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METABOLISM

# An appetite for exercise

Exercise is one of the best remedies for obesity and conditions associated with it, such as type 2 diabetes. However, the mechanisms underlying these beneficial effects — apart from increasing energy expenditure — are not well understood. Ropelle *et al*. now show that exercise directly affects hypothalamic neurons involved in the regulation of food intake and energy metabolism, through an interleukin-6 (IL-6)-mediated mechanism.

The authors rendered rats obese by feeding them a high-fat diet. This altered hypothalamic mRNA levels of neuropeptide Y and pro-opiomelanocortin (POMC), two neuropeptides involved in food intake regulation, and impaired insulin and leptin signalling in the hypothalamus. A session of swimming or treadmill running countered these effects and reduced food intake in obese rats but had no effect in lean rats.

In agreement with findings from previous studies, obese rats showed increased inhibitor of κB kinase β (IKKβ)–nuclear factor κB (NF-κB) signalling and endoplasmatic reticulum (ER) stress in the hypothalamus compared with lean rats. These responses are known to impair insulin and leptin signalling. The authors showed that exercise normalized the level of IKKβ–NF-κB signalling and reduced ER stress. It also increased serum and hypothalamic levels of the cytokine IL-6 to a greater extent in obese than in lean rats. Importantly, intrahypothalamic injections of IL-6 in obese rats mimicked the effect of exercise on IKKβ–NF-κB signalling and ER stress. Conversely, an IL-6-specific antibody administered before the exercise session blocked the effects of exercise in obese rats.

The authors next induced ER stress and IKKβ–NF-κB signalling in the hypothalamus of lean rats by injecting thapsigargin. Exercise or an intrahypothalamic IL-6 infusion reversed the cellular stress induced by thapsigargin, and the effect of exercise was blocked by intrahypothalamic infusion of the IL-6-specific antibody. Together, these findings indicate that exercise reduces ER stress through an IL-6-mediated mechanism.

Exercise-induced increases in plasma IL-6 levels are known to be followed by increases in plasma levels of the anti-inflammatory cytokine IL-10. The authors found that exercise also induced IL-10 expression in the hypothalamus, to a greater extent in obese than in lean rats. Intrahypothalamic injections of IL-10 reduced food intake and reduced hypothalamic IKKβ–NF-κB signalling and ER stress in obese rats. Moreover, knocking down IL-10 expression in the hypothalamus using an antisense oligonucleotide prevented the effects of exercise or IL-6 infusions, suggesting that IL-10 acts downstream of IL-6 to mediate the effects of exercise on ER stress and food intake.

Finally, the authors showed that, similar to a single exercise session, chronic (4-week) exercise reduced food intake and body weight, increased hypothalamic IL-6 and IL-10 levels and decreased IKKβ–NF-κB signalling and ER stress in obese, but not in lean rats. These effects were most pronounced on the first day of exercise.

These findings provide further insight into the complex relationship between inflammation, cellular stress, insulin sensitivity and food intake, all of which have a role in obesity. They suggest that, in addition to exercise, modulation of hypothalamic IL-6 and IL-10 levels might be a potential target for countering obesity.

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**ORIGINAL RESEARCH PAPER** Ropelle, E. R. *et al.* IL-6 and IL-10 anti-inflammatory activity links exercise to hypothalamic insulin and leptin sensitivity through IKKβ and ER stress inhibition. *PLoS Biol.* **8**, e1000465 (2010)

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