Molecule shuts down food intake and turns on 'siesta mode'

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Researchers have identified a molecule that tells your brain your stomach is full – signaling that it's time to say no to a second piece of pumpkin pie and push back from the Thanksgiving table.

In studies with mice and rats, researchers have found that a chemical messenger called NAPE is made in the small intestine after the animals ate a greasy meal. After eating, NAPE – N-acylphosphatidylethanolamine, a mouthful in itself -- enters the blood and travels to the brain, where it quashes hunger signals. Rats treated with extra NAPE for five days ate less and lost weight, hinting that studying NAPE could help researchers design better appetite suppressants or obesity drugs.

Howard Hughes Medical Institute investigator Gerald Shulman at Yale School of Medicine led the research team, which reported its findings in the November 26, 2008, issue of the journal *Cell*. Shulman's research group is well known for its work on understanding how insulin resistance develops and leads to diabetes. In the course of that research, his team developed a sensitive system to identify and measure lipids in tissue samples. After seeing the power of that system in his diabetes research, Shulman was eager to see if it might also be applied to understanding obesity.

Some 300 million adults worldwide are severely overweight and at risk for life-threatening illnesses such as type 2 diabetes and cardiovascular disease. But obesity is difficult to treat. "We do not have good medical

therapies for obesity," Shulman says, noting that the small number of diet drugs on the market now come with intolerable side effects and have only modest impacts on weight. "It's very important to find other targets that might affect food intake."

Despite many years studying the physiology of appetite and hunger, researchers still do not have a clear picture of how the brain keeps tabs on fat consumption. Fat is effective at satisfying hunger, so Shulman and his colleagues at Yale and the University of Cincinnati decided to see if they could find out whether the brain senses lipid intake directly. If they could learn how that happens, they suspected, their findings might point toward a new treatment for obesity.

The team used Shulman's lipid analysis system to investigate what happens to fat that enters the blood after ingesting a high-fat meal. The scientists reasoned that the fat derivatives that enter the bloodstream might themselves serve as messengers to signal the brain that the body has been fed. They used this approach to compare the lipids present in blood plasma from rats that had fasted or eaten, and they zeroed in on NAPE.

They found only low levels of NAPE in the blood of rats that had fasted for 12 hours. The level of NAPE shot up 40 to 50 percent in animals that had dined on high-fat chow. Furthermore, NAPE didn't increase in rodents that ate only protein or carbohydrate, suggesting that NAPE levels reflect the amount of fat eaten in a meal.

The researchers found that when they injected synthetic NAPE into the abdominal cavity or blood, the rodents' appetites diminished substantially. The more NAPE they received, the less food they ate. "It's really quite effective," Shulman says. "At the highest doses, it keeps the animals from eating for up to 12 hours." At a low dose—comparable to the spike in NAPE that occurs naturally after a meal—the rodents still

ate 25 percent less than controls. They even acted full, going into "siesta mode" as if they had just eaten, Shulman says, noting that additional tests confirmed that the animals were only lethargic, not ill or incapacitated.

When the researchers delivered tiny amounts of NAPE directly into the brain, it had the same effect as a larger dose delivered to the blood. This suggests that the compound communicates directly with the brain, Shulman says.

Indeed, they found that NAPE injected into the blood did cross the blood-brain barrier and was concentrated in the hypothalamus, a specific region of the brain that governs hunger. There, they found that NAPE calmed neurons that stimulate appetite. The team made those conclusions after inspecting brain samples that had been stained to reveal the cells in which NAPE was active. "Most appetite regulation is hypothalamic, so we were excited that [NAPE] was working centrally," Shulman says. "That suggests [NAPE] is involved in the gut-brain axis. It's a way the gut communicates to the brain that there's energy coming in and you need to shut down food intake."

The team next wanted to know if NAPE would stay effective with longer-term treatment, so they outfitted 22 rats with vests that allowed them to move freely in their cages while they hooked up to an IV that dispensed NAPE. The vests permitted the rats to eat, sleep, and rest while still receiving infusions of NAPE. Over five days, control rats continued to gain weight normally, but NAPE-treated rats ate less and lost ten percent of their body weight—while appearing otherwise well and healthy.

Shulman and his team are now monitoring NAPE levels in humans, to see if they rise after a meal the same way they do in rodents. They also plan to test NAPE for effects on appetite in non-human primates. If these studies parallel the results they have observed in mice and rats,

Shulman says, a clinical trial with NAPE or NAPE-like compounds may be on the horizon.

Source: Howard Hughes Medical Institute