Why diets don't work? Starved brain cells eat themselves

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A report in the August issue of the Cell Press journal *Cell Metabolism* might help to explain why it's so frustratingly difficult to stick to a diet. When we don't eat, hunger-inducing neurons in the brain start eating bits of themselves. That act of self-cannibalism turns up a hunger signal to prompt eating.

"A pathway that is really important for every cell to turn over components in a kind of housekeeping process is also required to regulate appetite," said Rajat Singh of Albert Einstein College of Medicine.

The cellular process uncovered in neurons of the brain's hypothalamus is known as autophagy (literally self-eating.) Singh says the new findings in mice suggest that treatments aimed at blocking autophagy may prove useful as hunger-fighting weapons in the war against obesity.

The new evidence shows that lipids within the so-called agouti-related peptide (AgRP) neurons are mobilized following autophagy, generating free fatty acids. Those fatty acids in turn boost levels of AgRP, itself a hunger signal.

When autophagy is blocked in AgRP neurons, AgRP levels fail to rise in response to starvation, the researchers show. Meanwhile, levels of another hormone, called □-melanocyte stimulating hormone, remain elevated. That change in body chemistry led mice to become lighter and leaner as they ate less after fasting, and burned more energy.

Autophagy is known to have an important role in other parts of the body as a way of providing energy in times of starvation. However, unlike other organs, earlier studies had shown the brain to be relatively resistant to starvation-induced autophagy.

"The present study demonstrates the unique nature of hypothalamic neurons in their ability to upregulate autophagy in response to starvation that is consistent with the roles of these neurons in feeding and energy homeostasis," the researchers wrote.

Singh said he suspects that fatty acids released into the circulation and taken up by the hypothalamus as fat stores break down between meals may induce autophagy in those AgRP neurons. Singh's research earlier showed a similar response in the liver.

On the other hand, he says, chronically high levels of fatty acids in the bloodstream, as happens in those on a high-fat diet, might alter hypothalamic lipid metabolism, "setting up a vicious cycle of overfeeding and altered energy balance." Treatments aimed at the pathway might "make you less hungry and burn more fat," a good way to maintain energy balance in a world where calories are cheap and plentiful.

The findings might also yield new insight into metabolic changes that come with age given that autophagy declines as we get older. "We already have some preliminary evidence there might be changes with age," Singh said. "We are excited about that."

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