New model system may better explain regulation of body weight

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A new mathematical model of the physiological regulation of body weight suggests a potential mechanism underlying the difficulty of losing weight, one that includes aspects of two competing hypotheses of weight regulation. In the January issue of *Cell Metabolism*, Massachusetts General Hospital (MGH) investigators outline a system in which there may be several steady states to which an animal's weight tends to gravitate, rather than a single "set point."

"There are problems with both of the current hypotheses for how the body balances energy intake and expenditure to maintain a stable weight," explains Joshua Tam, a doctoral student working in the Steele Laboratory in the MGH Department of Radiation Oncology, lead author of the study. "While our model has its own limitations, if it holds up, it may help us better understand the body's system for weight regulation."

The well-known tendency for body weight to remain stable in spite of changes in diet or energy expenditure - observed in both humans and other mammals - led to the development of the "set-point" hypothesis, which holds that an individual's metabolism acts to oppose changes to a physiologically predetermined body weight. Opponents of that theory, who argue that a natural set-point would prevent the development of obesity in the first place, argue that the body's weight "settling point" is determined solely by environmental factors, such as the availability of food, along with physical activity and other behavioral factors. Opposing the settling point theory are study results showing that, if given access only to low-calorie foods, some animals will maintain their weight by increasing the amount of food they consume, supporting a tendency to return to an established weight.

Earlier attempts to develop mathematical models of metabolic weight regulation did not specifically include the neuroendocrine signals that act on the central nervous system to control both food intake and energy expenditure. Tam's model focuses on the pathway controlled by leptin, a hormone produced by fat cells that helps to regulate energy metabolism. Although low leptin levels are a starvation signal leading to increased food consumption and reduced energy expenditure, mutations that disable the leptin pathway are extremely rare. In fact, obese individuals usually have elevated leptin levels and show evidence of resistance to leptin's effects.

The equations Tam used to model energy regulation in mice were based on two sets of assumptions - one based on the set-point hypothesis, the other on the settling point theory. But neither of the models accurately reflected experimental data from earlier studies, and both continued to have the previously mentioned limitations. However, a model that combined aspects of both theories did seem to fit. Under that combination model, set-point-maintaining signals only become active when leptin levels drop below a defined threshold, at normal leptin levels, weight varied depending on the animals' food intake and activity level.

When adjusted to account for leptin resistance, the model predicted that resistance-susceptible animals that had elevated leptin levels would tend to maintain an elevated weight. Only if leptin levels could be brought below what the researchers call the tipping point would resistant animals be able to reach and maintain a stable reduced weight. This model accounts for both those fortunate, leptin-sensitive individuals who stay at a normal body no matter their food intake and leptin-resistant individuals who find it difficult to achieve and maintain weight loss.

"Our animal model was based on limited data, so its predictive value needs to be verified experimentally, and it can be further improved by the inclusion of other physiological factors," says Tam, a student in the Harvard-MIT Health Sciences and Technology Program. "If human body weight exhibits the multi-steady-state phenomenon that our model predicts, and if methods could be developed - either drugs or lifestyle changes - to ease the transition between those states, it may be possible to develop new therapies to help reduce body weight and sustain those changes."

Source: Massachusetts General Hospital

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