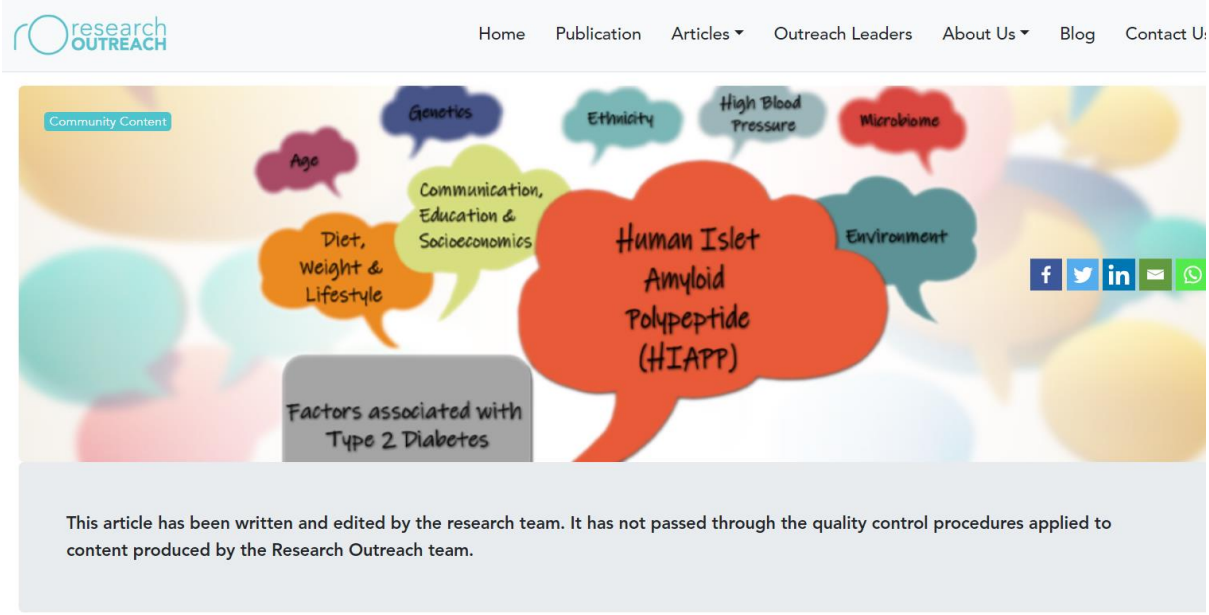
Proteins behaving badly: The role of human Islet Amyloid Polypeptide (hIAPP) in type 2 diabetes

[Proteins behaving badly: The role of (hIAPP) in type 2 diabetes (researchoutreach.org)]



Type 2 diabetes is a complex condition. It can result in complications that affect different parts of the body. Currently there is no cure, but there are treatments can manage the condition, although they are not perfect. Our understanding of the condition at the molecular level is limited. Here we summarise the important role of a protein called human Islet Amyloid Polypeptide (hIAPP) in sugar regulation and when it malfunctions, its role in type 2 diabetes. Understanding how this protein works may help with earlier diagnosis and the development of medications to manage the condition better.

A global issue

There are over 400 million people currently living with diabetes, 1.5 million of them will die from it every year. The majority of people (over 90%) have type 2 diabetes. Globally, over 800 billion US dollars is spent annually on treating diabetes, mainly on diabetes-related complications. Cases of type 2 diabetes (including children) are rising fast worldwide, especially in low and middle-income countries. This is linked to socioeconomics, obesity and lifestyle factors and highlights the need for better education and investment in affordable and accessible healthcare. Better screening methods are also needed to diagnose people earlier to ensure they get the support they need.

So what is type 2 diabetes and what causes it?

Essentially, Type 2 Diabetes Mellitus (T2DM) is a condition where either the pancreas cannot produce enough fully functioning insulin, or the body stops responding to insulin. Insulin is needed to control the body's sugar levels which normally rise after we eat. Sugar is taken

from the blood so it can be used for energy. If sugar levels remain high in the body for a long time, it can result in serious complications such as permanent damage to our eyes, nerve damage in our feet and hands, organ failure, and can even be life-threatening. With proper treatment however, people with T2DM can keep their sugar levels within a safe range and live a relatively normal life. Many factors increase the risk of getting T2DM. Some of them we can do nothing about (ethnicity, age, genetics) but some factors, e.g. weight and diet, are manageable with the right support.

Proteins and sugars

We are interested in better understanding the link between one of our own molecules, a protein called human Islet Amylogenic PolyPeptide (or hIAPP for short!) and T2DM. Normally, this protein is important for regulating digestion and is released with insulin to help regulate sugar levels in the body. It regulates the feeling of being full after eating, regulates the emptying of the stomach contents and prevents another molecule glucagon – which increases sugar levels - from being released. In those with T2DM, hIAPP levels fluctuate and it forms the wrong shape – or 'misfolds' - so cannot function correctly. Misfolded hIAPP molecules clump together, accumulate and can damage the pancreatic islet cells that produce insulin. This leads to impaired sugar regulation that can lead to T2DM. We are trying to identify what causes hIAPP to form these clumps and the specific steps involved. Our recent review summarises the complexity of this (1). Research suggests that pancreatic cells are damaged when hIAPP activates certain molecules or when hIAPP physically interacts with them. hIAPP also interferes with regulatory systems causing miscommunication between cells and failure to remove misfolded forms of the protein, all resulting in T2DM.

By changing different parts of the hIAPP protein ('amino acids') we also hope to understand what parts of the protein are involved in forming these clumps (2). We already know that certain hIAPP amino acids found in some Chinese and Japanese populations cause hIAPP clumping and early onset T2DM. Also, certain species such as rats, do not get T2DM. This is thought to be because their IAPP, with some differences in amino acids compared with hIAPP, does not misfold or clump. This suggests the protein itself is linked to T2DM, thus warranting the need for further research.

Treatment for type 2 diabetes

We would like to use hIAPP as a treatment for T2DM as we know it is essential for regulating sugar levels (and is defective in those with T2DM) but of course, we need to modify the protein first so that it won't form clumps. We can easily change the amino acids that cause clumping then test whether clumps form using established methods in the laboratory. hIAPP is a good molecule for treating T2DM as it is already found naturally in the human body, so it is less likely to cause unwanted side effects such as nausea and diarrhoea currently attributed to existing chemical drugs. Also, it can be used to control weight gain. hIAPP can slow the emptying of the stomach helping people feel fuller for longer, so could be given in combination with insulin to better manage sugar levels and obesity.

If we understand the clumping process better, we can target the clumping process early on, at the beginning of T2DM. Hopefully this will treat the condition early before cellular and organ damage occurs. Being able to stop hIAPP misfolding may also prevent disease onset and /or progression of other conditions such as Alzheimer's disease where there is an imbalance of sugar and insulin resistance in the brain (often referred to as 'type 3 diabetes').

This is because hIAPP causes other proteins that are linked to other conditions to clump ('protein misfolding disorders', of which there are over 40) and explains why having T2DM puts people at higher risk of these other conditions.

References

1) Sevcuka A, White K, Terry C, (2022) Factors That Contribute to hIAPP Amyloidosis in Type 2 Diabetes Mellitus. *Life* 12(4):583. https://doi.org/10.3390/life12040583

2) Hassan S, White K, Terry C (2022) Linking hIAPP misfolding and aggregation with type 2 diabetes mellitus: a structural perspective. *Biosci Rep* 42(5): BSR20211297. https://doi:10.1042/BSR20211297

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