Rare leptin variants found in two children, leading to hyperphagia and obesity

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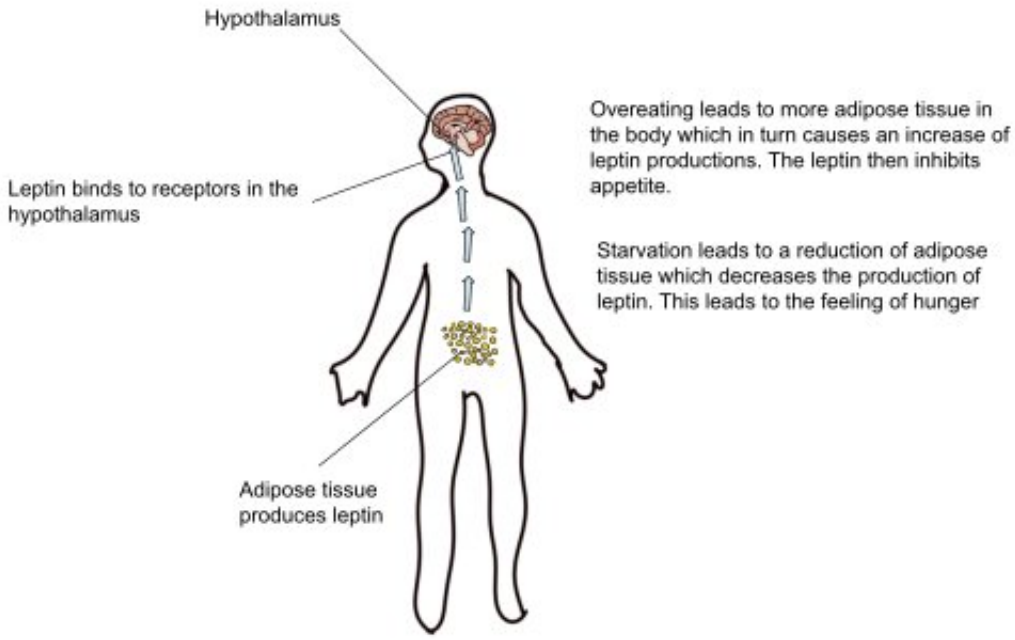

Diagram representing the production of the leptin hormone in the human body. It shows the affected organ and explains how leptin affects the human body. Credit: Andrmuno704/Wikimedia Commons, CC BY-SA

An international team of doctors and medical scientists has found two rare leptin variants in two children. Both variants led to hyperphagia and

obesity. In their study, reported in *The New England Journal of Medicine*, the group found mutations in genes responsible for leptin production and explored how they impacted eating behavior in the patients.

In this effort, the research team were presented with two children, one a 14-year-old boy, the other a 2-year-old girl. Both were suffering from obesity and hyperphagia, in which the desire to eat is not suppressed once food is consumed. The work began with a look at the genetic profiles of both patients—both were found to have mutations in the genes responsible for producing leptin, a hormone that under normal circumstances sends signals to the brain telling it to suppress hunger pangs. The two mutations were not the same, but both led to the same problem—overeating.

Next, blood tests showed that both children had abnormally high levels of leptin in their systems, an indication that the hormone was clearly attempting to tell the brain to suppress the urge to eat. This finding ruled out diseases such as Bardet-Biedl and Prader-Willi syndrome.

The team then tested the behavior of leptin samples from both children in a petri dish. They found that binding occurred between leptin proteins and receptors, as was expected. But they also found that the leptins were not able to send signals, which explained why the children always felt like they were starving.

To treat the problem, the team gave both patients metreleptin, a synthetic type of leptin. Initial testing showed no improvements, prompting the team to raise the dose. Soon thereafter, both children began to lose weight. In addition to the metreleptin, both children were put on a diet and exercise regimen to stimulate proper signaling and eating. Over time, both slimmed down to normal weights for their age groups as their appetites waned.

The research team says that both patients began producing metreleptin antibodies, which lessened the lifespan of the hormone, but not enough to prevent them from signaling.

More information: Jan-Bernd Funcke et al, Rare Antagonistic Leptin Variants and Severe, Early-Onset Obesity, *New England Journal of Medicine* (2023). DOI: 10.1056/NEJMoa2204041