A metabolic switch to turn off obesity

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This is an image of a weight scale. Credit: CDC/Debora Cartagena

You've tried all the diets. No matter: you've still regained the weight you lost, even though you ate well and you exercised regularly! This may be due to a particular enzyme in the brain: the alpha/beta hydrolase domain-6 enzyme, better known as ABHD6. A study published this week in *Cell Reports* demonstrates that when this enzyme is blocked in certain neurons of the mouse hypothalamus, it becomes impossible for them to lose weight, even if they adhere to an ideal regimen... ideal for mice that is!

A research team at the University of Montreal Hospital Research Centre (CRCHUM) has generated genetically engineered mice, deprived of the ABHD6 enzyme in a localized area of the brain, namely in a specific population of hypothalamic neurons. Alexandre Fisette, postdoctoral researcher at CRCHUM and first author of the study, explains that, "under normal conditions of housing and food, these mice are identical to normal mice. However, when challenged, they are unable to adapt. They no longer consume food after a fast, they cannot maintain their body temperature during exposure to cold, and they are more susceptible to become obese when fed a high-fat diet. What's more, once they are obese and we try to make them lose weight by feeding them a normal diet, they do not lose weight."

The researchers have discovered that this enzyme acts as a sort of switch for the body's adjustment to extremes. "It is a mechanism we had not suspected. Strikingly, the absence of one single enzyme within a precise region of the brain completely disrupts the normal metabolism and prevents the mice from losing weight," comments Thierry Alquier, CRCHUM researcher and professor at the University de Montréal.

Is there an identical process taking place in humans? Thierry Alquier thinks that clinical studies will be required to find out. However, according to Alquier, "ABHD6 has a key role in the rebound effect that is often observed after a dietary regimen. People who experience difficulty losing weight might have a deficiency of this enzyme."

Weight is controlled by several signals. Scientists have known for a long time that endocannabinoids - molecules secreted by the brain - are involved in the ingestion of nutrients and the expenditure of energy. The endocannabinoids stimulate appetite. Thus, this is an interesting area of exploration in the search for an appetite-suppressant drug. But all the products developed until now have been associated with serious side effects.

The pursuit of the ABHD6 enzyme appears to be promising. In 2014, the team of Marc Prentki, another CRCHUM researcher, discovered that this enzyme breaks down endocannabinoids. Blocking ABHD6 in peripheral organs and adipose tissues protects against obesity and against type 2 diabetes.

"We know today that ABHD6 plays a completely different role in certain neurons of the hypothalamus. Blocking the enzyme in this location promotes obesity, whereas blocking it elsewhere in the body has beneficial effects," emphasizes Stephanie Fulton, CRCHUM researcher and study co-author.

Multiple signals and neuronal networks are involved in regulating the balance of energy so as to maintain a stable body weight. "We have shown the critical part played by the ABHD6 enzyme in preserving homeostasis in specific neurons of the hypothalamus. But we don't know what happens when we block the enzyme in the entire brain. This is what we are currently investigating in an ongoing study," the researcher explains.

Many more years of research will be needed to develop an effective treatment for obesity. As science advances, we learn that weight management does indeed take place inside the head, but that it is not necessarily a question of lack of will.

More information: Alexandre Fisette et al, α/β-Hydrolase Domain 6 in the Ventromedial Hypothalamus Controls Energy Metabolism Flexibility, *Cell Reports* (2016). DOI: 10.1016/j.celrep.2016.10.004

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