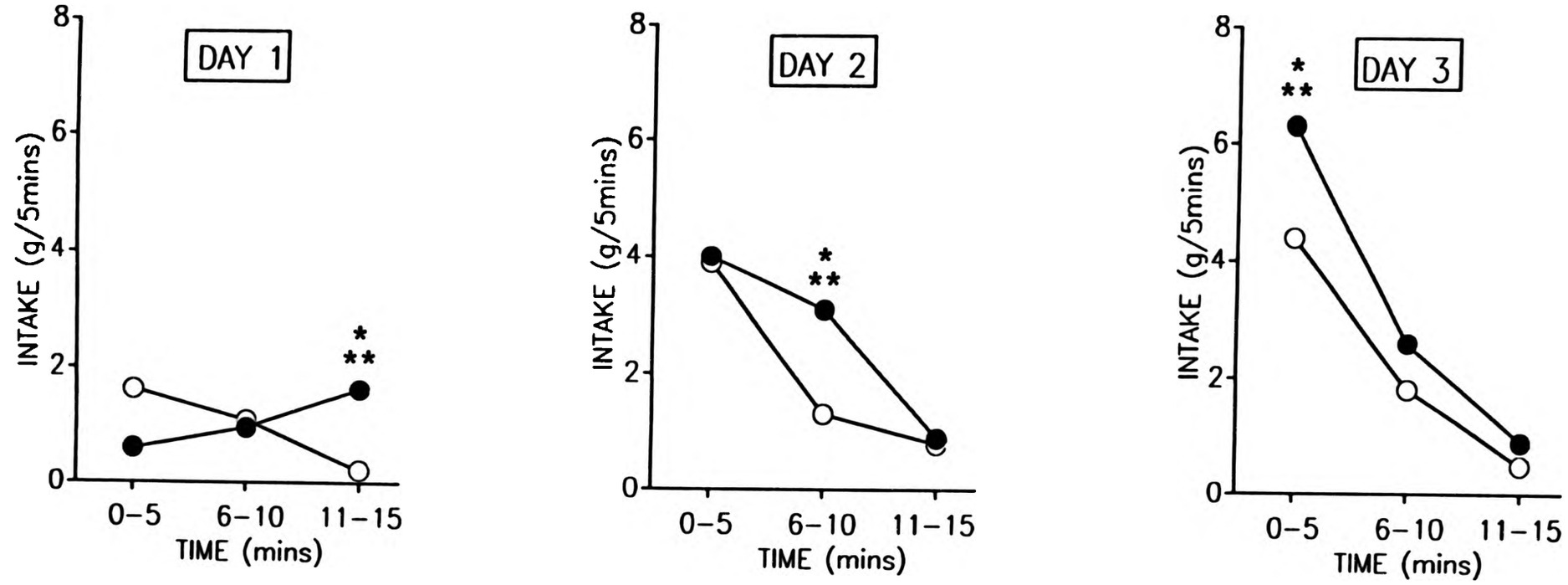


FIG. 5.5. Effects of raclopride upon 34% sucrose intake during the initial three days of exposure to sucrose, presented as the first 15mins of each 1h session, in 5min bins. **Open circles**, vehicle; **filled circles**, 150ug/kg raclopride. Values are means. Stars indicate statistical significance of drug effects; ***, $p<0.001$.

5.4 DISCUSSION

5.4.1 Effect of choice upon preference

Presentation of a single sucrose concentration yielded an inverted-U-shaped concentration-intake function: intake was highest for the intermediate (7%) sucrose concentration, and similarly low for 0.7% and 34% sucrose. These effects were comparable to those previously observed in operant performance maintained by sucrose pellets varying in concentration (Chapter 4). However, when all three concentrations were presented concurrently, all animals showed a striking preference for 34% sucrose over the two lower concentrations. Indeed, intake of the 34% solution was remarkably constant across 2-bottle (sucrose vs. water) and 3-bottle conditions (compare top panels, Fig. 5.1). A similar finding, of greater preference for sweeter solutions (in the range 4% to 50%), under conditions of concurrent, or near concurrent presentation, has been observed in previous studies (Flaherty et al., 1979; Hammer, 1968; Young, 1949; Young & Greene, 1953). In the light of these preference data, it is clear that the descending limb of the single-bottle concentration-intake curve can not be explained away by hypothesising that very sweet solutions are aversive.

As noted in the previous chapter, other paradigms provide analogous data. Using ICSS, Hodos & Valenstein (1962) found a similar inverted-U-shaped function, relating rate of lever pressing to current intensity. However, a strong preference was found for descending limb current intensities over ascending limb intensities, and intensities yielding maximal response rates under no-choice conditions. This was so for both areas studied (posterior hypothalamus and septal area). It was concluded that regardless of the no-choice response rate, the higher the current intensity the greater the preference for it. Inverted-U-shaped functions have also been observed in operant responding for

sweet solutions (Guttman, 1953) or sweet pellets (Chapter 4). In both cases, descending limb concentrations yield the highest response rates upon their unexpected withdrawal, indicative of a high degree of frustration (Coe *et al.*, 1983; Daly & Daly, 1982; Rescorla & Wagner, 1972). Thus, the descending limb of the intensity/performance function observed in a variety of different paradigms can not be explained by aversive effects.

Satiety provides another potential explanation. Again, however, this seems unlikely: in the present experiments, the difference in intake between 7% and 34% sucrose was apparent within the first 5 minutes of the session, and did not increase thereafter. Furthermore, a satiety hypothesis cannot explain the descending limb observed in ICSS experiments (Hawkins & Pliskoff, 1964; Hodos & Valenstein, 1962; Lyons & Freedman, 1982). Rather, it appears that, in some sense, very intense rewards may saturate the brain mechanisms mediating reward, such that further rewards obtained by increased response rates become superfluous (Waraczynski *et al.*, 1987; Miliaressis & Malette, 1987).

5.4.2 Overall effects of raclopride

When presented with a single concentration of sucrose (and water as an alternative), raclopride reduced intake of 0.7% sucrose, but increased consumption of 34% sucrose, at the same time as reducing water intake. Moreover, the identical pattern of effects emerged when all concentrations were presented concurrently: raclopride again reduced consumption of 0.7% sucrose and increased consumption of 34% sucrose. Clearly, increases in consumption of 34% sucrose rule out serious motor impairment by raclopride: therefore, such a straightforward disability cannot explain concurrent decreases in intake of 0.7% sucrose. Decreases in the intake of, and preference for,

weak (0.7-1%) sucrose solutions have previously been reported using other DA antagonists (Muscat & Willner, 1989; Towell *et al.*, 1987). These effects are compatible with the hypothesis that DA antagonists blunt the rewarding properies of sweet solutions (Bailey *et al.*, 1986; Geary & Smith, 1985; Towell *et al.*, 1987; Xenakis & Sclafani, 1981; but see Berridge et al., 1989).

Using the 2-bottle test (sucrose and water), it has also reported that other neuroleptic drugs (pimozide and sulpiride) also increased the intake of 34% sucrose intake (Muscat & Willner, 1989; Willner *et al.*, 1990b). However, this effect was not observed in a single bottle procedure (Muscat & Willner, 1989; Towell *et al.*, 1987). The reason for this discrepancy is not clear. Although water is available in the 2-bottle test, during the early portions of the session when enhancements of intake occur, relatively little water is consumed. Also, water is not available in the 3-concentration sucrose choice procedure, (in which raclopride also increased consumption of the 34% solution), and animals do not appear to utilise 0.7% sucrose as a substitute, as negligible quantities of this concentration are consumed during a session. It should also be noted that analogous increases in behaviour were observed following pimozide or raclopride treatment in animals consuming solid 95% sucrose pellets (Chapters 3 and 4).

Comparison of the within-session intake functions for 7% and 34% sucrose (Fig. 5.1, bottom panels) suggests that raclopride causes animals to react to 34% sucrose as though it were of a lower concentration. Given that intake of a less preferred 0.7% sucrose solution is reduced by raclopride, the overall effects of raclopride on the intake of sucrose solutions may be viewed as a shift to the right in the inverted-U-shaped concentration/intake function (see Fig.4.6). However, it has been shown previously that pimozide had no effect upon either the threshold of sweetness perception, or the just-

noticeable sweetness difference (Willner *et al.*, 1990b). Therefore, the enhanced intake of a preferred 34% sucrose solution following raclopride pretreatment may reflect a reduction in reactivity to sweetness, rather than a reduction in the perception of sweetness at the sensory level. This conclusion is consistent with a number of earlier studies (see Sections 1.2.3 and 7.3).

Significantly, the efficacy of raclopride did not extend to a blunting of the direct impact of an aversive stimulus. A low (0.001%) concentration of quinine-adulterated water caused a mild reduction in intake compared with water alone. If the effects of raclopride upon reactivity were nonspecific, then the drug would be expected to ameliorate the impact of quinine and increase the volume of quinine-adulterated water ingested. In fact raclopride had no effect upon quinine intake, nor did it affect water intake. Nevertheless, raclopride reduced intake of a 0.7% sucrose solution in the same animals.

5.4.3 Within-session effects of raclopride

Reductions in the intake of 0.7% sucrose, together with enhanced intake of 34% sucrose, occurred immediately in both the 2-bottle and 3-bottle procedures. Immediate enhancements in 34% sucrose intake weigh against an inhibition of postingestional satiety, as such an effect would be expected to preferentially evolve only much later in a session. Interestingly, intake of 7% sucrose under raclopride showed both effects. Raclopride dose-dependently reduced intake of 7% sucrose at first, but enhanced intake later in the session. These effects suggest that reactivity to sucrose may be a rather more dynamic process than overall measures suggest. Immediate raclopride-induced reductions of 7% sucrose intake are reminiscent of effects under 0.7% sucrose, whereas later

enhancements of intake reliably occur under 34% sucrose. Thus, the within-session effects of raclopride on 7% sucrose consumption may indicate a time-dependent shift from the ascending to the descending portion of the concentration-intake function. It was also observed in Chapter 4 that responding for 10% sucrose pellets was suppressed by raclopride early in the session, but enhanced later in the session (as compared to responding for 95% sucrose pellets, which at the same dose was enhanced early in the session, but later in the session was unaffected).

In contrast to the immediate enhancement of 34% sucrose intake in sucrose-experienced animals, sucrose-naive animals did not show this effect until 11-15 minutes into the session. Following the first day of exposure, the onset of the effect advanced towards the beginning of the session by 5 minutes each day, until by the third day of sucrose exposure, the enhancement of intake occurred during the first 5 minutes of the session, as in sucrose-experienced animals. This increase in 34% sucrose intake by raclopride appeared to depend upon some form of learning. In this context it may be significant that on day 1, during the first 5 minutes of the session there was no difference in intake of the three concentrations (0.7%, 7% and 34% sucrose). This was not so for later portions of the session, nor on subsequent days of exposure, when 34% sucrose was clearly preferred. It seems clear that both preference for sweeter sucrose solutions, and concomittant concentration-dependent enhancements in intake induced by raclopride are acquired. However, the mechanisms by which these changes occur remain to be determined, and is further discussed in Section 7.3.

CHAPTER 6

ANATOMICAL SUBSTRATES FOR NEUROLEPTIC-INDUCED REWARD ATTENUATION AND NEUROLEPTIC-INDUCED RESPONSE DECREMENT

6.1 INTRODUCTION

It was demonstrated in Chapters 2 and 3 that pimozide caused a time-dependent decrement in operant performance maintained by food reinforcement, a finding in accord with previous work (see Chapter 1, Section 1.2.2). In Chapter 4, it was observed that raclopride induced a within-session response decrement in the absence of primary reinforcement. In addition, while the further effect on response rate of removal of conditioned reinforcement was most pronounced early in the experimental session, raclopride-induced response decrements occurred much later.

In conjunction with other findings (eg. Phillips & Fibiger, 1990), these data were taken to suggest that neuroleptic-induced within-session decrements are unlikely to arise from an interaction with reward processes. However, other evidence was consistent with this interpretation. Operant responding for, or consumption of sucrose exhibits a concentration-dependent inverted-U-function. In Chapters 3 and 4, it was found that neuroleptic drugs decreased responding for a concentration of sucrose situated on the ascending limb of the function, but increased responding for a concentration of sucrose situated on the descending limb of the function. Analogous data obtained in a consummatory procedure were presented in Chapter 5: these effects were interpreted as a shift to the right of the sucrose concentration-intake function (Chapters 4 and 5).

Thus, neuroleptic drugs impair rewarded behaviour by what appear to be two distinct actions: within-session performance decrements and an interaction with

reinforcement mechanisms. In this Chapter, the technique of intracranial drug administration was used to investigate whether these two effects have different neural substrates, using sulpiride, a relatively selective DA D2 receptor antagonist (Jenner & Marsden, 1981).

The nucleus accumbens (NAS) is closely associated with motivational and reinforcement processes (see Chapter 1; and see also Willner & Scheel-Kruger, 1990). Conversely, the anterior caudate nucleus, is usually considered to be more closely involved in sensorimotor functioning (see Chapter 1, Section 1.1.2). It was therefore predicted that sulpiride-induced within-session decrements would be obtainable from the anterodorsal striatum (ADS), and effects on sucrose consumption from the NAS.

Rats with amygdala lesions have been shown to drink less of an 8% sucrose solution (Kemble & Schwarzbaum, 1969), whereas lesions of the basolateral amygdaloid nucleus enhanced intake of a more concentrated 25% sucrose solution (Rolls & Rolls, 1973). These effects resemble those observed following systemic neuroleptic administration (see Chapters 4 and 5). Administration of sulpiride to the basolateral amygdala caused a release of DA in the NAS (Louilot *et al.*, 1985). Accordingly, to assess a potential role of the amygdala in the behavioural effects of neuroleptics, a third group was included, with cannulae in the basolateral amygdala (BLA).

Behavioural methods were chosen on the basis of previous studies in this laboratory, and on work presented in previous chapters. Responding under a random-interval (RI) 30sec schedule is roughly constant, and systemically administered pimozide induces a clear within-session decrement in responding under these conditions (Willner *et al.*, 1988; Willner & Phillips, 1989). Hence, this schedule was utilised to assess the potential contribution of each area to sulpiride-induced within-session response decrements. The

consumption of sucrose at different concentrations was used as a simple test of the effect of sulpiride on reward processes (see Chapter 5). During these experiments, it was observed that sulpiride administered to the NAS markedly reduced home cage activity. 6-OHDA-induced lesions of the the NAS are known to suppress spontaneous or stimulant-induced locomotor activity (Kelly *et al.*, 1975; Koob *et al.*, 1978). The effect of sulpiride on locomotor activity was therefore also assessed.

6.2 METHODS

Subjects

Subjects were 27 male Lister hooded rats (NIMR, Mill Hill, London). Animals weighed 270-310g at the start, and were singly housed under a 12h light/dark cycle (lights on 08.00h) at a constant temperature of 22°C. During experiment 6.1, excepting a pre- and post-operative recovery period (see below), food access was restricted to 60min at the end of daily experimental sessions (18.00-19.00h), water being freely available in the home cage. Following experiment 6.1, access to both food and water was restricted to 120min at the end of daily experimental sessions (17.00-19.00). All experiments were carried out between 13.00 and 17.00h, daily baseline runs continuing 7 days per week.

Apparatus

Experiment 6.1 was conducted in eight identical operant chambers (Campden Instruments Ltd, London), each delivering a standard 45mg food pellet reinforcer (Campden Instruments Ltd, London). A mean force of 9g was required to depress the lever. An Acorn System 4 microcomputer (Acorn Computers, Cambridge) was used to

record lever presses and to control pellet delivery. Lever presses by each animal were recorded as 30min totals, and in 5min time bins.

In experiments 6.2, 6.4 and 6.5, fluid intakes were measure using 250ml white polypropylene bottles with 2" stainless steel spouts, each containing a ball-bearing and held in the bottle by tight fitting rubber bungs (NKP Cages Ltd, Dartford, Kent). Sucrose was of commercial grade.

Experiment 6.3 was conducted in five identical chambers, 96cm long, 24cm wide and 29cm high, which were constructed of natural wood, with a grey plastic floor and a smoked plastic lid. The floor was in three 32cm sections, each of which was mounted on a spring at each corner. Downward displacement of the floor panels was detected by optical switches, and counted by BBC microcomputers connected in an Econet. Intercount times (ICTs) were recorded in 0-0.5, 0.5-1, 1-1.5, 1.5-2, 2-5, 5-10, 10-20 and >20s bins.

Experiment 6.1

During each 30min run in the operant chambers, the houselight was illuminated, and for initial training under continuous reinforcement (3 sessions), a 50ms 800Hz sinusoidal tone sounded at 1s intervals. Reinforcer delivery was signalled by a tray light of 0.5s duration, and noise from pellet delivery mechanisms. From session 4, animals were placed under a random- interval (RI) 30sec schedule of food reinforcement, in which reinforcement was delivered for the first lever press occurring after an interval that varied randomly between 2sec and 60sec. The tone signalling the session now sounded at 8sec intervals. Following the attainment of asymptotic performance (7 sessions) the 27 animals were divided into three matched groups of 9, and placed on free feed for five

days. Indwelling cannulae were then implanted in the ADS, NAS, or BLA (see below, Surgery). Animals were given a minimum of five days recovery time, following which food access was again restricted. After a period of retraining and readjustment to food deprivation (8 sessions), over the following two test sessions each animal was administered either 0.625ug sulpiride or vehicle. A higher dose of 2.5ug sulpiride, and vehicle, were administered over the next two test sessions.

Experiment 6.2

The second experiment commenced immediately following the end of experiment 6.1, on postoperative day 20. During initial training, each animal was presented in the home cage with a solution of either 0.7% or 34% sucrose (weight/volume), together with water as an alternative. Bottle position (sucrose to left or right) was counterbalanced across animals and days. Bottles were reweighed at 5min intervals for the first 15min, and at the end of the one hour session. The same solution was presented to each animal in subsequent sessions. Following stabilisation of intake (4 sessions), animals were administered 0.625ug sulpiride or vehicle on the following two test sessions. Each animal was then presented with the alternative sucrose concentration, and the above procedure was repeated. Subsequently, a second dose of 1.25ug sulpiride, and vehicle was administered according to the same method.

Experiment 6.3

Measurement of locomotor activity commenced on postoperative day 50. Following stabilisation of activity counts (7 sessions), over the following two 30min test sessions animals were administered 0.625ug sulpiride or vehicle.

Experiments 6.4 and 6.5

On postoperative day 65, animals were reintroduced to 0.7% sucrose, according to the method described in experiment 6.2. Stable intakes ensued after 6 sessions. Over the following two test sessions, animals were administered 0.625ug sulpiride or vehicle. However, test onset was delayed for 1h; thus sucrose was not presented until the time at which it had previously been removed (experiment 6.2).

Finally, animals were familiarised with a 7% sucrose solution until intakes stabilised (4 sessions), again according to the method described in experiment 6.2. Over the following two test sessions (postoperative days 80 and 85), animals were administered 0.625ug sulpiride or vehicle. One week later, this procedure was repeated using 1.25ug sulpiride.

Surgery

Mean body weight was 280.3g at the time of surgery (atlas weight = 290g). Animals were pretreated 50min prior to anaesthetic with scopolamine methyl bromide (50ug/kg, i.p., Sigma Chemical Co., Poole, UK), a cholinergic antagonist with minimal central activity, to preempt breathing difficulties associated with the onset of bronchial congestion. A 21:1 air-breathing mixture of medical grade oxygen (BOC Ltd, Guildford, UK) and halothane anaesthetic (RMB Animal Health Ltd, Dagenham, UK) was then administered. Using a miniature spirit level, the upper incisor bar was individually adjusted to maintain a horiontal plane between the skull reference points Bregma and Lambda, as required by the atlas of Paxinos & Watson (1986). Indwelling cannulae were then implanted (Plastic Products Ltd, New Jersey, USA) in the NAS, ADS or BLA. Coordinates were: ADS, AP +1.2, L +/-3.0, DV -3.0; NAS, AP +1.2, L

+/-1.5, DV -6.0; and BLA, AP -2.8, L +/-5.0, DV -7.5mm relative to Bregma. Injection cannulae projected from the guide cannulae by 1mm, and to maintain the patency of guide cannulae, screw-in dummy cannulae were otherwise in place.

Drug and Injections

dl-Sulpiride (Sigma Chemical Co, Poole, UK) was dissolved in a single drop of glacial acetic acid (42ul approx.), and made up to 8ml volume with phosphate buffer saline (NaCl, 8.0g/l; KCl, 0.2g/l; $MgCl_2.6H_2O$, 0.1g/l; KH_2PO_4, 0.2g/l; $Na_2HPO_{4\cdot2}O$, 1.15g/l; pH, 7.4), which also served as vehicle. Injections were in a volume of 0.2ul, and were allowed to infuse for 1min before removing the injection cannulae. Test sessions were separated by at least four drug-free days, and drug or vehicle were administered in a counterbalanced order across animals and days. With the exception of experiment 6.4 (see below), sessions commenced immediately following drug infusion.

Histology

For histological examination of cannula placements, animals were sacrificed with 2ml pentobarbital, and the brains were immediately removed and stored in 5% formalin. 20um sections were stained using cresyl fast violet (Lamb, Sunbeam Rd, London), and placements were verified histologically (Fig.6.1) with reference to the atlas of Paxinos & Watson (1986).

Analysis

Data were subjected to analysis of variance, supplemented where appropriate by tests of simple main effects and planned comparisons. For experiments 6.2, 6.4 and 6.5,

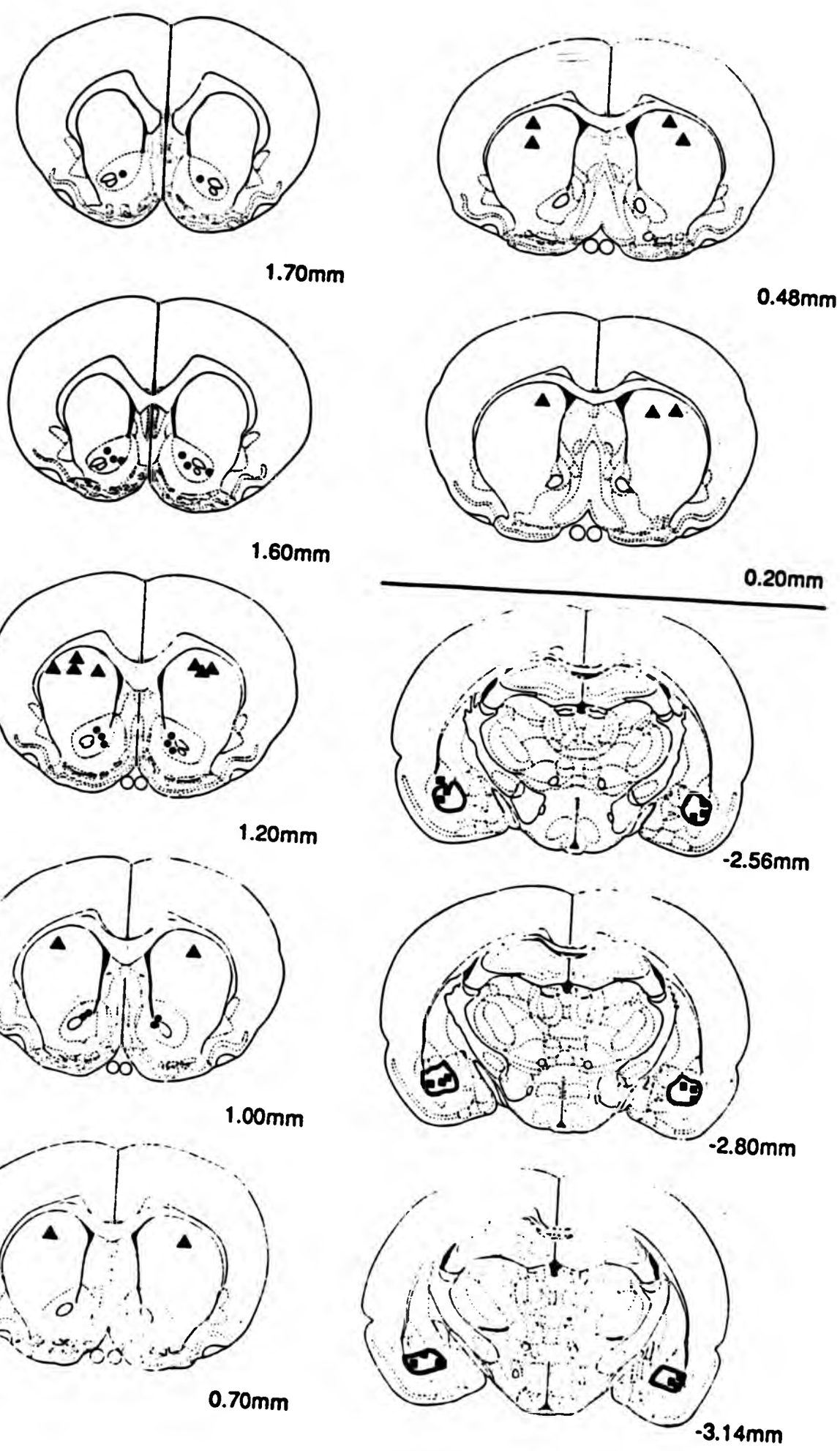


Fig.6.1 Serial sections through the rat brain derived from the atlas of Paxinos & Watson (1986). Sections run vertically from top left (anterior) to bottom right (posterior). Numbers indicate distance from Bregma; horizontal line indicates a large transition between striatal implantation sites and the basolateral amygdala. Cannulae placements: **circles**, nucleus accumbens; **triangles**, anterodorsal striatum; **squares**, basolateral amygdala (site outlined for clarity).

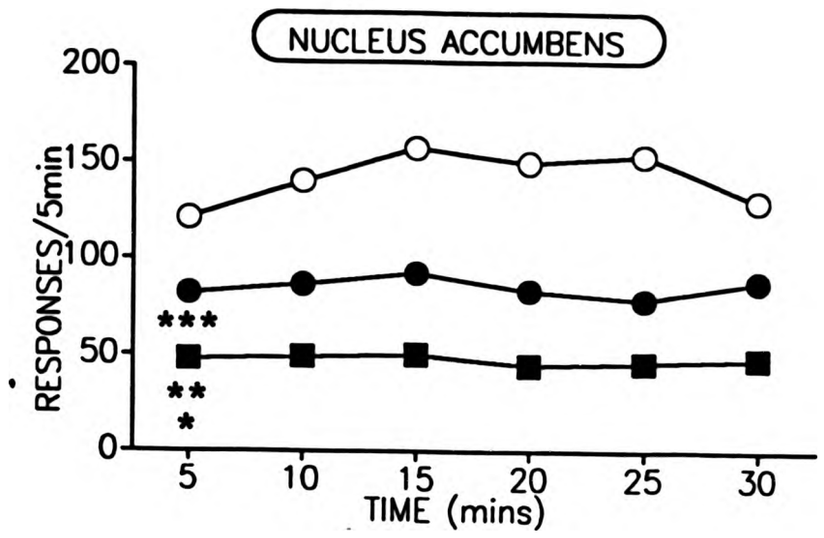
separate analyses were carried out on consumption of sucrose and water, total fluid intake, and sucrose preference, calculated according to the formula: Preference(%) = (sucrose intake/total intake) x 100.

