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Review

Oleoylethanolamide: A fat ally in the fight against obesity

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ABSTRACT

Obesity is a pandemic, gateway disease that has thrived in modern, sedentary, high calorie-eating societies. Left unchecked, obesity and obesity-related diseases will continue to plague future generations with heavy burdens on economies, healthcare systems, and the quality of life of billions. There is a significant need to elucidate basic physiological mechanisms and therapies that address this global health care crisis. Oleoylethanolamide (OEA) is an endocannabinoid-like lipid that induces hypophagia and reduces fat mass in rodents. For over a decade, PPAR-α has been the most widely accepted mediator of the hypophagic action of OEA via signaling to homeostatic brain centers. Recent evidence suggests that OEA may also reduce food intake via effects on dopamine and endocannabinoid signaling within hedonic brain centers. Limited study of OEA supplementation in humans has provided some encouraging insight into OEA-based weight loss therapy, but more thorough, controlled investigations are needed. As a potential link between homeostatic and hedonic regulation of food intake, OEA is a prime starting point for the development of more effective obesity therapies.

Contents

1. Introduction

During the latter half of the 20th century, obesity quickly became pandemic. In 2014, the World Health Organization (WHO) reported that global obesity had more than doubled since 1980 and that 1.9 billion adults (18+ years) were overweight, with 600 million of those individuals being obese [1]. Obesity is a gateway disease that greatly elevates the risk of developing chronic diseases such as type 2 diabetes (T2D), cardiovascular disease, certain types of cancer, and neurodegenerative diseases [2]. Obesity and obesity-related diseases lower physical and mental quality of life [3]; create a worldwide economic burden of roughly $2 trillion annually; tax healthcare systems; and lower workforce productivity [4]. As we look to the future, it is worrisome that 41

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million children (under 5 years) are considered overweight or obese [1]. This is significant since increasingly younger children are now at elevated risk for developing obesity-related diseases that were only previously seen in adults [5–8]. For example, at the 2015 European Association for the Study of Diabetes annual meeting, a case report was presented about the youngest person ever to be diagnosed with T2D, a 3-year-old girl from Texas who weighed 77 lbs [9]. With predictions forecasting that 3.3 billion individuals will be overweight or obese by 2030 [2], there is a significant need to elucidate the basic pathophysiology of obesity with the goal of developing more effective therapies that address this global health care crisis. In this review, we will highlight the findings that make OEA, a lipid-derived messenger, a viable starting point for the development of more effective obesity therapies (Fig. 1).

By its simplest definition, body weight is determined by the energy balance ratio of energy intake (*i.e.*, food and beverage consumption) to energy expenditure (*i.e.* physical activity, exercise, metabolic rate). Though straightforward in theory, raising energy expenditure and decreasing energy intake to aid in weight loss is complicated due to the abundant availability of calorically-dense foods that have become modern staples for a highly-sedentary society. Over the years, our research ventures have focused on analyzing both sides of the energy balance equation by examining the molecular physiology and behaviors that govern our motivation to eat [10–14] and to be physically active [15–19]. The modulation of caloric intake is governed by a complex network that integrates homeostatic and non-homeostatic signaling in brain circuitry (See reviews [20,21]). The basic energy homeostatic model suggests that short-term caloric intake is integrated with long-term adiposity signals, such as leptin, that are released in proportion to body fat mass. The non-homeostatic model comprises additional factors that mediate energy intake including stress, learning/experience, social situations, biological rhythms, and hedonics/reward. The gut-brain axis is an essential component of the physiological network responsible for modulating energy balance. The sensing of ingested nutrients and their digestive products by specialized cells in the small intestine known as enteroendocrine cells (EECs) leads to the mobilization of various peptides—cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), peptide tyrosine-tyrosine (PYY), and oxyntomodulin—that each communicate nutrient status to the brain via humoral or afferent signaling (See review [22]). These peptides form an important interface that encodes the amount and composition of nutrient load and contributes to the control of food intake and energy homeostasis [23,24].

