Naturally occurring peptide may tackle the 'root cause' of obesity-related conditions

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Research published today in *Clinical and Experimental Immunology* shows that a peptide (small protein) called PEPITEM could provide a revolutionary approach to reducing the risk of type 2 diabetes and other

obesity-related diseases such as hepatic steatosis (fatty liver).

The researchers used an animal model of obesity to investigate whether PEPITEM, delivered by a slow-release pump, could prevent or reverse the effects that a high-fat diet has on the pancreas. Excitingly, the results showed that administration of PEPITEM significantly reduced the enlargement of insulin-producing cells in the pancreas and also significantly reduced immune cell migration into various tissues.

The research team was led by Dr. Helen MCGettrick and Dr. Asif Iqbal from the University of Birmingham's Institute of Inflammation and Ageing and Institute of Cardiovascular Sciences. Dr. McGettrick said, "We have found a new therapeutic approach that could provide new drugs to tackle the root cause of obesity-related conditions by preventing the damage caused by systemic inflammation.

PEPITEM was first identified in 2015 by Birmingham researchers who described its role in the adiponectin-PEPITEM pathway, which is involved in controlling the onset and severity of auto-immune and chronic inflammatory diseases.

Obesity causes complex and dramatic changes in metabolism in adipose (fat) tissue, damage to the pancreas, reduced insulin sensitivity and eventually the hyperglycemia that underpins type 2 diabetes. It also causes a low-level inflammatory response across the body, encouraging white blood cells to enter into many tissues, including the visceral adipose tissue (fat stored deep inside the body wrapped around the organs, including the liver and gut) and peritoneal cavity (a thin membrane that encompasses the gut).

The latest research shows that the adiponectin-PEPITEM pathway also connects obesity, the low-level inflammatory response that is driven by it, and changes in the pancreas that precede diabetes.

The results showed that dosing with PEPITEM while the mice were on a high-fat diet significantly reduced the enlargement of insulin-producing beta cells in the pancreas and the number of white blood cells in the visceral adipose tissue and peritoneal cavity, compared to controls.

The researchers also looked at the potential of PEPITEM to reverse the changes brought on by obesity, by feeding the animals a high-fat diet prior to treating with PEPITEM. Excitingly, they saw similar results. Dr. Asif Iqbal commented, "Until now we have understood very little about how the inflammation that accompanies obesity drives pathology. These results show us that PEPITEM can both prevent and reverse the impact that obesity has on metabolism. The next stage is to translate these exciting results into therapeutics that can be used in humans."

Professor Ed Rainger from Birmingham's Institute of Cardiovascular Sciences led the team that first identified PEPITEM. He commented, "We are all very excited about these latest results. PEPITEM is a naturally occurring peptide. We have already shown it has effects on several organs and now for the first time, we have shown that PEPITEM is effective in a model of a disease process that is not driven by the immune system alone."

University of Birmingham Enterprise had already filed patent applications covering PEPITEM compositions and therapeutic uses, and has now filed a further application covering its use in the use in the prophylaxis or treatment of obesity-associated inflammatory conditions including chronic low-grade systemic inflammation and pancreatic beta-cell damage.

More information: PEPITEM modulates leukocyte trafficking to reduce obesity-induced inflammation, *Clinical and Experimental Immunology* (2023). DOI: 10.1093/cei/uxad022

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