Improved understanding of appetite-control proteins suggest treatment of obesity

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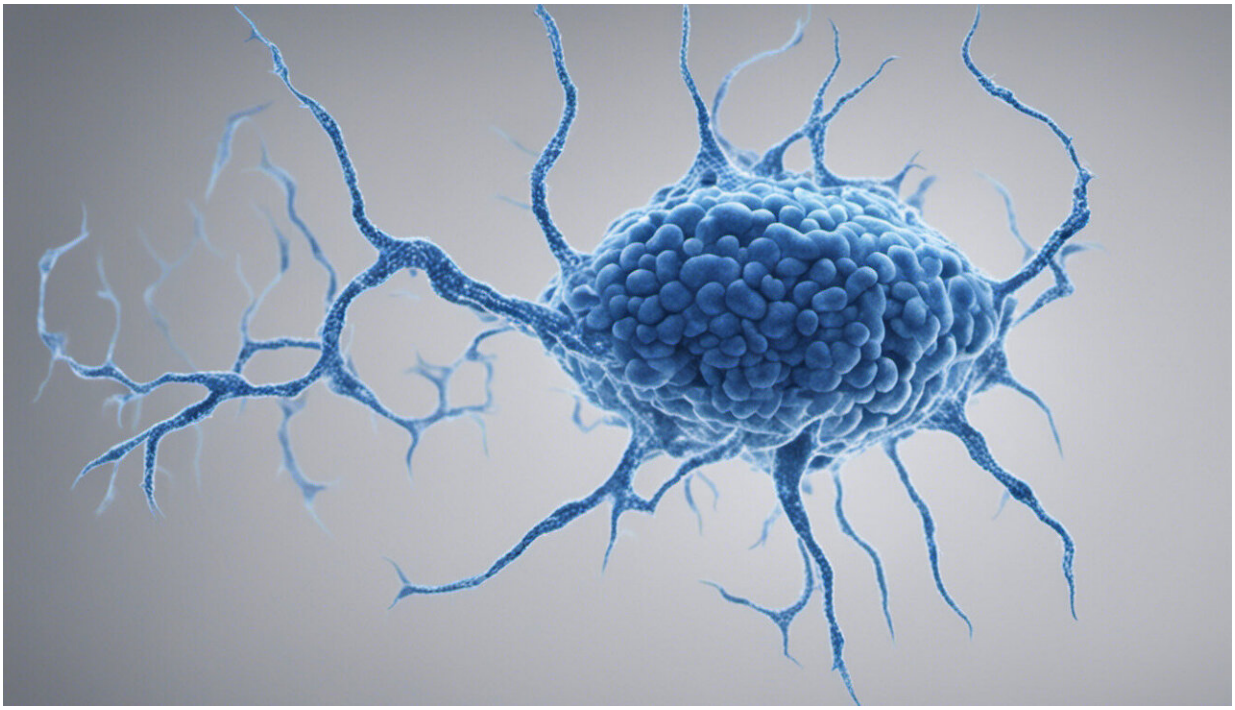

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The main cause of weight gain, and ultimately obesity, is an energy imbalance in the body triggered by increased food intake, often coupled with reduced energy expenditure. Two hormones called leptin and α-MSH (α-melanocyte-stimulating hormone) regulate the so-called 'energy homeostasis' in the body by influencing the brain to control appetite,

metabolism and behavior.

The hormone leptin acts on at least two sets of neurons in the brain, including a group called the pro-opiomelanocortin (POMC) neurons. Scientists know that impaired POMC regulation leads to leptin resistance and obesity, but are unclear about the exact mechanism by which this occurs.

Now, Weiping Han and colleagues at the A*STAR Singapore Bioimaging Consortium and Institute of Molecular and Cell Biology, together with co-workers from Hungary and the United States, have shown that deleting a protein called methyl-CpG-binding protein 2 (MeCP2) can promote weight gain and obesity in mice.

The team previously investigated the onset of leptin resistance during a high fat diet. "We examined whether epigenetic changes, such as DNA methylation, could alter the gene expression of the critical regulators of energy homeostasis," notes Han. "POMC neurons are regulated by MeCP2, so we chose to investigate what would happen if this relationship was disrupted."

The team bred genetically altered mice that had MeCP2 deleted specifically in the POMC neurons in the hypothalamus region of the brain. Their growth and feeding behavior on a high fat diet were then compared to their littermate control group with fully functioning MeCP2. After eight months, the MeCP2-knockout mice showed higher levels of leptin circulating in the blood, alongside increased body weight and fat levels.

Under normal physiological conditions, MeCP2, along with other factors, allows increased expression of POMC. "This occurs in response to cues from hormones such as leptin," explains Han. "POMC is then processed to generate α-MSH, which is released from POMC neurons to

control appetite and feeding behavior."

The researchers found that without MeCP2 to increase POMC expression in response to rising leptin levels, not enough α-MSH was released to stem the appetite. This led to all of the MeCP2-knockout mice becoming overweight.

"Knowing that increased DNA methylation in POMC promoters may lead to leptin resistance and weight gain provides new options for weight management," states Han. "Targeting epigenetic modification and regulation might be a viable approach to treat obesity."

Hoping to better understand the onset of obesity, the team is now researching other proteins that might affect the neurons and hormonal pathways in the brain.

More information: Wang, X., Lacza, Z., Sun, Y. E. & Han, W. "Leptin resistance and obesity in mice with deletion of methyl-CpG-binding protein 2 (MeCP2) in hypothalamic pro-opiomelanocortin (POMC) neurons." *Diabetologia* 57, 236–245 (2014). dx.doi.org/10.1007/s00125-013-3072-0

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