Why our brain cells may prevent us burning fat when we're dieting

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A study carried out in mice may help explain why dieting can be an inefficient way to lose weight: key brain cells act as a trigger to prevent us burning calories when food is scarce.

"Weight loss strategies are often inefficient because the body works like a thermostat and couples the amount of calories we burn to the amount of calories we eat," says Dr Clémence Blouet from the Metabolic Research Laboratories at University of Cambridge. "When we eat less, our body compensates and burns fewer calories, which makes losing weight harder. We know that the brain must regulate this caloric thermostat, but how it adjusts calorie burning to the amount of food we've eaten has been something of a mystery."

Now, in research published in the open access journal *eLife*, a team of researchers has identified a new mechanism through which the body adapts to low caloric intake and limits weight loss in mice. Mice share a number of important biological and physiological similarities with humans and so are a useful model for studying how our bodies work.

The researchers tested the role of a group of neurons in a brain region known as the hypothalamus. These 'agouti-related neuropeptide' (AGRP) neurons are known for their major role in the regulation of appetite: when activated, they make us eat, but when fully inhibited they can lead to almost complete anorexia.

The team used a genetic trick to switch the AGRP neurons 'on' and 'off' in mice so that they could rapidly and reversibly manipulate the neurons' activity. They studied the mice in special chambers than can measure energy expenditure, and implanted them with probes to remotely measure their temperature, a proxy for energy expenditure, in different contexts of food availability.

The researchers demonstrated that AGRP neurons are key contributors to the caloric thermostat that regulates our weight, regulating how many calories we burn. The findings suggest that when activated, these neurons make us hungry and drive us to eat - but when there is no food available, they act to spare energy, limiting the number of calories that we burn

and hence our weight loss.

As soon as food becomes available and we start eating, the action of the AGRP neurons is interrupted and our energy expenditure goes back up again to normal levels.

In addition, the researchers also describe a mechanism through which AGRP neurons regulate their activity by detecting how much energy we have on-board and then controlling how many calories we burn.

"Our findings suggest that a group of neurons in the brain coordinate appetite and energy expenditure, and can turn a switch on and off to burn or spare calories depending on what's available in the environment," says Dr Blouet, who led the study. "If food is available, they make us eat, and if food is scarce, they turn our body into saving mode and stop us from burning fat."

"While this mechanism may have evolved to help us cope with famine, nowadays most people only encounter such a situation when they are deliberately dieting to lose weight. Our work helps explain why for these people, dieting has little effect on its own over a long period. Our bodies compensate for the reduction in calories."

Dr Luke Burke, the study's first author, adds: "This study could help in the design of new or improved therapies in future to help reduce overeating and obesity. Until then, best solution for people to lose weight - at least for those who are only moderately overweight - is a combination of exercise and a moderate reduction in caloric intake."

More information: Luke K Burke et al, mTORC1 in AGRP neurons integrates exteroceptive and interoceptive food-related cues in the modulation of adaptive energy expenditure in mice, *eLife* (2017). DOI: 10.7554/eLife.22848

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