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Brain Molecules and Appetite: The Case of Oleoylethanolamide

Andrea Sarro-Ramírez[1], Daniel Sánchez-López[1], Alma Tejeda-Padrón[1], Carmen Frías[2], Jaime Zaldívar- Rae[3] and Eric Murillo-Rodríguez[1,*]

[1]*Laboratorio de Neurociencias Moleculares e Integrativas. Escuela de Medicina, División Ciencias de la Salud. Universidad Anáhuac Mayab. Mérida, Yucatán. México;* [2]*Laboratorio de Neurobiología del Sistema Olfatorio. Escuela de Medicina, División Ciencias de la Salud. Universidad Anáhuac Mayab. Mérida, Yucatán. México;* [3]*Escuela de Psicología, División Ciencias Jurídicas, Universidad Anáhuac Mayab. Mérida, Yucatán. México*

Abstract: The neurobiological mechanisms of feeding involve the activity of several brain areas as well as the engagement of endogenous compounds such as ghrelin, melanin-concentrating hormone, orexin, neuropeptide Y, leptin, vasoactive intestinal peptide, cholecystokinin, among others. Furthermore, the family of food-intake modulators has been enlarged due to the inclusion of lipids such as *N*-arachidonoylethanolamide (anandamide), as well as oleoylethanolamide (OEA). In this regard, the food-intake suppressing properties of OEA have been described since pharmacological administration of this compound induces anorexia. It has been suggested that satiety induced by OEA may be through the activation of peroxisome proliferator-activated receptor-α (PPAR-α), a ligand-activated transcription factor that modulates several pathways of lipid metabolism. The mechanism of action of OEA remains unknown, it has been suggested that the ingestion of dietary fat stimulates epithelial cells of the small intestine and promotes the synthesis and release of OEA. Upon its release, this lipid acts within the gut engaging sensory fibers of the vagus nerve to diminish food-intake. Here, recent advances in our understanding of the neurobiological role of OEA in modulation of feeding will be reviewed. Also, we highlight the emerging molecular mechanism of anorexia induced by OEA.

Keywords: Anorexia, central nervous system, endocannabinoids, feeding, hypothalamus.

OLEOYLETHANOLAMIDE

Since endogenous lipids display biological functions, they have been the recent focus of interest. Among these molecules are the endogenous agonist for cannabinoid receptors, arachidonoylethanolamide (also named anandamide (ANA) [1, 2]), the pain modulator lipid palmitoylethanolamide [3, 4] as well as the amide of oleic acid and ethanolamine, oleoylethanolamide (OEA, [5]). Regarding this last compound, the biosynthesis pathway described suggests that oleic acid obtained from diet serves as a precursor of *N*-oleoyl-phosphatidylethanolamine, which is then cleaved by *N*-acyl-phosphatidylethanolamine-selective phospholipase D (PLD) to release OEA [6, 7]. This biochemical process occurs in absorptive epithelial cells of the small intestine [6-10], (Fig. **1**). Thus, feeding stimulates OEA mobilization in the mucosal layer of rat duodenum and jejunum but not in other sections of the gastrointestinal tract, including the stomach.

On the other hand, the hydrolysis of OEA is catalyzed by an intracellular enzyme known as fatty acid amide hydrolase (FAAH; for a comprehensive review see [11]). Pharmacological experiments have shown that endogenous levels of OEA are increased by using highly selective FAAH inhibitors [12, 13], such as URB597 [13-18]. The study of the pharmacological effects of the blockade of FAAH on enhancement of OEA levels represents a new horizon to explore the potential role of this lipid on modulation of several neurophysiological functions, including food-intake.

*Address correspondence to this author at the Laboratorio de Neurociencias Moleculares e Integrativas, Escuela de Medicina, División Ciencias de la Salud, Universidad Anáhuac Mayab, Carretera Mérida-Progreso Km. 15.5, Apartado Postal 96 Cordemex C.P. 97310, Mérida, Yucatán. México; Tel: + 52 (999) 942-4800 Ext. 664; E-mail: eric.murillo@anahuac.mx;
web: http://www.anahuacmayab.mx/318-1-Escuela+de+Medicina.html

OLEOYLETHANOLAMIDE AND FEEDING

Upon OEA release, it is up-taken by a specific transport system yet to be cloned and modulates several neurobiological functions. The spectrum of OEA-mediated biological actions includes its circadian rhythm [19], it affects memory consolidation [20], modulates stress [21], promotes alertness [22], induces of cellular death [23], enhances dopamine release [18], it has been linked with sleep deprivation [24], activates nuclear receptors [25] and suppresses feeding [6]. The role of OEA in feeding has been described by several groups. In this regard, systemic administration of OEA induces a dose- and time-dependent diminution in food-intake and this effect has been also described in experimental models of obesity. For example, Izzo and coworkers (2010) described that in ad libitum fed Zucker rats, levels of OEA were up to tenfold higher in the duodenum and slightly higher in the brainstem. Remarkably, it was also found that fasting/ refeeding-induced changes in OEA levels were maintained in the duodenum, and liver [26].

