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How fat might be controlled through the body clock

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Australian researchers have shed more light on an underexplored aspect of the important brain-signaling system that controls appetite, body composition and energy use. Their findings suggest that a specific gene regulating our body clock may play a central role in determining how fat we become.

Evolution has preserved the 'neuropeptide Y (NPY) system', as it is known, in most species – indicating its importance – and much of our understanding comes from studying it in mice. There is one important difference, however, between the NPY system in mouse and man.

In man, the neurotransmitter NPY communicates with four well-known 'cell surface receptors' in the brain (Y1, Y2, Y4 and Y5), which in turn trigger the system's effects.

The new study has shown that mice have an additional receptor, Y6, which has profound effects on their body composition. Y6 is produced in a very small region of the brain that regulates the body clock, as well as growth hormone production.

PhD student Ernie Yulyaningsih, Dr Kim Loh, Dr Shu Lin and Professor Herbert Herzog from Sydney's Garvan Institute of Medical Research, together with Associate Professor Amanda Sainsbury-Salis, now at the University of Sydney, deleted the Y6 gene from mice to understand its effects. Their study showed that mice without the Y6 gene were smaller, and had less lean tissue, than normal mice. On the other hand, as they

aged, these 'knockout mice' grew fatter than the normal mice, especially when fed a high-fat diet. In that case, they became obese and developed metabolic problems similar to diabetes. These findings are now published online in the prestigious international journal, *Cell Metabolism*.

While the gene encoding the Y6 receptor is altered in man, Professor Herzog believes it would be unwise to ignore it because the development of anti-obesity drugs relies heavily on mouse studies.

"It is now clear to us that signaling through the Y6 receptor system is critical for the ways in which energy is used at different times of the day," said Professor Herbert Herzog.

"Our work shows that Pancreatic Polypeptide has a very high affinity for Y6 in mice. It's a satiety signal, and probably controls the circadian aspect of food intake – because the same amount of calories eaten at different times of the day has different effects on body weight."

"The Y6 gene is highly expressed in a part of the brain called the 'hypothalamic suprachiasmatic nucleus', which is known to control the body's circadian rhythm and may also critically modulate metabolic processes in response to food. The gene stimulates higher levels of certain peptides, including vasoactive intestinal peptide (VIP) – which controls growth hormone release."

"While it is not clear whether the Y6 receptor is fully active in humans, Pancreatic Polypeptide is highly expressed – even more so than in mice – and it's possible that another receptor to which the peptide has high affinity, such as Y4, could have taken over this function."

Associate Professor Amanda Sainsbury-Salis expressed surprise at the impact of the Y6 gene deletion on mice, commenting "I find it amazing that one gene, which is expressed in the small part of the brain that

controls the body clock, has such a profound impact on how much fat is stored on the body, and how much lean tissue is maintained."

"Importantly, we use mice as models of human beings in research, and so when looking for anti-obesity drugs, we need to fully understand the function of the NPY system in this animal model to understand how similar circuits in humans connect with the body clock."

Provided by Garvan Institute of Medical Research