Growth hormone acts to prevent weight loss

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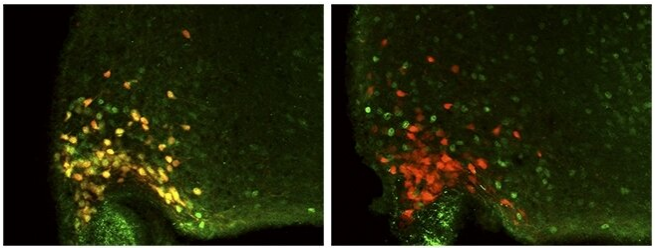

A Brazilian study shows that, like leptin, growth hormone contributes directly to energy conservation when the body loses weight . Credit: AgRP neurons in GH receptor knockout mice (right); AgRP neurons in control mice (left) / *Nature Communications*

Researchers at the University of São Paulo (USP) in Brazil have discovered that growth hormone (GH), which stimulates skeletal maturation and linear bone growth, as well as helping maintain tissue and organs throughout life, also acts directly on the brain to conserve energy when the body loses weight.

A paper on the discovery has just been published in the journal *Nature Communications*. "Growth hormone has been known for decades, but our discovery shows it does a lot more than was thought," said José Donato Junior, a professor at the University of São Paulo's Biomedical Science Institute (ICB-USP) and one of the authors of the paper.

"GH receptors are found in large quantities in muscle and tissue, in the liver, and in organs directly involved in growth metabolism, but we found that the brain is also full of GH receptors. This is entirely new," Donato said.

"We also found that brain GH is not only involved in growth metabolism, but above all, influences the metabolic responses that conserve energy when we're hungry or on a diet. This discovery, which is also new to science, has important implications in terms of understanding why it's so hard to lose weight."

In addition to researchers affiliated with ICB-USP, the group also included scientists at the University of São Paulo's Ribeirão Preto Medical School (FMRP-USP), Argentina's La Plata National University (UNLP), and Ohio University in the United States.

"For decades, scientists have been trying to understand why it's so difficult to maintain the weight achieved after the sacrifices of a successful diet and why it's so easy to regain the lost weight. Leptin has hitherto been considered the main hormone that acts to conserve energy when we're hungry," Donato said.

Bloodstream leptin levels are known to fall in response to weight loss, he explains, but this knowledge has never resulted in the creation of a successful diet or therapy with leptin that could enable subjects to lose weight and not regain it soon afterwards.

"The weight loss process evidently involves several metabolic processes and several hormones besides leptin. This is where GH comes in. We found that in response to weight loss, GH acts on the brain in a similar way to leptin. However, while leptin levels fall, the opposite happens to GH. Weight loss triggers a rise in bloodstream levels of GH," Donato said. "In the recently published article, we show that central growth hormone signaling also promotes neuroendocrine adaptations during food deprivation."

GH receptors in the brain are located in the hypothalamus, the highest center of the autonomic nervous system. Impulses from the hypothalamus influence the cells of the neurovegetative system and regulate smooth muscle tissue in the gut and blood vessels, cardiac muscle, all glands, and the kidneys, among other organs.

The researchers found that GH receptors in the

hypothalamus specifically activate a small population of neurons called AgRP, which is short for agouti-related protein. AgRP neurons in turn increase the production of AgRP, which increases appetite and diminishes energy metabolism and expenditure.

"AgRP is one of the most powerful appetite stimulants. It's curious to see how a small number of AgRP neurons, only a few thousand out of the billions of neurons in the hypothalamus, can play such an important role," Donato said.

Energy conservation

To conduct a detailed study of the influence of GH signaling on AgRP neurons, the scientists at USP and colleagues bred genetically modified mice with AgRP-specific GH receptor ablation (called AgRP GHR knockout mice). Their experiments also used a control group comprising wild-type mice that were not genetically modified.

In various experiments, the researchers measured whole-body energy expenditure in the two groups of mice when subjected to a diet with 60 percent food restriction. Their aim was to determine whether a lack of adaptive response to the resulting energy deficit would have a significant impact on energy balance.

They found that the control mice decreased energy expenditure during food restriction, which is consistent with the adaptive responses that conserve energy in this situation.

Energy expenditure by the AgRP GHR KO mice during food restriction decreased significantly less, suggesting that they did not save energy as efficiently as the control mice.

As a result, the AgRP GHR KO mice displayed a higher rate of weight loss, owing primarily to decreased fat mass (energy reserves) but also to loss of lean mass (vital organs, bone, muscle, ligaments, tendons, and body fluids).

"In other words, we discovered that weight loss triggers an increase in hypothalamus GH levels, which activates the AgRP neurons, making weight loss harder and intensifying the sense of hunger. That's precisely the same function leptin performs," Donato said.

Energy conservation is so important to the organism, he added, that evolution has endowed humans with two energy conservation mechanisms, one activated by leptin and the other by GH.

"One functions as a backup for the other. This is why weight loss treatments based solely on leptin don't work. The GH mechanism has to be dealt with at the same time," Donato said.

More information: Isadora C. Furigo et al, Growth hormone regulates neuroendocrine responses to weight loss via AgRP neurons, *Nature Communications* (2019). DOI: 10.1038/s41467-019-08607-1

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