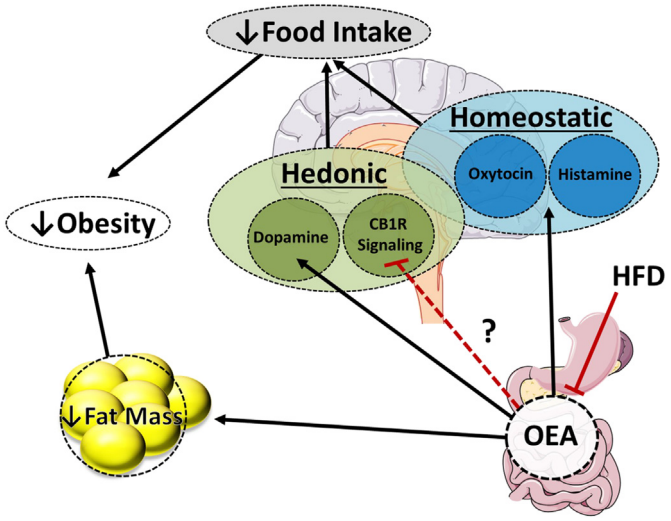

Fig. 1. The anti-obesity actions of oleoylethanolamide (OEA). OEA is synthesized and mobilized in the proximal small intestine from diet-derived oleic acid. High-fat diet (HFD) can inhibit OEA production in the intestine. OEA reduces food intake by activating homeostatic oxytocin and histamine brain circuitry as well as hedonic dopamine pathways. There is evidence that OEA may also attenuate hedonic cannabinoid receptor 1 (CB1R) signaling, the activation of which is associated with increased food intake. OEA reduces lipid transport into adipocytes to decrease fat mass. Further elucidation of the effects of OEA on food intake and lipid metabolism will aid in the determination of physiological mechanisms that can be targeted to develop more effective obesity therapies.

In addition to gut hormones, nutrients themselves play an important signaling role in the control of caloric intake. While consuming fat has been stigmatized in contemporary society for causing obesity, it has long been known that direct infusion of lipid emulsions into the small intestine can potently suppress food intake in rodents and humans [25–27]. One critical link explaining the relationship between fat ingestion and reduced food intake was identified in 2001 when Danielle Piomelli's group demonstrated that exogenous OEA, an endocannabinoid-like lipid, reduced food intake in rats [28]. Since this initial discovery, various groups have examined the mechanisms underlying the anorectic function of OEA. Herein, we discuss some of the history and recent developments in OEA research with respect to: 1) the physiological regulation of OEA production; 2) currently known mechanisms by which exogenous OEA mediates food intake and fat mass; and 3) how OEA research is providing insights into leveraging gut lipid signaling as a basis for more effective weight loss strategies.

2. Synthesis and degradation pathways of OEA in the intestine

OEA is a member of the *N*-acylethanolamines (NAEs), a family of saturated or unsaturated fatty acid amides with an ethanolamine moiety. Included among these bioactive lipids are the well-known polyunsaturated arachidonoylethanolamide (AEA, anandamide), which serves as an endogenous ligand for cannabinoid receptors [29], and endocannabinoid-like lipids such as saturated palmitoylethanolamide (PEA) [30], polyunsaturated linoleoyethanolamide (LEA) and monounsaturated OEA [31], whose actions are not mediated by cannabinoid receptors. NAEs are found in various tissues including brain, intestine, and immune cells [32,33], where they play an important role in many biological functions such as pain [34,35], inflammation [36], and the regulation of energy balance [28,37]. Among them, OEA has been studied mainly as an endogenous lipid mediator involved in the control of food intake [11,28,31]. Intestinal OEA levels decrease during food deprivation, whereas endogenous levels of OEA in the mucosal layer of the proximal small intestine (duodenum and jejunum) increase with nutrient availability [28,38]. A study that examined duodenal infusion of individual nutrients showed that dietary fat, but not protein or carbohydrate, is the major macromolecule stimulus for intestinal OEA production [39]. On the other hand, the prolonged consumption of high dietary fat reduces the jejunal levels of NAEs such as OEA, PEA, and LEA ([40–43] see below in Section 5).

Production of endogenous OEA involves multiple biochemical reactions that utilize oleic acid and phosphatidylethanolamine as substrates [38,44–47]. The first step requires transmembrane movement of oleic acid into enterocytes through apical membrane glycoprotein CD36 [39,45]. The transported oleic acid is then targeted to an enzymatic pathway catalyzed by a calcium-dependent *N*-acyltransferase (NAT) enzyme to generate *N*-oleoyl-phosphatidylethanolamine (NOPE) [48,49]. In the last step, NOPE is hydrolyzed by a specific *N*-acyl-phosphatidylethanolamine phospholipase D (NAPE-PLD) to produce OEA [38,50]. The increases in endogenous intestinal levels of selective NAEs such as OEA, LEA, and PEA [28,38,51] in response to food intake are concomitant with enhanced accumulation of NAPE-PLD [38] and the corresponding NAPE precursors [51]. Further, whole body ablation of the NAPE-PLD gene in mice reduces biosynthesis of various NAEs including OEA; however, OEA is not completely suppressed in these mice, suggesting a role for a NAPE-PLD-independent biosynthetic pathway [52,53]. Though fat ingestion is a major stimulus for OEA production and mobilization, findings that surgical sympathetic superior mesenteric ganglionectomy (SGX) as well as antagonism of β_2-adrenergic receptors attenuated

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food-induced OEA synthesis in the jejunum support the involvement of the sympathetic nervous system in endogenous OEA production [54].

