Ghrelin likely involved in why we choose 'comfort foods' when stressed

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We are one step closer to deciphering why some stressed people indulge in chocolate, mashed potatoes, ice cream and other high-calorie, high-fat comfort foods.

UT Southwestern Medical Center-led findings, in a mouse study, suggest that ghrelin – the so-called "hunger hormone" – is involved in triggering this reaction to high stress situations.

"This helps explain certain complex eating behaviors and may be one of the mechanisms by which obesity develops in people exposed to psychosocial stress," said Dr. Jeffrey Zigman, assistant professor of internal medicine and psychiatry and senior author of a study appearing online today and in a future print edition of the *Journal of Clinical Investigation.* "We think these findings are not just abstract and relevant only to mice, but likely are also relevant to humans."

Scientists know that fasting causes ghrelin to be released from the gastrointestinal tract, and that the hormone then plays a role in sending hunger signals to the brain. Dr. Zigman's laboratory has previously shown that chronic stress also causes elevated ghrelin levels, and that behaviors generally associated with depression and anxiety are minimized when ghrelin levels rise. In mice, these stress-induced rises in ghrelin lead to overeating and increased body weight, suggesting a mechanism for the increased prevalence of weight-related issues observed in humans with chronic stress and depression.

For this investigation, the researchers developed a mouse model to determine which hormones and what parts of the brain may play a role in controlling more complex eating behaviors that occur upon stress, particularly those that lead to the indulgence of comfort foods.

They subjected mice to a standard laboratory technique that induces social stress by exposure to more dominant "bully" mice. Such animals have been shown to be good models for studying depression and the effects of chronic stress and depression in humans.

Wild-type mice subjected to the stress gravitated toward a chamber where they had been trained to find pleasurable, fatty food – the mouse equivalent of "comfort food." However, genetically-engineered mice, which were not able to respond to stress-induced increases in ghrelin, showed no preference toward the fatty food-paired chamber, and when exposed to the fatty food, did not eat as much as the wild-type animals.

"Our findings show that ghrelin signaling is crucial to this particular behavior and that the increase in ghrelin which occurs as a result of chronic stress is probably behind these food-reward behaviors," Dr. Zigman said.

The study also showed that these effects of ghrelin are due to direct interaction with a subset of neurons that use catecholamines as a neurotransmitter. These include dopaminergic neurons in the brain's ventral tegmental area, which is known to be associated with pleasure and reward behaviors.

The findings, he said, may make sense when considered from an evolutionary standpoint.

Our hunter-gatherer ancestors needed to be as calm as possible when it was time to venture out in search of food, or risk becoming dinner

themselves, said Dr. Zigman, who pointed out that ghrelin's anti-depressant effects and its actions to help efficiently secure calorically-dense, tasty foods may have provided a survival advantage.

"Though it might have been beneficial to have these actions of ghrelin linked, now it seems to be a cause of a lot of morbidity in our modern society," Dr. Zigman said. "Ultimately, these linkages also may present a large challenge to the development of therapeutics to treat and/or prevent obesity."

The researchers next plan to investigate the molecular mechanisms by which ghrelin acts to cause these stress-associated food-reward behaviors.

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