This Week in The Journal

Warm-Sensitive Preoptic Neurons Express Leptin Receptors

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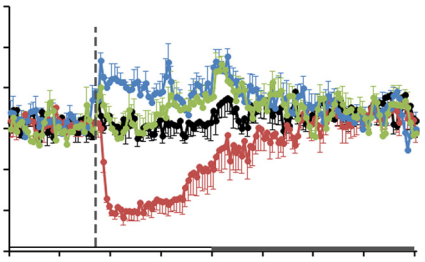
(see pages 5034–5046)

Body temperature is regulated by the preoptic area of the hypothalamus. Different populations of preoptic neurons are activated by increases and decreases in body temperature, and they evoke counteracting behavioral and physiological responses, such as vasodilation or constriction, sweating or shivering, and increased or decreased heat generation by brown adipose tissue. Because adaptive thermogenesis is energy intensive, it is inhibited when energy reserves are low, and it can be activated to prevent weight gain when energy intake is high. This energy-dependent regulation of thermogenesis is mediated by leptin, a hormone secreted by fat cells. Previous work has shown that leptin facilitates adaptive thermogenesis by acting on leptin receptors (LepRbs) in the dorsomedial and arcuate nuclei of the hypothalamus. Yu et al. now show that LepRb-expressing neurons in the preoptic area inhibit thermogenesis.

Yu et al. used pharmacogenetic (DREADDs) technology to selectively activate LepRb-expressing preoptic neurons. This caused mice to exhibit behavioral and physiological changes normally associated with increases in ambient temperatures: mice stretched their bodies and were less active, and both their body temperature and their energy expenditure (as measured by oxygen consumption) decreased. The latter effects were attenuated by blocking ß3 adrenergic receptors, suggesting they were mediated in part by decreases in adaptive thermogenesis. Activating LepRb-expressing preoptic neurons also reduced food intake, causing mice to lose weight despite decreased energy expenditure. A similar decrease in energy expenditure and food consumption occurred when ambient temperature was raised from 22 to 30°C, and this temperature elevation also activated LepRb-expressing preoptic neurons.

Previous work suggested that warm-sensitive preoptic neurons reduce thermogenesis by inhibiting neurons in the dorsomedial hypothalamus and rostral medulla that promote thermogenesis. But Yu et al. found that most LepRb-expressing preoptic neurons were glutamatergic, and thus likely excitatory. Moreover, pharmacogenetic activation of glutamatergic preoptic neurons mimicked the effects of activating LepRb-expressing neurons, whereas activating GABAergic neurons did not.

Together, these results indicate that leptin receptors in the preoptic area are expressed primarily on warm-sensitive, glutamatergic neurons, and suggest these neurons elicit behavioral and physiological actions to lower body temperature when ambient temperature rises. Because these effects include reducing food intake, activating this pathway could potentially be used to combat diet-induced obesity.



Activating LepRb-expressing preoptic neurons (red, activation starting at dashed vertical line) reduced energy expenditure, as indicated by a drop in oxygen consumption. No drop occurred in control mice (black) or in mice given a ß3 adrenergic receptor antagonist (red and green). See Yu et al. for details.

Dopamine Reduction May Underlie Apathy in Huntington's

Dan P. Covey, Hannah M. Dantrassy, Natalie E. Zlebnik, Iness Gildish, and Joseph F. Cheer

(see pages 4993–5002)

Huntington's disease (HD) is best known for producing involuntary twisting and jerking movements (chorea), but it also has cognitive and psychiatric effects (including apathy, depression, and obsessions) that typically emerge before motor impairment. The disease is caused by expansion of a polyglutamine sequence in huntingtin protein, and the motor symptoms result from degeneration of medium spiny neurons in the dorsal striatum. Dopamine signaling in the striatum is also impaired in HD patients, and like psychiatric symptoms, this impairment is detectable before the onset of motor symptoms. Therefore, psychiatric symptoms may result from impaired dopamine signaling.

Because increases in dopamine release in the ventral striatum (nucleus accumbens) are associated with increased willingness to exert effort to obtain rewards, Covey et al. hypothesized that decreased dopamine release in the accumbens contributes to motivational impairments in HD. They tested this hypothesis by measuring dopamine release in the nucleus accumbens as mice with or without a huntingtin mutation performed a task in which the effort (number of lever presses) required to obtain a reward increased exponentially over time. Reward receipt resulted in dopamine release in the nucleus accumbens in both mutant and wild-type mice, and on early trials, the amount of dopamine release in the two groups was not significantly different. On later trials however, when the number of lever presses required to obtain reward was high, dopamine release was greater in wild-type mice than in HD mice. With further increases in the number of required lever presses, HD-model mice stopped completing the task sooner than wild-type mice.

These data suggest that HD-model mice were less willing than wild-type mice to exert a large amount of effort to obtain a reward. They also suggest that insufficient dopamine release in the nucleus accumbens of HD mice may underlie this difference. These results have significant clinical implications, because the only FDA-approved treatment for Huntington's chorea is an inhibitor of vesicular monoamine transporter 2, which reduces dopamine release. Thus, this treatment may worsen motivation deficits and other psychiatric symptoms in patients with HD.

This Week in The Journal is written by Teresa Esch, Ph.D.