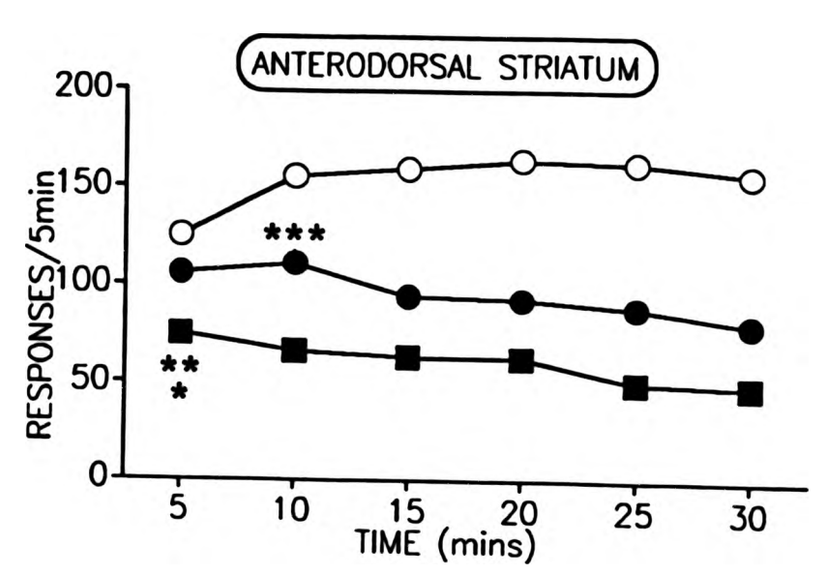
In the Figures, vehicle scores represent the mean of the vehicle treatments corresponding to each of the drug doses, and the scores for each drug dose have been adjusted to preserve the quantitative relationships to its own vehicle scores. The analyses, however, were carried out on unadjusted raw scores.

6.3 RESULTS

6.3.1 Effects of sulpiride on operant behaviour

Response rates in the three groups were very similar following vehicle treatment ($F(2,24) = 0.6$, N.S.). Sulpiride did not affect responding when administered to the BLA ($F(1,24) = 0.22$, N.S.). However, sulpiride dose-dependently reduced responding when administered to the ADS ($F(1,24) = 164$, $p<0.001$) and NAS ($F(1,24) = 160$, $p<0.001$), and to a similar overall extent (response rates under drug: $F(1,24) = 0.9$, N.S.). Nonetheless, within-session data revealed a clear difference between the two groups (Fig.6.2). Whereas sulpiride administered to the NAS caused a constant impairment (drug x time interaction: $F(5,120) = 0.7$, N.S.), administration within the ADS caused a time-dependent response decrement (drug x time interaction: $F(5,120) = 4.0$, $p<0.01$). At the lower dose of sulpiride administered to the ADS, behaviour was not significantly impaired at the start of the session (first 5min: $F(1, 24)=3.0$, N.S.). The gradual onset of the effects of sulpiride when administered to the ADS are seen most clearly when the data are expressed as proportional changes relative to scores under vehicle treatment (Fig.6.3). During the early portions of the session, both 0.625ug and 2.5ug





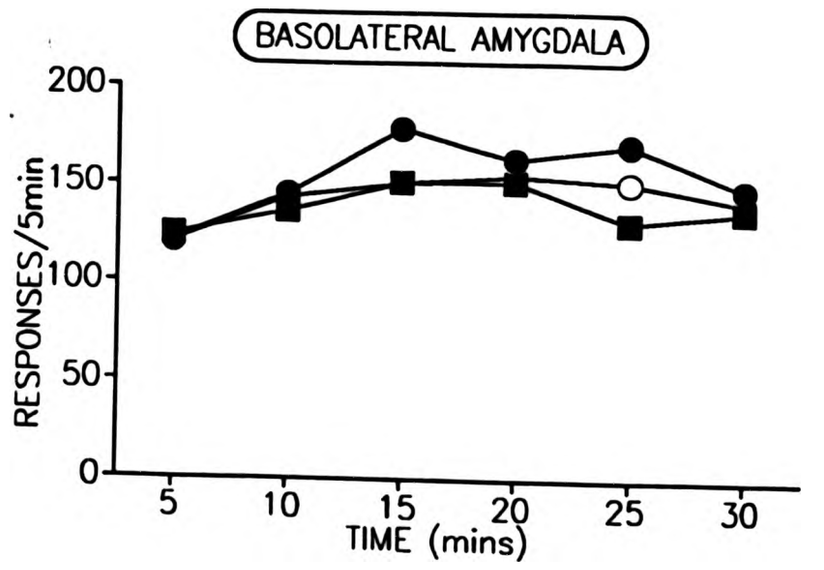
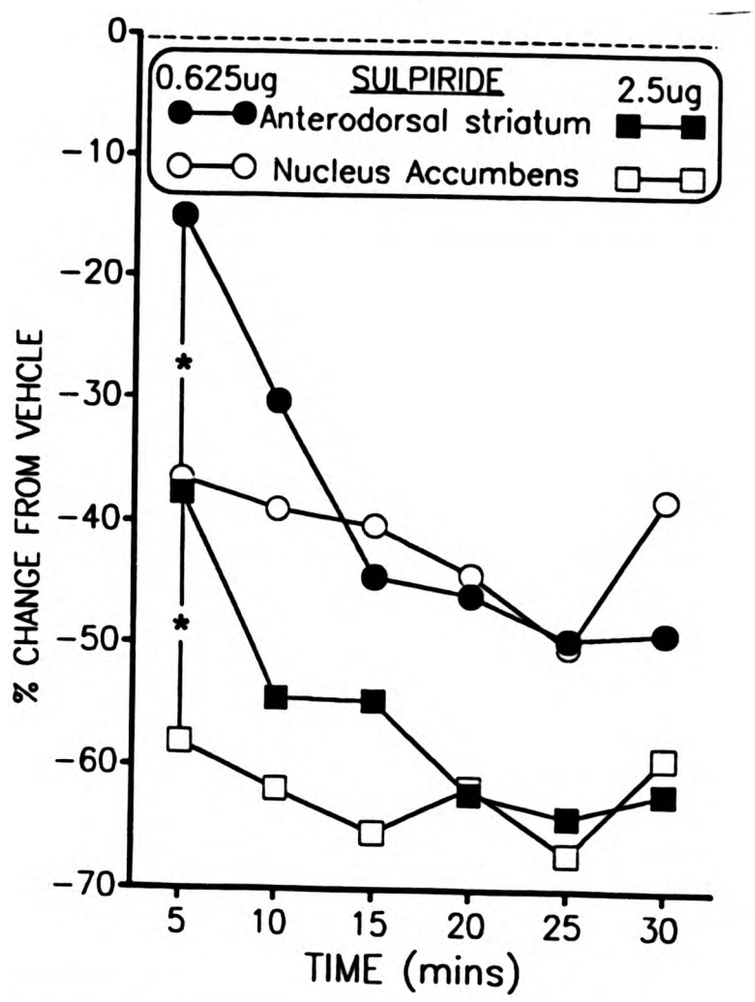


Fig.6.2 Within-session effects of sulpiride infusion to the nucleus accumbens, anterodorsal striatum or basolateral amygdala upon responding under a random-interval 30s schedule for food reinforcement. Open circles, vehicle; filled circles, 0.625ug sulpiride; filled squares, 2.5ug sulpiride. Values are means. Stars indicate statistical significance of drug effects; ***, $p<0.001$.



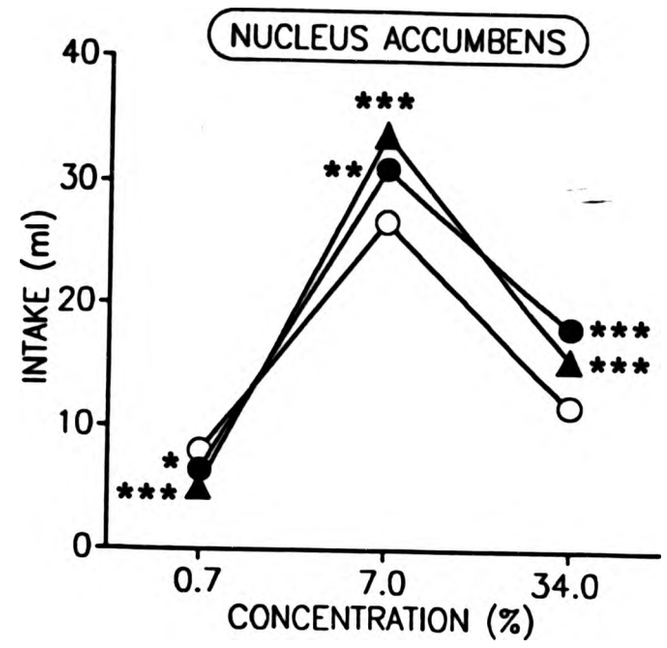
Linear trends:
Anterodorsal striatum: $F(1,120)= 38.9$, $p<0.001$.
Nucleus accumbens: $F(1,120)= 0.03$, n.s.

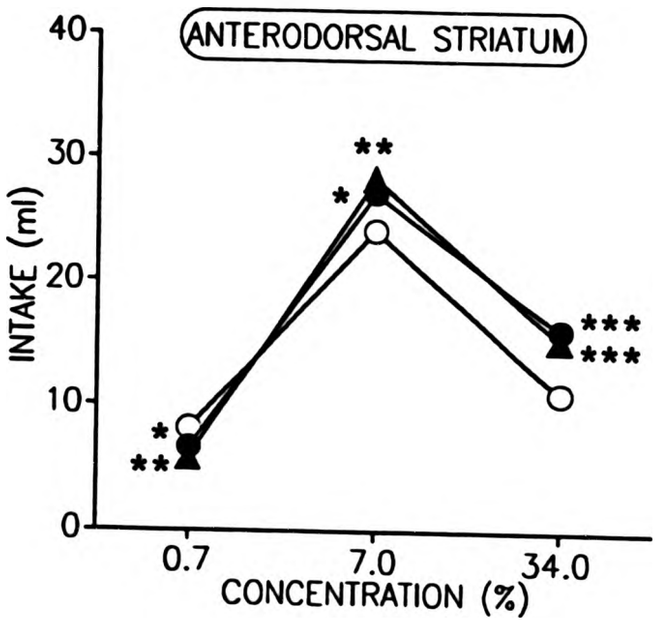
Fig.6.3 Within-session effects of sulpiride infusion to the nucleus accumbens or anterodorsal striatum upon responding under a random-interval 30s schedule for food reinforcement. Data are expressed as percentage change from vehicle. Values are means. Stars indicate statistical significance of drug effects; *, $p<0.05$.

sulpiride caused significantly less impairment when administered within the ADS than when administered within the NAS (first 5min: $F(1, 24) = 5.4, 4.9$, for 0.625 and 2.5ug respectively, $p < 0.05$). In short, sulpiride caused a time-dependent decline in responding when administered within the ADS (linear trend: $F(1, 60) = 38.9$, $p < 0.001$), but a time-independent reduction in response rate when administered within the NAS (linear trend: $F(1, 60) = 0.03$, N.S.).

6.3.2 Effects of sulpiride on consummatory behaviour

Overall, the effects of sulpiride (0.625,1.25ug) on sucrose intake appeared broadly similar when administered to the NAS and ADS (Fig.6.4). Sulpiride reduced intakes of 0.7% sucrose (NAS: $F(1,21) = 18.7$, $p < 0.001$; ADS: $F(1,21) = 15.1$, $p < 0.001$) and increased consumption of concurrently available water (not shown, (but cf. Fig.6.5); NAS: $F(1,21) = 14.4$, $p < 0.001$; ADS, 1.25ug dose only: $F(1,21) = 6.2$, $p < 0.05$); neither dose affected the total volume of 0.7% sucrose and water consumed by any group (largest $F(1,21) = 2.7$, N.S.). Conversely, consumption of 7% sucrose was enhanced by sulpiride in both groups ($F(1,21) = 35.0$, $p < 0.001$), though to a lesser degree in the ADS group (NAS vs. ADS group: $F(1,21) = 7.2$, $p < 0.01$). Intake of 34% sucrose was also enhanced ($F(1,21) = 216$, $p < 0.001$), to a comparable degree in both NAS and ADS groups ($F(1,21) = 3.3$, N.S.); when not restrictively low, consumption of associated water was reduced (not shown; ADS: $F(1,21) = 5.8$, $p < 0.05$). By contrast, sulpiride had relatively little effect when administered to the BLA. No changes in intake of 0.7% sucrose were observed, and sulpiride enhanced intake of 34% sucrose to a lesser degree than in the other groups (BLA vs. NAS: $F(1,21) = 16.2$, $p < 0.001$; BLA vs. ADS: $F(1,21) = 4.9$, $p < 0.05$).





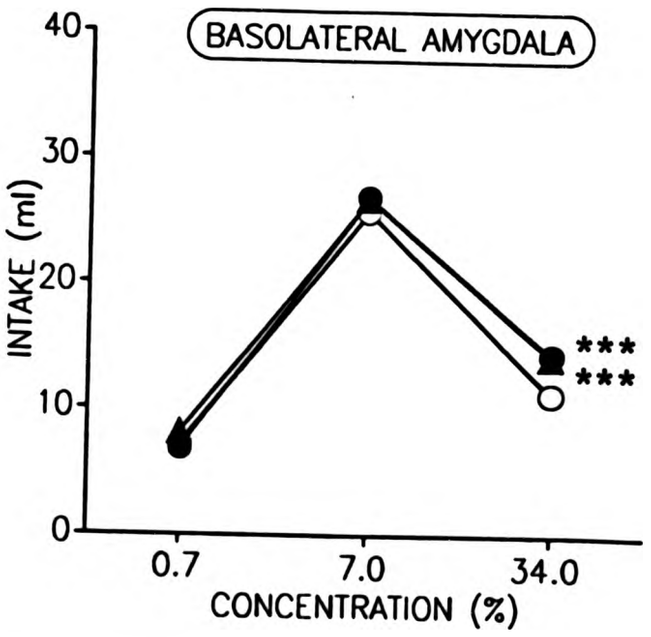


Fig.6.4 Effects of sulpiride infusion to the nucleus accumbens, anterodorsal striatum or basolateral amygdala upon intake of 0.7%, 7% or 34% sucrose over 1h. **Open circles**, vehicle; **filled circles**, 0.625ug sulpiride; **filled triangles**, 1.25ug sulpiride. Values are means. Stars indicate statistical significance of drug effects; *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$.

Although sulpiride reduced consumption of 0.7% sucrose in both NAS and ADS groups, within-session data indicate that this occurred through very different mechanisms (Fig.6.5, top panel). Sulpiride administered to the NAS dose-dependently reduced intake of sucrose, and increased the intake of concurrently available water, during the first 5min of the session, resulting in a highly significant decrease in preference for 0.7% sucrose (first 5min: $F(1,21) = 36.5, p < 0.001$). However, neither sucrose nor water intake were affected during later time periods (16-60mins: 0.7% sucrose, $F(1, \ ) = 2.6$, N.S.; water, $F(1,21) = 0.4$, N.S.). Conversely, administration of sulpiride to the ADS had no effect on sucrose intake during the first 5 minutes ($F(1, \ ) = 0.9$, N.S.). In this group, sucrose intake was reduced towards the end of the session (16-60mins: $F(1, \ ) = 22.4$, $p < 0.001$), and this effect was not accompanied by an increase in water consumption ($F(1,21) = 0.2$, N.S.).

Identical results were obtained when this experiment was repeated (seven weeks later), using a 1h pretreatment time (Fig.6.5, bottom panel). Administration of 0.625ug sulpiride to the NAS again reduced 0.7% sucrose intake and increased concurrently available water consumption, but only during the first 5min of the session (0.7% sucrose: $F(1,15) = 125, p < 0.001$; water: $F(1,15) = 75.2, p < 0.001$). Conversely, sulpiride in the ADS had no early effects (first 5min: sucrose, $F(1,15) = 2.5$, N.S.; water, $F(1,15) = 0.6$, N.S.), but again selectively reduced 0.7% sucrose consumption, without increasing water intake, later in the session (16-60mins: 0.7% sucrose, $F(1,15) = 9.5, p < 0.01$; water, $F(1,15) = 0.1$, N.S.).

The increased intake of 7% sucrose following sulpiride administration to the NAS or ADS (Fig.6.4) was also to some extent time- and site-dependent (Fig.6.6, top panel). Significant increases were first seen 11-15min into the session (NAS: $F(1,15) = 13.1$,

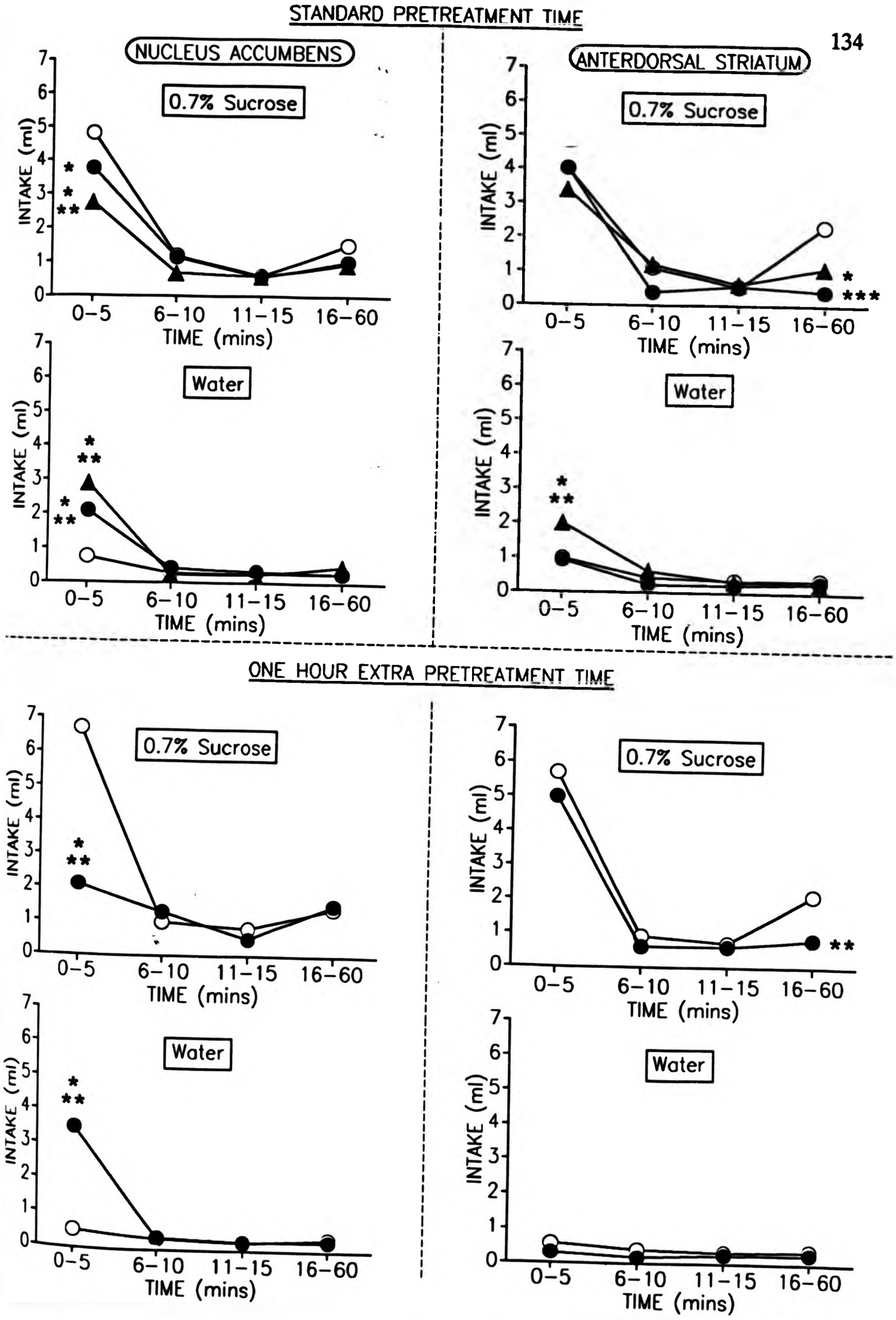


Fig.6.5 Within-session effects of sulpiride infusion to the nucleus accumbens or anterodorsal striatum upon intake of 0.7% sucrose and concurrently available water. **Top panel:** standard pretreatment time; **bottom panel:** one hour additional pretreatment time. Vehicle, **open circles;** 0.625ug sulpiride, **filled circles;** 1.25ug sulpiride, **filled triangles.** Values are means. Stars indicate statistical significance of drug effects; ***, $p<0.01$; ****, $p<0.001$.

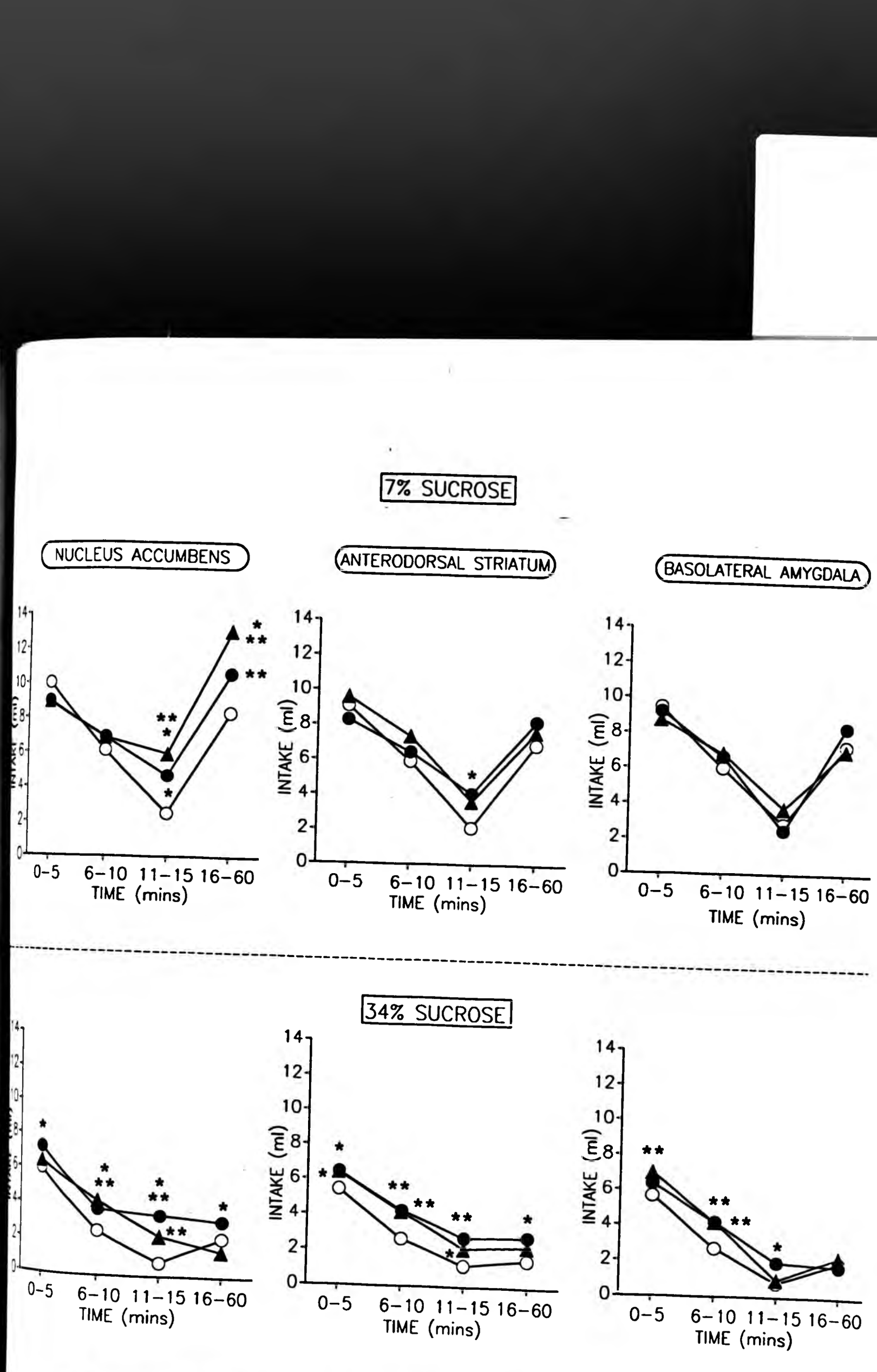


Fig.6.6 Within-session effects of sulpiride infusion to the nucleus accumbens, anterodorsal striatum or basolateral amygdala upon intake of 7% sucrose (top panel) or 34% sucrose (bottom panel). Vehicle, open circles; 0.625ug sulpiride, filled circles; 1.25ug sulpiride, filled triangles. Values are means. Stars indicate statistical significance of drug effects; ***, $p<0.001$.

$p<0.001$; ADS: $F(1,15)= 5.2$, $p<0.05$), but while the NAS group sustained this effect during the latter portion of the session, the ADS group did not (16-60min: NAS vs. ADS: $F(1,15)= 16.6$, $p<0.001$). However, effects on consumption of 34% sucrose were similar in all three groups (Fig.6.6, bottom panel): sulpiride increased intake of 34% sucrose during the first 5min (NAS, $F(1,21)= 6.5$, $p<0.05$; ADS, $F(1,21)= 9.5$, $p<0.01$; BLA, $F(1,21)= 9.3$, $p<0.001$), and enhanced intakes were robustly maintained for at least the first 15min of the session.

6.3.3 Effect of sulpiride on spontaneous locomotion

Administration of sulpiride to the ADS or BLA did not visibly affect behaviour in the home cage at any time. However, administration to the NAS caused a noticeable, and often profound akinesia, which continued for the remainder of the day. Animals showed a strikingly diminished responsiveness to sensory stimulation, eg. rattling of cage bars. Head turn in response was often noted, but whole body reaction was frequently absent unless sensory stimulation was repeated.

