

How the brain controls peripheral metabolism in humans

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Over the last years, the human brain has been recognized as an insulin sensitive organ. Of note, only a limited number of brain areas respond to the peptide hormone. These include prefrontal areas that are crucial for the inhibitory control of behavior as well as higher visual areas where food stimuli are processed by the brain. One important function of insulin in those regions appears to be the modulation of eating behavior. Insulin also acts in the hippocampus, an important area for memory and cognition. Just as in animals, the human hypothalamus responds to insulin. This brain area is the center for the homeostatic control of the rest of the body and contributes to the modulation of peripheral insulin sensitivity as well as glucose fluxes throughout the body.

Similar to the periphery, the brain can become insulin resistant. This condition is associated with abdominal obesity, increasing age, elevated levels of circulating saturated free fatty acids as well as a number of genetic variants that predispose for obesity.

Research from our department and others demonstrated that brain insulin action improves peripheral insulin sensitivity in humans. Brain-derived signals reach peripheral tissues mainly via the autonomic nervous system.

Using hyperinsulinemic-euglycemic clamps, we recently demonstrated that insulin administration to the human brain improves peripheral insulin sensitivity by suppressing endogenous glucose production and stimulating glucose uptake into tissue. This mechanism is, however, only detectable in lean and healthy but not in obese volunteers (who are brain insulin resistant).

The modulation of peripheral insulin sensitivity by brain insulin action appears to be strongly dependent on the prandial state. In the postprandial situation (where brain insulin action occurs in physiology), brain-derived outflows improve peripheral insulin sensitivity to suppress endogenous glucose production and stimulate glucose uptake into tissue. In contrast, under fasting conditions, the brain responds to insulin and parasympathetic outflows are activated, however, this does not translate into beneficial metabolic effects.

Thus, overcoming brain insulin resistance will likely result in metabolic benefits like improved glucose tolerance and reduced dia-

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betes risk. Besides these metabolic effects, restored brain insulin action will have positive results also directly in the brain where it could shift eating behavior towards a healthy diet, improve cognitive function and even reduce the risk for neurodegenerative processes. Strategies to improve brain insulin sensi-

tivity that are currently investigated include weight loss as well as the applications of various types of antidiabetic drugs.

Thus, the brain as the metabolic mastermind is an excellent novel target to prevent and treat metabolic diseases and complications thereof.