

OEA - A New Player in Appetite Regulation Answers Old Questions



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In last month's *Viewpoint* I wrote about the endocannabinoids—molecules that look like the active component of marijuana and stimulate receptors in the brain to promote appetite. The relevance to obesity and type 2 diabetes is obvious—find a drug that blocks the endocannabinoids from working, and you might have a pretty good appetite suppressant.

The story has gotten even more interesting in the short time since I wrote that piece. In an attempt to find new members of the endocannabinoid family, a group of researchers identified a molecule called oleylethanolamide, or OEA. OEA is made by cells in the small intestine in response to food. This makes it different than most endocannabinoids, which are primarily made in the brain. There are other critical differences as well, but none more important than the fact that OEA actually *inhibits* food intake, an effect completely opposite to that of other known endocannabinoids. In addition, it was recently shown that OEA does not work by binding the known endocannabinoid receptors, and it has been unclear which receptor OEA does bind and activate. More on that in a moment.

OEA is also interesting because it is made in the small intestine. How does the OEA signal get to the brain to tell it to stop eating? Well, it appears that OEA activates nerves in the wall of the intestine, sending a direct signal to the parts of the brain that control food intake. This is in sharp contrast to most other molecules that affect appetite, such as leptin or ghrelin, which exert their effects by circulating in the blood until they hit the brain. In fact, one of the hallmarks of leptin, ghrelin, and other such molecules is that they work just as well if injected directly into the brain as they do when injected into the blood. OEA, on the other hand, works only if injected in the intestine; injection into the brain has no effect whatsoever. It turns out this is because the OEA receptor, unlike the leptin or ghrelin receptors, is located outside the brain.

As I alluded to earlier, one of the big mysteries about OEA has been the identity of its receptor. In new work published in the journal *Nature*, the same team of researchers that discovered the anti-appetite activity of OEA has solved this puzzle, and I believe the answer will have a profound impact on the field of diabetes and obesity out of proportion to the importance of OEA *per se*. I say this because the OEA receptor turns out to be a protein called PPAR-alpha, and PPAR-alpha is already well known to be intricately involved in the handling of fats in the blood and liver.

PPAR-alpha is the target of drugs called fibrates, such as gemfibrozil (Lopid™) and fenofibrate (Tricor™). These agents are used to lower triglyceride levels in blood, and have beneficial effects on cholesterol as well. These drugs do not appear to affect

appetite, however, probably because their interactions with PPAR-alpha are relatively weak. In fact, the new study shows that stronger PPAR-alpha agonists now being developed by drug companies to lower blood lipids do, in fact, reduce appetite in rodents, as would be predicted from the OEA work. The most impressive data linking OEA to PPAR-alpha, however, were from studies performed in mice genetically engineered to lack PPAR-alpha. These mice are immune to the effects of OEA, proving conclusively the requirement for PPAR-alpha in mediating OEA's effects on satiety.

Perhaps the most important aspect of the story lies outside the role of OEA in appetite suppression, and has more to do with the identity of OEA as a natural PPAR activator. For years, drug companies and academic laboratories have invested millions of dollars in the hunt for the natural compounds that activate all three forms of the PPAR molecule: PPAR-alpha, PPAR-delta, and PPAR-gamma. Some candidates have been identified, but none of them satisfy all the criteria for a *bona fide* PPAR activator. OEA, on the other hand, does meet these criteria. It is produced in high concentrations in the very cells that contain PPAR-alpha, it binds to the receptor with high affinity, it does not bind to any appreciable degree with the other two forms of PPAR, and its effects are not seen when the receptor is not present. The discovery of OEA as a true PPAR-alpha activator will surely spur the hunt for similar molecules that might bind PPAR-delta and PPAR-gamma as well. PPAR-gamma is of particular interest, since it is the protein activated by the thiazolidinedione anti-diabetic drugs Avandia™ and Actos™. The discovery of a natural PPAR-gamma activator would teach us an awful lot about what goes wrong in type 2 diabetes, and could lead to the development of new and more powerful insulin-sensitizing agents.

So the story can be summed up as follows: researchers note that marijuana smoking increases appetite, which leads to the discovery of endocannabinoids, natural compounds that induce food intake. A new endocannabinoid-like molecule is discovered (OEA) which unexpectedly *blocks* appetite. Furthermore, the effects of OEA are found to be carried by nerves in the gut, and not by receptors in the brain. Finally, OEA is discovered to work by binding and activating PPAR-alpha, providing scientists with their first look at a true, high-affinity specific ligand for a PPAR protein.

What this will ultimately mean for patients is not altogether clear, but I would predict rapid advancement in the development of drugs that work on all three forms of PPAR, with benefits on appetite reduction, lipid lowering, and, probably, new oral anti-diabetics as well.

References:

F. Rodríguez de Fonseca, M. Navarro, R. Gómez, L. Escuredo, F. Nava, J. Fu, E. Murillo-Rodríguez, A. Giuffrida, J. LoVerme, S. Gaetani, S. Kathuria, C. Gall, D. Piomelli. An anorexic lipid mediator regulated by feeding. *Nature* 414, 209 - 212 (08 Nov 2001).

Jin Fu, Silvana Gaetani, Fariba Oveisi, Jesse Lo Verme, Antonia Serrano, Fernando Rodríguez de Fonseca, Anja Rosengarth, Hartmut Luecke, Barbara Di Giacomo, Giorgio Tarzia, Daniele Piomelli. Oleylethanolamide regulates feeding and body weight through activation of the nuclear receptor PPAR- alpha. *Nature* 425, 90 - 93 (04 Sep 2003).

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