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Oleoylethanolamide: a new player in energy metabolism control. Role in food intake

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Oleoylethanolamide (OEA) is a lipid amide produced by enterocytes upon the absorption of dietary fat and participates in the induction of satiety. Through indirect pathways, probably depending on the local activation of peroxisome-proliferator-activated receptor-alpha and involving afferent vagus nerve fibers, OEA signal is transmitted to the brain-stem and the hypothalamus, where it stimulates the release of oxytocin from magnocellular neurons.

OEA mechanism might, thus, provide a novel target for the design of therapies controlling appetite.

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Introduction

The spread of 'obesity epidemic' and the poor efficacy of many anti-obesity therapies highlight the need to identify novel mechanisms controlling feeding and energy balance. One such mechanism involves oleoylethanolamide (OEA), the monounsatured analogue of the endocannabinoid anandamide. OEA is one of the N-acylethanolamides (NAEs) present in all living organisms that are synthesized from the precursors N-acylphosphatidylethanolamines (NAPEs), through the actions of the enzymes N-acyltransferase and NAPE-phospholipase D (NAPE-PLD), and hydrolyzed intracellularly by fatty acid amide hydrolase enzymes [1]. OEA has no affinity for cannabinoid receptors nor it induces cannabimimetic effects and its biological role remained elusive for long. During the last decade it has clearly emerged that OEA is a gut-derived satiety factor controlling appetite and energy balance. The present review will summarize our knowledge on the role of OEA in the regulation of feeding, by focusing our attention on the gastrointestinal and the central levels.

OEA is characterized by satiety-inducing properties

OEA shows all of the defining characteristics of a 'satiety factor': (1) it inhibits feeding by prolonging the interval to the next meal; (2) its synthesis is regulated by nutrient availability and (3) its levels undergo circadian fluctuations.

Pharmacological studies have shown that OEA causes a dose-dependent and time-dependent decrease in food intake in starved and free-feeding rats and mice [2–5]. These effects are structurally and behaviorally selective. They are not followed by compensatory hyperphagia, are not caused by the induction of visceral malaise, anxiety or stress-response, nor they are paralleled by alterations of the body temperature, pain threshold, plasma levels of glucose, insulin and leptin [2]. Behavioral analyses of the feeding pattern of free-feeding rats and mice treated with OEA at the onset of the dark phase revealed that the hypophagic effect is due to the selective

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prolongation of feeding latency and post-meal interval with no effect on the meal size [3,6] and with the resulting decrease of meal frequency. These effects are suggestive of enhanced across-meal satiety and are evident following either intraperitoneal or oral administration of OEA [3,4,6]. Conversely, they are not observed after intracerebroventricular injection of the drug, thus suggesting that its primary sites of action are located outside the central nervous system [2].

Mice over-expressing in their duodenum the enzyme NAPE-PLD are characterized by increased OEA mobilization in the small intestine and show reduced food intake with respect to control mice [7]. Their hypophagia appears behaviorally identical to that elicited by peripherally administered OEA [7]. This observation may indicate that the increase of intestinal OEA levels is sufficient to influence across-meal satiety, supporting the idea that OEA may act as a gut-derived satiety factor [7].

In accordance with this hypothesis, nutrient availability can control OEA levels in the proximal intestine. In fact, OEA intestinal levels decrease during food deprivation and increase upon re-feeding in various vertebrate species [2,8,9]. In rats feeding stimulates OEA mobilization in the mucosal layer of duodenum and jejunum but not in the serosal layer from the same intestinal segments, in other sections of the gastrointestinal tract (stomach, ileum and colon) or in a broad series of internal organs and tissues (e.g. liver, brain, heart and plasma) [9]. Feeding-induced OEA mobilization is paralleled by enhanced accumulation of OEA precursors, increased activity and expression of NAPE-PLD, and decreased activity and expression of fatty acid amide hydrolase in intestinal enterocytes and lamina propria cells [9].