Objective measurement confirmed these observations (Fig.6.7). Sulpiride (0.625ug) had no effect on locomotion when administered to the ADS or BLA ($F(1,15)= 0.2$, 0.7 respectively, N.S.), but markedly reduced locomotion when infused within the NAS ($F(1,15)= 91.3$, $p<0.001$). Baseline ICTs were bimodal; relatively more short (<0.5s) and long (>2s) ICTs were recorded than moderate ones (Fig.6.8, top panel; quadratic trend: $F(1,70)= 47.8$, $p<0.001$). Sulpiride administered to the NAS did not differentially affect the bimodal ICT frequency distribution curve, but induced a proportionately comparable decrement across all ICTs (Fig.6.8, bottom panel; linear trend: $F(1,35)= 0.1$, N.S.).

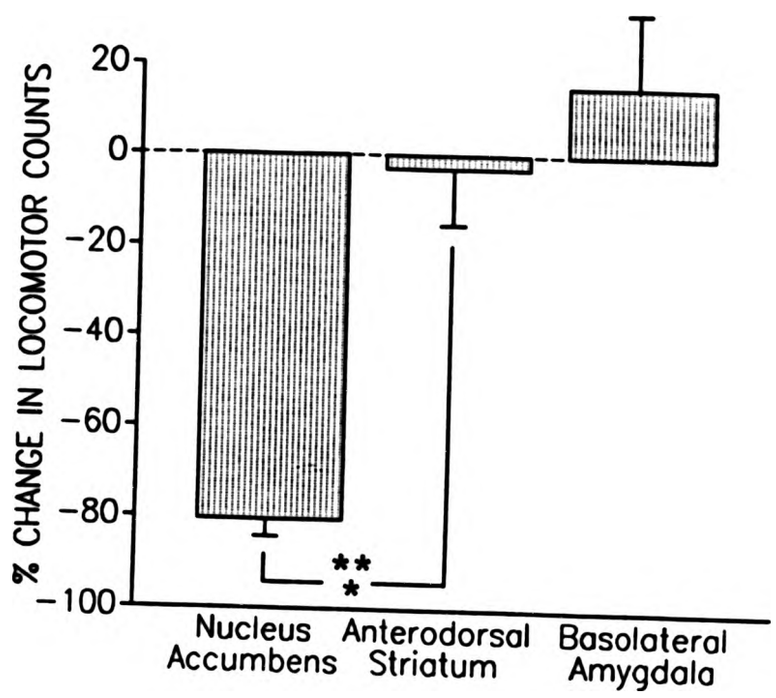
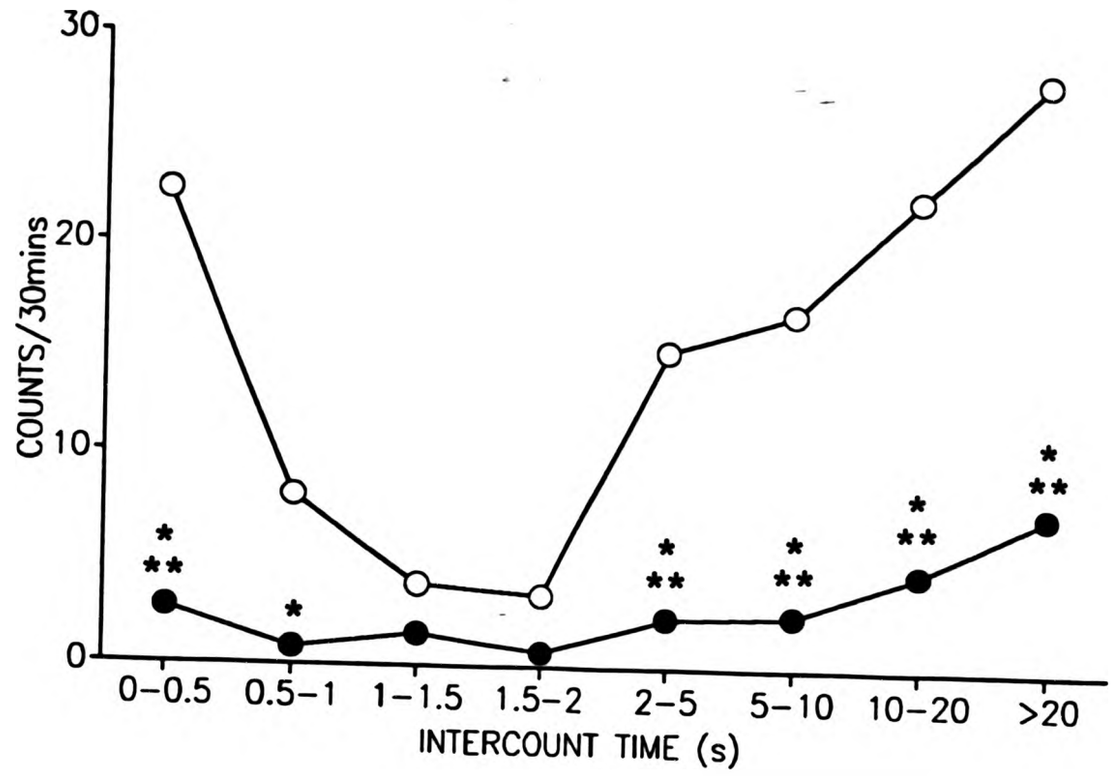


Fig.6.7 Effects of sulpiride infusion (0.625ug) to the nucleus accumbens, anterodorsal striatum or basolateral amygdala upon 30min spontaneous locomotion. Values denote mean percentage change from vehicle +/-1SEM. Stars indicate statistical significance of drug effects; ***, $p<0.001$.



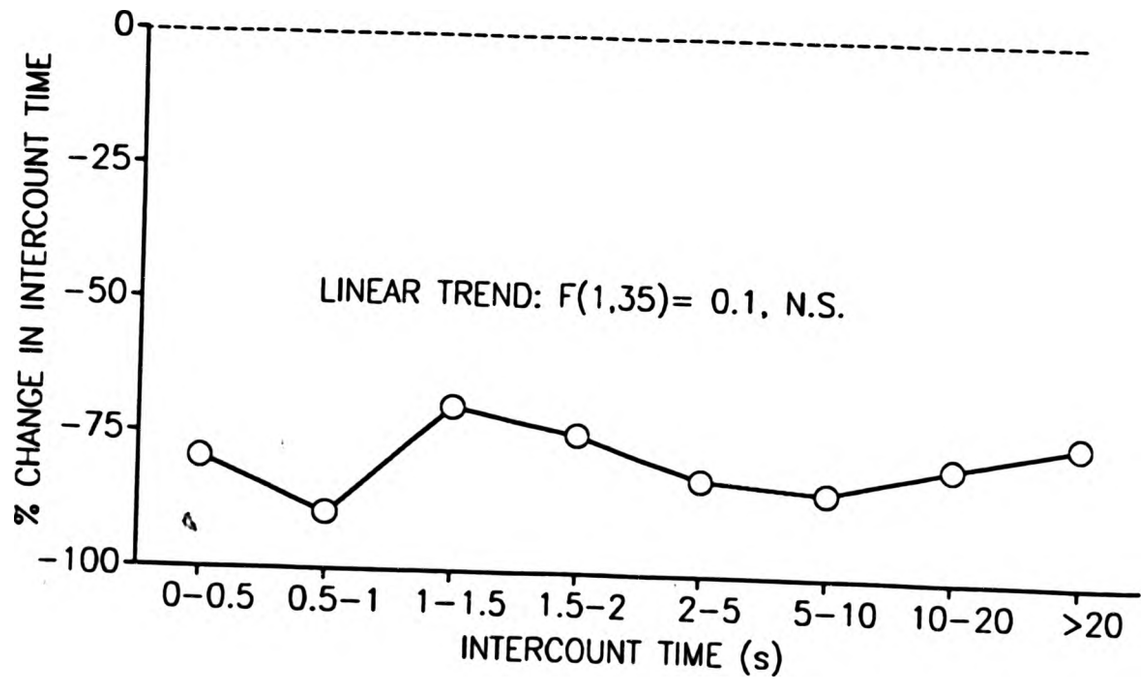


Fig.6.8 Effects of intra-accumbens infusion of 0.625ug sulpiride upon 30min spontaneous locomotion. **Top figure**, binned intercount times (s); **bottom figure**, percent change from vehicle. **Open circles**, vehicle; **filled circles**, sulpiride. Values are means. Stars indicate statistical significance of drug effects; *, $p<0.05$; ***, $p<0.001$.

6.4 DISCUSSION

As predicted, administration of sulpiride to the NAS caused a selective decrease in preference for a weak (0.7%) sucrose solution. As the reduction in sucrose consumption was matched by an increase in water consumption, with no change in total fluid intake, these changes can not be explained in terms of motor impairment. It was argued in Chapter 5 (see also Chapter 1, Section 1.2.3) that this reduction in preference for sucrose may be best seen as a reduction in the reinforcing properties of sucrose.

Within the NAS, sulpiride also caused a time-independent suppression of operant behaviour, and decreased locomotor activity. This decrease in locomotor activity was not specific to either very short (<0.5sec) or relatively long (>2sec) ICTs, but nonspecifically reduced the number of locomotor counts observed. Very short ICTs may reflect continuous sequences of locomotor behaviour, whereas longer ICTs may represent newly initiated bouts of locomotor behaviour. In any case, sulpiride administered to the NAS caused a global deficit in behavioural output. Sulpiride has recently been observed to suppress the exploratory behaviour of rats in a water maze, during the inter-trial interval on the platform; as in the present study, this effect was not observed following sulpiride administration to the ADS (Klimek *et al.*, 1989). A decrease in spontaneous or stimulant-elicited locomotion following destruction of the mesolimbic DA system innervating the NAS is well established (Kelly *et al.*, 1975; Koob *et al.*, 1978).

By contrast, a major effect of sulpiride administration to the ADS, but not the NAS, was a time-dependent suppression of operant responding, which was previously observ-ed following systemic neuroleptic administration (see Chapters 2, 3 and 4; see also Chapter 1, Section 1.2.2). Consumption of 0.7% sucrose was also suppressed by

sulpiride administration to the ADS. However, unlike the effect observed in the NAS, the decrease in the ADS was unaccompanied by an increase in water intake, and appeared only towards the end of the experimental session. This late onset did not result from diffusion of the drug to a distant site of action, since it was independent of the time of drug administration (compare Fig.6.5, upper and lower panels). Rather, the late suppression of 0.7% sucrose intake appears to be a further example of a time-dependent response decrement, and may be the first demonstration of such an effect on consummatory behaviour.

To summarize: these data demonstrate a double dissociation between the effects of sulpiride administered to the NAS and ADS. Within the NAS, sulpiride decreased the reinforcing properties of 0.7% sucrose, accompanied by reduced locomotor activity and a time-independent decrease in operant performance; within the ADS, sulpiride caused time-dependent response decrements in both operant responding and consumption of 0.7% sucrose.

The effects of sulpiride on consumption of 7% and 34% sucrose fit less well with this neuroanatomical dissociation. Administration of sulpiride to both the NAS and ADS increased intake of 7% sucrose 11-15min into the session: and to a very similar extent. Precisely the same effect on 7% sucrose intake was previously observed following systemic administration of raclopride (Chapter 5), and also in an operant procedure using 10% sucrose pellets (Chapter 4). However, although the NAS group maintained their increased consumption throughout the latter portion of the session (16-60mins), the ADS group did not; this may reflect the underlying time-dependent response decrement noted for 0.7% sucrose (see above; Chapter 7 for further discussion).

Infusion of sulpiride to all three areas increased consumption of 34% sucrose within

the first 5min, an effect which was consistently maintained for at least the first 15min of the session. The effects were smallest within the BLA (consistent with a lack of effect of sulpiride within this area on consumption of 0.7% and 7% sucrose solutions). In Chapters 4 and 5, it was reported that systemic injection of raclopride also caused an immediate increase both in the consumption of 34% sucrose solutions and in operant responding reinforced with 95% sucrose pellets, and this behaviour was seen as compensatory to a blunting of the reward process.

According to this interpretation of the data, the involvement of DA in the rewarding effects of a weak (0.7%) solution is localized within the NAS, but at higher concentrations the substrate for reinforcement is more widely distributed. Although recent studies of the brain mechanisms of reward have tended to focus on the mesolimbic DA innervation of the NAS, (see Willner & Scheel-Kruger, 1990), the diverse locations at which reinforcing intracranial self-stimulation (ICSS) may be elicited has been the subject of some discussion (eg. Phillips, 1984; Phillips & Fibiger, 1989; Shizgal & Murray, 1989), and ICSS is reliably obtained from all three areas investigated in the present study (eg. accumbens, Mogenson et al., 1979; striatum, Phillips *et al.*, 1976; amygdala, Prado-Alcala & Wise, 1984). While an involvement of the NAS and the BLA in reinforcement processes is well established, evidence implicating the ADS is far weaker. However, neural activity in the caudate nucleus does to some extent correspond to behavioural manifestations of food preference and sensory-specific satiety (Nishino *et al.*, 1984), and there is evidence for a direct involvement of the ADS in the reinforcing properties of certain drugs (Glick *et al.*, 1975; Ng *et al.*, 1988; Smith *et al.*, 1980). Nonetheless, a definitive answer to the question of whether neuroleptic-induced increases in the consumption of a 34% sucrose solution reflect an

attenuation of its rewarding properties remains the subject of future study.

CHAPTER 7

CONCLUDING DISCUSSION

7.1 SUMMARY OF CONCLUSIONS

Three issues were identified in Chapter 1 that were to be addressed in this thesis:

1. The nature of neuroleptic-induced within-session response decrements.

2. Clarification of neuroleptic effects on reward processes.

3. The use of quantitative methods to distinguish motor vs. non-motor explanations of drug-induced performance changes.

The studies described have addressed each of these issues, with the following conclusions, which are discussed in detail in the three following sections:

1. Using the Herrnstein matching law, the effects of neuroleptic drugs were compatible with, at low doses, a reduction in reinforcer efficacy, and at higher doses, an additional motor impairment. However, the Herrnstein matching law was found to be prone to artifactual error; in particular, reductions in reinforcer efficacy were time-dependent. These problems compromise the use of the Herrnstein matching law to dissociate motoric from motivational explanations of drug-induced performance changes.

2. Under reinforcement-lean conditions, neuroleptic drugs decreased behaviour in a time-dependent manner. This effect also occurred in the absence of both primary and secondary reinforcement. Within-session decrements in both operant and consummatory behaviour were observed following administration of sulpiride to the anterodorsal striatum (ADS) but not following administration of sulpiride to the nucleus accumbens (NAS). Neuroleptic-induced within-session decrements may reflect a Parkinsonian-like

deficit in the maintenance of behaviour.

3. Consumption of sucrose and operant responding maintained by sucrose pellets follow an inverted-U-shaped concentration-intake function. Systemic administration of raclopride shifted the curve to the right. It is argued that this curve shift reflects an impairment in the primary reward process. Effects of intracranial neuroleptic action on sucrose reward were restricted to the NAS at a low concentration of sucrose, but were also observed within the ADS and basolateral amygdala (BLA) at higher concentrations. It was suggested that at lower concentrations, the rewarding effects of a low concentration of sucrose are confined to the NAS, but at higher concentrations the substrate for reinforcement may be more widely distributed.

7.2 THE HERRNSTEIN MATCHING LAW

A recurrent problem in the assessment of neuroleptic effects on behaviour has been the discrimination of drug effects on reinforcement processes from effects of the drug that are not directly related to the impact of the reinforcer (see Section 1.2). A potential resolution of this problem was suggested to be provided by the Herrnstein matching law, which states that response rate rises to an asymptote as a negatively accelerating function of increasing density of reinforcement (Herrnstein, 1970), and is expressed mathematically as Herrnstein's equation (see Sections 1.2.4B and 2.1). Two parameters may be derived from Herrnstein's equation: K, (the asymptote of the response-reinforcement matching curve) which is selectively affected by motoric manipulations such as increasing the response force requirement; and Re (the lateral position of the rising portion of the curve) which is affected by motivational factors such

as the degree of food deprivation (see Chapter 2; see also Bradshaw *et al.*, 1983a,b; Hamilton *et al.*, 1985; Heyman & Monaghan, 1987; McSweeney, 1978; and see reviews by Davison & McCarthy, 1988; de Villiers & Herrnstein, 1976, de Villiers, 1977). In order to compute the parameters Re and K, data must be obtained from sufficient response-reinforcement points to allow derivation of the hyperbolic curve. Various methods have been utilised in this pursuit, but possess the disadvantage of requiring a great deal of training, and are often not readily learned by rats (see Section 1.2.4B, Chapters 2 and 3).

However, it has also been suggested that in order to dissociate motoric from motivational influences on behaviour, it may not be strictly necessary to derive the response-reinforcement matching curve (see Chapter 2; see also Bradshaw & Szabadi, 1989; Morley *et al.*, 1984, 1985). A change in Re depends upon a relatively larger change in responding contingent on lower reinforcement densities, while a change in K is reflected in changes in response rate that are independent of the reinforcement density in operation. From this, it been suggested that only two schedules need be employed, and effects on Herrnstein's parameters inferred from differential changes in responding under the two densities of reinforcement (Morley et al., 1984, 1985). Thus, in Chapter 2, an inferential 2-point method was employed, in which two RI schedules of widely differing reinforcement densities (RI7.5s and RI300s) were presented on alternate days (ALT-2 procedure). Under the ALT-2 procedure, the effects of experimental manipulations on the performance of rats under the two schedules were compared. Increasing the number of hours of access to food (from 1h to 4h) preferentially reduced response rates under the reinforcement-lean schedule, consistent with a reduction in the motivation to respond (Morley *et al.*, 1984, 1985). By contrast, increasing the response

force requirement nonselectively reduced response rates under both schedules, consistent with a reduction in the motor parameter K (Morley *et al.*, 1984, 1985).

These data suggested that the ALT-2 procedure could provide a robust method for dissociating drug-induced motoric from motivational effects on behaviour. Fluoxetine has previously exerted effects in consummatory procedures that were interpretable as an enhancement of satiety (Clifton *et al.*, 1989; Willner *et al.*, 1990c). Consistent with this, in the ALT-2 procedure, fluoxetine preferentially suppressed responding under reinforcement-lean conditions. By contrast, although its precise mechanisms of anorectic action are not well understood, fenfluramine does not appear to enhance satiety (Montgomery & Willner, 1988; Willner *et al.*, 1990c). In agreement with these data, fenfluramine nonselectively reduced responding in the ALT-2 procedure under both reinforcement-rich and reinforcement-lean conditions.

At low doses, the neuroleptic drugs SCH-23390 and sulpiride preferentially reduced responding in the ALT-2 procedure under reinforcement-lean conditions, consistent with a reduction in the motivation to respond, but at higher doses both drugs reduced response rates under the reinforcement-rich schedule, consistent with an additional reduction in the ability to respond. Analogous data have been reported by this laboratory using an ALT-3 procedure, a more sophisticated variant of the ALT-2 procedure, in which the parameters of Herrnstein's equation may be derived directly. At low doses, both drugs selectively affected Re, indicating a reduction in the motivation to respond (Willner *et al.*, 1990a). However, both drugs were also shown to affect Re in a time-dependent manner, a mechanism of action which severely compromises the use of the Herrnstein matching law (for further discussion, see below). In addition, the majority of other drugs tested in Chapter 2 produced effects in the

ALT-2 procedure that can at best be described as artifactual. Matching interpretations of the effects of metergoline and clonidine were inconsistent with the literature on these agents (see Chapter 2). The most serious problem arose in the case of methyl-scopolamine, which selectively reduced responding under reinforcement-lean conditions to such an extent that responding at RI7.5s was significantly lower than at RI300s. These data were not interpretable using the matching law (see Table 2.I, and Fig.2.3). It is clear from these data that the ALT-2 procedure is prone to artifactual distortion. However, the ALT-2 rationale derives directly from the Herrnstein matching law itself (Morley *et al.*, 1984, 1985). Therefore, the source of the problem may not lie in the procedural method, but rather in the underlying assumptions.

7.2.1 Independence of Herrnstein's parameters

The use of the Herrnstein matching law depends upon the reported independence of the parameters Re and K (Bradshaw et al., 1983a,b; Hamilton *et al.*, 1985; Heyman & Monaghan, 1987; McSweeney, 1978). In fact, attempts to demonstrate the independence of these parameters have not always met with success. In Chapter 2, it was reported that increasing feeding time from 1 to 4 hours selectively suppressed responding under the reinforcement-lean schedule on the following day, which is consistent with a reduction in the motivation to respond. However, in other experiments (not reported in detail), feeding time was extended to 17, 20 or 21 hours (i.e. no deprivation), and a selective suppression of responding under reinforcement-lean conditions was not observed (see Fig.7.1). Apparent confirmations of the Herrnstein methodology by this route in fact point to the fragility of the procedure. For example, Bradshaw *et al.*, (1983b) demonstrated a selective increase in Re by increasing body

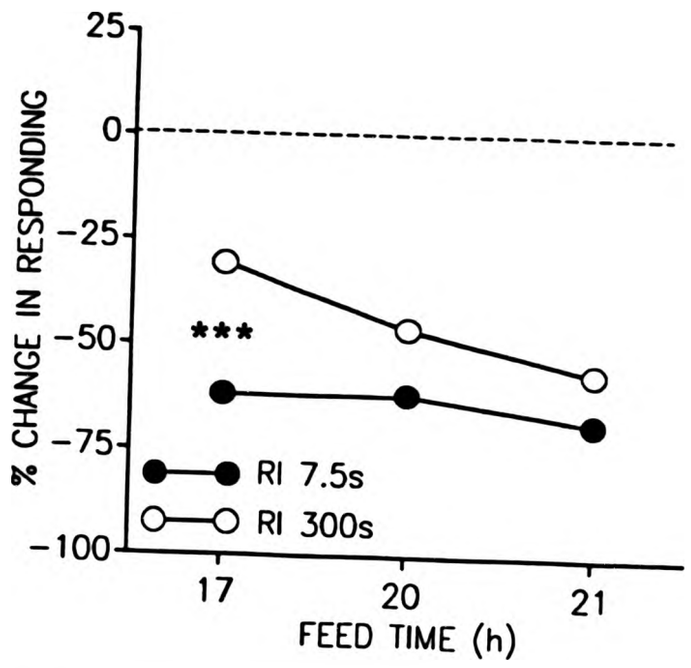


FIG. 7.1. Effects of extended period of food access on performance in the ALT-2 procedure, shown as proportional decrease in responding relative to 1h food access (21h food deprivation). Values are means. Stars indicate statistical significance of drug effects, ***, $p<0.001$. Unpublished data; Willner, Phillips, Sampson & Muscat.

weight, but from 80% to 90% of free feeding weight only. In agreement with the data shown in Figure 7.1, increasing body weight to 100% free feeding weight has been shown to decrease K (McSweeney, 1975). Similar conclusions may be drawn from the multiple-schedule procedure described in Chapter 3 (Fig.3.3). For the most part, in proportional terms response reductions in reinforcement-rich and reinforcement-lean density components were very comparable. Only in the final 5mins did responding decline to a significantly larger extent under reinforcement-lean conditions; and even this result must be viewed with caution (see Section 7.2.4). Heyman & Monaghan (1987) allowed performance to stabilise at three levels of water deprivation; 47.5h, 23.5h and 6h. Reducing the deprivation level did selectively increase Re in this study, but the procedure was flawed in that the period of water exposure differed between the three conditions.

7.2.2 The Interpretation of K

A further problem concerning the presumed independence of Herrnstein's parameters may be illustrated by the effects of yohimbine (Chapter 2). At low doses (0.5-1mg/kg) yohimbine enhanced responding, while at higher doses (2-4mg/kg) response rate declined. Proportionately, this effect was not specific to either reinforcement-lean, or reinforcement-rich conditions. Matching analysis of 2-schedule performance (Morley *et al.*, 1984, 1985) suggests these effects are interpretable as changes in the parameter K, or motor ability. However, intraventricular infusion of yohimbine yielded a similarly non-monotonic action upon spontaneous locomotor activity (Zebrowska-Lupina & Kleinrok, 1973), and systemic administration also exerted a non-monotonic effect upon the acquisition of an operant response (Huang *et al.*,

1987). Thus, yohimbine modulates behavioural arousal. This observation is clearly of relevance to the interpretation of the matching law.

The standard method of validation of K is to increase the response force requirement, which implies that K provides a measure of the physical ability to respond. However, strictly speaking, this interpretation of K is incorrect. Herrnstein's equation indicates that K is not a measure of the theoretical physical maximum rate of responding, but rather, the total amount of ongoing behaviour (see Section 2.1). The first assumption that underpins the matching law is that in a given situation, the total output of all behaviours remains the same; the allocation of behaviour may only be redistributed amongst available possibilities. However, if the total output of all behaviours does not remain constant under all circumstances, then K cannot simply be assumed to measure motor ability. Indeed, even Herrnstein has suggested that such a modification of K may prove necessary (Herrnstein, 1981). Nonspecific arousal may be expected by definition to affect all behaviours equally, hence the nonspecific enhancement in responding engendered by low doses of yohimbine. Amphetamine has also been found to increase K in some studies (eg. Heyman & Seiden, 1985). Again, an interpretation of these data in terms of non-specific arousal, rather than an increase in motor ability, is equally plausible.

If K is seen as a measure of arousal, and not simply a measure of the physical ability to respond, then a number of apparently rogue results may be explicable. Snyderman (1983) reported that reducing body weight from 90% to 70% free feeding weight did cause a reduction in Re as might be expected, but also increased K. He asks: "Is it conceivable that increasing deprivation also leads to an overall increase in motor activity (arousal) and therefore to a change in the asymptotic rate of responding [?]." Snyderman

alternatively cites Killeen's (1982) 2-process model of incentive, in which reinforcement has both an arousing and a response directing effect. In this context, it is significant that increasing the magnitude of the reward has also been found to increase K (humans, money: McDowell & Wood, 1984, 1985), while reducing the magnitude of the reward has been found to reduce K (rats, sucrose concentration: Bradshaw *et al.*, 1978).

In the light of this discrepancy, Bradshaw *et al.*, (1978) made a crucial modification to equation 3 (see also McDowell, 1986), and suggested that:

$$Bo = \frac{(e.K).Ro}{(Ro+Re)} \qquad (6)$$

where the novel variable 'e' refers to the efficacy of the reinforcer. The relationship between e, and Re was not made clear, and has not been followed up in subsequent research. However, this modification severely compromises the apparent utility of the Herrnstein matching law as a method of dissociating motor capacity from reinforcer efficacy. In effect, K and Re may not be truly independent measures of motor capacity and reinforcer efficacy, but rather are inextricably linked.