In regards to OEA degradation, two structurally different intracellular enzymes, fatty acid amide hydrolase (FAAH) [55,56] and *N*-acylethanolamine-hydrolyzing acid amidase (NAAA) [57], hydrolyze OEA to oleic acid and ethanolamine [38]. NAAA is a lysosomal cysteine hydrolase that is highly localized in macrophages and that displays a high preference for saturated NAEs such as PEA [57–59]. In contrast, mono- and polyunsaturated NAEs such as OEA and AEA are primarily hydrolyzed by FAAH, which is an intracellular membrane-bound serine hydrolase mainly located in the endoplasmic reticulum [60,61]. Genetic studies have demonstrated that intestinal OEA levels are elevated in FAAH knockout mice as would be predicted, yet the time-course for elimination of exogenous OEA in the intestine of FAAH knockout mice is similar to that observed in wild-type mice [62]. Furthermore, the pharmacological FAAH inhibitor URB597 enhances levels of AEA and OEA in the liver and brain, but not in the intestine [62]. Together, these data suggest that an additional hydrolase enzyme participates in the intestinal deactivation of these NAEs. In contrast, another FAAH inhibitor, AA-5-HT, was shown to increase intestinal levels of AEA and PEA [63]. Although levels of OEA were not measured in this latter study, the inconsistences in the effects of FAAH inhibitors on intestinal NAE levels warrants further investigation into the precise mechanisms mediating tissue-specific inactivation and elimination of OEA.

3. The effects of OEA on homeostatic and hedonic food intake

There are still many unanswered questions about how the specific physiological mechanisms that control our need (*i.e.*, homeostatic) versus want (*i.e.*, hedonic/reward) to eat contribute to the onset and maintenance of obesity. During the progression towards obesity, the status of available energy substrates (*e.g.*, fat stored in adipose tissue) may become "invisible" to homeostatic systems due to the development of resistance in the brain to peripheral signals (*e.g.*, leptin and insulin). Alternatively, or in addition to this, hedonic systems may overwhelm homeostatic control mechanisms in the brain [64]. Therefore, physiological mechanisms that restore "visibility" of energy stores and/or lower the hedonic response to palatable foods are prime targets for anti-obesity therapy development. Herein, we discuss how OEA interacts with homeostatic and hedonic systems to reduce food intake.

3.1. Homeostatic regulation of food intake by OEA

Rodriguez et al. [28] showed for the first time that intraperitoneal (IP) administration of OEA causes a sustained inhibition of food intake in rats. Subsequent studies showed that the eating-inhibitory effect of exogenous OEA depends on the feeding state (*i.e.*, fed vs. fasted) of the animals. In *ad libitum*-fed rats, IP or oral administration of OEA delays eating onset without affecting meal size [11,65,66], indicating that the hypophagic effect of OEA is due to a prolongation of satiety (*i.e.*, the state of fullness after eating) rather than satiation (*i.e.*, the state of meal termination). In food-deprived rats, IP-administered OEA delays eating onset and reduces meal size [11,66], suggesting that OEA also affects meal size perhaps when larger meals are consumed as occurs after food deprivation. Importantly, the eating-inhibitory effect of OEA does not induce visceral illness, anxiety-like behavior, or stress hormone release [28,67], implying that the observed effects are not due to pain or other non-physiological factors. In addition to exogenous OEA, transient overexpression of NAPE-PLD in the duodenum of rats was associated with an increase in intestinal OEA levels and a concomitant decrease in food intake, which provides further evidence for the hypophagic action of endogenous OEA [68].

Several lines of evidence suggest that the satiety effect of exogenous OEA is mediated by activation of peroxisome proliferator-activated receptor-α (PPAR-α), a major transcriptional regulator of lipid metabolism and energy balance [31,50]. First, OEA is a potent activator of PPAR-α *in vitro*, whereas other natural ligands with close structural homology to OEA such as LEA and PEA activate PPAR-α to a lesser degree [30,31,43]. Although LEA is the most abundant endogenous NAE identified in intestinal sections of mice and rats [43,51], exogenous OEA reduces food intake to a greater degree than LEA [51]. Second, OEA administration causes hypophagia with similar behavioral features as those produced by the synthetic PPAR-α agonists WY-14643 and GW-7647 [13,31]. In addition to PPAR-α, OEA binds with two other known receptors with moderate potency, namely the G protein-coupled receptor 119 (GPR119), which is expressed in pancreatic β-cells and intestinal L-cells [69], and the capsaicin receptor transient receptor potential vanilloid-1 (TRPV1) [70,71]. Both receptors have been implicated in the biological actions of OEA (37, 38). However, studies in PPAR-α-null mice show that the satiety effect of exogenous OEA is absent [31], but OEA still inhibits eating in mice with a genetic deletion of GPR119 or TRPV1 [72,73]. These findings indicate that the involvement of GPR119 and TRPV1 is not necessary for the eating-inhibitory effect of OEA.

