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New data analysis supports hedonic overdrive model in high-fat diet-induced mice

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High-fat diets cause obesity in male mice. The underlying mechanism, however, remains controversial. After assessing three contrasting ideas, researchers have determined that the hedonic overdrive model provides

the best fit, according to a new study.

The study, titled "The Hedonic Overdrive Model Best Explains High-Fat Diet-Induced Obesity in C57BL/6 Mice" appears in the journal *Obesity*.

"Our work provides some direction as to why high-fat/high-carb macronutrient combinations stimulate overconsumption. The study is in mice so we need to be cautious about extrapolating to humans. However, if the effect is repeated in humans, avoiding the macronutrient combos that stimulate us to overeat would seem a good strategy to prevent obesity," said John R. Speakman, director of the Shenzhen Key Laboratory of Metabolic Health, Center for Energy Metabolism and Reproduction, Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Shenzhen, China. Speakman is the corresponding author of the study.

Experts explain that when fed a diet containing more than 40% fat by calories, the males of many strains of mice deposit large amounts of body fat. However, the effects in females are smaller. The underlying mechanism generating the obesity effect in males is not well understood because studies have not performed measurements frequently enough or used a sufficient range of different diets to test among alternative ideas.

In the current study, researchers assessed the responses of 240 individually-housed 12-week-old C57BL/6 male mice against 3 patterns predicted by hedonic overdrive, reverse causality and passive overconsumption models. A baseline period of 7 days took place, feeding all the mice a standard low-fat diet that contained 10% fat, 20% protein and 70% carbohydrate by energy. The mice were then exposed to 12 different diets that varied in their fat, protein and carbohydrate contents for 30 days. All the diets analyzed had more than 40% fat by calories.

Body weight and food intake were measured daily over the baseline period and after switching to the experimental diets for 30 days. Food intake was measured from the weight of food that went missing from the food hopper each day. Mice occasionally pulled pellets of food through the hopper bars or ground their food; therefore, a thorough search of the cage was made to return any uneaten food to the hopper before weighing.

Results showed that the hedonic overdrive model provided the best fit for the data analysis. The reverse causality and passive overconsumption models were not well supported. After exposure to the diets, energy intake increased first and body weight followed later. Intake then declined. The peak energy intake was dependent on both dietary protein and carbohydrate, but not the dietary fat and energy density, whereas the rate of decrease in intake was only related to dietary protein.

On the high-fat diets, the weight of food intake declined, but despite this average reduction of 14.4 g in food intake, the mice consumed on average 357 kJ more energy than at baseline. The fact that they gained weight in this situation is a direct refutation of the mass balance model of obesity.

"Using multiple defined diets varying in macronutrient composition followed by statistical modeling of food intake patterns in male mice over a 30-day period, this study reinforces the idea that diet palatability, and not energy content, drive overconsumption beyond actual caloric needs. As the authors acknowledge, the study also reveals that the analysis of food intake patterns requires even more sophisticated statistical modeling methods to better understand the role of each macronutrient in both the initiation and cessation of eating," said Professor Catherine M. Kotz, Ph.D., of the University of Minnesota. Kotz was not associated with the research.

The study's authors noted that it remains a mystery as to why female C57BL/6 mice do not have the same magnitude of response to overconsumption when exposed to high-fat diets, and added that this would be a profitable area for further research.

More information: The Hedonic Overdrive Model Best Explains High-Fat Diet-Induced Obesity in C57BL/6 Mice, *Obesity* (2024). onlinelibrary.wiley.com/doi/10.1002/oby.23991

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