7.2.3 The problem of non-monotonicity

A related problem with the Herrnstein matching law is the assumption that response rate rises monotonically to an asymptote with increasing contingent reinforcement density. Using a multiple schedule, it was reported in Chapter 3 that substitution of 95% sucrose pellets for standard, 10% sucrose pellets did not increase response rates, but instead, responding declined. This was so even during the first 5min of the session (see below). Reviews of the literature (de Villiers & Herrnstein, 1976; de Villiers, 1977) do not suggest there may be serious problems with the assumption monotonicity. Whilst one

would hesitate to quarrel with their overall thrust, not every apparently confirming instance is as straightforward as claimed. Snyderman (1983) criticised the elimination of nonmonotonic data points by de Villiers & Herrnstein (1976). On rather dubious grounds, Heyman & Monaghan (1987) applied the same technique to the work of Snyderman (1983). Also, in de Villiers (1977), Guttman (1953) was cited in confirmation of the matching law. The majority of this paper in fact concerns the apparently valid nonmonotonic relationship between response rate and sucrose concentration (see Chapter 5).

It was reported in Chapters 4 and 5 that CRF responding for, or consumption of sucrose followed an inverted-U-shaped concentration-intake function. As previously shown using a multiple schedule, the inverted-U-shaped function was apparent within 5min of the session start. This observation weighs against postingestional satiety being the causal agent for the descending limb of the concentration-intake function. Indeed, this mechanism is ruled out by the fact that the 10% and 95% sucrose pellets used in these experiments had an almost identical calorie content (see Section 7.4.1). Increased consummatory time for very intense sucrose concentrations may be a second mechanism for the descending limb. However, analogous inverted-U-shaped functions have been shown using ICSS, in which the stimulation time was kept constant, and the current intensity varied (Hawkins & Pliskoff, 1964; Hodos & Valenstein, 1962). It is therefore possible that the inverted-U-shaped concentration-intake function may genuinely reflect a monotonic reward process. If so, then these data are a further problem for the monotonic nature of the Herrnstein matching law.

7.2.4 Time-dependency and contrast effects

Multiple schedules are often used to obtain the data necessary for calculation of Herrnstein's parameters (see Section 1.2.4B, see also Chapter 3), and necessarily involve the sequential presentation of components. Clearly, in order to obtain valid estimates of drug effects on Herrnstein's parameters, it is essential that drug effects be constant over time. However, neuroleptic drugs cause a time-dependent increase in the parameter Re. Underlying an increase in Re is a larger suppression of responding relative to baseline under reinforcement-lean, low response rate conditions. Therefore, a sequential presentation of components of differing reinforcement density would be expected to compromise the validity of the obtained parameter changes. In a nonrandom multiple schedule procedure, under conditions in which reinforcement density (and response rate) increased during the session, pimozide appeared selectively to decrease motor ability (Willner *et al.*, 1987). However, if reinforcement density (and response rate) decreased during the session, then pimozide appeared selectively to reduced the motivation to respond. Both of these effects would be expected if the suppressive effects of pimozide increased during the course of the experimental session.

This hypothesis was addressed in Chapter 3. In order to distinguish effects on time from those of component presentation order, two schedules of reinforcement density were devised in which both ascending and descending sequences of reinforcement density were presented in different parts of the session. It was shown that the response suppressions induced by pimozide, and SCH-23390 were time-dependent, such that decrements in responding were smallest early in the experimental session, and largest later in the session. Nevertheless, the effects of pimozide and SCH-23390 were also schedule-dependent: the time-dependent suppressions in response rates were largest

under reinforcement-lean conditions. The contamination by time-dependency of drug effects on Herrnstein's parameters were assessed was examined in detail for SCH-23390. In the RLR schedule, SCH-23390 decreased K in the first half of the experimental session, which consisted of an ascending order of reinforcement densities, but increased K in the second half of this schedule, which consisted of a descending order of reinforcement densities. A motor deficit that depends upon the order of component presentation is as implausible as its apparently temporary nature.

Multiple schedule procedures are also subject to the phenomenon of behavioural contrast (Reynolds, 1961), in which response rate in the component under consideration is influenced by its temporal context. The influence of the following component is usually greater than that of the prece-ding components (Reynolds, 1961). The interpretation of behavioural contrast is a complex and controversial issue (Herrnstein, 1970; MacLean & White, 1983; Williams & Wixted, 1986), and an accepted modification of Herrnstein's equation to take account of this phenomenon has yet to be developed. It was reported in Chapter 3 that response rate under a moderate reinforcement-density component was higher if it preceded a reinforcement-rich component than if it followed the reinforcement-rich component. This finding is consistent with the literature on behavioural contrast (Reynolds, 1961). However, valid calculation of Herrnstein's parameters depends upon data obtained at each reinforcement density reflecting only that reinforcement density.

Moreover, a potential interaction of behavioural contrast with the effects of experimental manipulations would be difficult to assess. Increasing body weight to 100% free feeding weight nonselectively reduced responding during the early and middle portions of the multiple schedule session, but during the latter portion of the session

reduced responding to a larger degree under reinforcement-lean conditions, under which no further significant amounts of reinforcement would be anticipated. It cannot be ruled out that this may reflect the operation of behavioural contrast. It follows that this possibility also compromises interpretation of the apparently time-dependent reductions in responding obtained following neuroleptic drug administration. However, it should be noted that this latter finding is in agreement with a substantial literature demonstrating a time-dependent action of neuroleptic drugs in single schedules (see Section 1.2.2).

7.2.5 Summary

The Herrnstein matching law was advanced as a quantitative method for dissociating motoric from motivational drug-induced performance changes. However, the majority of drugs tested produced results that are best seen as artifactual, and analyses of the effects of neuroleptic drugs were confounded by the time-dependent mechanism of action of this class of drug. The apparent unreliability of the matching procedure often necessitates comparison with other paradigms for interpretation of the data. In the words of Wise (1989, with reference to the place preference procedure): "We are happy...so long as it gives us empirical results consistent with..[other].. paradigms, but as soon as it gives us results that do not agree with those from..[other]..studies, my guess it that we will challenge its legitimacy ..." In the same review, Wise (1989) places great reliance on the matching paradigm to give definitive answers. This confidence may be misplaced.

7.3 NEUROLEPTIC-INDUCED WITHIN-SESSION RESPONSE DECREMENTS

Despite a substantial research effort, the nature of neuroleptic-induced within-session response decrements remains an enigma (see Section 1.2.2). Although originally suggested to reflect a neuroleptic-induced state of 'anhedonia' (Wise *et al.*, 1978a), this hypothesis has since been rejected (Section 1.2.2). It was reported in Chapter 4 that time-dependent reductions in responding under raclopride can be observed following prolonged extinction (see also Phillips & Fibiger, 1990). Moreover, whereas the effects of conditioned reinforcement were confined to the initial period of the experimental session, raclopride-induced decrements in responding were present only much later. It was therefore suggested that neuroleptic-induced within-session response decrements do not reflect changes in reinforcer efficacy.

The mechanism of these effects at the neuronal level is unknown. Fowler (1990) suggested that response decrements arise because the pool of available dopamine is depleted, as neuroleptics increase DA turnover in the striatum (Carlsson, 1978; Lane & Blaha, 1987). This arises partly from blockade of DA autoreceptors, and partly from indirect inhibition of the striato-nigral feedback pathway (Bunney *et al.*, 1987). According to Fowler's (1990) account, arousing stimulation from handling, apparatus cues and motor activity may cause the further release of dopamine within the striatum, accounting for relatively normal response rates early in the session, but depleted supplies may be only temporarily sufficient to adequately maintain behaviour in neuroleptic-treated animals. However, this account is almost certainly mistaken. Gallistel *et al.*, (1982) trained rats to self-stimulate by turning a running wheel. Following a specified, large number of turns, the rats were transferred to an alleyway procedure, in which running also obtained ICSS. If motor activity caused a significant release of DA,

then following wheel running, administration of pimozide would not be expected to cause a within-session response decrement in alleyway running: activity should be decreased from the outset. However, despite running at least 55 metres in the running wheel, pimozide induced a typical within-session decrement in subsequent alley running, by comparison with alley running alone. Within-session response decrements do not therefore reflect a depletion of striatal DA.

The independence of raclopride-induced within-session decrements from the effects of reward-associated cues (Chapter 4) emphasises that the essential nature of a neuroleptic-induced within-session decrement is not one directly related to reinforcement processes. Fowler (1990) has suggested that the deficit is essentially Parkinsonian in nature: a failure to maintain behaviour is one symptom of PD (Schwab, 1972). Consistent with this interpretation, it was reported in Chapter 6 that administration of sulpiride to the ADS caused a time-dependent reduction in both operant and consummatory behaviour. By contrast, sulpiride administered to the NAS induced a constant, time-independent reduction in response rate.

The dorsal striatum is critically involved in the organization of behaviour under the guidance of internal cues (Cools *et al.*, 1989). Cools (1980) observed the escape strategies used by rats in a swim tank. At first, no escape was possible, and the rats were observed to sample a characteristic sequence of escape strategies. It is important to note that as no escape was at first possible, the initiation of each strategy may be interpreted as arising from factors intrinsic to the rat. Administration of haloperidol to the dorsal striatum reduced the number of escape strategies; often the repertoire under haloperidol was restricted to the first strategy attempted. Thus, haloperidol administered to the dorsal striatum reduced the number of switches between strategies initiated by factors

intrinsic to the rat. However, if an external escape stimulus was made available (a climbing rope), then the escape latencies of the haloperidol-treated animals were normal. Thus, haloperidol administered to the dorsal striatum had no effect on the selection of a strategy based on an external stimulus. In a second study, Jaspers *et al.*, (1984) studied the behaviour of cats on a treadmill. A food hopper was situated at one end of the treadmill. Two distinct forms of behaviour were observed; externally oriented locomotor accelerations (fixation on, and approach of the food hopper), and internally generated locomotor accelerations (no observable stimulus attended to, and food hopper not approached). Haloperidol administered to the dorsal striatum had no effect on the former, externally oriented behaviour; but greatly reduced the number of the latter, internally generated accelerations observed (see also Gelissen & Cools, 1988). It was suggested that DA blockade in the dorsal striatum reduces the ability to arbitrarily switch to non-stimulus directed behaviours.

Parkinson's patients exhibit a similar deficit of internally generated behaviour, but this problem may be ameliorated using an external stimulus (Cools *et al.*, 1984). Indeed, Parkinson's patients have even been reported to create imaginary stimuli to this end (Stern *et al.*, 1980). Electrophysiological studies have found that of the caudate nucleus is responsive to conditioned stimuli (eg. Cherkes *et al.*, 1984; Nishino *et al.*, 1984; Shugalev 1983; Suvarov et al., 1984). However, the role of caudate DA in this response is less certain (Blackburn et al., 1989; Taylor & Robbins, 1984, 1986, see Section 1.2.3). A possible neuroanatomical basis for this deficit was described in Section 1.1.3. Briefly, it has been proposed that dysfunction of the dorsal striatal DA system leads to excessive inhibition of the thalamus-to-cortex stage of the cortico-striato-thalamo-cortical motor circuit (Alexander *et al.*, 1986). Kirkpatrick & Fowler (1989) suggested that this

mechanism underlies the response decrements seen following neuroleptic administration to rats. In the 'peak force' paradigm, the force applied to the lever, and the duration which the lever was depressed, were both found to increase as the session progressed. It was suggested that the gradual onset of these abnormalities was due to a perceived mismatch between the intention to act, and feedback from the resulting action. Experience of this deficit was hypothesised to cause the observed progressive reduction in responding.

Frith & Done (1988) have put forward an analogous mechanism for the positive symptoms of schizophrenia, which were suggested to result from a failure in the system for the central monitoring of actions (positive symptoms). The positive symptoms of schizophrenia were suggested to apply particularly to self-generated acts. One outcome of a deficiency in the central monitoring system may be a confusion of self-generated actions and stimuli of external origin, leading to delusions of control and thought. There appears to be two dissociable aspects to this problem, at both the psychological and neuroanatomical level (Goldberg, 1985). First, the planning and execution of actions involves the prefrontal cortex, and the efferent 'limbic' circuit respectively (see Section 1.1.3); and an underlying deficit in this system would be expected to lead to a difficulty of initiating planned activities, which is manifested in the negative symptoms of schizophrenia (Frith & Done, 1988). The positive symptoms of schizophrenia have been suggested to involve the hippocampal-septal, 'comparator' system (Gray, 1982). The similarity of the behavioural effects of hippocampal lesions to those of high doses of amphetamine is significant in this regard (eg. Devenport et al., 1981). Gray has suggested that information concerning planned acts are normally passed from the prefrontal cortex to the hippocampus monitoring system (Gray & Rawlins, 1986). Subsequently, Frith &

Done (1988) suggested that neuroleptics reduce the positive symptoms of schizophrenia by decreasing activity in the prefrontal cortex: fewer self-generated acts are initiated, hence there is less likelihood of a monitoring failure occurring.

In sum, neuroleptic-induced within-session response decrements may reflect an underlying mismatch between an internally generated act and subsequent motor feedback, this problem arising at the level of the dorsal striatum.

7.4 DOPAMINE AND REINFORCEMENT

7.4.1 Neuroleptic-induced behavioural increments for natural reward.

Consumption of sucrose solutions or operant responding maintained by sucrose pellets follows a concentration-dependent inverted-U-function. It was shown in Chapters 4 and 5 that administration of raclopride reduced operant responding for, or consumption of, a low concentration of sucrose situated on the ascending limb of the concentration-intake function, but increased responding for, or consumption of, a concentration of sucrose situated on the descending limb of the concentration-intake function. These effects were together interpreted as a shift in the function to the right: in effect, animals under raclopride appeared to react towards sucrose as though it were less concentrated (see also Geary & Smith, 1985; Xenakis & Sclafani, 1981). However, it has been shown that pimozide did not affect the threshold for sucrose discrimination, nor did it affect the just-noticeable-difference between sucrose concentrations (Willner *et al.*, 1990b). Hence, the effects of raclopride on sucrose-dependent behaviour are unlikely to reflect a sensory discrimination deficit. It was reported in Chapter 6 that administration of sulpiride to the ADS or BLA did not affect preference for a low concentration of sucrose over water. However, administration of sulpiride to the NAS

markedly reduced preference for 0.7% sucrose. The total volume of fluid consumed was not affected, hence the reduction in sucrose consumption can not be seen as a reduction in motor ability. The NAS mediates the organisation of behaviour under the guidance of external cues (see Sections 1.2.3 and 7.4.5; Cools *et al.*, 1989; Robbins *et al.*, 1989; Scheel-Kruger & Willner, 1990). The effect of sulpiride administered to the NAS on preference for a low concentration of sucrose is consistent with this interpretation.

The potential contribution of a number of artifacts to data obtained on the descending limb of the sucrose concentration-intake function were assessed in Chapters 4 and 5. Aversion to concentrated sucrose was identified as one such artifact which may give rise to the descending limb of the function. However, in an operant procedure, withdrawal of 95% sucrose pellets, situated on the descending limb of the function, increased responding, whereas withdrawal of standard, 10% sucrose pellets, which supported higher rates of reinforced responding did not (Chapter 4). More conclusive evidence was provided by a consummatory sucrose choice test: a concentration of sucrose situated on the descending limb of the function was found to be the most preferred (see Chapter 5; see also Young, 1949; Young & Greene, 1953). Hence, aversion can not account for the descending limb of the function. Satiation due to the caloric content of concentrated sucrose was the second artifact addressed. However, in sucrose-experienced animals, onset of the descending limb, and behavioural increments engendered by raclopride occurred within 5min of the session start. Furthermore, it was reported in Chapter 4 that following transfer from 10% to 95% sucrose pellets, reductions in response rate were also apparent within 5min of the session start. Finally, the caloric content of the 10% sucrose pellets and 95% sucrose pellets used in Chapter 4 was in fact almost identical. Hence, increments in behaviour following administration

of raclopride could not be caused by an inhibition of postingestional satiety.

Nonetheless, acquisition of sucrose preference, and raclopride-induced increases in consumption were not immediately apparent, but required experience. It is possible that this reflects a process of 'conditioned' satiation. If this were so, then experience of a non-nutritive solution (saccharin) should lead to an extinction of the consummatory response. Carper & Polliard (1953) tested the hypothesis that saccharin may be seen as a secondary reinforcer, but found no evidence for an extinction process. Moreover, others have noted that preference for saccharin also increases with experience (Capaldi *et al.*, 1990; Domjan & Gillan, 1976; unpublished personal observations). Nonetheless, in contrast with sucrose, higher concentrations of saccharin may not be preferred, an effect attributable to its 'dual' taste (Mook, 1974). In recent (unpublished) experiments in this laboratory raclopride did not increase consumption of a high, but nonpreferred concentration of saccharin (unpublished observations). Moreover, if an initially preferred high concentration of sucrose was adulterated with quinine so that it was no longer preferred, then raclopride did not increase consumption. It is clear that effects of raclopride on sucrose consumption do not relate to its caloric content. An alternative explanation is outlined in Section 7.4.3.

7.4.2 Neuroleptic-induced increases in drug self-administration

In contrast with the novelty of neuroleptic-induced increases in behaviour for sucrose reinforcement, enhanced responding for stimulant drug reinforcement following neuroleptic treatment is well established (see Sections 1.2.1 and 1.2.2). Low doses of antagonist challenge induce a sustained increase in response rate, while higher doses may result in a 'frustrative' burst, followed by a cessation of responding (de Wit & Wise,

1977; Pickens *et al.*, 1968; Yokel & Wise, 1975, 1976). In this respect, antagonist challenge mimics substitution of saline for reinforcing drug, and has been suggested to indicate a reduction in the reward value of the self-administered drug (Yokel & Wise, 1975, 1976). These data provide further evidence that neuroleptics do not simply impair motor ability, and stand in marked contrast with the near-catalepsy that may ensue following neuroleptic treatment under noncontingent conditions (see Chapter 6; Janssen *et al.*, 1965). However, given that response rate for stimulant self-administration commonly shows an inverse relationship to unit dose (eg. Glick *et al.*, 1975; Yokel & Pickens, 1973), it is hardly surprising that partial DA blockade leads to an increase in responding.

Nevertheless, while these effects are consistent with a reduction in reinforcer efficacy, other interpretations are possible. Following drug infusion, there is typically a pause in responding, which is directly related to the unit dose of drug (Pickens & Thompson, 1968). This post-reinforcement pause, which is largely responsible for the descending limb of overall response rate for drug self-administration, may often be caused by so-called 'direct', drug side-effects (Katz, 1989). Spealman & Kelleher (1979) studied the effects of cocaine under a multiple schedule, in which components of response-dependent shock alternated with components of response-dependent cocaine infusion. Despite the use of a constant shock intensity, responding in both shock and drug components showed an inverted-U-function with increasing dose of cocaine. If cocaine availability was instead made response-independent, then responding in the cocaine component extinguished, but response-produced shock continued to exhibit an inverted-U-function with increasing dose of cocaine infusion. In addition, response-independent cocaine administration also resulted in the temporary cessation of

responding for food (Pickens & Thompson, 1968). These data would suggest that the post-reinforcement pause, and the consequent descending limb of the self-administration dose-response function may be the outcome of drug side-effects. Hence, response increments induced by DA blockade may simply arise from the amelioration of these side effects.

However, there is evidence that direct drug effects are not the sole contributor to the descending limb for drug self-administration. Wise *et al.*, (1977) utilised a concurrent schedule, in which rats responded on one lever to obtain an infusion of amphetamine, and on a second lever to obtain ICSS. High response rates for ICSS were observed during the post-reinforcement pause following amphetamine infusion (Wise *et al.*, 1977). This would not be expected if the post-reinforcement pause were solely the outcome of a motor disability. It is unlikely that amphetamine-induced stereotypy can explain high response rates for ICSS during the drug post-reinforcement pause, since termination of current resulted in extinction of responding on the ICSS lever, and if the lever contingencies were reversed, then response choice also reversed. Furthermore, if the descending limb were simply the outcome of some form of drug-induced disability, then such a state would presumably be an aversive one. However, there is little evidence that this is so. In rats, Pickens & Thompson (1975) were unable to demonstrate any consistent preference for one dose of cocaine over another. Nevertheless, a consistent finding in monkeys has been that irrespective of response rate during drug availability, the higher the dose of stimulant drug, the greater is the preference for it (Iglauer & Woods, 1974; Johanson & Schuster, 1975; Llewellyn *et al.*, 1976).

It is clear that the response decrements observed at high doses in the

self-administration paradigm may not in all instances be explained by direct effects of the drug. Rather, neuroleptic-induced increments in drug-rewarded behaviour may be seen as an attempt to compensate for a blunting of the rewarding aspect of the drug. In humans, the subjective experience of amphetamine euphoria was blocked by administration of pimozide (Gunne *et al.*, 1972). Given that stimulant drugs release DA, blockade of DA receptors may be overcome by increased self-administration of a stimulant drug.

7.4.3 Neurochemical basis of the interaction between neuroleptics and natural reward.

While it seems relatively clear that neuroleptic-induced response increments in drug self-administration can be interpreted at least in part as a compensation for loss of the rewarding properties of the drug, it is less clear whether such a mechanism underlies neuroleptic-induced behavioural increments for sucrose reward. It was reported in Chapter 6 that sulpiride administered to either the NAS or ADS increased consumption of sucrose. If these effects are to be seen as analogous to those of drug self-administration, then sucrose consumption would be expected to cause a release of DA in these areas. Following neuroleptic challenge, increased sucrose consumption would cause a further release of DA, and ameliorate DA receptor blockade. However, Blackburn *et al.*, (1989) reported that an unsignalled meal did not lead to an increase in the DOPAC/DA ratio in either the NAS or ADS. By contrast, presentation of a conditioned stimulus in the absence of primary reinforcement did increase DA turnover in both areas (19.9% and 17.3% respectively; although greater variability in the ADS group prevented data from this group reaching statistical significance in a 2-tailed test).

It was suggested that in relation to natural reinforcement, DA release corresponds to preparatory behaviours that may lead to a consummatory response, but does not correspond to the consummatory response itself. However, precisely the opposite results were reported by Hernandez & Hoebel (1988a). Following 20min of CRF for food, DA release in the NAS increased by up to 50% for 40min or more following consumption. No changes in DA activity were found following presentation of a conditional stimulus alone. The main cause of this apparent discrepancy may be the large difference in sample times employed in the two studies. Whereas Blackburn *et al.* were able to detect changes in DA turnover after just 4min exposure to the conditional stimulus (by immediate sacrifice and dissection of area), the in vivo microdialysis technique of Hernandez & Hoebel required a full 20min sampling time to obtain sufficient quantities of DA and metabolites. Using a longer sampling time, (1h consumption of a liquid diet), Blackburn *et al.*, (1986) reported an increase in DA turnover in both the NAS and ADS. Nonetheless, the data of Hernandez & Hoebel would indicate that increases in DA turnover following presentation of a conditional stimulus is a relatively short-lived affair, whereas increased DA release following primary reinforcement may last much longer. It is possible that this long-term effect in some manner reflects the postingestional consequences of consumption, as in one study saccharin consumption was not found to increase DA turnover (Blackburn *et al.*, 1986). However, Hernandez *et al.*, (1990) found that consumption of saccharin does indeed lead to a delayed increase in DA turnover. Furthermore, rats will self administer amphetamine directly into the NAS (Hoebel *et al.*, 1983), and the resultant increase in DA release is equally long-lasting (40min or more) (Hernandez & Hoebel, 1988b). This may imply that reinforcing drugs to an extent mimic the effects of food ingestion. Alternatively, food

consumption could be seen as reinforcing in a manner similar to that of stimulant drug.

DA release in the NAS does not necessarily correspond with increased behavioural output. Whereas administration of amphetamine to the NAS does increase spontaneous locomotor activity (Carr & White, 1987; Pijnenberg *et al.*, 1976), Hernandez & Hoebel (1988a) noted that sustained increases in DA release in the NAS following 20min CRF corresponded with an **absence** of activity: animals were reportedly 'quiescent' during this period (see also Segal and Kuczenski, 1990). In this laboratory, responding under CRF maintained by sucrose pellets, or consumption of sucrose solutions declines to very low levels after 20min exposure, and animals are also relatively quiescent; the data of Hernandez & Hoebel (1988a) suggest that this pattern of behaviour may be correlated with increased release of DA. Moreover, a sustained release of DA in the NAS does not depend upon caloric intake. Tail pinch caused a similar prolonged elevation of DA release in the NAS (Louilot *et al.*, 1986), and was also accompanied by immobility.

In common with tail pinch, schedule-induced polydipsia (SIP) appears to be mediated, at least in part through the release of mesolimbic DA in the NAS (Robbins & Koob, 1980; Wallace *et al.*, 1983). SIP has been interpreted as a coping response to an aversive state (Brett & Levine, 1979). However, Mittleman *et al.* (1990) reported that prior learning of amphetamine self-administration enhanced acquisition of SIP, whereas the prior development of SIP retarded the acquisition of amphetamine self-administration. In humans, subsequent drug abuse is predictable to a large extent by the degree of reinforcement obtained from the initial drug experience (Haertzen *et al.*, 1983; see also Bardo & Neisewander, 1986). One possibility may be that the initial experience of DA release in the NAS is in fact subjectively neutral. Whether enhanced DA release is positively, or negatively reinforcing may depend upon learning processes. This may

partly involve the operation of conditioned stimuli. Significantly, amphetamine has been shown to potentiate the behavioural effects of conditioned reinforcement, when administered to either the NAS and dorsal striatum (Taylor & Robbins, 1984, see Section 1.2.3). However, other possibilities can not be excluded at this stage. For instance, in contrast with the reported effects of positive reinforcement on DA release (see above), the effects of stress on DA release are largest in the mesocortical DA system (Zacharko & Anisman, 1990), and stress also causes the additional release of serotonin in the NAS (Willner et al., 1990d). It has been proposed that the consequences of DA release in the NAS may therefore depend on the balance of neurotransmitter release within the NAS, or on the balance of activity throughout the brain (Scheel-Kruger & Willner, 1990). However, resolution of this problem awaits further investigations.

7.4.4 Experience and rewarding efficacy

A more fundamental process may also operate to modulate the reinforcing efficacy of a stimulus: repetition. It was reported in Chapter 5 that sucrose-experienced rats showed a marked preference for 34% sucrose over 0.7% or 7% sucrose throughout an experimental session. However, sucrose-naive rats did not at first show a preference for 34% sucrose: intakes of the three concentrations were very comparable in the first 5min of exposure to the 3-bottle test (0.7%, 1.1ml; 7%, 1.1ml; 34%, 1.6ml). Furthermore, the onset of raclopride-induced increments in intake depended upon acquisition of this preference; on the first day raclopride did not increase intakes of 34% sucrose until 11-15min into the session. Three experimental sessions were required before raclopride increased intakes of 34% sucrose during the first 5min of the session, as typically found using sucrose-experienced animals (Chapter 5). This may have reflected an initial

neophobic response to the sweet-tasting stimulus. However, if this were so then the neophobic response should have shown some concentration-dependency: the avoidance response should have been most marked for 34% sucrose, and least for 0.7% sucrose, given its relative similarity to water.