Most evidence supports a model whereby OEA promotes satiety via PPAR-α-mediated activation of afferent vagal fibers from the small intestine to the brain. Initially, the observations that total subdiaphragmatic vagotomy (TVX) and treatment with the neurotoxin capsaicin abolish the satiety effect of exogenous OEA suggested that OEA exerts its effects via activation of vagal sensory afferents [28,31]. With TVX, both vagal afferents and efferents are removed. However, we showed that OEA does not require intact abdominal vagal afferents to reduce food intake by using the surgical procedure of subdiaphragmatic vagal deafferentation (SDA), which selectively eliminates all abdominal vagal afferents while retaining about half of the vagal efferents intact [11]. SDA allows the specific effects of afferent versus efferent signaling to be distinguished and is the most complete and selective abdominal vagal deafferentation technique available [74,75]. The presence of OEA-induced hypophagia in SDA rats implies that other pathways are involved in transmitting the hypophagic signaling of OEA. We partially addressed this by showing that peripherally administered OEA activates *c-Fos* expression in the area postrema (AP), a circumventricular organ that lacks a functional blood brain barrier (BBB), and in the subpostremal nucleus of the tractus solitarius (NTS) [12]. This observation brought up the possibility that OEA may promote hypophagia by directly engaging brain circuitry. Indeed, one study showed that peripheral administration of OEA reduced *c-Fos* staining in the lateral hypothalamus (LH) and that targeting OEA to the LH reduced food intake [76]. However, other evidence needs to be considered. First, direct injection of OEA into the lateral ventricles had no effect on food intake [28]. Second, fasting and refeeding only modestly affect plasma OEA levels [38]. Together, these studies argue against the direct action of OEA in the brain to promote hypophagia. Additionally, there is a possibility that elevations in plasma NAPEs could engage satiety centers to reduce food intake. Studies have demonstrated that plasma NOPE increases after fasting/refeeding [54], HFD, or intraduodenal lipid infusion [77]. However, an anorectic effect of exogenously-administered NAPE was only shown for the C16:0 NAPE species which is a precursor for PEA, not OEA [77]. Furthermore, a true anorectic effect of exogenous NAPE has been disputed [78,79].

An alternative, and not mutually exclusive possibility, is that elevations in intestinal OEA may stimulate the production and/or release of other humoral mediators that act as satiety signals. Given the known regulatory function of PPAR-α in lipid metabolism and its localization in the proximal intestine, where digestion of dietary fats and uptake of long-chain fatty acids occur [80], it is possible that OEA controls food intake by selectively activating intestinal PPAR-α signaling that stimulates fatty acid oxidation (FAO) and ketogenesis. Indeed, we and others provide evidence that elevations in intestinal FAO and ketogenesis can decrease food intake [13,81]. Furthermore, we demonstrate that administration of exogenous OEA causes an acute spike in plasma levels of the ketone body beta-hydroxybutyrate (BHB) [11]. Thus, the possibility of

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other OEA-induced humoral mediators that may contribute to extravagal communication between gut and brain needs further investigation.

Within the brain, two pathways are known to contribute to the hypophagic action of OEA. First, the neuropeptide oxytocin is involved in the central nervous system (CNS) mediation of the eating-inhibitory effect of OEA. IP administration of OEA enhances the expression of oxytocin in neurons within the paraventricular (PVN) and supraoptic nuclei (SON) of the hypothalamus, two nuclei that are critically involved in eating and energy homeostasis [82]. Moreover, injection of the selective oxytocin receptor antagonist L-368,899 via intracerebroventricular (ICV) infusion abolished the satiety effect of OEA, suggesting that the activation of oxytocin in the CNS is required [82]. Second, there is evidence that brain histamine transmission is also involved in OEA's satiety effect. Provensi et al. [83] demonstrated that ablation of the histamine-synthesizing enzyme histidine decarboxylase (HDC) as well as targeted pharmacological blockade of brain HDC reduced the anorectic effect of OEA. Additionally, OEA induced histamine release in the brain and promoted *c-Fos* expression in oxytocin neurons of wild type mice but not in HDC knockout mice.

3.2. Engagement of hedonic/reward systems by OEA to regulate food intake

In addition to homeostatic "need to eat" signaling, the rewarding effects of palatable foods add a challenging level of complexity in the quest to understand the mechanisms that regulate caloric intake. While much progress has been made in understanding the effects of OEA on homeostatic eating, less is known about how OEA responds to and interacts with hedonic signaling associated with food intake. Though in its infant stages of investigation, there is evidence to suggest that OEA links homeostatic systems with classical hedonic systems to promote hypophagia.

