# Insulin action in the brain can lead to obesity

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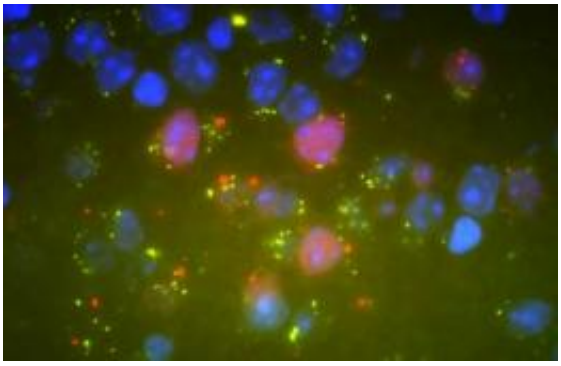

This is a visualization of how insulin affects the SF-1 neurons of the hypothalamus. After stimulation with insulin, the SF-1 cells (red) form the signaling molecule PiP3 (green). (Blue: cell nucleus) Credit: Max Planck Institute for Neurological Research

Fat-rich food makes you fat. Behind this simple equation lie complex signalling pathways, through which the neurotransmitters in the brain control the body's energy balance. Scientists at the Cologne-based Max Planck Institute for Neurological Research and the Cluster of Excellence in Cellular Stress Responses in Ageing-associated Diseases (CECAD) at the University of Cologne have clarified an important step in this complex control circuit.

They have succeeded in showing how the hormone insulin acts in the part of the brain known as the ventromedial hypothalamus. The consumption of high-fat food causes more insulin to be released by the pancreas. This triggers a signalling cascade in special nerve cells in the

brain, the SF-1 neurons, in which the enzyme P13-kinase plays an important role. Over the course of several intermediary steps, the insulin inhibits the transmission of nerve impulses in such a way that the feeling of satiety is suppressed and energy expenditure reduced. This promotes overweight and obesity.

The hypothalamus plays an important role in energy homeostasis: the regulation of the body's energy balance. Special neurons in this part of the brain, known as POMC cells, react to neurotransmitters and thus control eating behaviour and energy expenditure. The hormone insulin is an important messenger substance. Insulin causes the carbohydrate consumed in food to be transported to target cells (e.g. muscles) and is then available to these cells as an energy source. When high-fat food is consumed, more insulin is produced in the pancreas, and its concentration in the brain also increases. The interaction between the insulin and the target cells in the brain also plays a crucial role in the control of the body's energy balance. However, the precise molecular mechanisms that lie behind the control exercised by insulin remain largely unclear.

A research group led by Jens Brüning, Director of the Max Planck Institute for Neurological Research and scientific coordinator of the CECAD (Cellular Stress Responses in Aging-Associated Diseases) cluster of excellence at the University of Cologne has achieved an important step in the explanation of this complex regulatory process. As the scientists have shown, insulin in the SF-1 neurons – another group of neurons in the hypothalamus – triggers a signalling cascade. Interestingly, however, these cells appear only to be regulated by insulin when high-fat food is consumed and in the case of overweight. The enzyme P13-kinase plays a central role in this cascade of messenger substances. In the course of the intermediary steps in the process, the enzyme activates ion channels and thereby prevents the transmission of nerve impulses. The researchers suspect that the SF-1 cells communicate

in this way with the POMC cells.

Kinases are enzymes that activate other molecules through phosphorylation – the addition of a phosphate group to a protein or other organic molecule. "If insulin binds to its receptor on the surface of the SF-1 cells, it triggers the activation of the PI3-kinase," explains Tim Klöckener, first author of the study. "The PI3-kinase, in turn, controls the formation of PIP3, another signalling molecule, through phosphorylation. PIP3 makes the corresponding channels in the cell wall permeable to potassium ions." Their influx causes the neuron to 'fire' more slowly and the transmission of electrical impulses is suppressed.

"Therefore, in overweight people, insulin probably indirectly inhibits the POMC neurons, which are responsible for the feeling of satiety, via the intermediary station of the SF-1 neurons," supposes the scientist. "At the same time, there is a further increase in food consumption." The direct proof that the two types of neurons communicate with each other in this way still remains to be found, however.

In order to find out how insulin acts in the brain, the Cologne-based scientists compared mice that lacked an insulin receptor on the SF-1 neurons with mice whose insulin receptors were intact. With normal food consumption, the researchers discovered no difference between the two groups. This would indicate that insulin does not exercise a key influence on the activity of these cells in slim individuals. However, when the rodents were fed high-fat food, those with the defective insulin receptor remained slim, while their counterparts with functional receptors rapidly gained weight. The weight gain was due to both an increase in appetite and reduced calorie expenditure. This effect of insulin could constitute an evolutionary adaptation by the body to an irregular food supply and extended periods of hunger: if an excess supply of high-fat food is temporarily available, the body can lay down energy reserves particularly effectively through the action of insulin.

It is not currently possible to say whether the findings of this research will eventually help to facilitate targeted intervention in the body's energy balance. "We are currently still very far away from a practical application," says Jens Brüning. "Our objective is to find out how hunger and the feeling of satiety arise. Only when we understand the entire system at work here, we will be able to start developing treatments."

**More information:** Tim Klöckener, Simon Hess, Bengt F. Belgardt, Lars Paeger, Linda A.W. Verhagen, Andreas Husch, Jong-Woo Sohn, Brigitte Hampel, Harveen Dhillon, Jeffrey M. Zigman, Bradford B. Lowell, Kevin W. Williams, Joel K. Elmquist, Tamas L. Horvath, Peter Kloppenburg, Jens C. Brüning, High-fat Feeding Promotes Obesity via Insulin Receptor/P13k-Dependent Inhibition of SF-1 VMH Neurons, *Nature Neuroscience*, June 5th 2011

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