

SYSTEMS NEUROSCIENCE

No food in the CART

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Appetite is regulated by the actions of hormones, neuropeptides and neurotransmitters, including serotonin and cocaine- and amphetamine-regulated transcript (CART), in the hypothalamus. Serotonin (5-hydroxytryptamine, 5-HT) receptor 4 (5HTR₄) and CART are also present in the nucleus accumbens (NAc), a brain area that is part of the reward system. Compan and colleagues now demonstrate that CART- and 5-HT-expressing neurons in the NAc play a part in appetite regulation and amphetamine-induced anorexia in mice.

The authors injected a 5HTR₄ agonist into the NAc, and found that it reduced food intake in mice that had been fed normally and in mice that had been deprived of food for 24 hours. Administration of a 5HTR₄ agonist increased CART mRNA levels in the NAc, and injecting CART directly into the NAc also reduced appetite in both normal and starving mice. Conversely, when the authors blocked 5HTR₄ or reduced CART levels in the NAc, food intake increased in mice that had been fed normally, but not in food-deprived mice. These findings indicate that 5-HT and CART in the NAc have a role in regulating appetite and, importantly, show that stimulating this system reduces food intake even in food-deprived mice that really need the energy.

Amphetamines, such as ecstasy (3,4-methylenedioxymethamphetamine, MDMA) have food-suppressant effects. Does MDMA, which acts in the NAc (as well as in other regions), inhibit appetite through this pathway? The authors found that intraperitoneal injections of MDMA suppressed food intake in food-deprived wild-type mice, but not in starved mice that lacked 5HTR₄, indicating that the anorectic effect of MDMA is mediated by 5HTR₄. Interestingly, MDMA injections also increased

CART mRNA in the NAc. Again, this was observed only in wild-type mice, indicating that MDMA-induced CART gene transcription is dependent on the presence of 5HTR₄. Moreover, reducing CART in food-deprived mice through RNA silencing abolished the anorectic effects of a 5HTR₄ agonist and of MDMA (completely and partly, respectively), indicating that CART in the NAc mediates the appetite-suppressing effect of MDMA.

These findings show that in normal conditions CART acts in the NAc to suppress food intake, and that MDMA-induced anorexia involves 5HTR₄-mediated up-regulation of CART in this area. It is possible that dysregulation of 5HTR₄ and CART in the NAc has a role in eating disorders, such as anorexia nervosa. Considering that the NAc is part of the reward pathway, it is tempting to speculate that the disorder might have an addictive component, which would confirm the anecdotal evidence that anorexia sufferers might be hooked on the self-starvation and self-control involved in the disorder.

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ORIGINAL RESEARCH PAPER Jean, A. *et al.* Anorexia induced by activation of serotonin 5-HT₄ receptors is mediated by increases in CART in the nucleus accumbens. *Proc. Natl Acad. Sci. USA* **104**, 16335–16340 (2007)



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