3.2.1. Dopamine signaling

At the center of the hedonic regulation of food intake and other addictive behaviors is the neurotransmitter dopamine [84]. Currently, there is a supported theory that, in some cases, obesity can occur due to dysfunctional dopamine signaling, which results in compensatory overeating [85,86]. Dopamine engages pathways in the nucleus accumbens, a region of the ventral striatum that mediates pleasure and reward signaling [87], and the dorsal striatum (DStr), a brain area housing the circuitry that mediates motivation of goal-directed behaviors such as eating [88]. Pharmacological inhibition (via ablation of dopaminergic neurons by 6-hydroxydopamine) and genetic ablation (*i.e.*, tyrosine hydroxylase knockout) of dopamine signaling leads to hypophagia and early death due to starvation [89,90]. Interestingly, restoration of dopamine signaling in tyrosine hydroxylase knockout mice via viral delivery of the tyrosine hydroxylase gene to the DStr, but not to the nucleus accumbens, rescues hypophagia, suggesting that dopamine signaling in the DStr is essential for proper control of food intake [89,91]. Furthermore, knockdown of dopamine receptors in the DStr of rats mimicked the compulsive food intake observed in obese rats fed a cafeteria diet [86]. In humans, there are reports of dopamine receptor deficiency and attenuated striatal responses to food stimuli in obese and overweight individuals, respectively [92–95].

In 2013, Tellez et al. published an elegant study that measured the effect of OEA on extracellular dopamine levels of the dorsal striatum in normal chow- and high-fat diet- (HFD)-fed mice [96]. In that study, intragastric infusions of lipid were coupled with microdialysis sampling of extracellular dopamine in the DStr. Intragastric lipid infusion promoted an increase in DStr dopamine in normal chow-fed mice, but not in HFD mice, providing evidence that HFD disrupts dopamine signaling in the DStr. Importantly, IP administration of OEA prior to lipid infusion rescued this dopamine deficiency in HFD mice in a PPARα- and afferent innervation-dependent manner. OEA lowered oral intake of both low- and high-calorie emulsion in normal chow-fed mice. Strikingly, in HFD-fed mice, OEA reduced high-calorie emulsion intake, but increased low-calorie emulsion intake. These data suggest that OEA may shift preference towards low-calorie foods. Furthermore, others have shown that OEA dose-dependently increases dopamine in the nucleus accumbens [97] and attenuates cocaine-induced locomotor activity [98], a behavioral phenotype that is dependent on dopamine signaling in the nucleus accumbens [99].

3.2.2. Endocannabinoid signaling and taste perception

Sensitivity to specific tastes is an important component of hedonic hunger and obesity [100–104]. In recent years, the array of known sensations that our taste buds perceive has been extended beyond the basic tastes of sweet, sour, bitter, salty, and umami [105,106] to now include oleogustus—the taste of fatty acids [107]. Within this taste system, endocannabinoids play a key role in the regulation of hedonic hunger, intake of dietary sugar and fat, and obesity progression. The endocannabinoids AEA and 2-arachidonoylglycerol (2-AG) promote food intake and increase adiposity through activation of the cannabinoid receptor 1 (CB1R) in hedonic and homeostatic brain centers as well as in peripheral sites [32,108,109]. In rats, administration of endocannabinoids or exogenous cannabinoids increased preference for sucrose and dose-dependently increased carbohydrate, but not protein or fat, consumption [110–112]. Furthermore, the sucrose-induced activity of the chorda tympani, a branch of the facial nerve that transmits taste signals from the tongue to the brain, becomes increasingly dependent on lingual cannabinoid receptor activation and less dependent on leptin signaling during the development of diet-induced obesity (DIO) [113].

The endocannabinoid system is also involved in oleogustus sensation. Indeed, a line of evidence by DiPatrizio and colleagues illustrates this concept. Importantly, it was shown in a sham-feeding rat model—a method that uncouples oral taste sensations from post-ingestive effects (See review [114])— that oral exposure to dietary fat, but not protein or carbohydrates, causes a doubling of AEA and 2-AG specifically in the proximal small intestine (*i.e.*, jejunum) in a CB1R- and vagus nerve-dependent manner [115]. Further evidence pointed to oral sensing of unsaturated, but not saturated, dietary fats as a major stimulus driving this increase in jejunal endocannabinoids [116]. A direct connection between peripheral endocannabinoid signaling and hyperphagia associated with obesity was shown by targeted blockade of peripheral CB1R with AM6545 which resulted in hypophagia of obese mice fed a Western diet (40% kcal from fat) for 60 days, but not of lean mice fed standard chow [117]. With respect to OEA, oral fat exposure also promotes an elevation in jejunal NAPE-PLD activity, the enzyme that converts NOPE into OEA, and a decrease in FAAH, the enzyme that hydrolyses and inactivates OEA [115]. Though it could be hypothesized that jejunal OEA may also be elevated in this model, no data were presented to determine this point. Overall, these studies demonstrate the important integration between taste perception and food intake by the endocannabinoid system and highlights this system as a target for the development of more effective obesity therapies.