Although a neophobic response by sucrose-naive rats can not be ruled out at this stage, it may be that the reward value of a stimulus can be enhanced simply by its repetition. Robinson *et al.*, (1988) subjected rats to a chronic, escalating regimen of amphetamine treatment. Three weeks after termination of amphetamine treatment, DA activity in the NAS was measured by in vivo microdialysis. Basal extracellular levels were normal. However, acute amphetamine challenge strikingly enhanced DA release in the NAS (and locomotor activity), over and above that shown by controls. Using in vivo voltammetric methodology, Justice *et al.*, (1990) measured DA activity in the NAS following (suprathreshold) electrical stimulation of the medial forebrain bundle (MFB). Chronic treatment with cocaine enhanced the effect of MFB stimulation on release of DA in the NAS, by comparison with acute treatment. Gratton *et al.*, (1988) electrically stimulated MFB or VTA sites at currents previously demonstrated to engender high rates of responding (the majority of animals were pretrained to self-stimulate), and measured DA release in a number of forebrain areas. Experimenter-induced stimulation of the VTA or MFB caused a release of DA in the NAS, ADS, and prefrontal cortex. It was noted however, that DA release was far more readily detectable in pretrained animals, by comparison with naive subjects. It is possible then that mere repetition of a DA-mediated stimulus event is sufficient to potentiate the response of DA neurons, but the direction of change in reinforcing value may again depend upon the context. Nonetheless, chronic treatment with either amphetamine or cocaine has

also been shown to raise the threshold for ICSS (Kokkinidis & Zacharko, 1980; Koob, 1989), implying a reduction in the effectiveness of the reinforcing stimulation.

Further, the reinforcing properties of a stimulus are not determined solely by that stimulus alone. In preparation for testing the effect of raclopride upon intake of a quinine solution (Chapter 5), it was observed that following 21h food and water deprivation, naive animals consumed approximately 8ml of water in one hour. However, given just one exposure to 0.7% sucrose, intake of water halved to 4ml on subsequent days, and remained at this level despite identical deprivation conditions throughout. This is likely to reflect a process of negative contrast (see Flaherty, 1982). Behavioural contrast is a ubiquitous feature of reinforced behaviour (see Chapter 3, and Reynolds, 1961; Flaherty, 1982). In fact, intake of each of the three solutions tested (quinine, water and 0.7% sucrose) was to some extent dependent upon prior exposure to the other two. Similarly, in the ICSS autotitration-of-threshold procedure, reset threshold is not an absolute value, but depends upon the maximum current value obtainable upon reset (Fouriezos & Nawiesnak, 1982): the higher the maximum obtainable value, the higher the apparent threshold. Contrast effects may be especially difficult to assess between qualitatively different forms of reinforcement, eg. drug and ICSS. Nonetheless, raised ICSS thresholds following repeated stimulant administration may be a negative contrast effect, and would be less likely to occur using suprathreshold current values, and in these cases (see above), sensitization following stimulant treatment was observed. In this manner, apparent subsensitivity to a rewarding stimulus may not be a purely pharmacokinetic context, but may more accurately reflect the organism's evaluation of the stimulus in the light of previous experience. Further work is clearly needed in order more fully to characterise the reward process.

7.4.5 Conclusions: The role of dopamine in rewarded behaviour

Operant responding maintained by, or consumption of, sucrose has been shown to follow an inverted-U-shaped concentration-intake function. Administration of raclopride, a DA D2 antagonist, reduced contingent behaviour for a concentration of sucrose situated on the ascending limb of the concentration-intake function, but increased contingent behaviour for a concentration of sucrose situated on the descending limb of the concentration-intake function. It was argued that these effects represented a shift of the inverted-U-shaped function to the right, reflecting an impairment of the reward process, as first suggested by Wise *et al.*, (1978). This conclusion is consistent with data derived from other experimental methods: for example, the effects of neuroleptic drugs on sucrose consumption have been shown to be analogous to those of dilution (Geary & Smith, 1985; Xenakis & Sclafani, 1981). It has also been shown that neuroleptic treatment during operant training extends the subsequent period of responding under extinction, an effect analogous to training under a partial reinforcement schedule of reinforcement (Ettenberg & Camp, 1986a,b). And as discussed in detail earlier, in the matching paradigm, neuroleptics affect operant responding under lean-reinforcement conditions to a larger extent than response rates under reinforcement-rich condtions (see Section 7.2; see also Willner et al., 1987, 1990a), this effect is compatible with a shift in the response-reinforcement matching curve to right, and a reduction in reinforcer efficacy.

However, a number of studies are apparently inconsistent with the conclusion that neuroleptics impair the reward process. These merit detailed consideration. In one such study, Berridge *et al.*, (1989) lesioned the substantia nigra of rats, and recorded the effects of this on the consummatory responses to various taste stimuli (sweet, sour, salt

and bitter). It was hypothesised that if DA modulates the 'hedonic' impact of positive reinforcers, then DA depletion should result in a reduction in the responsivity to the sucrose stimulus. It was found that DA depletion had no effect on responsivity to the sweet taste, and it was concluded that DA does not modulate the 'hedonic' impact of positive reinforcement. However, it was reported in Chapter 6 that sulpiride administered to the dorsal striatum did not affect the consumption of a weak concentration of sucrose: this area, innervated by the substantia nigra, did not appear to exert a major impact on consummatory behaviour, in contrast to the nucleus accumbens which receives its major DA innervation from the VTA. Further, only 1ml of each solution was given, which would mitigate against observing an impact of the lesion. Finally, consummatory responses were simply recorded as the number of observations, rather than the intensity of each response. This categorical form of data collection would be relatively insensitive to subtle changes in consummatory reactivity. Therefore, it is not surprising that Berridge *et al.*, (1989) did not find a positive result.

In another apparently contradictory study, Martin-Iversen *et al.*, (1987) measured the effects of DA manipulations on the perceived quantity of food made available. Whereas amphetamine produced effects compatible with a reduction in the perceived quantity, and interpreted as an increase in the 'hedonic' properties of the food, haloperidol did not. The reason for this asymmetry was not clear to the authors. However, the relevance of the perception of food quantity to primary reinforcement processes is also obscure: the data of Martin-Iversen *et al.*, (1987) may be more relevant to the effects of neuroleptics on discriminability. In this respect, it is significant that pimozide did not affect the discriminability of threshold concentrations of sucrose, nor did it affect the just-noticeable difference between sucrose concentrations. However, in

the same study, pimozide did cause a rightward shift in the sucrose concentration-intake function (Willner et al., 1990b).

It should be emphasised in this context that the effects of neuroleptics on sucrose intake are highly concentration-dependent: data obtained from only one limb of the inverted-U-shaped sucrose concentration-intake function could therefore lead to erroneous interpretations. Much of the work in this area has not addressed this issue adequately. For instance, Kirkpatrick & Fowler (1989) found that pimozide did not differentially affect performance maintained by 8% or 24% sucrose in the 'peak force' paradigm. It was concluded that therefore pimozide did not affect the reinforcing properties of sucrose. However, it was shown subsequently that performance in the 'peak force' paradigm was not in fact sensitive to manipulations of sucrose concentration (Fowler & Kirkpatrick, 1989); therefore, the lack of effect of pimozide is beside the point. Similarly, Blackburn *et al.*, (1987) found that pimozide increased the latency to approach a food hopper upon presentation of a conditional stimulus, but had no effect on consumption itself. However, an unspecified 'liquid diet' was used as the consummatory stimulus, and no other forms of diet were assessed. In the present studies, raclopride had only minimal effects on operant responding reinforced by standard (10%) sucrose pellets, but from the effects of raclopride on higher sucrose concentrations is clear that the lack of effect at 10% sucrose is related to the composition of this particular diet.

However, Blackburn *et al.*, (1987) did show that administration of pimozide increased the latency to approach the food hopper. In related vein, Salamone (1986, 1988) demonstrated that haloperidol reduced the amount of conditioned activity engendered by food presentation, but the rats nevertheless remained in the proximity of

the food dispenser. Salamone (1987) argued that motivated behaviour has both a directional, and an activational aspect, and that neuroleptic drugs impair the latter, but not the former aspect of behaviour. It is widely accepted that DA modulates the behavioural activation engendered by conditioned reinforcement (eg. Robbins, 1978; Robbins *et al.*, 1983a,b). It is important, therefore, to relate these findings to those reported for sucrose consumption.

Raclopride reduced contingent behaviour for a concentration of sucrose situated on the ascending limb of the inverted-U-shaped concentration-intake function. In the context of other effects on the descending limb of the function, this was interpreted as a blunting of the primary reward process. However, there is an alternative explanation. Reference to Figure 4.1 (bottom panel, day 17) indicates that the within-session patterns of responding for 10% and 95% sucrose were essentially parallel throughout the session: response rates were initially high, but declined as the session progressed. However, the through-session pattern for 1% sucrose can be seen to be quite different: response rates at the beginning of the session were no higher that at the end. This may reflect a floor effect towards the end of the experimental session. However, despite this problem, some decline in responding would still be expected earlier in the session, but was not evident. It is possible that raclopride-induced reductions in contingent behaviour reinforced by a low concentration of sucrose do not reflect a blunting of the primary reinforcing aspects of the stimulus, but rather reflect an impairment of its incentive value, consistent with the work cited above. In this context, it is significant that sulpiride administered to the NAS (but not to other areas) so clearly reduced the preference for it. The NAS is believed to be crucially involved in the organisation of behaviour under the guidance of external cues (Cools et al., 1989; Robbins et a., 1989; Scheel-Kruger & Willner, 1990).

Thus, neuroleptic-induced reductions in contingent behaviour for rewards situated on the ascending limb of the function may reflect an impairment of the activating, and response-directing characteristics of incentive stimuli.

By contrast, raclopride and other neuroleptics increased the consumption of more concentrated sucrose. This process appeared to be widely distributed: intracranial adminstration of sulpiride increased the consumption of more concentrated sucrose solutions when administered to the nucleus accumbens, anterodorsal striatum, and also (to a lesser degree) the basolateral amygdala. The numerous anatomical locations for ICSS have also been the subject of comment (eg. Phillips, 1984; Phillips & Fibiger, 1989; Shizgal & Murray, 1989). The increased sucrose consumption following raclopride treatment was interpreted as a compensatory behaviour in response to a partial blockade of reward-related neuronal processes. Again however, there is an alternative interpretation. DA is widely accepted to modulate the switching between behaviours, under the control of both external, and internal cues (Cools et al., 1990; Oades, 1985; Robbins et al., 1989; Scheel-Kruger & Willner, 1990). Thus, increased consumption of concentrated sucrose could reflect a neuroleptic-induced deficit in switching away from the intense stimulus. However, observation of rats drinking concentrated sucrose solutions indicated that, even without neuroleptic treatment animals engage solely in consummatory behaviour for at least the first 5 minutes. As raclopride increased the consumption of sucrose during this period (see Chapter 5), a neuroleptic-induced switching deficit seems unlikely. In addition, a clear prediction can be made that will dissociate these alternatives. A keystone of the reward impairment hypothesis is that for neuroleptic-induced increments in sucrose-dependent behaviour to be seen as compensatory, consumption of concentrated sucrose must lead to a release of DA.

Further, it was reported in Chapters 4, 5 and 6 that the time of onset of neuroleptic-induced increases in sucrose-dependent behaviour were concentration-dependent: increments were delayed for 7% sucrose, but occurred within the first 5min of the session start for 34% sucrose. It follows that the speed of DA release should also be concentration-dependent, and be very rapid indeed using 34% sucrose. These are very clear predictions, which do not apply to a neuroleptic-induced switching deficit. If neuroleptic-induced increases in sucrose-dependent behaviour are to be seen as reflecting a primary reward impairment, this hypothesis is clearly in need of urgent investigation.

7.5 CLINICAL IMPLICATIONS OF DOPAMINE DYSFUNCTION

It was reported in Chapter 4 that time-dependent reductions in responding under raclopride can be observed following prolonged extinction. In addition, whereas the behavioural impact of conditioned reinforcement was confined to the initial period of the experimental session, raclopride-induced decrements in response rate did not ensue until much later. It was further reported in Chapter 6 that within-session performance decrements were obtainable following intracranial administration of sulpiride to the ADS, but not following administration of sulpiride to the NAS. It was therefore argued in Section 7.3 that neuroleptic-induced within-session decrements may reflect a Parkinsonian-like deficit in the maintenance of behaviour under the guidance of internal stimuli.

However, sulpiride-induced "motor-like" deficits were not confined to nigrostriatal DA terminal areas: administration of sulpiride to the NAS resulted in a striking reduction in locomotor activity. The mesolimbic DA system has long been implicated in locomotion (Iversen & Koob, 1977; Kelly *et al.*, 1975; Koob *et al.*, 1978), and the

initiation of behaviour (Blackburn *et al.*, 1987, 1989; Carey 1983; Johnels 1982). Except under unusually motivating circumstances (Schwab, 1972), persons affected by Parkinson's Disease (PD) also experience difficulty in initiating behaviour. Although PD is more commonly associated with the nigrostriatal DA system, some suggest an additional influence of the mesolimbic DA system in the behavioural aspects of PD (eg. DeLong, 1990; Koob *et al.*, 1984; Swerdlow & Koob, 1987; Yang & Mogenson, 1989). Indeed, detailed postmortem examination indicates that in fact damage to the mesolimbic DA system in PD may be more common, and more extensive than often supposed (Bogerts *et al.*, 1983; Javoy-Agid & Agid, 1980; Torack & Morris, 1988; Uhl *et al.*, 1985).

Administration of sulpiride to the NAS also strikingly impaired the rewarding impact of sucrose solutions. The relative inability to experience pleasure is a cardinal trait of depression (Willner, 1983). Up to 90% of persons affected by PD experience marked depression (Asnis, 1977; Brown *et al.*, 1984; Knight *et al.*, 1988), which does not appear to be reactive in nature (Horn, 1974; Mayeux *et al.*, 1981; Robins, 1976). In fact, depressive symptoms may often precede the onset of overt Parkinsonian symptoms (Santamaria *et al.*, 1986; Todes & Lees, 1985). Degeneration of the ventral tegmental area and consequent denervation of DA input to the NAS has been suggested to account for affective deficits in PD (eg. Fibiger, 1984; Lieberman, 1987; Rosse & Peters, 1986). It is significant that such striking locomotor and reward impairments were both obtainable from the NAS, and from the same cannula placement.

Chronic mild stress (CMS) also reduces reactivity to rewards, and this effect appears to be mediated within the NAS (Willner *et al.*, 1990d). CMS-induced reward impairment has been proposed as a model for the anhedonic aspect of endogenous depression, and

is reversed by antidepressant treatment (Willner *et al.*, 1990d). It is significant that motor retardation is a second trait of endogenous depression (Willner, 1983). However, although administration of sulpiride to the ADS did not affect the rewarding impact of a low sucrose concentration, it did impair the impact of a concentrated sucrose solution. It should be noted that this area is also implicated in Parkinsonian depression (Mayeux *et al.*, 1984, 1986; Raisman *et al.*, 1986).

Clearly, both the mesolimbic and nigrostriatal DA systems may be involved in motoric, motivational, and affective functioning. Although the precise roles of each of these systems remains to be determined, this thesis has demonstrated the feasibility of discriminating between all these aspects of experience. Perhaps, as originally stated by Balzac as long ago as 1839, "The day may not be far off when we shall discover by just what chemical means feeling is condensed into a fluid, similar perhaps to electricity."

REFERENCES

Adams, P.M. (1977) Effects of anticholinergic and cholinesterase blocking drugs on appetitive behaviour under different deprivation conditions. Life Sciences 21, 129-136.

Albin, R.L., Young, A.B. and Penney, J.B. (1989) The functional anatomy of basal ganglia disorders. Trends in Neurosciences 12, 366-375.

Alexander, G.E. & DeLong, M.R. (1985a) Microstimulation of the primate neostriatum: II. Somatotopic organization of striatal microexcitable zones and their relation to neuronal response properties. Journal of Neurophysiology 53, 1433-1446.

Alexander, G.E. & DeLong, M.R. (1985b) Microstimulation of the primate neostriatum: I. Physiological properties of striatal microexcitable zones. Journal of Neurophysiology 53, 1417-1432.

Alexander, G.E., DeLong, M.R. & Strick, P.L. (1986) Parallel organization of functionally segregated ciruits linking basal ganglia and cortex. Annual Review of Neuroscience 9, 357-381.

Alexander, G.E. & Crutcher, M.D. (1990) Functional architecture of basal ganglia ciruits: Neural substates of parallel processing. Trends in Neurosciences 13, 266-271.

Anden, N.-E., Carlsson, A., Dahlstrom, A., Fuxe, K., Hillarp, N.A. & Larsson, K. (1964) Demonstration and mapping out of nigro-neostriatal dopamine neurons. Life Sciences 3, 523-530.

Anden, N.-E., Dahlstrom, A., Fuxe, K., Larsson, K., Olson, L. & Ungerstedt, U. (1966) Ascending monoamine neurons to the telencephalon and diencephalon. Acta Physiol. Scand. 67, 313-326.

Arnt, J.+Hyttel, J. (1984) Differential inhibition by dopamine D1 and D2 antagonists of circling behaviour induced by dopamine agonists in rats with unilateral 6-hydroxydopamine lesions. Journal of Pharmacology 102, 349-354.

Arnt, J. (1985) Behavioural stimulation is induced by separate dopamine D1 and D2 receptors in reserpine-pretreated but not in normal rats. European Journal of Pharmacology 113, 79.

Asin, K.E. & Wir shafter, D. (1985) Clonidine produces a conditioned place perference in rats. Psychopharmacology 85, 383-385.

Asnis, G. (1977) Parkinson's disease, depression, and ECT: A review and case study. American Journal of Psychiatry 134, 191-195.

Bailey, C.S., Hsiao, S. & King, J.E. (1986) Hedonic reactivity to sucrose in rats: Modification by pimozide. Physiology and Behavior 38, 447-452.

Balaydier, C. & Mauguiere, F. (1980) The duality of the cingulate gyrus in the monkey, neuroanatomical study and functional hypothesis. Brain 103, 525-554.

Balzac, H. de, (1839) A Harlot High and Low, pp.493. Penguin Books (1970 edition), London.

Bankiewicz, K.S., Oldfield, E.H., Chiueh, C.C., Doppman, J.L., Jacobwitz, D.M. & Kopin, I.J. (1986) Hemiparkonsonism in monkeys after unilateral internal carotic artery infusion of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Life Sciences 39, 7-16.

Bardo, M.T. & Neisewander,J.L. (1986) Single-trial conditioned place preference using intravenous morphine. Pharmacology Biochemistry & Behavior 25, 1101-1105.

Barone, P., Davis, T.A., Braun, A.R. and Chase, T.N. (1986) Dopaminergic mechanisms and motor functions: Characterisation of D1 and D2 receptor interactions. European Journal of Pharmacology, in press.

Beckstead, R.M. (1976) Convergent thalamic and mesencephalic projections to the anterior medial cortex in the rat. Journal of Comparative Neurology 166, 403-416.

Beckstead, R.M., Domesick, V. & Nauta, W.J.H. (1979) Efferent connections of the substantia nigra and ventral tegmental area in the rat. Brain Research 175, 191-217.

Beninger, R.J. & Phillips, A.G. (1981) The effects of pimozide during pairing on the transfer from classical conditioning to an operant discrimination. Pharmacology Biochemistry & Behavior 14, 101-105.

Beninger, R.J., Hoffman, D.C. & Mazurski, E.J. (1989) Receptor subtype-specific dopaminergic agents and conditioned behaviour. Neuroscience and Biobehavioural Reviews 13, 113-122.

Beninger, R.J., Cheng, M., Hahn, B.L., Hoffman, D.C., Mazurski, E.J., Morency, M.A. & Ramm, P. (1987) Effects of pimozide, SCH-23390, and metoclopramide on food-rewarded operant responding of rats. Psychopharmacology 92, 343-349.

Beninger, R.J. (1990) Receptor subtype-specific dopamine agonists and antagonists and conditioned behaviour. In: P. Willner, J. Scheel-Kruger (Eds.) The Mesolimbic Dopamine System: From Motivation to Action. Wiley, Chichester. In press.

Berger, B., Thierry, A.M., Tassin, J.P. & Myre, M.A. (1976) Dopaminergic innervation of the rat prefrontal cortex: A fluorescence histochemical study. Brain Research 106, 133-145.

Bergman, J., Kamien, J.B. & Spealman, R.D. (1990) Antagonism of cocaine self-administration by selective dopamine D_1 and D_2 antagonists. Behavioural Pharmacology 1, 355-363.

Berridge, K.C., Vernier, I.L. & Robinson, T.E. (1989) Taste reactivity analysis of 6-hydroxydopamine-induced aphagia: Implications for arousal and anhedonia hypotheses of dopamine function. Behavioral Neuroscience 103, 36-45.

Biber, M.P., Kneisley, L.W. & LaVail, J.H. (1978) Cortical neurons projecting to the cervical and lumbar enlargements of the spinal cord in young and adult rhesus monkeys. Experimental Neurology 59, 492-508.

Bindra, D.A. (1974) A motivational view of learning, performance, and behavior modification. Psychological Review 81, 199-213.

Bjorklund, A. & Lindvall, O. (1986) Catecholaminergic brainstem regulatory systems. In V.B. Mountcastle, F.E. Bloom & S.R. Geiger (Eds.) Handbook of physiology: The nervous system, Volume 4. Intrinsic systems of the brain. American Physiological Society, Bethesda.

Blackburn, J.R., Phillips, A.G., Jakubovic, A. & Fibiger, H.C. (1986) Increased dopamine metabolism in the nucleus accumbens and striatum following consumption of a nutitive meal but not a palatable non-nutritive saccharin solution. Pharmacology Biochemistry & Behavior 25, 1095-1100.

Blackburn, J.R., Phillips, A.G. & Fibiger, H.C. (1987) Dopamine and preparatory behaviour: I. Effects of pimozide. Behavioural Neuroscience 101, 352-360.

Blackburn, J.R., Phillips, A.G., Jakubovic, A. & Fibiger, H.C. (1989) Dopamine and preparatory behaviour: II. A neurochemical analysis. Behavioural Neuroscience 103, 15-23.

Blundell, J.E. & Latham, C.J. (1980) Behavioural pharmacology of feeding. In: T. Silverstone (Ed.) Drugs and Appetite. Academic Press, London.

Bogerts, B., Hantsch, J. & Herzer, M. (1983) A morphometric study of the dopamine-containing cell groups in the mesencephalon of normals, Parkinson patients, and schizophrenics. Biological Psychiatry 18, 951-969.

Bowers, W., Hamilton, M., Zacharko, R.M. & Anisman, H. (1985) Differential effects of pimozide on response-rate and choice accuracy in a self-stimulation paradigm in mice. Pharmacology Biochemistry & Bevhaior 22, 521-526.

Bozarth, M.A. & Wise, R.A. (1981) Intracranial self-administration of morphine into the ventral tegmental area in rats. Life Sciences 28, 551-555.

Bradshaw, C.M., Szabadi, E. & Bevan, P. (1978) Relationships between response rate and reinforcement frequency in variable-interval schedules: The effect of the concentration of sucrose reinforcement. Journal of the Experimental Analysis of Behavior 19, 447-452.

Bradshaw, C.M., Szabadi, E. & Ruddle, H.V. (1983a) Herrnstein's equation: Effect of response force requirement on performance in variable-interval schedules. Behaviour Analyis Letters 3, 93-100.

Bradshaw, C.M., Szabadi, E., Ruddle, H.V. & Pears, E. (1983b) Herrnstein's equation: Effect of deprivation level on performance in variable-interval schedules. Behaviour Analysis Letters 3, 267-273.

Bradshaw, C.M. & Szabadi, E. (1989) Central neurotransmitter systems and the control of operant behaviour by 'natural' positive reinforcers. In: J.M. Liebman, S.J. Cooper (Eds.) The Neuropharmacological Basis of Reward. Oxford University Press, Oxford.

Branch, M.N. (1983) Rate dependency, behavioural mechanisms, and behavioral pharmacology. Journal of the Experimental Analysis of Behavior 42, 511-522.

Breese, G.R., and Mueller, R.A. (1985) SCH-23390 antagonism of a D2 dopamine agonist depends upon catecholaminergic neurons. European Journal of Pharmacology 113, 109.

Brett, L.P. & Levine, S. (1979) Schedule-induced polydipsia suppresses pituitary-adrenal activity in rat. Journal of Comparative and Physiological Psychology 93, 946-956.

Brown, J.H. and Makman, M.H. (1972) Stimulation by dopamine of adenylate cyclase in retinal homogenates and of adenosine 3', 5'-cyclic monophosphate formation in intact retina. Proceedings of the National Academy of Sciences of the USA 69, 539.

Brown, R.G., Marsden, C.D., Quinn, N. & Wyke, M.A. (1984) Alterations in cognitive performance and affect-arousal state during fluctuations in motor function in Parkinson's disease. Journal of Neurology, Neurosurgery, and Psychiatry 47, 454-465.

Bunney, B.S., Sesack, S.R. & Silva, N.L. (1987) Midbrain dopaminergic systems: Neurophysiology and pharmacology. In H.Y. Meltzer (Ed.) Psychopharmacology: The Third Generation of Progress. New York: Raven Press, 113-126.

Burns, R.S., Chiueh, C.C., Markey, S.P., Ebert, M.H., Jacobowitz, D.M. & Kopin, I.J. (1983) A primate model of parkinsonsism: Selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Proceedings of the National Academy of Sciences of the USA 80, 4546-4550.

Cador, M., Robbins, T.W., Everitt, B.J., Simon, H., Le Moal, M. & Stinus, L. (1990) Limbic-striatal interactions in reward-related processes: Modulation by the dopaminergic system. In: P. Willner, J. Scheel-Kruger (Eds.), The Mesolimbic Dopamine System: From Motivation to Action. Wiley, Chichester. In press.

Capaldi, E.D., Bradford, J.P., Sheffer, J.D. & Pulley, R.J. (1989) The rat's sweet tooth. Learning and motivation 20, 178-190.

Carey, R.J. (1983) Differential effects of limbic versus striatal dopamine loss on motoric function. Behavioural Brain Research 7, 283-296.