In humans, fluctuations of OEA plasma levels were observed following meal consumptions, resulting down- or up-regulated under conditions of transient or chronic hyperglycemia, respectively [10].

Circadian variations of small-intestinal OEA levels have been detected, resulting higher during the daytime (when animals are satiated), and lower during the night (when animals are actively feeding) [11]. A parallel diurnal cycle of OEA content was observed in rat white adipose tissue [12] and in some areas of the rat and mouse brain, such as the pons and the hypothalamus. In particular, in the pons the maximum levels were observed during the dark phase, whereas in the hypothalamus they were detected at the end of the dark phase [13].

OEA receptors

OEA has been hypothesized to activate different receptors. OEA showed low efficacy for the vanilloid receptor TRPV1 (*in vitro* EC_{50} 2 μM) and was able to excite vagal sensory neurons and induce visceral pain via activation of this receptor [14,15]. However, discrepant findings are reported, because OEA was also found to produce antinociceptive effects in animal models of visceral and inflammatory pain [16]. Like all TRPV1 agonists, particularly the lipophilic ones, OEA can also immediately desensitize this receptor [17], thus possibly explaining these discrepant observations. The involvement of TRPV1 receptor in OEA hypophagic action is suggested by the lack of effects in TRPV1 null mice [15], although opposite results were also reported [12].

Based on *in vitro* evidence, OEA was shown to activate the orphan receptor GPR119, with higher affinity (EC_{50} 3 μM) than 1-oleoyl-lysophosphatidylcholine, previously known as its most potent endogenous agonist [18]. Recent data from C3H mice showed a positive correlation between GPR119 upregulation in the intestine and decrease of body fat pads induced by chronic oral administration of OEA [19]. However, not all GPR119 synthetic agonists mimic OEA effects on feeding. Whether this receptor is essential for the anorexiant action of OEA remains to be demonstrated (for review see [1]).

A large body of evidence indicate that OEA is able to engage peroxisome-proliferator-activated receptor-alpha (PPAR-alpha), a lipid-activated nuclear receptor that regulates several aspects of lipid metabolism and that appear to mediate the satiety-inducing effects of OEA. (1) OEA binds with high affinity and activates with high potency (EC_{50} 120 nM) PPAR-alpha-driven transactivation in a heterologous expression system [11]. (2) The concentrations reached by endogenous OEA in the rodent small-intestinal mucosa after feeding (200–400 nM) [9] are sufficient to fully activate PPAR-alpha receptor, which is highly expressed in the small intestine [11] but not to affect the other putative OEA receptors, such as GPR119 and TRPV1. (3) OEA treatment *in vivo* affects the expression of different PPAR-alpha target genes, such as those encoding for PPAR-alpha itself, fatty acid translocase (FAT/CD36), fatty acid transport protein 1 (FATP1), inducible nitric oxide synthase (iNOS) [11]. Similar observations can be made in the small intestine of mice over-expressing NAPE-PLD in their duodenum [7]. (4) Intestinal PPAR-alpha expression parallels the circadian fluctuations of OEA levels, whereas the expression of its trans-repression target iNOS shows opposite pattern [11], thus suggesting that food-induced OEA production in the proximal small intestine may regulate satiety through a local autocrine or paracrine mechanism. (5) Synthetic PPAR-alpha agonists, such as the compounds GW7647 and Wy-14643, closely mimic OEA effects on both the intestinal expression of PPAR-alpha-regulated genes and on the eating pattern of free-feeding mice [11]. (6) PPAR-alpha knock out (PPAR-alpha$^{-/-}$) mice do not respond to OEA or synthetic PPAR-alpha agonists [11,20], are more vulnerable to diet-induced obesity, and display an altered feeding pattern with respect to wild type mice [21]. In particular, free-feeding PPAR-alpha$^{-/-}$ mice on a standard lab chow were found to start earlier their nocturnal consummatory activity and with a higher meal frequency, while eating comparable amount of food at each meal, with respect to wt mice [22].