

Diet switching can activate brain's stress system, lead to 'withdrawal' symptoms

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In research that sheds light on the perils of yo-yo dieting and repeated bouts of sugar-bingeing, researchers from The Scripps Research Institute have shown in animal models that cycling between periods of eating sweet and regular-tasting food can activate the brain's stress system and generate overeating, anxiety, and withdrawal-like symptoms.

The research is being published in an advance, online Early Edition of the journal *Proceedings of the National Academy of Sciences* (PNAS) the week of November 9, 2009.

"When many people diet, they try to avoid fattening foods that taste good, but ultimately end up going back to their regular eating habits," said senior author Eric Zorrilla, Ph.D., an associate professor and member of the Pearson Center for Alcoholism and Addiction Research and Harold L. Dorris Neurological Research Institute at Scripps Research. "We found that rats cycled in this way between palatable food and less tasty, but otherwise acceptable, food, begin to binge on the sweet food, stop eating their regular food, and show withdrawal-like behaviors often associated with drug addiction. As in addiction to drugs or ethanol, the brain's stress system is involved in each of these changes."

"Our research suggests that this eating pattern leads to a vicious circle," explained Pietro Cottone, Ph.D., who is co-first author of the paper with Valentina Sabino, Ph.D.; both are former postdoctoral fellows at Scripps Research who are now assistant professors and co-directors of the Laboratory of Addictive Disorders at Boston University School of

Medicine. "The more you cycle this way, the more likely it is you cycle again. Having a 'free day' in your diet schedule is a risky habit."

Seeking Pleasure, Avoiding Pain

According to the U.S. Department of Health and Human Services, about two-thirds of the adult population of the United States is overweight or obese, conditions that cost the country an estimated \$117 billion in terms of medical expenses and lost productivity. Understanding the factors that underpin overeating and that undermine attempts at weight loss is important for addressing this major public health concern.

Instead of focusing on the positive motivation derived from eating pleasurable food—which had previously been the gist of much research in the field—the Scripps Research team took a new tack and focused on the questions of whether negative reinforcement, which is thought to drive compulsive drug intake, may play a similar role in excessive eating and whether the brain's stress system was involved in this process.

Cottone explained, "For example, I can be motivated to work hard because I get praise from my boss—that's positive reinforcement. Conversely, I can work hard to avoid being fired—that's negative reinforcement. Similarly, I can either eat a lot for the pleasure of eating, or I can eat a lot to relieve the stress of not having certain foods. We wanted to know if negative factors were involved."

To examine this question, the researchers divided the rats into two groups. The first group was fed alternating cycles of five days of regular chow and two days of sweet chow. The second group ate only regular-tasting food. The amount of food consumed was not restricted for either group.

When the researchers examined the results, they found that the two

groups showed different patterns of behavior. When the diet-cycled rodents were fed regular chow, they put less effort into obtaining the previously acceptable food, ate less, and were more likely to avoid anxiety-provoking situations. When they returned to a diet of sweet food, their anxiety-related behaviors returned to normal, but they ate more than they needed. The control group showed none of these effects.

A Diet that Causes Stress

Next, the researchers looked at the involvement of the brain's stress system—which had been shown to contribute to patterns of drug and alcohol binging and withdrawal—in underpinning these behaviors.

To do this, the team measured levels of stress-related corticotropin-releasing factor (CRF) mRNA and peptide in an area of the brain known as the central amygdala, which is involved in fear, anxiety, and stress responses. Indeed, the researchers found that the diet-cycled group on normal chow displayed five times the control group's levels of CRF. Only when the diet-cycled group was fed sweet food did CRF levels return to normal.

"CRF is a key stress neuropeptide," said Cottone. "In observing the activation of the amygdaloid CRF system during abstinence from sweet foods, we understood the causes of recurrent dieting failures."

Zorrilla pointed out that the increase in stress was due to the withdrawal state, rather than to outside factors.

"People will often say they are eating bad foods or fail a diet because they 'are stressed,'" he said. "Our findings suggest that intermittently eating sweet food changes the brain's stress system so that you might feel stressed, even though nothing that terrible has happened. In other words, you might be self-medicating stress-like symptoms of abstinence with

that piece of pie. Or, the adaptations in your brain stress system might make you more reactive to otherwise minor stressors."

To confirm these results and to see whether blocking CRF could reverse some of the effects of diet cycling, the researchers turned to a compound called R121919 (a small molecule CRF1 receptor antagonist).

When administered to the diet-cycled rats, the compound blunted the bingeing on sweet chow, as well as the lackluster pursuit of regular chow and the anxiety-associated behaviors during this part of the diet cycle. As in similar studies modeling alcoholism, on a molecular level diet-cycled rats showed greater sensitivity to the ability of the CRF1 receptor antagonist to reduce central amygdala synaptic transmission of the neurotransmitter GABA, which plays an important role in regulating neuronal excitability.

"We believe we may have identified part of the neurochemical basis underlying behavioral adaptations that can result from yo-yo dieting," said Zorrilla. "The mechanism corresponds to what is colloquially known as the 'dark side' of addiction to drugs of abuse or ethanol, supporting the idea that the brain shows addiction-like adaptations to intermittent eating of palatable food."

An Unhealthy Cycle

While many questions remain, the study helps explain how a pattern yo-yo dieting can be established and why it is usually ineffective in promoting weight loss. The study also underlines the health risks of such an eating pattern, as activation of the brain's [stress](#) system has been linked not only to emotional disorders, but also to conditions such as heart disease.

"The findings suggest that frequent dieting with frequent relapse is

worse than dieting by itself," said Cottone.

In addition, the research opens the door to potential development of a drug therapy to assist people escape an unhealthy cycle of eating.

Source: The Scripps Research Institute ([news](#) : [web](#))

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