Carlsson, A., Falck., B. & Hillarp, N.-A. (1962) Cellular localization of of brain monoamines. Acta Pysiol. Scand. Suppl. 196, 1-28.

Carlsson, A. (1978) Mechanism of action of neuroleptic drugs. In M.A. Lipton, A.D. DiMascio, K.F. Killam (Eds.) Psychopharmacology: A Generation of Progress. New York: Raven Press, 1057-1070.

Carpenter, M.B., Nakano, K. & Kim, R. (1976) Nigrothalamic projections in the monkey demonstrated by autoradiographic technics. Journal of Comparative Neurology 165, 401-416.

Carper, J.W. & Polliard, F. (1953) A comparison of the intake of glucose and saccharin solutions under conditions of caloric need. American Journal of Psychology 66, 479-482.

Carr, G.D. & White, N.M. (1983) Conditioned place preference from intra-accumbens but not intra-caudate amphetamine injections. Life Sciences 33, 2551-2557.

Carr, G.D. & White, N.M. (1986) Anatomical dissociation of amphetamine's rewarding and aversive effects: An intracranial microinjection study. Psychopharmacology 89, 340-346.

Carr, G.D. & White, N.M. (1986) Contribution of dopamine terminal areas to amphetamine-induced anorexia and adipsia. Pharmacology Biochemistry & Behavior 25, 17-22.

Carr, G.D. & White, N.M. (1987) Effects of systemic and intracranial amphetamine injections on behavior in the open field: A detailed analysis. Pharmacology Biochemistry & Behavior 27, 113-122.

Carr, G.D., Phillips, A.G. & Fibiger, H.C. (1988) Independence of amphetamine reward from locomotor stimulation demonstrated by conditioned place preference. Psychopharmacology 94, 221-226.

Carr, G.D., Fibiger, H.C. & Phillips, A.G. (1989) Conditioned place preference as a measure of drug reward. In: J.M. Liebman, S.J. Cooper (Eds.), The Neuropharmacological Basis of Reward. Oxford University Press, Oxford.

Carter, D.A. & Fibiger, H.C. (1977) Ascending projections of presumed dopamine-containing neurons in the ventral tegmentum of the rat as demonstrated by horseradish peroxidase. Neuroscience 2, 569-576.

Catania, A.C. & Reynolds, G.S. (1968) A quantitative analysis of the responding maintained by interval schedules of reinforcement. Journal of the Experimental Analysis of Behavior 11, 327-383.

Cherkes, V.A., Lukhanina, E.P. & Litvinova, A.N. (1984) Activity of neurons of the caudate nucleus during goal-directed and imposed limb movements in waking cats. Zhurnal Vysshei Nervnoi Deyatel'nosti 34, 265-272.

Christensen, A.V., Arnt, J., Hyttel, J., Larsen, J.-J. & Svendsen, O. (1984a) Pharmacological effects of a specific dopamine D1 antagonist SCH-23390 in comparison with neuroleptics. Life Sciences 34, 1529.

Christensen, A.V., Arnt, J. & Svendsen, O. (1984b) Behavioural correlates to the dopamine D1 and D2 antagonists. Polish Journal of Pharmacology and Pharmacy 36, 249.

Clark, D. & White, F.J. (1987) Review: D1 dopamine receptor - The search for a function: A critical evaluation of D1/D2 dopamine receptor classification and its functional implications. Synapse 1, 347-388.

Clement-Cormier, Y.C., Kebabian, J.W., Petzold, G.L. & Greengard, P. (1974) Dopamine-sensitive adenylate cyclase in mammalian brain: A possible site of action of antipsychotic drugs. Proceedings of the National Academy of Science of the USA 71, 1113.

Clifton, P.G., Barnfield, A.M.C. & Philcox, L. (1989) A behavioural profile of fluoxetine-induced anorexia. Psychopharmacology 97, 89-95.

Coe, C.L., Stanton, M.E. & Seymour, L. (1983) Adrenal responses to reinforcement and extinction: Role of expectancy versus instrumental responding. Behavioural Neuroscience 97, 654-657.

Cools, A.R. (1980) Role of the neostriatal dopaminergic activity in sequencing and selecting behavioural strategies: Facilitation of processes involved in selecting the best strategy in a stressful situation. Behavioural Brain Research 1, 361-378.

Cools, A.R., Van den Berken, J.H.L., Horstink, M.W.I., Van Spaendonck, K.P.M. & Berger, H.J.C. (1984) Cognitive and motor shifting aptitude disorders in Parkinson's disease. Journal of Neurology and Neurosurgical Psychiatry 47, 443-453.

Cools, A.R., Brachten, R., Heeren, D., Willemen, A. & Ellenbroek, B. (1990) Search after neurobiological profile of individual-specific features of Wistar rats. Brain Research Bulletin 24, 49-69.

Cormier, S.M. (1981) A match-mismatch theory of limbic system function. Physiological Psychology 9, 3-36.

Crutcher, M.D. & DeLong, M.R. (1984a) Single cell studies of primate putamen. I. Functional organization. Experimental Brain Research 53, 233-243.

Crutcher, M.D. & DeLong, M.R. (1984b) Single cell studies of the primate putamen. II. Relations to direction of movements and pattern of muscular activity. Experimental Brain Research 53, 244-258.

Dahlstrom, A. & Fuxe, K. (1964) Evidence for the existence of monoamine containing neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies of brain stem neurons. Acta.Physiol.Scand. 62 (Suppl. 232), 1-55.

Daly, H.B. & Daly, J.T. (1982) A mathematical model of reward and aversive nonreward: Its application in over 30 appetitive learning situations. Journal of Experimental Psychology: General 111, 441-480.

Davison, M & McCarthy, D. (1988) The matching law: A research review. Lawrence Erlbaum Associates, New Jersey.

DeLong, M.R. & Georgopoulos, A.P. (1981) Motor functions of the basal ganglia. In: J.M. Brookhart, V.B. Mountcastle, & V.B. Brooks (Eds.) Handbook of Physiology, Section 1, The Nervous System, Volume 2, Motor Control, Part 2, pp.1017-1061. American Physiological Society, Bethesda.

DeLong, M.R. (1990) Primate models of movement disorders of basal ganglia origin. Trends in Neurosciences 13, 281-285.

de Paulis, T., Kumar, Y., Johansson, L., Ramsby, S., Hall, H., Sallemark, M., Angeby-Moller, K., Ogren, S.O. (1986) Potential neuroleptic agents. 4. Chemistry, behavioural pharmacology and blocking of ^{3}H-spiperone binding of 3,5-disubstituted N-[(1-ethyl-2- pyrrolidinyl)methyl] -6- methoxy-salicylamide. Journal of Medical Chemistry 29, 61-69.

de Villiers, P.A. & Herrnstein, R.J. (1976) Towards a law of response strength. Psychological Bulletin 83, 1131-1153.

de Villiers, P.A. (1977) Choice in concurrent and a quantitative formulation of the law of effect. In Honig, W.K. & Staddon, J.E.R. (Eds.), Handbook of operant behaviour. Prentice-Hall, New Jersey, USA.

Devenport, L.D., Devenport, J.A. & Holloway, F.A. (1981) Reward-induced stereotypy: Modulation by the hippocampus. Science 212, 1288-1289.

DeVito, J.L.+Anderson, M.E. (1982) An autoradiographic study of efferent connections of the globus pallidus in Macaca mulatta. Experimental Brain Research 46, 107-117.

de Wit, H. & Wise, R.A. (1977) Blockade of cocaine reinforcement in rats with the dopamine blocker pimozide, but not with the noradrenergic blockers phentolamine and phenoxybenzamine. Canadian Journal of Psychology 31, 195-203.

Domesick, V.B., Beckstead, R.M. & Nauta, W.J.H. (1976) Some ascending and descending projections of the substantia nigra and ventral tegmental area in the rat. Neuroscience 61, Abstract II.

Domjan, M. & Gillan, D. (1976) Role of novelty in the aversion for increasingly concentrated saccharin solutions. Physiology & Behavior 16, 537-542.

Edmonds, D.E., and Gallistel, C.R. (1974) Parametric analysis of brain stimulation reward in the rat: Effect of performance variables on the reward summation function. Journal of Comparative and Physiological Psychology 87, 876-883.

Edmonds, D.E. and Gallistel, C.R. (1977) Reward versus performance in self-stimulation: Electrode-specific effects of a-methyl-p-tyrosine on reward in the rat. Journal of Comparative and Physiological Psychology 91, 962-974.

Epstein, A.N. (1982) Instinct and motivation as explanations for complex behaviour. In: D. Pfaff (Ed.) The Physiological Mechanisms of Motivation. Springer-Verlag, New York.

Ettenberg, A., Cinsavich, S.A. & White, N. (1979) Performance effects with repeated-response measures during pimozide-produced dopamine receptor blockade. Pharmacology Biochemistry & Behavior 11, 557-561.

Ettenberg, A. & Camp, C.H. (1986a) Haloperidol induces a partial reinforcement extinction effect in rats: Implications for a dopamine involvement in food reward. Pharmacology Biochemistry & Behavior 25, 818-822.

Ettenberg, A. & Camp, C.H. (1986b) A partial reinforcement extinction effect in water-reinforced rats intermittently treated with haloperidol treatment. Pharmacology Biochemistry & Behavior 25, 1231-1235.

Ettenberg, A., Koob, G.G. & Bloom, F.E. (1981) Response artifact in the measurement of neuroleptic-induced anhedonia. Science 209, 357-359.

Ettenberg, A. (1989) Dopamine, neuroleptics and rewarded behaviour. Neuroscience and Biobehavioural Reviews 13, 105-111.

Evenden, J.L. & Robbins, T.W. (1983) Dissociable effects of d-amphetamine, chlordiazepoxide and alpha-flupenthixol on choice and rate measures of reinforcement in the rat. Psychopharmacology 79, 180-186.

Everitt, B.J., Cador, M. & Robbins, T.W. (1989) Interactions between the amygdala and ventral striatum in stimulus-reward associations: Studies using a second order schedule of sexual reinforcement. Neuroscience 30, 63-75.

Fallon, J.H. & Moore, R.Y. (1978) Catecholamine innervations of the basal forebrain. IV. Topography of the dopamine projection to the basal forebrain and neostriatum. Journal of Comparative Neurology 180, 545-580.

Fallon, J.H., Koziell, D.A. & Moore, R.Y. (1978) Catecholamine innervation of the basal forebrain. II. Amygdala, suprarhinal cortex and entorhinal cortex. Journal of Comparative Neurology 180, 509-532.

Fallon, J.H. (1981) Collateralization of monoamine neurons: Mesotelencephalic dopamine projections to caudate, septum, and frontal cortex. The Journal of Neuroscience 1, 1361-1368.

Feldon, J., Katz, Y. & Weiner, I. (1988) The effects of haloperidol on the partial reinforcement extinction effect (PREE): Implications for neuroleptic drug action on reinforcement and nonreinforcement. Psychopharmacology 95, 528-533.

Ferster, C.B. & Skinner, B.F. (1957) Schedules of reinforcement. N.Y.: Appleton-Century-Crofts.

Fibiger, H.C., Carter, D.A. & Phillips, A.G. (1976) Decreased intracranial self-stimulation after neuroleptics or 6-hydroxydopamine: Evidence for mediation by motor deficits rather than reduced reward. Psychopharmacology 47, 21-27.

Fibiger, H.C. (1984) The neurobiological substrates of depression in Parkinson's disease: A hypothesis. Canadian Journal of Neurological Sciences 11 (Suppl.1), 105-107.

Fibiger, H.C. & Phillips, A.G. (1986) Reward, motivation, cognition: Psychobiology of mesotelencephalic dopamine systems. In: V.B. Mountcastle, F.E. Bloom & S.R. Geiger (Eds.) Handbook of physiology: The nervous system, Volume 4. Intrinsic systems of the brain. American Physiological Society, Bethesda.

Fibiger, H.C., Jakubovic, A. & Phillips, A.G. (1987) The role of dopamine in intracranial self-stimulation of the ventral tegmental area. Journal of Neuroscience 7, 3888-3896.

Filion, M., Boucher, R. & Bedard, P. (1985) Globus pallidus unit activity in the monkey during the induction of Parkinsonism by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Society for Neuroscience 11(2), (Abstr.) pp. 1160.

Flaherty, C.F., Wrightson, J., Deptula, D. & Duston, C. (1979) Chlordiazepoxide does not influence simultaneous gustatory contrast. Bulletin of the Psychonomic Society 14, 216-218.

Flaherty, C.F. (1982) Incentive contrast: A review of behavioural changes following shifts in reward. Animal Learning and Behavior 10, 409-440.

Florio, V., Bianchi, L. & Longo, V.G. (1975) A study of the central effects of sympathomimetic drugs: EEG and behavioural investigations on clonidine and naphazoline. Neuropharmacology 14, 707-714.

Fouriezos, G. & Wise, R.A. (1976) Pimozide-induced extinction of intracranial self-stimulation: Response-patterns rule out motor performance deficits. Brain Research 103, 377-380.

Fouriezos, G., Hansson, P. & Wise, R.A. (1978) Neuroleptic-induced attenuation of brain-stimulation reward. Journal of Comparative and Physiological Psychology 92, 659-669.

Fouriezos, G. & Nawiesniak, E. (1982) Comparison of two methods of estimating thresholds of intracranial self-stimulation. Neuroscience Abstracts 8, 624.

Fowler, S.C. & Kirkpatrick, M.A. (1989) Behavior-decrementing effects of low doses of haloperidol result from disruptions of response force and duration. Behavioural Pharmacology 1, 123-132.

Fowler, S.C. (1990) Neuroleptics produce within-session decrements: Facts and theories. Drug Development Research, 20, 101-116.

Franklin, K.B.J. (1978) Catecholamines and self-stimulation: Reward and performance deficits dissociated. Pharmacology Biochemistry & Behavior 9, 813-820.

Franklin, K.B.J. & McCoy, S.N. (1979) Pimozide-induced extinction in rats: Stimulus control of responding rules out a motor deficit. Pharmacology Biochemistry & Behavior 11, 71-75.

Freedman, S.B. & Woodruff, G.N. (1986) Brain dopamine receptors. In: W. Winlow, R. Markstein (Eds.), The Neurobiology of Dopamine Systems. Manchester University Press, Manchester.

Fuxe, K. (1965) Evidence for the existence of monoamine nerve terminals in the central nervous system. IV. Distribution of dopamine nerve terminals in the central nervous system. Acta. Physiol. Scand. 64 (Suppl.247), 39-85.

Gallistel, C.R., Boytim, M., Gomita, Y. & Klebanoff, L. (1982) Does pimozide block the reinforcing effect of brain stimulation? Pharmacology Biochemistry & Behavior 17, 769-781.

Gallistel, C.R. (1986) The role of dopaminergic projections in MFB self-stimulation. Behavioural Brain Research 22, 97-105.

Gallistel, C.R. & Freyd, G. (1987) Quantitative determination of the effects of catecholaminergic agonists and antagonists on the rewarding efficacy of brain stimulation. Pharmacology Biochemistry & Behavior 26, 731-741.

Geary, N. & Smith, G.P. (1985) Pimozide decreases the positive reinforcing effect of sham fed sucrose in the rat. Pharmacology Biochemistry & Behavior 22, 787-790.

Gelissen, M. & Cools, A. (1988) Effect of intracaudate haloperidol and apomorphine on switching motor patterns upon current behaviour of cats. Behavioural Brain Research 29, 17-26.

Gerber, G.J., Singh, J. & Wise, R.A. (1981) Pimozide attenuates lever pressing for water in rats. Pharmacology Biochemistry & Behavior 14, 201-205.

Gessa, G.L. & Mereu, G. (1984) Electrophysiological and functional effects of selective blockade of D1 and D2 receptors. Clinical Neuropharmacology 7, Suppl.1, S46.

Gilbert, D.B., Demski, J.E., Stein, L. & Beluzzi, J.D. (1986) Dopamine and reward: Conditioned place preference induced by dopamine D2 receptor agonist. Society for Neuroscience Abstracts 12, 938.

Glick, S.D., Cox, R.S. & Crane, A.M. (1975) Changes in morphine self-administration and morphine dependence after lesions of the caudate nucleus in rats. Psychopharmacologia 41, 219-224.

Goeders, N.E., Lane, J.D. & Smith, J.E. (1984) Intracranial self-administration of methionine enkaphalin into the nucleus accumbens. Pharmacology Biochemistry & Behavior 20, 451-455.

Gramling, S.E., Fowler, S.C. & Collins, K.R. (1984) Some effects of pimozide on nondeprived rats licking sucrose solutions in an anhedonia paradigm. Pharmacology Biochemistry & Behavior 21, 617-624.

Gratton, A., Hoffer, B.J. & Gerhadt, G.A. (1988) Effects of electrical stimulation of brain reward sites on release of dopamine in rat: An in vivo electrochemical study. Brain Research Bulletin 21, 319-324.

Gray, T. & Wise, R.A. (1980) Effects of pimozide on lever-pressing behaviour maintained on an intermittent reinforcement schedule. Pharmacology Biochemistry & Behavior 12, 931-935.

Gray, T. (1982) The Neuropsychology of Anxiety: An Enquiry into the Functions of the Septo-Hippocampal System. Clarendon Press, Oxford.

Gray, T. & Rawlins, J.N.P. (1986) Comparator and buffer memory: An attempt to integrate two models of hippocampal function. In: R.L. Isaacson, K.H. Pribram (Eds.) The Hippocampus. Plenum Press, New York.

Graybiel, A.M. & Ragsdale Jr., C.W. (1983) Biochemical anatomy of the striatum. In: P.C. Emson (Ed.) Chemical Neuroanatomy. Raven Press, New York.

Gunne, L.M., Anggard, E. & Jonsson, L.E. (1972) Clinical trials with amphetamine-blocking drugs. Psychiatria, Neurologia, Neurochirurgia 75, 225-226.

Guttman, N. (1953) Operant conditioning, extinction, and periodic reinforcement in relation to concentration of sucrose used as reinforcing agent. Journal of Experimental Psychology 46, 213-224.

Haertzen, C.A., Kocher, T.R. & Miyasato, K. (1983) Reinforcements from the first drug experience can predict later drug habits and/or addiction: Results with coffee, cigarettes, alcohol, barbiturates, minor and major tranquilizers, stimulants, marijuana, hallucinogens, heroin, opiates and cocaine. Drug and Alcohol Dependency 11, 147-165.

Hamilton, A.L., Stellar, J.R. & Hart, E.B. (1985) Reward, performance, and the response strength method in self-stimulating rats: Validation and neuroleptics. Physiology and Behavior 35, 897-904.

Hammer, L.R. (1968) Relationship of reinforcement value to consummatory behaviour. Journal of Comparative and Physiological Psychology 66, 667-672.

Hawkins, T.D. & Pliskoff, S.S. (1964) Brain-stimulation intensity, rate of self-stimulation, and reinforcement strength: An analysis through chaining. Journal of the Experimental Analysis of Behavior 7, 285-288.

Heimer, L. & Wilson, R.D. (1975) The subcortical projections of the allocortex. Similarities in the neural associations of the hippocampus, the piriform cortex, and the neocortex. In M. Santini (Ed.) Golgi Centennial Symposium: Perspectives in Neurology, pp.177-193. Raven Press, New York.

Heimer, L., Switzer, R.D. & Van Hoesen, G.W. (1982) Ventral striatum and ventral pallidum: Components of the motor system? Trends in Neurosciences 5, 83-87.

Hemphill, M., Holm, G., Crutcher, M., DeLong, M.R. & Hedreen, J. (1981) Afferent connections of the nucleus accumbens in the monkey. In R. Chronister, J. DeFrance (Eds.) Neurobiology of the Nucleus Accumbens, pp.75-81. Haer Institute Press, Maine, US.

Herkenham, M. (1977) The connections of the nucleus reuniens thalami: evidence for a direct thalamo-hippocampal pathway in the rat. Journal of Comparative Neurology 177, 589-610.

Hernandez, L. & Hoebel, B.G. (1988a) Feeding and hypothalamic stimulation increase dopamine turnover in the accumbens. Physiology & Behavior 44, 599-606.

Hernandez, L. & Hoebel, B.G. (1988b) Food reward and cocaine increase extracellular dopamine in the nucleus accumbens as measured by microdialysis. Life Sciences 42, 1705-1712.

Herrnstein, R.J. (1961) Relative and absolute strength of response as a function of frequency of reinforcement. Journal of the Experimental Analysis of Behavior 4, 267-272.

Herrnstein, R.J. (1970) On the law of effect. Journal of the Experimental Analysis of Behavior 13, 243-266.

Herrnstein, R.J. (1981) Punishment and avoidance - Chairman's comments. In C.M. Bradshaw, E. Szabadi and C.F. Lowe (Eds), Quantification of steady-state operant behaviour (pp.165-173). Amsterdam: Elsevier/North-Holland.

Heyman, G.M. (1983) A parametric evaluation of the hedonic and motoric effects of drugs: Pimozide and amphetamine. Journal of the Experimental Analysis of Behavior 40, 113-122.

Heyman, G.M. & Seiden, L.S. (1985) A parametric description of amphetamine's effects on response rate: Changes in reinforcement efficacy and response topography. Psychopharmacology 85, 346-353.

Heyman, G.M., Kinzie, D.L. & Seiden, L.S. (1986) Chlorpromazine and pimozide alter reinforcement efficacy and motor performance. Psychopharmacology 88, 346-353.

Heyman, G.M. & Monaghan, M. (1987) Effects of changes in response requirement and deprivation on the parameters of the matching law equation: New data and review. Journal of Experimental Psychology 13, 384-394.

Hillegaart, V., Ahlenius, S., Magnusson, O. & Fowler, C.J. (1987) Repeated testing of rats markedly enhances the duration of effects induced by haloperidol on treadmill locomotion, catalepsy, and a conditioned avoidance response. Pharmacology Biochemistry & Behavior 27, 159-164.

Hodos, W. & Valenstein, E.S. (1962) An evaluation of response rate as a measure of rewarding intracranial stimulation. Journal of Comparative and Physiological Psychology 53, 502-508.

Hokfelt, T., Skirboll, L., Rehfeld, J.F., Goldstein, M., Markey, K. & Dann, O. (1980) A Subpopulation of mesencephalic dopamine neurons projecting to limbic areas contains a cholecystokinin-like peptide: Evidence from immunohistochemistry combined with retrograde tracking. Neuroscience 5, 2093-2124.

Hong, J.S., Yoshikawa, K., Kanamatsu, T. & Sabol, S.L. (1985) Modulation of striatal enkephalinergic neurons by antipsychotic drugs. Federation Proceedings 44(9), 2535-2539.

Horn, S. (1974) Some psychological factors in Parkinsonism. Journal of Neurology, Neurosurgery, and Psychiatry 37, 27-31.

Hornykiewicz, O. (1966) Dopamine (3-hydroxytyramine) and brain function. Pharmacological Review 18, 925-964.

Horvitz, J.C. & Ettenberg, A. (1988) Haloperidol blocks the response-reinstating effects of food reward: A methodology for separating neuroleptic effects on reinforcement and motor processes. Pharmacology Biochemistry & Behavior 31, 861-865.

Hsaio, S. & Tuntland, P. (1971) Short-term satiety signals generated by saccharin and glucose solutions. Physiology & Behavior 7, 287-289.

Huang, M., Messing, R.B. & Sparber, S.B. (1987) Learning enhancement and behaviuoral arousal induced by yohimbine. Life Sciences 41, 1083-1088.

Iglauer, C. & Woods, J.H. (1974) Concurrent performance: Reinforcement by different doses of intravenous cocaine in rhesus monkeys. Journal of the Experimental Analysis of Behavior 22, 179-196.

Ilinsky, I.A., Jouandet, M.L., Goldman-Rakic, P.S. (1985) Organization of the nigrothalamocortical system in the rhesus monkey. Journal of Comparative Neurology 236, 315-330.

Iorio, L.C., Barnett, A., Leitz, F.H., Houser, V.P. & Kordula, C.A. (1983) SCH-23390, a potential benzazepine antipsychotic with unique interactions on dopaminergic systems. Journal of Pharmacology and Experimental Therapeutics 226, 462.

Iversen, S.D. (1977) Brain dopamine systems and behaviour. In: L.L. Iversen, S.D. Iversen, S.H. Snyder (Eds.) Handbook of Psychopharmacology, Vol.8, pp.333-384. Plenum Press, New York.

Iversen, L.L., Rogawski, M.A. & Miller, R.J. (1976) Comparison of the effects of neuroleptic drugs on pre- and postsynaptic dopaminergic mechanisms in the rat striatum. Molecular Pharmacology 12, 251.

Iversen, S.D. & Koob, G.F. (1977) Behavioural implications of dopaminergic neurons in the mesolimbic system. Advances in Biochemical Psychopharmacology 17, 209-214.

Janssen, P.A.J., Niegemeers, C.J.E. & Schellekens, K.H.L. (1965) Is it possible to predict the clinical effects of neuroleptic drugs (major tranquilisers) from animal data? Arzneimittel-Forschung 15, 104-117.

Jasper, R., Schwarz, M., Sontag, K.H. & Cools, A.R. (1984) Caudate nucleus and programming behaviour in cats: Role of dopamine in switching motor patterns. Behavioural Brain Research 14, 17-28.

Javoy-Agid, F. & Agid, Y. (1980) Is the mesocortical dopaminergic system involved in Parkinson's Disease. Neurology 30, 1326-1330.

Jenner, P. & Marsden, C.D. (1981) Substituted benzamide drugs as selective neuroleptic agents. Neuropharmacology 20, 1285-1293.

Johanson, C.E. & Schuster, C.R. (1975) A choice procedure for drug reinforcers: Cocaine and methylphenidate in the rhesus monkey. Journal of Pharmacology and Experimental Therapeutics 193, 675-688.

Johnels, B. (1982) Locomotor hypokinesia in the reserpine-treated rat: Drug effects from the corpus striatum and nucleus accumbens. Pharmacology Biochemistry & Behavior 17, 283-289.

Johnson, R.P., Sar, M. & Stumpf, W.E. (1980) A topographic localization of enkephalin on the dopamine neurons of the rat substantia nigra and ventral tegmental area demonstrated by combined histofluoresence-immunocytochemistry. Brain Research 194, 566-571.

Jones, E.G., Coulter, J.D., Burton, H. & Porter, R. (1977) Cells of origin and terminal distribution of corticostriatal fibers arising in the sensory-motor cortex of monkeys. Journal of Comparative Neurology 173, 53-80.

Jones, D.L. & Mogenson, G.J. (1980a) Nucleus accumbens to globus pallidus GABA projection: Electrophysiological and iontophoretic investigations. Brain Research 188, 93-105.

