



Hungry for rewards - insulin in the midbrain influences eating behaviour

Researchers at the Max Planck Institute for Neurological Research and the University of Cologne discover that insulin acts as a messenger in neurons of the midbrain and find a connection with the brain's reward system

Still hungry - or already full? The brain controls eating behaviour and curbs our appetite when the body has consumed enough energy. It obtains its information about the degree of satiety from various messenger substances, of which insulin plays an important role. Scientists at the Max Planck Institute for Neurological Research and the Cluster of Excellence in Cellular Stress Responses in Aging-associated Diseases (CECAD) at the University of Cologne have now discovered that in mice, insulin not only acts as a metabolic signal transmitter in the hypothalamus, a fact that is already known, but also in the dopamine-producing cells of the midbrain. The switching off of the insulin receptors in these neurons causes gluttony and overweight.

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The hormone insulin, which is produced in the pancreas, plays a key role in the regulation of blood sugar levels. Malfunctions of this system can result in overweight and diabetes mellitus. Researchers have already known for some years that this regulation of the body's energy balance is not limited to muscle and fat tissue. The research team working with Jens Brüning, Director of the Max Planck Institute for Neurological Research and scientific coordinator of the Cluster of Excellence in Cellular Stress Responses in Aging-associated Diseases (CECAD) at the University of Cologne, succeeded in demonstrating that insulin receptors are found in certain cells of the hypothalamus – an important 'command centre' in the midbrain. Insulin thus passes the blood-brain barrier, binds to nerve cells and gives the signal for satiety. If these receptors are not available, the brain lacks the crucial information that enables it to set the course for satiety: more food is consumed, the result of which is weight gain.

In the recently published study, the Cologne-based scientists report on their discovery of another insulin-dependent control circuit in the brain, namely in the dopaminergic cells of the midbrain. "We discovered a mechanism that is superior to the mechanism in the hypothalamus," explains Christine Köhner, first author of the publication and a member of Jens Brüning's research team in Cologne. A link with the brain's reward system was also established as the examined neurons contain dopamine: a neurotransmitter that is known as the "happy hormone" and which plays a role in addictive behaviour. Whether insulin has an inhibitory or stimulating effect on dopaminergic cells was unknown up to now. The scientists are certain that they have now identified another important tile in the complex mosaic of the regulation of the body's energy balance.

The researchers in Cologne availed of the knockout mouse method for their study. In order to examine the role of insulin in the living animal, the insulin receptors in the dopamine-producing neurons of the mice's midbrain were switched off. The insulin receptors are formed in these cells together with tyrosine hydroxylase – a key enzyme and marker for dopamine synthesis. The main result of the experiments was that the knockout mice became more gluttonous and gained more weight and body fat than their non-manipulated counterparts with intact insulin

receptors. Therefore, insulin clearly also plays a crucial role in these cells in the control of food consumption and energy balance. In addition, under certain test conditions, the knockout mice reacted differently to a sugar solution and cocaine. Both results indicate to the scientists that insulin plays a direct role as a transmitter in the brain's reward system.

Some questions remain to be answered. The scientists cannot currently explain precisely why the brain has an additional regulatory system. Their working hypothesis is that the hypothalamus maintains the stability of the energy balance, and the body's food intake and energy metabolic rate are adapted accordingly to the energy status. The brain therefore appears to incorporate the signals of the reward system via the dopaminergic cells of the midbrain. "The signals from the midbrain can overrun the hypothalamic system," explains Könner. Thus, with the availability of the corresponding reward, increased food intake may perhaps occur even if sufficient energy is already available. In other words, despite having long reached satiety, we still eat chocolate.

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