

# Vicious cycle: Obesity sustained by changes in brain biochemistry

May 16 2013

---

With obesity reaching epidemic levels in some parts of the world, scientists have only begun to understand why it is such a persistent condition. A study in the *Journal of Biological Chemistry* adds substantially to the story by reporting the discovery of a molecular chain of events in the brains of obese rats that undermined their ability to suppress appetite and to increase calorie burning.

It's a [vicious cycle](#), involving a breakdown in how [brain cells](#) process key proteins, that allows obesity to beget further obesity. But in a finding that might prove encouraging in the long term, the researchers at Brown University and Lifespan also found that they could intervene to break that cycle by fixing the [core protein](#)-processing problem.

Before the study, scientists knew that one mechanism in which obesity perpetuates itself was by causing resistance to leptin, a hormone that signals the brain about the status of fat in the body. But years ago senior author Eduardo A. Nillni, professor of medicine at Brown University and a researcher at Rhode Island Hospital, observed that after meals obese [rats](#) had a dearth of another key hormone—alpha-MSH—compared to rats of normal weight.

Alpha-MSH has two jobs in parts of the [hypothalamus](#) region of the brain. One is to suppress the activity of food-seeking brain cells. The second is to signal other brain cells to produce the hormone TRH, which prompts the [thyroid gland](#) to spur calorie burning activity in the body.

In the obese rats alpha-MSH was low, despite an abundance of leptin and despite normal levels of [gene expression](#) both for its biochemical [precursor protein](#) called pro-opiomelanocortin (POMC) and for a key enzyme called PC2 that processes POMC in brain cells. There had to be more to the story than just leptin, and it wasn't a problem with expressing the needed genes.

Nilni and his co-authors, including lead authors Isin Cakir and Nicole Cyr, conducted the new study to find out where the alpha-MSH deficit was coming from. Nilni said he suspected that the problem might lie in the brain cells' mechanism for processing the POMC protein to make alpha-MSH.

## **Protein processing problems**

To do their work, the team fed some rats a high-calorie diet and fed others a normal diet for 12 weeks. The overfed rats developed the condition of "diet-induced obesity." The team then studied the hormone levels and brain cell physiology of the rats. They also tested their findings by experimenting with the biochemistry of key individual cells on the lab bench.

They found that in the obese rats, a key "machine" in the brain cells' assembly line of protein-making, called the endoplasmic reticulum (ER), becomes stressed and overwhelmed. The overloaded ER apparently fumbles the proper handling of PC2, perhaps discarding it because it can't be folded up properly. The PC2 levels they measured in obese rats, for example, were 53 percent lower than in normal rats. Alpha-MSH peptides were also barely more than half as abundant in obese rats as they were in healthy rats.

"In our study we showed that what actually prevents the production of more alpha-MSH peptide is that ER stress was decreasing the

biosynthesis of POMC by affecting one key enzyme that is essential for the formation of alpha-MSH," Nillni said. "This is so novel. Nobody ever looked at that."

Novel as it was, the story—a stressed ER mishandles PC2, which leaves POMC unfolded, which impedes alpha-MSH production—needed experimental confirmation.

The team provided that confirmation in several ways: In obese rats they measured elevated levels of known markers of ER stress. They also purposely induced ER stress in cells using pharmacological agents and saw that both PC2 and Alpha-MSH levels dropped.

Next they conducted an experiment to see if fixing ER stress would improve alpha-MSH production. They treated lean and obese rats for two days with a chemical called TUDCA, which is known to alleviate ER stress. If ER stress is responsible for alpha-MSH production problems, the researchers would see alpha-MSH recover in obese rats treated with TUDCA. Sure enough, while TUDCA didn't increase alpha-MSH production in normal rats, it increased it markedly in the obese rats.

Similarly on the benchtop they took mouse neurons that produce PC2 and POMC and pretreated some with a similar chemical called PBA that prevents ER stress. They left others untreated. Then they induced ER stress in all the cells. Under that ER stress, those that had been pretreated with PBA produced about twice as much PC2 as those that had not.

Nilni cautioned that although his team found ways to restore PC2 and alpha-MSH by treating [ER stress](#) in living rats and individual cells, the agents used in the study are not readily applicable as medicines for treating obesity in humans. There could well be unknown and unwanted side effects, for example, and TUDCA is not approved for human use by

the U.S. Food and Drug Administration.

But by laying out the exact mechanism responsible for why the brains of the obese rats failed to curb appetite or spur greater calorie burning, Nilni said, the study points drug makers to several opportunities where they can intervene to break this new, vicious cycle that helps obesity to perpetuate itself.

"Understanding the central control of energy-regulating neuropeptides during diet-induced obesity is important for the identification of therapeutic targets to prevent and or mitigate [obesity](#) pathology," the authors wrote.

Provided by Brown University

Citation: Vicious cycle: Obesity sustained by changes in brain biochemistry (2013, May 16) retrieved 27 April 2024 from

<https://medicalxpress.com/news/2013-05-vicious-obesity-sustained-brain-biochemistry.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.