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Marijuana flips appetite switch in brain

Sudden attacks of 'the munchies' are triggered by a change in the hormone released by neurons.

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18 February 2015

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Understanding how pot sparks hunger has wider implications for the study of appetite control.

Smoking marijuana may stoke a yearning for crisps, but understanding how it affects hunger is relevant not just to those who indulge in it. The drug has yielded a ripe target for scientists who seek to stimulate or suppress appetite: the receptor CB1, found in cells throughout the body.

When activated by the anti-nausea drug dronabinol — which is also a component of marijuana (*Cannabis sativa*) — CB1 prompts the release of hunger-promoting hormones[1]. And suppressing its activity is thought to aid in weight loss[2]. But the mechanism by which the receptor kills or kindles appetite is not entirely understood.

Now neuroscientist Tamas Horvath, of Yale University in New Haven, and colleagues report in *Nature* that nerve cells called pro-opiomelanocortin (POMC) neurons play a key role in this process[3]. POMC had generally been thought to promote satiation, but Horvath's team found that POMC neurons in the brain release not just a hunger-suppressing hormone, but also one that promotes appetite.

Which hormone is secreted is regulated by a protein in the cells' mitochondria, structures that regulate energy levels. When the CB1 receptor is activated, this mitochondrial protein induces POMC to switch from secreting the substance that suppresses gorging to one that encourages it.

The finding is intriguing, says Uberto Pagotto, a neuroscientist at the University of Bologna who has studied cannabinoids for many years. “It gives us a different starting point to look at CB1 receptors and the mitochondria,” he says.

Change in attitudes

Research into manipulating the cannabinoid system to regulate appetite is once again gaining favour, having been starved of support for years. Marijuana use is becoming increasingly acceptable and that means that “people are coming to see studying [cannabinoids] and how they’re processed as a natural and beneficial thing to pursue”, says Horvath. The biggest hurdle was not the legal status, he adds, but the fact that drug firms have been cautious about funding such work after problems arose with weight-loss drugs that worked by targeting CB1.

In 2008, for example, Sanofi-Aventis was forced to withdraw rimonabant after studies showed that the weight-loss drug was linked to depression. As a result, pharmaceutical firms including Merck, Pfizer and AstraZeneca stopped their research on similar compounds. Some of these potential treatments were in late stages of development, and pulling them likely cost the industry several billion dollars, reckons Steven Heymsfield, an obesity researcher now at Pennington Biomedical Research Centre in Baton Rouge, who had worked on Merck’s CB1 drug, taranabant.

“Until recently, many people I've been speaking to have lamented that it has been incredibly hard to get funding to do this research,” says George Kunos, an expert on cannabinoids and appetite at the US National Institutes of Health in Bethesda, Maryland. But some companies have renewed their interest. One possible approach is to target only the receptors present in the peripheral nervous system, so as to avoid the psychiatric side effects of inhibiting CB1 in the brain.

But much remains unknown about how the body processes cannabinoids, Kunos says. For example, activating CB1 with a drug, as Horvath’s team did, may cause a different reaction from when it is stimulated with cannabinoids the body naturally produces.

“This was high-calibre work that fits well and adds to the research that has been going on,” says Pagotto, “but how it can be practically applied may still be some ways off.”

Nature | doi:10.1038/nature.2015.16957

References

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