Though OEA is the monounsaturated analogue of AEA, it is not a ligand for the CB1R. In fact, OEA acts more like an anti-endocannabinoid with respect to food intake as it promotes hypophagia rather than hyperphagia. In the small intestine, AEA and OEA exhibit reciprocal concentrations during fasting (↑ AEA, ↓ OEA) and refeeding (↓ AEA, ↑ OEA) [38,118]. Within the last 15 years, CB1R antagonists have been investigated as potential anti-obesity therapies due to their ability to promote hypophagia in rodents [119]. At one time, it was proposed that co-administration of CB1R antagonists and OEA could be an effective anti-obesity therapy [120]. However, the significant adverse psychiatric effects (*e.g.*, increased depression and anxiety) associated with the CB1R antagonist rimobanant led to its rapid removal from clinical use [121,122]. Side-by-side comparison of OEA and rimobanant in male, C57BL6/J mice demonstrated that OEA was as

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anorectically potent as rimobanant but did not change feeding-related behaviors (*e.g.*, grooming, locomotor activity) as was seen with rimobanant [123], indicating that OEA may be a safer alternative to CB1R antagonists.

Recently, a study by Kang et al. [124] highlights the possibility that OEA may inhibit CB1R signaling in areas of the brain that mediate communication between gastrointestinal and gustatory signaling. They demonstrated that OEA attenuates AEA-induced coordination between the gastrointestinal autonomic insula (GI-Au-I) and the gustatory insula (Gu-I) [124], regions of the brain that integrate taste information from taste buds in the tongue and gastrointestinal mechano-/chemo-sensory information, respectively, to create sensations of hunger or satiety. In rat brain slice preparations, OEA attenuated AEA-mediated θ-oscillations (measured with a voltage dye) between the GI-Au-I and Gu-I in the presence of GW6471, a PPAR-α antagonist, but not in the presence of arvanil, a GPR119 antagonist. This suggests that GPR119, but not PPAR-α, mediates the disruption of AEA-mediated θ-oscillations by OEA. As these experiments were performed in rat brain slices without *in vivo* follow-up, future studies should investigate whether the inhibition CB1R signaling in the insular region, and potentially other brain regions, is a component of OEA-induced hypophagia. This is a plausible hypothesis as OEA plasma levels are positively associated with food-related brain activation of the insula and suppression of food-liking reactions in normal weight, but not obese, humans [125].

Together, these studies provide evidence that OEA can engage hedonic and homeostatic circuitry to mediate food intake and that OEA could act as a negative feedback signal to reduce additional consumption of high-calorie foods. The exact mechanism for how OEA engages and links homeostatic and hedonic circuitry is still unknown.

4. The effect of OEA on fat mass

In addition to acting as a satiety signal, OEA also plays an important regulatory role in lipid metabolism in genetically obese rats and DIO mice [126,127]. Chronic treatment with OEA reduces serum lipid levels and hepatic lipid accumulation, possibly through the direct activation of PPAR-α [126]. OEA-induced reductions in adipose FAT/CD36 reduce lipid transport into adipose tissue of HFD-fed mice, contributing to lower adiposity in these mice [128]. Additionally, a newly identified role of chronically-administered OEA in reducing HFD-induced inflammation and nonalcoholic fatty liver (NAFLD) in rats has been demonstrated [129]. Furthermore, OEA may contribute to reductions in inflammation associated with gastric bypass surgery (GBS). After GBS, morbidly obese patients exhibit unchanged levels of plasma OEA but elevated OEA in subcutaneous adipose tissue [130]. This group further demonstrated that OEA dose-dependently reduced the secretion of chemokine (C—C motif) ligand 2 (CCL2 or MCP1), an inflammatory cytokine that is elevated in obese patients and reduced post-GBS, from cultured adipocytes [130]. These findings highlight the therapeutic potential of OEA in the treatment of obesity and adipose-mediated inflammation.