Jones, D.L. & Mogenson, G.J. (1980b) Nucleus accumbens to globus pallidus GABA projection subserving ambulatory activity. American Journal of Psychology 238, R63-69.

Jones, D.L., Mogenson, G.J. & Wu, M. (1981) Injections of dopaminergic, cholinergic, serotoninergic and GABAergic drugs into the nucleus accumbens: Effects on locomotor activity in the rat. Neuropharmacology 20, 29-37.

Jurgens, U. (1983) Afferent fibers to the cingular vocalization region in the squirrel monkey. Experimental Neurology 80, 395-409.

Justice, J.B., Pettit, H.O., Menacherry, S. Pan, H., Brock, J. & Ng, J. (1990) In vivo measurements of cocaine and dopamine in acute, chronic and self-administration conditions. Abstract 23, British Association for Psychopharmacology, Summer Meeting, Cambridge, UK.

Katz, J.L. (1989) Drugs as reinforcers: pharmacological and behavioural factors. In: J.M. Liebman, S.J. Cooper (Eds.) The Neuropharmacological Basis of Reward. Oxford University Press, New York.

Kebabian, J.W., Petzold, G.L. & Greengard, P. (1972) Dopamine-sensitive adenylate cyclase in caudate nucleus of rat and its similarity to the "dopamine receptor". Proceedings of the National Academy of Science of the USA 69, 2145.

Kebabian, J.W. & Calne, D.B. (1979) Multiple receptors for dopamine. Nature, 277, 93.

Kelleher, R.T. & Morse, W.H. (1964) Escape behaviour and punished behaviour. Federation Proceedings 23, 808-817.

Kelleher, R.T. & Morse, W.H. (1968) Determinants of the specificity of behavioural effects of drugs. Ergebnisse der Physiologie Biologischen Chemie und Experimentellen Pharmakologie 60, 1-56.

Keller, F.S. & Schoenfeld, W.N. (1950) Principles of Psychology. N.Y.: Appleton-Century-Crofts.

Kelley, A.E. & Domesick, V.B. (1982) The distribution of the projection from the hippocampal formation to the nucleus accumbens in the rat: An anterograde- and retrograde-horseradish peroxidase study. Neuroscience 7, 2321-2335.

Kelley, A.E., Domesick, V.B. & Nauta, W.J. (1982) The amygdalostriatal projection in the rat: An anatomical study by anterograde and retrograde tracing methods. Neuroscience 7, 615-630.

Kelly, P.H., Seviour, P.W. & Iversen, S.D. (1975) Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. Brain Research 94, 507-522.

Kemble, E.D. & Schwarzbaum, J.S. (1969) Reactivity to tast properties of solutions following amygdaloid lesions. Physiology & Behavior 4, 981-985.

Killeen, P.R. (1982) Incentive theory. In D.J. Bernstein (Ed), Nebraska Symposium on Motivation 1981, Vol. 29, (pp. 169-216). Lincoln, Nebr.: University of Nebraska.

Kim, R., Nakano, K., Jayaraman, A. & Carpenter, M.B. (1976) Projections of the globus pallidus and adjacent structures: An autoradiographic study in the monkey. Journal of Comparative Neurology 169, 263-290.

Kirkpatrick, M.A. & Fowler, S.C. (1989) Force-proportional reinforcement: Pimozide does not reduce rats' emission of higher forces for sweeter rewards. Pharmacology Biochemistry & Behavior 32, 499-504.

Kish, S.J., Shannak, K. & Hornykiewicz, O. (1988) Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. The New England Journal of Medicine 318, 876-880.

Klimek, V., Krieger, R., Ryan, C.N. & Scheel-Kruger, J. (1989) The role of dopamine and glutamate in the nucleus accumbens and striatum for external and internal cue directed behaviour in the Morris water maze. Behavioural Pharmacology 1 (Suppl.1), Abstract 110 (European Behavioural Pharmacology Society, Malta, 1989).

Knight, R.G., Godfrey, H.P.D. & Shelton, E.J. (1988) The psychological deficits associated with Parkinson's disease. Clinical Psychology Review 8, 391-410.

Kohler, C., Hall, H., Ogren, S.O. & Gawell, L. (1985) Specific in vitro and in vivo binding of tritiated raclopride: A potent substituted benzamide drug with high affinity for dopamine D-2 receptors in the rat brain. Pharmacology 34, 2251-2259.

Koob, G.F., Riley, S.J., Smith, S.C. & Robbins, T.W. (1978) Effects of6-hydroxydopamine lesions of the nucleus accumbens septi and olfactory tubercle on feeding, locomotor activity and amphetamine anorexia in the rat. Journal of Comparative and Physiological Psychology 92, 917-927.

Koob, G.F., Stinus, L. & LeMoal, M. (1981) Hyperactivity and hypoactivity produced by lesions of the mesolimbic dopamine system. Behavioural Brain Research 3, 341-359.

Koob, G.F., Simon, H., Herman, J.-P. & le Moal, M. (1984) Neuroleptic-like disruption of the conditioned avoidance response requires destruction of both the mesolimbic and nigrostriatal dopamine systems. Brain Research 303, 319-329.

Koob, G.F., Vaccarino, F.J., Amalric, M. & Bloom, F.E. (1987) Positive reinforcement properties of drugs: Search for neural substrates. In: J. Engel, L. Oreland (Eds.), Brain Reward Systems and Abuse. Raven Press, New York.

Koob, G.F. & Goeders, N.E. (1989) Neuroanatomical substrates of drug self-administration. In: J.M. Liebman, S.J. Cooper (Eds.) The Neurpharmacological Basis of Reward. Oxford University Press, Oxford.

Krayniak, P.F., Meibach, R.C. & Siegel, A. (1981) A projection from the entorhinal cortex to the nucleus accumbens in the rat. Brain Research 209, 427-431.

Kunzle, H. (1975) Bilateral projections from precentral motor cortex to the putamen and other parts of the basal ganglia. An autoradiographic study in Macaca fascicularis. Brain Research 88, 195-209.

Kunzle, H. (1977) Projections from the primary somatosensory cortex to basal ganglia and thalamus in the monkey. Experimental Brain Research 30, 481-492.

Kunzle, H. (1978) An autoradiographic analysis of the efferent connections from premotor and adjacent prefrontal regions (areas 6 and 9) in Macaca fascicularis. Brain and Behavioural Evolution 15, 185-234.

Kuo, J.S. & Carpenter, M.B. (1973) Organization of pallidothalamic projections in the rhesus monkey. Journal of Comparative Neurology 151, 201-236.

Lane, R.F. & Blaha, C.D. (1987) Chronic haloperidol decreases dopamine release in striatum and nucleus accumbens in vivo: Depolarisation block as a possible mechanism of action. Brain Research Bulletin 18, 135-138.

Langston, J.W., Irwin, I. & Langston, E.B. (1984) A comparison of the acute and chronic effects of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP)-induced Parkinsonism in humans and the squirrel monkey. Neurology 34 (Suppl.1), 268.

Leone, P. & Di Chiara, G. (1987) Blockade of D-1 receptors by SCH-23390 antagonizes morphine- and amphetamine-induced place preference conditioning. European Journal of Pharmacology 135, 251-254.

Lieberman, A.N. (1987) Update on Parkinson's disease. New York State Journal of Medicine 87, 147-153.

Liebman, J. (1983) Discriminating between reward and performance: A critical review of self-stimulation methodology. Neuroscience and Biobehavioural Reviews 7, 45-72.

Lindvall, O. & Stenevi, U. (1978) Dopamine and noradrenaline neurons projecting to the septal area in the rat. Cell Tissue Research 190, 383-407.

Lindvall, O. & Bjorklund, A. (1979) Dopaminergic innervation of the globus pallidus by collaterals from the nigrostriatal pathway. Brain Research 172, 169-173.

Lindvall, O. & Bjorklund, A. (1983) Dopamine- and norepinephrine-containing neuron systems: Their anatomy in the rat brain. In: P.C. Emson (Ed.) Chemical Neuroanatomy. Raven Press, New York.

Lindvall, O., Bjorklund, A., Moore, R.Y. & Stenevi, U. (1974) Mesencephalic dopamine neurons projecting to neocortex. Brain Research 81, 325-331.

Llewellyn, M.E., Iglauer, C. & Woods, J.H. (1976) Relative reinforcer magnitude under a nonindependent concurrent schedule of cocaine reinforcement in rhesus monkeys. Journal of the Experimental Analysis of Behavior 25, 81-91.

Louilot, A., Simon, H., Taghzouti, K. & LeMoal, M. (1985) Modulation of dopaminergic activity in the nucleus accumbens following facilitation or blockade of the dopaminergic transmission in the amygdala: A study by in vivo differential pulse voltammetry. Brain Research 346, 141-145.

Louilot, A., LeMoal, M. & Simon, H. (1986) Differential reactivity of dopaminergic neurons in the nucleus accumbens in repsonse to different behavioral situations: An in vivo voltammetric study in free moving rats. Brain Research 397, 395-400.

Lyness, W.H., Friedle, N.M. & Moore, K.E. (1979) Destruction of dopaminergic nerve terminals in nucleus accumbens: Effect on d-amphetamine self-administration. Pharmacology Biochemistry & Behavior 11, 553-556.

Lyons, H.I. & Freedman, N.L. (1981) Task dependent properties of brain stimulation reward. Behavioural Brain Research 4, 339-358.

Mackey, W.B. & van der Kooy, D. (1985) Neuroleptics block the positive reinforcing effects of amphetamine but not of morphine as measured by place conditioning. Pharmacology Biochemistry & Behavior 22, 101-105.

Mackintosh, N.J. (1974) The Psychology of Animal Learning. Academic Press, London.

MacLean, A.P. & White, K.G. (1983) Temporal constraint on choice: Sensitivity and bias in multiple schedules. Journal of the Experimental Analysis of Behavior 39, 405-426.

MacPherson, J.M., Marangoz, C., Miles, T. & Wiesendanger, M. (1982) Microstimulation of the supplementary motor area (SMA) in the awake monkey. Experimental Brain Research 45, 410-416.

Mailman, R.B., Rollema, H., Shulz, D.W., Dettaven, D.L. & Lewis, M.H. (1984a) Dopamine receptor multiplicity: when the D1 antagonist is a D2 antagonist. Federation Proceedings 43, 1095.

Mailman, R.B., Shulz, D.W., Lewis, M.H., Staples, L., Rollema, H. & Dettaven, D.L. (1984b) SCH-23390: A selective D1 dopamine antagonist with potent D2 behavioural actions. European Journal of Pharmacology 101, 159.

Marshall, J.F., Richardson, I.S. & Teitelbaum, P. (1974) Nigrostriatal bundle damage and the lateral hypothalamic syndrome. Journal of Comparative and Physiological Psychology 88, 808-830.

Marshall, J.F. (1976) Activation-induced restoration of sensorimotor function in rats with dopamine-depleting brain lesions. Journal of Comparative and Physiological Psychology 90, 536-546.

Marshall, J.F., Berrios, N. & Sawyer, S. (1980) Neostriatal dopamine and sensory inattention. Journal of Comparative and Physiological Psychology 94, 833-846.

Martin-Iverson, M.T., Szostak, C. & Fibiger, H.C. (1986) 6-Hydroxydopamine lesions of the medial prefrontal cortex fail to influence intravenous self-administration of cocaine. Psychopharmacology 88, 310-314.

Martin-Iverson, M.T., Wilkie, D. & Fibiger, H.C. (1987) Effects of haloperidol and d-amphetamine on perceived quantity of food and tones. Psychopharmacology 93, 374-381.

Mason, S.T., Beninger, R.J., Fibiger, H.C. & Phillips, A.G. (1980) Pimozide-induced suppression of responding: Evidence against a block of food reward. Pharmacology Biochemistry & Behavior 12, 917-923.

Mayeux, R., Stern, Y., Rosen, J. & Leventhal, J. (1981) Depression, intellectual impairment, and Parkinson's disease. Neurology 31, 645-650.

Mayeux, R., Stern, Y., Cote, L. & Williams, J.B.W. (1984) Altered serotonin metabolism in depressed patients with Parkinson's disease. Neurology 34, 642-646.

Mayeux, R., Stern, Y., Williams, J.B.W, Cote, L., Frantz, A. & Dyrenfurth, I. (1986) Clinical and biochemical features of depression in Parkinson's disease. American Journal of Psychiatry 143, 756-759.

McDowell, J.J. & Wood, H.M. (1984) Confirmation of linear system theory prediction: Changes in Herrnstein's K as a function of changes in reinforcer magnitude. Journal of the Experimental Analysis of Behavior 41, 183-192.

McDowell, J.J. & Wood, H.M. (1985) Confirmation of linear system theory prediction: Rate of change in Herrnstein's k as a function of response-force requirements. Journal of the Experimental Analysis of Behavior 43, 61-73.

McDowell, J.J. (1986) On the falsifiability of matching theory. Journal of the Experimental Analysis of Behavior 45, 63-74.

McKearney, J.W. (1974) Effects of d-amphetamine, morphine and chlorpromazine on responding under fixed-interval schedules of food presentation or electric shock presentation. Journal of Pharmacology and Experimental Therapeutics 190, 141-153.

McSweeney, F.K. (1975) Concurrent schedule responding as a function of body weight. Animal Learning and Behavior 3, 264-270.

McSweeney, F.K. (1978) Prediction of concurrent key-peck and treadle press responding from simple schedule performance. Animal Learning and Behavior 6, 444-450.

Memo, M., Carboni, E., Trabucchi, M., Carruba, M.O. & Spano, P.F. (1985) Dopamine inhibition of neurotensin-induced increase in Ca^{2+} influx into rat pituitary cells. Brain Research 347, 253-257.

Miliaressis, E., Malette, J. & Coulombe, D. (1986) The effects of pimozide on the reinforcing efficacy of central gray stimulation in the rat. Behavioural Brain Research 21, 95-100.

Miliaressis, E. & Malette, J. (1987) Summation and saturation properties in the rewarding effect of brain stimulation. Physiology & Behavior 41, 595-604.

Mithani, S., Martin-Iversen, M.T., Phillips, A.G. & Fibiger, H.C. (1986) The effects of haloperidol on amphetamine- and methylphenidate-induced conditioned place preferences and locomotor activity. Psychopharmacology 90, 247-252.

Mittleman, G., Deminiere, J.M., Le Moal, M., Simon, H. & Piazza, P.V. (1990) Experiential and individual factors in the acquisition of amphetamine self-administration. Abstract 106, British Association for Psychopharmacology, Cambridge.

Mogenson, G., Takigawa, M., Robertson, A. & Wu, M. (1979) Self-stimulation of the nucleus accumbens and ventral tegmental area of Tsai attenuated by microinjections of spiroperidol into the nucleus accumbens. Brain Research 171, 247-259.

Mogenson, G.J., Jones, D.L. & Yim, C.Y. (1980) From motivation to action: Functional interface between the limbic system and the motor system. Progress in Neurobiology 14, 69-97.

Mogenson, G.J. & Nielsen, M.A. (1983) Evidence that an accumbens to subpallidal GABAergic projection contributes to locomotor activity. Brain Research Bulletin 11, 309-314.

Mogenson, G.J., Swanson, L.W. & Wu, M. (1983) Neural projections from the nucleus accumbens to globus pallidus, substantia innominata, and lateral preoptic-lateral hypothalamic area: An anatomical and electrophysiological investigation in the rat. Journal of Neuroscience Research 3, 189-202.

Mogenson, G.J. (1987) Limbic-motor integration. Progress in Psychology and Physiological Psychology 12, 117-170.

Mogenson, G.J. & Yim, C.C. (1990) Neuromodulatory functions of the mesolimbic dopamine system: Electrophysiological and Behavioural Studies. In: P. Willner, J. Scheel-Kruger (Eds.), The Mesolimbic Dopamine System: From Motivation to Action. Wiley, Chichester, in press.

Molloy, A.G. & Waddington, J.L. (1984) Dopaminergic behaviour stereospecifically promoted by the D1 agonist R-SK&F 38393 and selectively blocked by the D1 antagonist SCH-23390. Psychopharmacology, 82, 409.

Montagu, K.A. (1957) Catechol compounds in rat tissues and in brains of different animals. Nature 180, 244.

Montgomery, A., Willner, P. & Muscat, R. (1988) Behavioural specificity of 8-OH-DPAT-induced feeding. Psychopharmacology 94, 110-114.

Montgomery, A., Muscat, R. & Willner, P. (1989) 8-OH-DPAT reliably increases the consumption of solid but not liquid diets. In: Bevan, P., Cools, A. & Archer, T. (Eds.) Behavioural Pharmacology of 5-HT. Lawrence Erlbaum: Hillsdale, N.J., pp. 291-294.

Mook, D.G. (1974) Saccharin preference in the rat: Some unpalatable findings. Psychological Review 81, 475-490.

Mook, D.G., Bryner, C.A., Rainey, L.D. & Wall, C.L. (1980) Release of feeding by the sweet taste in rats: Oropharyngeal satiety. Appetite 1, 299-315.

Mook, D.G., Kushner, B.D. & Kushner, L.R. (1981) Release of feeding by the sweet taste in rats: The specificity of oral satiety. Appetite 2, 267-280.

Moore, R. & Bloom, F. (1978) Central catecholamine neuron systems: Anatomy and physiology of the dopamine system. Annual Review of Neuroscience 1, 129-169.

Morgan, M.J. (1974) Resistance to satiation. Animal Behavior 22, 449-466.

Morley, M.J., Bradshaw, C.M. & Szabadi, E. (1984) The effects of pimozide on variable-interval performance: a test of the anhedonia hypothesis of the mode of action of neuroleptics. Psychopharmacology 84, 531-536.

Morley, M.J., Bradshaw, C.M. & Szabadi, E. (1985) The effect of d-amphetamine on operant behviour maintained under variable-interval schedules of reinforcement. Psychopharmacology 87, 207-211.

Morley, M.J., Bradshaw, C.M. & Szabadi, E. (1987) Effects of 6-hydroxydopamine -induced lesions of the dorsal noradrenergic bundle on steady-state operant behaviour. Psychopharmacology 93, 520-525.

Morley, M.J., Shah, L., Bradshaw, C.M. & Szabadi, E. (1988) DSP4 and Herrnstein's equation: Further evidence for a role of noradrenaline in the maintenance of operant behaviour by positive reinforcement. Psychopharmacology 96, 551-556.

Murray, E.A. & Coulter, J.D. (1981) Organisation of corticospinal neurons in the monkey. Journal of Comparative Neurology 195, 339-365.

Muscat , R. (1987) Behav ioural Microanalysis of Dopamine Autoreceptor Fuction. Unpublished PhD thesis, City of London Polytechnic, London.

Muscat, R. & Willner, P. (1989) Effects of selective dopamine receptor antagonists on sucrose consumption and preference. Psychopharmacology 99, 98-102.

Muscat, R., Phillips, G., Nunn, J., Wood, N., Montgomery, A. & Willner, P. (1989) D1/D2 receptor interactions in the control of feeding and post-prandial satiety. Behavioural Pharmacology 1 (Suppl.1), Abstract 32 (European Behavioural Pharmacology Society, Malta, 1990).

Nakahara, D., Ozaki, N., Miura, Y., Miura, H., et al. (1989) Increased dopamine and serotonin metabolism in rat nucleus accumbens produced by intracranial self-stimulation of medial forebrain bundle as measured by in vivo microdialysis. Brain Research 495, 178-181.

Nakajima, S. (1985) Suppression of operant responding produced by blockade of dopamine D1 receptors with SCH-23390. Society for Neuroscience Abstr. 11, 717.

Nakajima, S. & McKenzie, G.M. (1986) Reduction of the neuroleptic effect of brain stimulation by a blockade of dopamine D1 receptors with SCH-23390.

Nauta, W.J.H. (1961) Fibre degeneration following lesions of the amygdaloid complex in the monkey. Journal of Anatomy 95, 515-531.

Nauta, W.J.H. (1962) Neural associations of the amygdaloid complex in the monkey. Brain 85, 505-520.

Nauta, W.J.H., Smith, G.P., Faull, R.L.M. & Domesick, V.B. (1978) Efferent connections and nigral afferents of the nucleus accumbens septi in the rat. Neuroscience 3, 385-401.

Ng, J.M., Ton, C., Gerhardt, G.A., Friedemann, M., Etgen, A.M., Rose, G.M., Sharpless, N.S. & Gardner, E.L. (1988) The effects of delta-9-tetrahydrocannabinol on potassium-evoked release of dopamine in the rat caudate nucleus: An in vivo microdialysis study. Brain Research 451, 59-68.

Nishino, H., Taketoshi, O., Sasaki, K., Fukuda, M. & Muramoto, K.-I. (1984) Caudate unit activity during operant feeding behaviour in monkeys and modulation by cooling prefrontal cortex. Behavioural Brain Research 11, 21-33.

Oades, R.D. (1985) The role of noradrenaline in tuning and dopamine in switching between signals in the CNS. Neuroscience & Biobehavioral Reviews 9, 261-282.

Olds, J. & Milner, P. (1954) Positive reinforcement from electrical stimulation of septal area and other regions of the rat brain. Journal of Comparative & Physiological Psychology 47, 419-427.

Onteniente, B., Simon, H., Taghzouti, K., Geffard, M., Le Moal, M. & Calas, A. (1987) Dopamine-GABA interactions in the nucleus accumbens and lateral septum of the rat. Brain Research 421, 391-396.

Palmer, C., Schmidt, E.M. & McIntosh, J.S. (1981) Corticospinal and corticorubral projections from the supplementary motor area in the monkey. Brain Research, 209, 305-314.

Pan, H.S., Penney, J.B. & Young, A.B. (1985) Gamma-aminobutyric acid and benzodiazepine receptor changes induced by unilateral 6-hydroxydopamine lesions of the medial forebrain bundle. Journal of Neurochemistry 45, 1396-1404.

Paxinos, G. & Watson, C. (1986) The rat brain in stereotaxic coordinates. Academic Press, Australia.

Penney, J.B. & Young, A.B. (1981) GABA as the pallidothalamic neurotransmitter: Implications for basal ganglia function. Brain Research 207, 195-199.

Pettit, H.O., Ettenberg, A., Bloom, F.E. & Koob, G.F. (1984) Destruction of dopamine in the nucleus accumbens selectively attenuates cocaine but not heroin self-administration in rats. Psychopharmacology 84, 167-173.

Phillips, A.G., Carter, D.A. & Fibiger, H.C. (1976) Dopaminergic substrates of intracranial self-stimulation in the caudate-putamen. Brain Research 104, 221-232.

Phillips, A.G. & Fibiger, H.C. (1978) Long-term deficits in stimulation-induced behaviors and self-stimulation after 6-hydroxydopamine adminstration in rats. Behavioral Biology 16, 127-143.

Phillips, A.G. & Fibiger, H.C. (1979) Decreased resistance to extinction after haloperidol: Implications for the role of dopamine in reinforcement. Pharmacology Biochemistry & Behavior 10, 751-761.

Phillips, A.G. (1984) Brain reward circuitry: A case for separate systems. Brain Research Bulletin 12, 195-201.

Phillips, A.G., Jakubovic, A. & Fibiger, H.C. (1987) Increased in vivo tyrosine hydroxylase activity in rat telencephalon produced by self-stimulation of the ventral tegmental area. Brain Research 402, 109-116.

Phillips, A.G. & Fibiger, H.C. (1989) Neuroanatomical bases of intracranial self-stimulation: Untangling the Gordian knot. In: J.M. Liebman, S.J. Cooper (Eds.) The Neuropharmacological Basis of Reward. Oxford University Press, Oxford.

Phillips, A.G. & Fibiger, H.C. (1990) Role of reward and enhancement of conditioned reward in persistence of responding for cocaine. Behavioural Pharmacology 1, 269-282.

Pickel, V.M., Towle, A.C., Joh, T.H. & Chan, J. (1987) Dual ultrastructural localization of tyrosine hydroxylase and GABA in rat nucleus accumbens: Presynaptic and postsynaptic interactions between dopamine and amino acid transmitters. Society for Neuroscience Abstr. 263.4

Pickens, R. & Thompson, T. (1968) Cocaine-reinforced behavior in rats: Effects of reinforcer magnitude and fixed-ratio size. Journal of Pharmacology and Experimental Therapeutics 161, 122-129.

Pickens, R., Meisch, R.A. & Dougherty, J.A. (1968) Chemical interactions in methamphetamine reinforcement. Psychological Reports 23, 1267-1270.

Pijnenberg, A.J.J. & Van Rossum, J. (1973) Stimulation of locomotor activity following injection of dopamine into the nucleus accumbens. Journal of Pharmacy and Pharmacology 25, 1003-1005.

Pijnenberg, A.J.J., Honig, W.M.M., van der Heyden, J.A.M. & van Rossum, J.M. (1976) Effects of chemical stimulation of the mesolimbic dopamine system upon locomotor activity. European Journal of Pharmacology 35, 45-58.

Pinel, J.P.J. & Treit, D. (1978) Burying as a defensive response in rats. Journal of Comparative & Physiological Psychology 92, 708-712.

Pliskoff, S.S., Shull, R.L. & Gollub, L.R. (1968) The relation between response rates and reinforcement rates in a multiple schedule. Journal of the Experimental Analysis of Behavior, 11, 271-284.

Powell, E.W. & Leman, R.B. (1976) Connections of the nucleus accumbens. Brain Research 105, 389-403.

Prado-Alcala, R. & Wise, R.A. (1984) Brain stimulation reward and dopamine terminal fields: I. Caudate-putamen, nucleus accumbens and amygdala. Brain Research 297, 265-273.

Pycock, C. & Hornton, R. (1976) Evidence for an accumbens-pallidal pathway in the rat and its GABAergic control. Brain Research 110, 629-634.

Raisman, R., Cash, R. & Agid, Y. (1986) Parkinson's disease: Decreased density of ^{3}H-imipramine and ^{3}H-paroxetine binding sites in the putamen. Neurology 36, 556-560.

Rech, R.H. & Commissaris, R.L. (1982) Neurotransmitter basis of the behavioral effects of hallucinogens. Neuroscience & Biobehavioral Reviews 6, 521-527.

Reicher, M.A. & Holman, E.W. (1977) Location preference and flavor aversion reinforced by amphetamine in rats. Animal Learning & Behavior 5, 343-356.

Reiner, A., Albin, R.L., Anderson, K.D., D'Amato, C.J., Penney, J.B. & Young, A.B. (1988) Differential loss of striatal projection neurons in Huntington disease. Proceedings of the National Academy of Sciences of the USA 85, 5733-5737.