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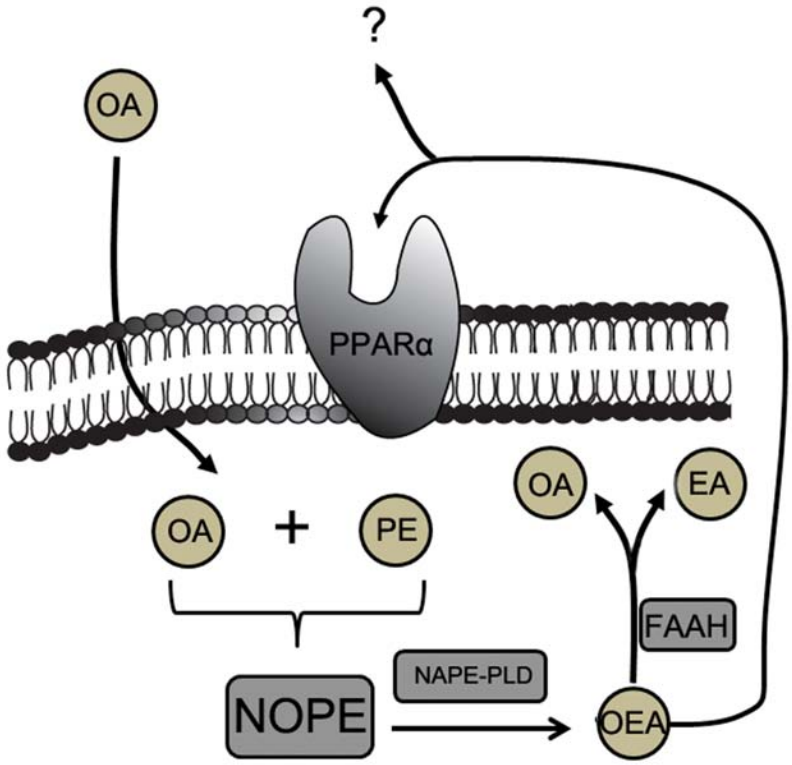

Fig. (1). Synthesis and degradation pathway of oleoylethanolamide. Current evidence suggests that enterocytes in duodenum and jejunum use food-derived oleic acid (OA) and phosphatidylethanolamine (PE) to generate the phospholipid *N*-oleoylphosphatidylethanolamine (NOPE), which is cleaved by *N*-acyl-phosphatidylethanolamine-selective phospholipase D (NAPE-PLD) to synthetize oleoylethanolamide (OEA). Once its formation, this lipid binds to the peroxisome proliferator-activated receptors-alpha (PPARα) to modulate feeding. The OEA biological signaling is terminated by its degradation into OA and PE through an enzyme-mediated hydrolysis, catalyzed by the fatty acid amide hydrolase (FAAH).

Taken together, the current data suggest that OEA induces satiety. But what might be the mechanism of action of this lipid on feeding suppression? It has been suggested that the anorexic effect caused by OEA requires intact sensory vagal fibers as well as an activation of the nucleus of the solitary tract in the brainstem and the paraventricular nucleus in the hypothalamus [6, 14]. In this regard, animals with lesion in the peripheral sensory fibers failed to respond to the pharmacological administrations of OEA [6] whereas surgical resection of the sympathetic celiac-superior mesenteric ganglion complex blocks feeding-induced OEA production in rat small-intestinal cells [27].

Additionally, it has been suggested that the food-intake suppression actions of OEA are mediated by the peroxisome proliferator-activated receptor-α (PPAR-α), a nuclear receptor linked to the regulation of absorption, storage and utilization of dietary fat [28, 29]. Regarding this, the hypophagic effects of OEA are abolished in PPAR-α-null mice whereas food suppression is mimicked by PPAR-α agonists [8, 30]. Overall, the above data suggest that OEA could be mediating anorexia via activation of PPAR-α receptors. However, further studies are needed to elucidate the mechanisms of action of PPAR-α in feeding.

