OBESITY

Long-lasting effects of obesity on appetite neurons


Credit: CamiloTorres/Getty

Neuronal circuits monitor the body's energy status and modulate food intake and metabolism accordingly. Several types of neuron are involved in this regulation, including the agouti gene-related peptide (AgRP) neurons. In lean organisms, AgRP neurons are activated in the absence of food to promote hunger, while food availability effectively inhibits AgRP neurons. It is not fully understood how obesity alters the activity of AgRP neurons in response to a meal, especially in the long term. Now, Zachary Knight and colleagues show that, in obese mice, the response of AgRP neurons to fat is blunted and that this blunted response persists in obese mice following weight loss.

The researchers fed lean mice a high-fat diet for several weeks, which resulted in weight gain, before feeding the animals with normal feed again, which partially reversed the weight gain. At the beginning of the study, as well as after weight gain and after partial weight loss, the researchers provided the animals with a meal and documented the response of AgRP neurons. "We used fibre photometry, which allows us to monitor AgRP neuron activity in real-time and during behaviour," explains Knight.

The team observed that presenting the mice with food rapidly inhibited AgRP neurons in lean animals, while this response was attenuated in obese mice. After obese mice lost weight, the response of AgRP neurons to a normal meal was partially restored, while the response to a high-fat meal remained attenuated. Interestingly, when the researchers infused different foods directly into the stomachs of obese mice, they observed that the response of AgRP neurons to protein or sugar was not altered. The response to lipids, however, was reduced. Furthermore, weight loss did not restore the neuronal response to lipids directly infused into the stomach.

"These data reveal that obesity can cause long-term changes in feeding circuits that predispose animals to weight regain," says Knight. The researchers are now planning to further investigate the underlying mechanisms. "Clarifying the mechanism by which diet or weight gain cause long-lasting deregulation of AgRP neurons might reveal new ways to treat obesity," concludes Knight.

Anna Kriebs, Associate Editor, Nature Communications

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Hyperglycaemia changes response to aerobic exercise

A high aerobic exercise capacity is associated with increased longevity. People with diabetes mellitus or pre-diabetes have reduced aerobic exercise capacity, but the mechanisms causing this reduction were unclear. Now, new research published in *Nature Metabolism* has described the exercise-related molecular and physiological changes that occur in response to hyperglycaemia.

"Performing regular aerobic exercise is the best way to improve our aerobic fitness level," explains corresponding author Sarah Lessard. "However, previous studies have shown that low aerobic fitness in people with metabolic disease is not due to reduced physical activity levels." The present study set about improving our understanding in this area. To test their aims, the team used mouse models, as well as tissue culture experiments and data collected from human participants. The mouse models partially reflect two major causes of hyperglycaemia in humans, that is, diet-induced insulin resistance or reduced insulin secretion.

The team report that hyperglycaemia can fundamentally change the response to aerobic exercise at the molecular and physiological levels. "We found that mice and humans with impaired glucose metabolism responded to aerobic exercise in a way that is more typical of resistance or strength training exercise," explains Lessard. These findings indicate that chronic exposure to high glucose causes muscle signals to get crossed." The authors note, however, that metabolic benefits such as improved glucose tolerance and decreased fat mass were observed with aerobic exercise training, even in models of chronic hyperglycaemia. "Based on this observation, this exercise

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New drug hope for diabetes mellitus

Currently, no therapies are available for diabetes mellitus that directly target the underlying processes of β-cell dysfunction and persistent α-cell secretion of glucagon. A new study published in *Cell Metabolism* describes a novel anti-diabetic small-molecule inhibitor of thioredoxin-interacting protein (TXNIP).

"We discovered *TXNIP* almost 20 years ago as the top gene upregulated by glucose in human islets and subsequently as a major factor contributing to islet cell death and dysfunction," explains corresponding author Anath Shalev. To identify molecules active against TXNIP, the authors performed high-throughput screening of 300,000 compounds followed by medicinal chemistry optimization, resulting in the lead compound SRI-37330. This compound specifically inhibited TXNIP expression and signalling in mouse and human islets, and had favourable pharmacological and safety profiles.

The oral administration of SRI-37330 to diabetic mice improved glucose homeostasis, decreased serum glucagon levels and reduced hepatic glucose production. "While elevated glucagon levels have been recognized as a major problem of diabetes mellitus for decades, therapeutic attempts of glucagon receptor antagonism have been hampered by associated compli cations such as hepatic steatosis, α-cell hyperplasia and worsening of hyperglucagonaemia," describes Shalev. "Of note, none of these problems were detected with SRI-37330." Importantly, SRI-37330 was protective in mouse models of both type 1 diabetes mellitus (streptozotocin-induced) and type 2 diabetes mellitus (obesity-induced).