It is worth noting that along with the regulatory role of OEA on lipid metabolism, its effect on glucose metabolism has also been investigated [127,131,132]. Although neither acute nor chronic OEA treatment affect basal plasma glucose concentration [126,127,131,132], one study showed that exposure of rats to acute OEA treatment induces glucose intolerance without affecting insulin levels [131]. In the same study, the authors showed that OEA reduced insulin-stimulated glucose uptake in isolated rat adipocytes possibly through a mechanism involving the activation of p38 and JNK kinase. Although these effects may partly explain the *in vivo* observations, the possible effect of OEA on muscle glucose uptake was not investigated. In contrast, another study has shown that OEA had no effect on glucose uptake or oxidation in both rat adipocytes or muscle [127].

5. The effects of diet on endogenous OEA

As we begin to discuss the effects of diet on endogenous OEA it should be noted that most human studies measure plasma-derived OEA and not intestinal OEA, which is the focus of this review [125, 133–137]. This is an important point to consider when drawing conclusions from correlation analyses as OEA found in the plasma is most likely a composite of spillover from multiple organs that generate OEA. Indeed, levels of OEA in plasma and tissues are not always reflective of one another and depend on diet or drug intervention. For instance, in rodents, while orally-administered OEA promoted a rise in intestinal and plasma OEA but not in brain or muscle, the drug URB597 caused an increase in endogenous OEA in the brain and liver but not the small intestine [62,65]. Furthermore, it has been shown that blood cells in rodents and humans contain large amounts of esterified NAEs, including OEA, suggesting that blood cells can potentially generate NAEs themselves and/or provide a storage compartment for NAEs released from tissues [138]. In that study, a diet intervention in mice also showed that fish oil dose-dependently decreased esterified and free OEA in plasma and blood cells [138]. Therefore, though plasma analyses can provide some information as to the effects of diet and drugs interventions on OEA levels, more specific analysis is required to determine how OEA levels in various tissues are affected.

The extent to which OEA is produced and mobilized in the gut can be affected by the type and the duration of specific diets. Various studies show that consumption of diets high in oleic acid elevate plasma OEA levels and reduce energy intake in humans [139–141]. Plasma OEA is lower in overweight males and females who received daily supplementation of either corn-safflower oil blend or flax-safflower oil blend compared to groups receiving oils with higher oleic acid content (*e.g.*, canola oil or high oleic acid canola oil) [139]. As olive oil consists of 55–83% oleic acid, it is possible that elevations in OEA may contribute to the improvements in weight and overall health experienced with transitioning to the Mediterranean diet in which foods with high in oleic acid (*e.g.*, avocados, olives, and olive oil) are staples [142–144].

Studies in rats show that as the percentage of ingested fat content increases, the anorectic jejunal NAEs decrease [42]. With respect to OEA, HFD rapidly (within 7 days) suppresses OEA mobilization in the intestine and continues to suppress OEA during chronic administration of HFD (15 weeks) [42,96]. Hansen and colleagues [42,43] showed that 7 days of exposure to high dietary fat decreases OEA levels in the jejunum of rodents regardless of the fat composition of the diet. They also showed that rats fed a HFD (45% energy from fat, energy density: 19.5 kJ/g) or a diet with the same energy density as regular chow (energy density: 12.5 kJ/g), but with 45% of the energy from fat, had reduced levels of OEA and ate more than normal chow-fed rats, indicating that NAE levels are regulated by dietary fat content and not by the energy density of the HFD [42]. In rodents fed normal chow, OEA levels in the jejunum are reduced 10-fold during a 24-h food deprivation and rebound to above free-feeding levels within 30 min of refeeding [40]. Further, acute duodenal infusion of Intralipid or oleic acid mobilizes jejunal OEA in lean rodents but not in DIO rodents fed either high-fat or high-sucrose diets (HSD) for 7 days [40]. The mechanism by which chronic exposure to dietary fat suppresses intestinal OEA levels is unclear, but this phenomenon might contribute to the overconsumption of high-caloric foods.

The presence of an intestinal fat sensor that detects increased luminal dietary fat might contribute to the observed effects described above. Recent work in mice lacking the intestinal LXR-responsive phospholipid-remodeling enzyme lysophosphatidylcholine acyltransferase 3 (Lpcat3), an enzyme that modulates passive fatty acid transport into enterocytes, showed enhanced jejunal and serum OEA in mice fed a 60% HFD but not a normal chow diet [145]. Strikingly, within 10 days of switching from normal chow to 60% HFD or to a western diet, mice lacking intestinal Lpcat3 (IKO) lost 20% of their body weight and were moribund. MRI analysis demonstrated that the major contributor to

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this HFD-induced weight loss in IKO mice was a large (almost 5-fold) reduction in fat mass. Though not directly tested, it is plausible that the elevated levels of OEA exhibited by IKO mice on HFD could contribute to their rapid weight loss. First, OEA directly engages systems that reduce food intake, as described above, but can also promote lipolysis. Second, OEA engages GPR119 in L-cells of the ileum to secrete GLP1, a gut hormone that carries out anorectic and insulinotropic functions [146]. GLP1 is also elevated in HFD-fed IKO mice. Administration of Exendin-9, a GLP1 receptor (GLP1R) antagonist, partially reversed the HFD-induced reductions in food intake in IKO mice, suggesting that GLP1-mediated anorexia could contribute, at least in part, to the rapid weight loss.