An attractive conceptual framework suggests that OEA might be inducing anorexia through different receptors. For instance, it is known that the transient receptor potential vanilloid subtype 1 (TRPV1) as well as GPR119 receptor have been linked with the anorexic effects caused by OEA [10, 28-30]. On the other hand, Aviello and coworkers (2008) found that OEA modulates gastric emptiness. According to the authors, the effects of OEA were unaffected by using several antagonist such as SR141716A (CB_1 cannabinoid receptor antagonist), SR144528 (CB_2 cannabinoid receptor antagonist), 5'-iodoresiniferatoxin (TRPV1 antagonist), or MK886 (PPAR-α receptor antagonist). Furthermore, compared to mice fed with standard diet, high-fat diet (HFD) mice showed higher levels of gastric OEA as well as a delay in gastric emptying. Importantly, HFD-induced enhancement in OEA levels was accompanied by increased in the expression of the *N*-acyl-phosphatidylethanolamine-selective PLD (the synthesizing enzyme for OEA) whereas promoted a diminution in the expression of the FAAH [31]. It may be conclude from these experiments that elevation of gastric OEA might likely contribute to the delayed gastric emptying as observed in HFD-fed mice.

Much progress has been made recently in identifying central or peripheral systems involved in the anorexic effects induced by OEA. In this regard, it is known that this lipid activates brain systems to modulate feeding. For instance, OEA recruits the activity of central nervous system nuclei as showed by an enhancement in *c*-Fos expression in areas such as nucleus of the solitary tract, paraventricular and supraoptic nuclei of the hypothalamus [6]. Moreover, Gaetani and coworkers

(2010) showed that systemic administration of OEA promotes expression of oxytocin in hypothalamus [32] whereas Serrano *et al.*, (2011) reported that injection of OEA in rats induced significant changes in hypothalamic monoaminergic activity as well as promoted the expression of the anorexigenic neuropeptide CART in the paraventricular nucleus. Furthermore, it has been described that OEA induced peripheral changes in gut peptides, such as PYY and ghrelin [33].

Finally, several further pieces of evidence support the role of molecular pathways involved in the anorexic-inducing effects of OEA. For instance, in a series of experiments, Yang and coworkers (2007) examined the effects of OEA on intestinal fatty acid uptake as well as fatty acid translocase (FAT/CD36; an 88-kDa integral membrane protein that facilitates free fatty acid uptake in adipocytes and myocytes). After intraperitoneal injection of OEA (5mg/kg) to rats, it was found a significantly increase of FAT/CD36 mRNA expression in isolated jejunal enterocytes as well as intestinal mucosa. Moreover, OEA also significantly enhanced fatty acid uptake in isolated enterocytes [34].

Recently, from a clinical perspective, Matias and coworkers (2012) reported the relationship between OEA and obesity. These authors found out that levels of OEA were quantifiable in saliva and its levels were significantly higher in obese than in normal weight subjects. Fasting salivary OEA levels directly correlated with body mass index as well as waist circumference. Moreover, the levels of OEA did not change in response to a meal [35]. Thus, taking together these results, it can be concluded that OEA could be regulating body weight by inducing alterations in peripheral lipid metabolism, such as increased lipolysis in adipocytes and enhancing fatty acid uptake in enterocytes.

The data reviewed here suggest that OEA displays hypophagic properties and involves peripheral and/or central mechanisms. The effects of OEA on receptors such as TRPV1, GPR119 or PPAR-α receptor on satiety have been described [36-38]. However, the functional relationship between these systems and OEA have not been studied in detail, in part because we lack of a clear conceptual framework of the links between the parallel and convergent functions of these neurobiological systems in food-intake modulation.

DISCUSSION

The increase in the prevalence of human obesity highlights the need to identify neuromolecular mechanisms involved in control of food-intake. Given the expansion of the knowledge in this area, it is ambitious to describe all the multitude of the neuroanatomical, neurochemical and genetic systems involved in feeding [39, 40]. However, it is known that several endogenous molecules are involved in feeding, and the nature of these compounds includes peptides, hormones and lipids [41-46]. With regard to the lipids, current evidence indicates the existence of endogenous lipid that promotes satiety: Oleoylethanolamide (OEA), which is produced primarily in the small intestine, has been identified to play an important role in the regulation of food-intake [5-10].

While the mechanism of action of OEA in anorexia remains to be described, it has been showed that this lipid activates several receptors, including PPAR-α receptor. The ingestion of dietary fat stimulates epithelial cells of the small intestine to synthetize OEA [6, 7], which behaves as an endogenous high-affinity agonist of the PPAR-α [27]. Upon its release, OEA acts within the gut engaging sensory fibers of the vagus nerve to promote anorexia [6, 14]. Current evidence suggests that feeding modulation by OEA may compromise peripheral and central mechanisms since it has been demonstrated that this lipid promotes expression c-*fos* gene in brain areas, including hypothalamus. Remarkably, the neurons in these brain nuclei express feeding-related peptides such as oxytocin and vasopressin. However, until more data are available on satiety effects of OEA, we cannot rule out the possibility that also feeding-related compounds such as ghrelin, leptin or nutritional status-dependent pathways might be under biological influence of OEA. Finally, the role of OEA as a potentially important key element in food-intake disorders has not yet been explored in detail.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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PATIENT CONSENT

Declared none.

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