Rescorla, R.A. & Wagner, A.R. (1972) A theory of Pavlovian conditioning: Variations in the effectiveness of reinforcement and nonreinforcement. In A.H. Black & W.F. Prokasy (Eds.), Classical conditioning II: Current Research and Theory. Appleton-Century-Crofts, New York.

Reynolds, G.S. (1961) Behavioral contrast. Journal of the Experimental Analysis of Behavior 27, 103-117.

Robbins, T.W. (1975) The potentiation of conditioned reinforcement by psychomotor stimulant drugs: a test of Hill's hypothesis. Psychopharmacology 45, 103-114.

Robbins, T.W. (1978) The acquisition of responding with conditioned reinforcement: Effects of pipradrol, methylphenidate, d-amphetamine, and nomifensine. Psychopharmacology 58, 79-87.

Robbins, T.W. & Koob, G.F. (1980) Selective disruption of displacement behaviour by lesions of the mesolimbic dopamine system. Nature 285, 409-412.

Robbins, T.W. & Everitt, B.J. (1982) Functional studies of the central catecholamines. International Review of Neurobiology 23, 303-365.

Robbins, T.W., Roberts, D.C.S. & Koob, G.F. (1983a) Effects of d-amphetamine and apomorphine upon operant behavior and schedule-induced licking in rats with 6-hydroxy-dopamine lesions of the nucleus accumbens. Journal of Pharmacology & Experimental Therapeutics 224, 662-673.

Robbins, T.W., Watson, B.A., Gaskin, M. & Ennis, C. (1983b) Contrasting interactions of pipradrol, d-amphetamine, cocaine, cocaine analogues, apomorphine and other drugs with conditioned reinforcement. Psychopharmacology 80, 113-119.

Robbins, T.W., Cador, M., Taylor, J.R. & Everitt, B.J. (1989) Limbic-striatal interactions in reward-related processes. Neuroscience and Biobehavioural Reviews 13, 155-162.

Roberts, D.C.S., Corcoran, M.E. & Fibiger, H.C. (1977) On the role of ascending catecholamine systems in self-administration of cocaine. Pharmacology Biochemistry & Behavior 6, 615-620.

Roberts, D.C.S. & Koob, G.F. (1982) Disruption of cocaine self-administration following 6-hydroxydopamine lesions of the ventral tegmental area in rats. Pharmacology Biochemistry & Behavior 17, 901-904.

Roberts, D.C.S., Loh, E.A. & Vickers, G. (1989) Self-administration of cocaine on a progressive ratio schedule in rats: Dose-response relationship and effect of haloperidol pretreatment. Psychopharmacology 97, 535-538.

Robins, A.H. (1976) Depression in patients with Parkinsonism. British Journal of Psychiatry 128, 141-145.

Robinson, T.E., Jurson, P.A., Bennett, J.A. & Bentgen, K.M. (1988) Persistent sensitization of dopamine neuro-transmission in ventral striatum (nucleus accumbens) produced by prior experience with (+)-amphetamine: A microdialysis study in freely moving rats. Brain Research 462, 211-222.

Rowland, N. & Engle, D.J. (1977) Feeding and drinking interactions after acute butyrophenone administration. Pharmacology Biochemistry & Behavior 7, 295-301.

Rolls, B.J. & Rolls, E.T. (1973) Effects of lesions in the basolateral amygdala on fluid intake in the rat. Journal of Comparative and Physiological Psychology 83, 240-247.

Rolls, E.T. & Rolls, B.J. (1973) Altered food preferences after lesions in the basolateral region of the amygdala in the rat. Journal of Comparative and Physiological Psychology 83, 248-259.

Rolls, E.T., Rolls, B.J., Kelly, P.H., Shaw, G., Wood, P.J. & Dale, R.I. (1974) The relative attenuation of self-stimulation, eating and drinking produced by dopamine-receptor blockade. Psychopharmacology 38, 219-230.

Rolls, E.T., Murzi, E., Yaxley, S. & Thorpe, S. (1986) Sensory-specific satiety: Food-specific reduction in responsiveness of ventral forebrain neurons after feeding in the monkey. Brain Research 368, 79-86.

Rolls, E.D., Sienkiewicz, Z.J. & Yaxley, S. (1989) Hunger modulates the responses to gustatory stimuli of single neurons in the caudolateral orbitofrontal cortex of the macaque monkey. European Journal of Neuroscience 1, 53-60.

Rosse, R.B. & Peters, J. (1986) Depression-dependent Parkinsonism: Case report. International Journal of Psychiatry in Medicine 16, 85-90.

Royce, G.J. (1978) Cells of origin of subcortical aferents to the caudate nucleus: A horseradish peroxidase study in the cat. Brain Research 153, 465-475.

Salamone, J.D. (1986) Different effects of haloperidol and extinction on instrumental behaviors. Psychopharmacology 88, 18-23.

Salamone, J.D. (1987) The actions of neuroleptic drugs on appetitive instrumental behaviors. In: L.L. Iversen, S.D. Iversen, S.H. Snyder (Eds.), Handbook of Psychopharmacology. Plenum Press, New York.

Salamone, J.D. (1988) Dopaminergic involvement in activational aspects of motivation: Effects of haloperidol on schedule induced activity, feeding, and foraging rats. Psychobiology 16, 196-206.

Sanger, D.J. (1986) Response decrement patterns after neuroleptic and non-neuroleptic drugs. Psychopharmacology 89, 98-104.

Sanger, D.J. (1988) The alpha-adrenoreceptor antagonists idazoxan and yohimbine increase rates of DRL responding in rats. Psychopharmacology 95, 413-417.

Santamaria, J., Tolosa, E. & Valles, A. (1986) Parkinson's disease with depression: A possible subgroup of idiopathic parkinsonism. Neurology 36, 1130-1133.

Schaefer, G.J. & Holtzmann, S.G. (1979) Free-operant and auto-titration brain self-stimulation procedures in the rat: A comparison of drug effects. Pharmacology Biochemistry & Behavior 10, 127-135.

Schaefer, G.J. & Michael, R.M. (1980) Acute effects of neuroleptics on brain self-stimulation thresholds in rats. Psychopharmacolgy 67, 9-15.

Schaefer, G.J. & Michael, R.M. (1985) The discriminative stimulus properties and detection thresholds of intracranial self-stimulation: Effects of d-amphetamine, morphine, and haloperidol. Psychopharmacology 85, 289-294.

Scheel-Kruger, J. & Willner, P. (1990) The mesolimbic system: Principles of Operation. In: P. Willner, J. Scheel-Kruger (Eds.) The Mesolimbic Dopamine System: From Motivation to Action. Wiley, Chichester. In press.

Schmidt, M.J. & Hill, L.E. (1977) Effects of ergots on adenylate cyclase activity in the corpus striatum and pituitary. Life Sciences 20, 789.

Schneider, L.H., Gibbs, J. & Smith, G.P. (1986) Selective D1 or D2 antagonists inhibit sucrose sham feeding in rats. Appetite 7, 294-295.

Schwab, R.S. (1972) Akinesia paradoxica. EEE and Clinical Neurophysiology, Suppl. 31, 87-92.

Schneider, L.H., Greenberg, D. & Smith, G.P. (1988) Comparison of the effects of selective D-1 and D-2 receptor antagonists on sucrose sham feeding and water sham drinking. Annals of the New York Academy of Science 537, 534-537.

Segal, D.S. & Kuczenski, R. (1990) Individual differences in response to amphetamine: Behavioural and neurochemical characteristics. Psychopharmacology 101 (Suppl.), Abstract 200 (European Behavioural Pharmacology Society, The Netherlands, 1990).

Seeman, P. (1980) Brain dopamine receptors. Pharmacological Review 32, 229.

Selemon, L.D. & Goldman-Rakic, P.S. (1985) Longitudinal topography and interdigation of cortico-striatal projections in the rhesus monkey. Journal of Neuroscience 5, 776-794.

Shearman, G.T., Hynes, M. & Lal, H. (1981) Self-administration of clonidine in the rat. In: Lal, H. & Fielding, S. (Eds.) Psychopharmacology of clonidine. Liss, New York.

Shizgal, P. & Murray, B. (1989) Neuronal basis of intracranial self-stimulation. In: J.M. Liebman, S.J. Cooper (Eds.) The Neuropharmacological Basis of Reward. Oxford University Press, Oxford.

Shugalev, N.P. (1983) Neurochemical mechanisms of participation of the caudate nucleus in food-getting behaviour. Neuroscience and Behavioural Physiology 13, 345-350.

Shulz, D.W., Staples, L. & Mailman, R.B. (1985) SCH-23390 causes persistent antidopaminergic effects in vivo: Evidence for a longterm occupation of receptors. Life Sciences 36, 1941-1948.

Smith, J.E., Co, C., Freeman, M.E., Sands, M.P. & Lane, J.D. (1980) Neurotransmitter turnover in rat striatum is correlated with morphine self-administration. Nature 287, 152-154.

Snyderman, M. (1983) Bodyweight and response strength. Behavior Analysis Letters 3, 255-265.

Spealman, R.D. & Kelleher, R.T. (1979) Behavioural effects of self-administered cocaine: Responding maintained alternately by cocaine and electric shock in squirrel monkeys. Journal of Pharmacology and Experimental Therapeutics 210, 206-214.

Spyraki, C., Fibiger, H.C. & Phillips, A.G. (1982) Attenuation by haloperidol of place preference conditioning using food reinforcement. Psychopharmacology 77, 379-382.

Stein, L. & Ray, O.S. (1960) Brain stimulation reward 'thresholds' self-determined in rat. Psychopharmacologia 1, 251-256.

Steiner, S.S., Beer, B. & Shaffer, M.M. (1969) Escape from self-produced rates of brain stimulation. Science 163, 90-91.

Stellar, J.R. & Rice, M.B. (1989) Pharmacological basis of intracranial self-stimulation reward. In: J.M. Liebman, S.J. Cooper (Eds.) The Neuropharmacological Basis of Reward. Oxford University Press, New York.

Stern, G.M., Lander, C.M. & Lees, A.J. (1980) Akinetic freezing and trick movements in Parkinson's disease. Psychoneural Transmissions (Suppl.16), 137-141.

Stoof, J.C. & Kebabian, J.W. (1981) Opposing roles for D1 and D2 dopamine receptors in efflux of cyclic AMP from rat striatum. Nature 294, 366-368.

Sugimoto, T. & Mizuno, N. (1987) Neurotensin in projection neurons of the striatum and nucleus accumbens, with reference to co-existence with enkephalin and GABA: Immunohistochemical study in the cat. Journal of Comparative Neurology 257, 383-395.

Suvorov, N.F., Yakimovsky, A.F. & Saulskaya, N.B. (1984) The nigro-striatal dopaminergic system and its role in adaptive conditioned behaviour. Fiziologicheskii Zhurnal SSSR 70, 594-600.

Swanson, L.W. & Cowan, W.M. (1975) A note on the connections and development of the nucleus accumbens. Brain Research 93, 324-330.

Swanson, L.W. (1976) An autoradiographic study of the efferent connections of the preoptic regions in the rat. Journal of Comparative Neurology 167, 227-256.

Swanson, L.W. (1982) The projections of the ventral tegmental area and adjacent regions: A combined fluorescent retrograde tracer and immunofluorescence study in the rat. Brain Research Bulletin 9, 321-353.

Swerdlow, N.R. & Koob, G.F. (1984) Restrained rats learn amphetamine-conditioned locomotion, but not place preference. Psychopharmacology 84, 163-166.

Swerdlow, N.R., Swanson, L.W. & Koob, G.F. (1984) Electrolytic lesions of the substantia innominata and lateral preoptic area attenuate the 'supersensitive' locomotor response to apomorphine resulting from degeneration of the nucleus accumbens. Brain Research 306, 141-148.

Swerdlow, N.R. & Koob, G.F. (1987) Dopamine, schizophrenia, mania and depression: Toward a unified hypothesis of cortico-striato-pallido-thalamic function. Behavioral and Brain Sciences 10, 197-245.

Taghzouti, K., et al. (1985) The effect of 6-OHDA lesions of the lateral septum on schedule-induced polydipsia. Behavioural Brain Research 15, 1-8.

Tassin, J.P., Cheramy, A., Blanc, G., Thierry, A.M. & Glowinski, J. (1976) Topographical distribution of dopaminergic innervation and of dopaminergic receptors in the rat striatum. I. Microestimation of [^{3}H]dopamine uptake and dopamine content in microdiscs. Brain Research 107, 291-301.

Taylor, J.R. & Robbins, T.W. (1984) Enhanced behavioural control by conditioned reinforcers following microinjections of d-amphetamine into the nucleus accumbens. Psychopharmacology 84, 405-412.

Taylor, J. & Robbins, T. (1986) 6-Hydroxydopamine lesions of the nucleus accumbens, but not the caudate nucleus, attenuate enhanced responding with reward-related stimuli by intra-accumbens d-amphetamine. Psychopharmacology 90, 390-397.

Thierry, A.M., Blanc, G., Sobel, A., Stinus, L. & Glowinski, J. (1973) Dopaminergic terminals in the rat cortex. Science 180, 499-501.

Thompson, T., Heistad, G.T. & Palermo, D.S. (1963) Effect of amount of training on rate and duration of responding during extinction. Journal of the Experimental Analysis of Behavior 6, 155-161.

Tobias, T.J. (1975) Afferents to prefrontal cortex from thalamic mediodorsal nucleus in the rhesus monkey. Brain Research 83, 191-212.

Todes, C.J. & Lees, A.J. (1985) The pre-morbid personality of patients with Parkinson's disease. Journal of Neurology, Neurosurgery, and Psychiatry 48, 97-100.

Tombaugh, T.N., Anisman, H. & Tombaugh, J. (1980) Extinction and dopamine receptor blockade after intermittent reinforcement training: Failure to find functional equivalence. Psychopharmacology 70, 19-28.

Tombaugh, T.N., Grandmaison, L.J. & Zito, K.A. (1982) Establishment of secondary reinforcement in sign tracking and place preference tests following pimozide treatment. Pharmacology Biochemistry & Behavior 17, 665-670.

Tomkins, S.S. (1962) Affect, Imagery, Consciousness. The Positive Affects, Volume 1. Springer, New York.

Torack, R.M. & Morris, J.C. (1988) The association of ventral tegmental area histopathology with adult dementia. Archives of Neurology 45, 497-501.

Towell, A., Muscat, R. & Willner, P. (1987) Effects of pimozide on sucrose consumption and preference. Psychopharmacology 92, 262-264.

Trabucchi, M., Spano, P.F., Tonon, G.C. & Frattol, L. (1976) Effects of bromocriptine on central dopaminergic receptors. Life Sciences 19, 225.

Uhl, G.R., Goodman, R.R., Kuhar, M.J., Childers, S.R. & Snyder, S.H. (1979) Immunohistochemical mapping of enkephalin containing cell bodies, fibres and nerve terminals in the brain stem of the rat. Brain Research 166, 75-94.

Uhl, G.R., Hedreen, J.C. & Price, D.L. (1985) Parkinson's disease: Loss of neurons from the ventral tegmental area contralateral to therapeutic surgical lesions. Neurology 35, 1215-1218.

Ungerstedt, U. (1971) Stereotaxic mapping of the monoamine pathways in the rat brain. Acta Physiol. Scand. (Suppl.367), 1-48.

Van Hoesen, G.W., Mesulam, M.M. & Haaxama,R. (1976) Temporal cortex projections to the olfactory tubercle in the rhesus monkey. Brain Research 109, 375-381.

Van Hoesen, G.W., Yeterian, E.H., Lavizzo-Mourney, R. (1981) Widespread cortico-striate projections from temporal cortex of the rhesus monkey. Journal of Comparative Neurology 199, 205-219.

Vallar, L. & Meldolesi, J. (1989) Mechanisms of signal transduction at the dopamine D_2 receptor. Trends in Pharmacological Sciences 10, 74-77.

Veening, J.G., Cornelissen, F.M. & Lieven, P.A.J.M. (1980) The topical organisation of the afferents to caudatoputamen of the rat. A horseradish peroxidase study. Neuroscience 5, 1253-1268.

Velley, L., Cardo, B. & Bockaert, J. (1981) Modulation of rat brain alpha-adrenoreceptor populations four weeks after stimulation of the nucleus locus coeruleus. Psychopharmacology 74, 226-231.

Versteeg, D.H.G., Van der Gugten, J., de Jong, W. & Palkovits, M. (1976) Regional concentrations of noradrenaline and dopamine in rat brain. Brain Research 113, 563-574.

Vives, F. & Mogenson, G.J. (1985) Electrophysiological evidence that the mediodorsal nucleus of the thalamus is a relay between the ventral pallidum and the medial prefrontal cortex in the rat. Brain Research 334, 329-337.

Vogt, B.A., Rosene, D.L. & Pandya, D.N. (1979) Thalamic and cortical afferents differentiate anterior from posterior cingulate cortex in the monkey. Science 204, 205-207.

Wallace, M., Singer, G., Finlay, J. & Gibson, S. (1983) The effect of 6-OHDA lesions of the nucleus accumbens septum on schedule-induced drinking, wheelrunning and corticosterone levels in the rat. Pharmacology Biochemistry & Behavior 18, 129-136.

Waraczynski, M.A., Stellar, J.R. & Gallistel, C.R. (1987) Reward saturation in medial forebrain bundle self-stimulation. Physiology & Behavior 41, 585-593.

Wauquier, A. & Niemegeers, C.J.E. (1979) A comparison between lick or lever-pressing contingent reward and the effects of neuroleptics thereon. Archives Internationales de Pharmacodynamie et de Therapie 239, 230-240.

Weatherford, S.C., Smith, G.P. & Melville, D. (1988) D-1 and D-2 receptor antagonists decrease corn oil sham feeding in rats. Physiology & Behavior 44, 569-572.

Weiner, N. & Molinoff, P.B. (1989) Catecholamines. In: G. Siegel, B. Agranoff, R.W. Albers, P. Molinoff (Eds.), Basic Neurochemistry. Raven Press, New York.

Wetherington, C.L. & Lucas, T.R. (1980) A note on fitting Herrnstein's equation. Journal of the Experimental Analysis of Behavior 34, 199-206.

White, F.J. & Wang, R.J. (1984) A10 dopamine neurons: Role of autoreceptors in determining firing rate and sensitivity to dopamine agonists. Life Sciences 34, 1161-1170.

Wilcove, W.G. (1973) Ingestion affected by the oral environment: The role of gustatory adaptation on taste reactivity in the rat. Physiology and Behavior 11, 297-312.

Wiley, J.L., Porter, J.H. & Faw, W.R. (1989) Haloperidol blocks reacquisition of operant running during extinction following a single priming trial with food reward. Bulletin of the Psychonomic Society 27, 340-342.

Williams, B.A. & Wixted, J.T. (1986) An equation for behavioural contrast. Journal of the Experimental Analysis of Behavior 45, 47-62.

Willner, P. & Towell, A. (1982) Microstructural analysis of the involvement of beta-receptors in amphetamine anorexia. Pharmacology Biochemistry & Behavior 17, 255-262.

Willner, P., Towell, T. & Muscat, R. (1987) Effects of amphetamine and pimozide on reinforcement and motor parameters in variable-interval performance. Journal of Psychopharmacology 1, 140-153.

Willner, P., Chawla, K., Sampson, D., Sophokleus, S. & Muscat, R. (1988) Tests of functional equivalence between pimozide pretreatment, extinction and free feeding. Psychopharmacology 95, 423-426.

Willner, P. & Phillips, G. (1989) Neuroleptic-induced response decrements: Two tests of the motor activation hypothesis. Behavioural Pharmacology 1 (Suppl.1), Abstract 127 (European Behavioural Pharmacology Society, Malta, 1989).

Willner, P., Phillips, G. & Muscat, R. (1989) Time-dependent and schedule-dependent effects of dopamine receptor blockade. Behavioural Pharmacology 1, 169-176.

Willner, P. & Scheel-Kruger, J. (1990) The Mesolimbic Dopamine System: From Motivation to Action. Wiley, Chichester, in press.

Willner. P., Sampson, D., Phillips, G. & Muscat, R. (1990a) A matching law analysis of the effects of dopamine receptor antagonists on reinforcement and motor parameters in variable-interval performance. Psychopharmacology 101, 560-567.

Willner, P., Papp, M., Phillips, G., Maleeh, M. & Muscat, R. (1990b) Pimozide does not impair sweetness discrimination. Psychopharmacology 102, 278-282.

Willner, P., McGuirk, J., Phillips, G. & Muscat, R. (1990c) A behavioural analysis of the anorectic effects of fenfluramine and fluoxetine. Psychopharmacology 102, 273-277.

Willner, P., Papp, M., Phillips, G. & Muscat, R. (1990d) Animal models of anhedonia. In: P. Simon, P. Soubrie, D. Widlocher (Eds.), Animal Models of Psychiatric Disorders, Vol.3. Karger, Basel, in press.

Willner, P., Phillips, G. & Muscat, R. (1990e) Suppression of rewarded behaviour by neuroleptic drugs: Can't or won't, or why? In: P. Willner, J. Scheel-Kruger (Eds.) The Mesolimbic Dopamine System: From Motivation to Action. Wiley, Chichester, in press.

Winn, P. & Robbins, T.W. (1985) Comparative effects of infusions of 6-hydroxydopamine into the nucleus accumbens and anterolateral hypothalamus induced by 6-hydroxydopamine on the response to dopamine agonists, body weight, locomotor activity and measures of exploration in the rat. Neuropharmacology 24, 25-31.

Wise, R.A., Yokel, R.A., Gerber, G.J. & Hansson, P. (1977) Concurrent intracranial self-stimulation and intravenous amphetamine self-administration in rats. Pharmacology Biochemistry & Behavior 7, 459-561.

Wise, R.A., Spindler, J., De Wit, H. & Gerber, G.J. (1978a) Neuroleptic-induced 'anhedonia' in rats: pimozide blocks the reward quality of food. Science 201, 262-264.

Wise, R.A., Spindler, J. & Legault, L. (1978b) Major attenuation of food reward with performance-sparing doses of pimozide in the rat. Canadian Journal of Psychology 32, 77-85.

Wise, R.A. (1982) Neuroleptics and operant behaviour: The anhedonia hypothesis. The Behavioral and Brain Sciences 5, 39-53.

Wise, R.A. (1989) The brain and reward. In J.M. Liebman & S.J. Cooper (Eds.), The pharmacological basis of reward (pp. 406). Oxford University Press, New York.

Wise, R.A. (1989) Intravenous drug self-administration: A special case of positive reinforcement. In M.A. Bozarth (Ed.), Methods of assessing the reinforcing properties of abused drugs. Springer-Verlag, New York.

Wolterink, G., Wolterink, J., Le Noury, J., Cador, M., Robbins, T.W. & Everitt, B.J. (1990) The role of D1 and D2 receptors and cholecysokinin in the ventral striatum in reward-related processes. Abstract 54, British Association for Psychopharmacology, Cambridge, 1990).

Woolverton, W.L., Goldberg, L.I. & Ginos, J.Z. (1984) Intravenous self-administration of dopamine receptor agonists by rhesus monkeys. Journal of Pharmacology and Experimental Therapeutics 230, 678-683.

Woolverton, W.L. & Virus, R.M. (1989) The effects of a D-1 and D-2 dopamine antagonist on behaviour maintained by cocaine or food. Pharmacology Biochemistry & Behavior 32, 691-697.

Xenakis, S. & Sclafani, A. (1981) The effects of pimozide on the consumption of a palatable saccharin-glucose solution in the rat. Pharmacology Biochemistry & Behavior 15, 435-442.

Yang, C.R. & Mogenson, G.J. (1987) Hippocampal signal transmission to the pedunculopontine nucleus and its regulation by dopamine D2 receptors in the nucleus accumbens: An electrophysiological and behavioural study. Neuroscience 23, 1041-1055.

Yang, C.R. & Mogenson, G.J. (1989) Ventral pallidal neuronal responses to dopamine receptor stimulation in the nucleus accumbens. Brain Research 489, 237-246.

Yeterian, E.H., & Van Hoesen, G.W. (1978) Cortico-striate projections in the rhesus monkey: The organization of certain cortico-caudate connections. Brain Research 139, 43-63.

Yim, C.Y. & Mogenson, G.J. (1980) Electrophysiological studies of neurons in the ventral tegmental area of Tsai. Brain Research 181, 301-313.

Yim, C.Y. & Mogenson, (1989) Low doses of accumbens dopamine modulate amygdala suppression of spontaneous exploratory activity in rats. Brain Research 477, 202-210.

Yokel, R.A. & Pickens, R. (1973) Self-administration of optical isomers of amphetamine and methylamphetamine by rats. Journal of Pharmacology and Experimental Therapeutics 187, 27-33.

Yokel, R.A. & Wise, R.A. (1975) Increased lever pressing for amphetamine after pimozide in rats: Implications for a dopamine theory of reward. Science 187, 547-549.

Yokel, R.A. & Wise, R.A. (1976) Attenuation of intravenous amphetamine reinforcement by central dopaminergic blockade in rats. Psychopharmacology 48, 311-318.

Young, P.T. (1949) Studies of food preference, appetite, and dietary habit. IX. Palatability versus appetite as determinants of the critical concentrations of sucrose and sodium chloride. Comparative Psychological Monographs 19, 1-44.

Young, P.T. & Greene, J.T. (1953) Quantity of food ingested as a measure of relative acceptability. Journal of Comparative and Physiological Psychology 46, 288-294.

Young III, W.S., Bonner, T.I. & Brann, M.R. (1986) Mesencephalic dopamine neurons regulate the expression of neuropeptide mRNAs in the rate forebrain. Proceedings of the National Academy of Sciences of the USA 83, 9827-9831.

Zaborsky, L., Alheid, G.F., Beinfield, M.C., Eiden, L.E., Heimer, L. & Palkovits, M. (1985) Cholecystokinin innervation of the ventral striatum: A morphological and biochemical study. Neuroscience 14, 427-453.

Zacharko, R.M. & Anisman, H. (1990) Stresor-evoked alterations of intracranial self-stimulation in the mesocorticolimbic dopamine system: An animal model of depression. In: P. Willner, J. Scheel-Kruger (Eds.) The Mesolimbic Dopamine System: From Motivation to Action. Wiley, Chichester, in press.

Zarevics, P. & Setler, P.E. (1981) Effects of GABAergic drugs on brain stimulation reward as assessed by a 'threshold' method. Brain Research 215, 201-209.

Zebrowska-Lupina, I. & Kleinrok, Z. (1973) Behavioural effects of yohimbine administered intraventricularly in the rat. Psychopharmacologia 33, 267-275.

TITLE

DOPAMINE AND REWARD:

EFFECTS OF DOPAMINE ANTAGONIST DRUGS

ON OPERANT AND CONSUMMATORY BEHAVIOURS

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