Anti-obesity drug improves associative learning in people with obesity: Study

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To control our behavior, the brain must be able to form associations. This involves, for example, associating a neutral external stimulus with a consequence following the stimulus (e.g., the hotplate glows red—you

can burn your hand). In this way, the brain learns what the implication of our handling of the first stimulus are.

Associative learning is the basis for forming neural connections and gives stimuli their motivational force. It is essentially controlled by a brain region called the dopaminergic midbrain. This region has many receptors for the body's signaling molecules, such as insulin, and can thus adapt our behavior to the physiological needs of our body.

But what happens when the body's insulin sensitivity is reduced due to obesity? Does this change our brain activity, our ability to learn associations and thus our behavior?

Researchers at the Max Planck Institute for Metabolism Research have now measured how well the learning of associations works in participants with normal body weight (high insulin sensitivity, 30 volunteers) and in participants with obesity (reduced insulin sensitivity, 24 volunteers), and if this learning process is influenced by the anti-obesity drug liraglutide. The research is published in *Nature Metabolism*.

Low insulin sensitivity reduces the brain's ability to associate sensory stimuli.

In the evening, they injected the participants with either the drug liraglutide or a placebo in the evening. Liraglutide is a so-called GLP-1 agonist, which activates the GLP-1 receptor in the body, stimulating insulin production and producing a feeling of satiety. It is often used to treat obesity and type 2 diabetes and is given once a day.

The next morning, the subjects were given a learning task that allowed the researchers to measure how well associative learning works. They found that the ability to associate sensory stimuli was less pronounced in

participants with obesity than in those of normal weight, and that brain activity was reduced in the areas encoding this learning behavior.

After just one dose of liraglutide, participants with obesity no longer showed these impairments, and no difference in brain activity was seen between participants with normal weight and obesity. In other words, the drug returned the brain activity to the state of normal-weight subjects.

"These findings are of fundamental importance. We show here that basic behaviors such as associative learning depend not only on external environmental conditions but also on the body's metabolic state," says study leader Marc Tittgemeyer from the Max Planck Institute for Metabolism Research.

"So, whether someone has overweight or not also determines how the brain learns to associate sensory signals and what motivation is generated. The normalization we achieved with the drug in subjects with obesity, therefore, fits with studies showing that these drugs restore a normal feeling of satiety, causing people to eat less and therefore lose weight."

"While it is encouraging that available drugs have a positive effect on brain activity in obesity, it is alarming that changes in brain performance occur even in young people with obesity without other medical conditions. Obesity prevention should play a much greater role in our health care system in the future. Lifelong medication is the less preferred option in comparison primary prevention of obesity and associated complications," says Ruth Hanßen, first author of the study and a physician at the University Hospital of Cologne.

More information: Liraglutide restores impaired associative learning in people with obesity, *Nature Metabolism* (2023). DOI: 10.1038/s42255-023-00859-y

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