It's eating fat that makes you fat, new mouse study suggests

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Credit: AI-generated image (disclaimer)

Worldwide obesity has tripled since 1975, with 1.9 billion adults considered overweight. The condition now kills more people across the globe than underweight and malnutrition.

One of the NHS's biggest cost burdens, a staggering 70% of UK adults

are expected to have overweight or obesity by 2034. Obesity is a problem of energy balance. If a person has more calories coming in than are going out, then the difference is generally stored as body fat. But what needs to be identified are the factors causing the imbalance of intake and spending in the first place. Why don't humans have a control system that allows them to eat exactly what they need and no more? Understanding the answer to this question may help tackle the obesity epidemic.

There have been several explanations of why people sometimes overconsume calories. These generally revolve around the macronutrient composition of our diets. Macronutrients consist of fats, protein and carbohydrates. One explanation for over-consumption of calories is called the protein leverage hypothesis. The idea is that we primarily eat food for its protein content. If the amount of protein falls in relation to the amount of fat and carbohydrate, then to meet our protein needs we overconsume calories.

An alternative is the carbohydrate-insulin model. This maintains that it is carbohydrates that make us fat, because when we eat them they stimulate the production of insulin, which promotes storage of the carbohydrates as fat and stimulates hunger to procure additional intake. This idea has become very popular in the wake of several books that have spawned the whole "high fat-low carb" (HFLC) diet movement.

The classic idea, however, is that what makes us fat is eating fat, because fat stimulates reward centres in our brains that encourage us to overeat. This has been called the hedonic over-ride hypothesis.

Of mice and men

You might think that testing between these ideas would be rather straightforward – simply expose people to the different diets and see

who gets fat. But a randomised controlled trial in humans would never get permission because ethically it would not be acceptable to expose anyone to a trial where the expected outcome is gross obesity and a threat to their health.

So the best we can do is trial the diets in animals such as mice and see what happens to give us some clues as to what may happen in humans. We have recently completed such a study using a total of 1,000 mice exposed to 30 different diets for three months (equivalent to nine years' exposure in a human).

The study included 12 diets where the protein content varied between 5% and 30% and 12 diets varying the fat content from 8.3% to 80%. The fat composition was designed to mimic the composition of the average American diet. In all these diets the sugar content was held constant at 5%.

Finally, in the last six diets we held the fat and protein constant and let the sugar vary from 5% to 30%. The balance in all cases was made up of highly processed carbohydrates such as corn starch. We repeated the study on five different strains of mice including ones considered to be prone or resistant to obesity. Food intake and body weights were measured every day, and each week we used a small mouse MRI machine to quantify how fat they were.

The results of this massive experiment were very clear. First, changing protein levels had minimal impact on total calorie intake and body fatness. So the protein leverage idea was not supported. Second, when we fixed the protein and fat levels, varying sugar also had no significant impact on body fatness, possibly because the other carbohydrates in the diet were already highly refined. Nevertheless, higher levels of these carbohydrates were on average protective against weight gain, which does not support the carbohydrate-insulin model.

In fact, the only thing that made the mice fat was eating more fat in their diets. But the relationship was not linear. With up to around 50%-60% fat in the diet, the mice ate more food and put on more weight. However, at higher levels of fat they gained less weight. A mouse eating 80% fat in its diet increased in weight by about the same amount as one eating 30% fat. We don't know exactly why, only that on these super high-fat diets the mice consumed fewer calories and didn't gain as much weight.

Looking at the results

There are several limitations to this work. Crucially, these experiments were done on mice. While convenient and we know lots about their genetics and physiology, it is possible that mice might respond differently to humans. However, a definitive experiment in humans cannot take place because of ethical concerns, so the hope is that mice can help us understand what is going on. There are a number of other limitations that are worth highlighting. Cost restrictions meant we were only able to study one sex of mice at a single age. So it's possible these results would not replicate at older ages and in the opposite sex.

We also only gave the mice sugar as part of their diet, but some studies suggest that delivering it in drinking water has a bigger effect on fatness in rodents. Higher sugar levels than 30% by calories may also be an issue but we didn't study them in this instance.

Overall our data suggests that if the responses of mice data do translate to humans, then if you are lean and want to avoid becoming fat, then the best strategy is to limit fat in your diet to less than 20% of overall calories. Sugar up to 30% of total calories in food may not be a major problem, but in liquid form it may be more of an issue. Protein levels appeared to make little difference.

But this advice applies only to people who are already lean and hoping to avoid putting on weight. Whether this is also the best strategy for someone who is already obese is not informed by our study. Fortunately, that is something that can be studied in human clinical trials.

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