The question remains: why does the ablation of intestinal Lpcat3 promote elevated levels of OEA when mice are given a HFD? It should be noted that IKO mice switched to a moderate fat diet (30% calories from fat) did not experience this rapid weight loss but did exhibit attenuated weight gain compared to control mice. The authors did not mention whether OEA and GLP1 levels were measured in moderate fat-fed mice, but the increased glucose tolerance of the moderate fat-fed mice suggests that at least GLP1 may be also elevated, potentially due to enhanced stimulation by above normal levels of OEA. Furthermore, this hypothesized increase in GLP1 release could be caused by diet-derived fat being hydrolyzed in more distal regions of the small intestine where 2-monoacylglycerol can stimulate GLP1 secretion, possibly via activation of GPR119 in L-cells [147]. The differences in how IKO mice respond to increasing percentages of fat in their diet suggests that Lpcat3 plays a role in the system that senses luminal dietary fat content and/or the integration of information about dietary fat that regulates OEA synthesis and mobilization. Whether Lpcat3 acts as a gating sensor in OEA synthesis and/or mobilization under high luminal content of dietary fat warrants additional investigations.

6. Incorporation of OEA into nutraceutical supplements and drug development

6.1. Nutraceutical supplements

The majority of OEA research studies in humans have highlighted the effect of diet on endogenous OEA or the correlations between endogenous, plasma OEA and measures such as BMI, % body fat, hunger, exercise, food palatability, and satiety [125,133–137]. The oral availability [65,148] and weight loss potential of OEA has led to the introduction of OEA to the weight loss supplement market. The supplement RiduZone (OEA [200 mg]/capsule) is currently the only FDA-acknowledged OEA supplement on the market. Data from a retrospective analysis of 42 patients (14 male, 28 female) who took RiduZone 2–3 times/day for 4–12 weeks was presented at the 2016 Obesity Medicine Association's Overcoming Obesity conference [149,150]. In that study, RiduZone elicited an average 7–8% decrease in BMI after 10 weeks of treatment. Other than one case of transient nausea, no other side effects were observed. It should be noted that this data set does not include a placebo group due to the retrospective analysis of patient records. Though these results are encouraging, there is a great need for more thorough, placebo-controlled investigations into the supplemental use of OEA for weight loss in humans.

6.2. Drug development

The action of OEA is relatively short due to its rapid hydrolysis [128,151]. Therefore, developing systems that reduce degradation of OEA by intrinsic processes will be useful to increase bioavailability of OEA as a method for enhancing its hypophagic and anorectic actions. In 2016, Younus and colleagues published a novel drug delivery system that incorporates OEA into lipid-based cubosomes that could potentially produce long-acting OEA *in vivo* [152]. Other labs have developed FAAH-resistant OEA analogues such as elaidyl-sulfamide and KDS-5104 [128,151] that demonstrate potent hypophagic function via PPAR-α activation. The safety of using long-acting OEA analogues must be demonstrated, however, as elaidyl-sulfamide also induces insulin resistance and hyperglycemia [153].

Aside from developing long-acting OEA analogues, there is the potential for OEA and other lipid molecules to be used to enhance the hypophagic and weight loss effects of endogenous satiety systems. In peptide drug development, the attachment of lipid moieties to peptides has traditionally been employed to increase circulating levels of peptide. For example, the peptide Liraglutide, a GLP1R agonist used to treat T2D (Victoza, Novo Nordisk) and obesity (Saxenda, Novo Nordisk), was developed by conjugating a palmitoyl group to a lysine residue in the GLP1 peptide sequence [154]. The palmitoylation of GLP1 increased its half-life from 1.5–5 min [155] to 10–14 h by promoting binding with albumin and decreasing GLP1 degradation by its intrinsic peptidase, dipeptidyl peptidase-IV (DPP-IV) [156–158]. As previously mentioned, OEA stimulates post-prandial GLP1 release from L cells [72,146]. However, in 2015, Cheng and colleagues unveiled another OEA-GLP1 relationship in that OEA enhances GLP1-mediated cAMP production (corroborated by our lab [data not published]) through what appears to be a direct interaction between GLP1 and OEA [159]. Interestingly, the enhancement of canonical GLP1R-mediated signaling by OEA occurred without changing the affinity of GLP1 for the GLP1R [159]. These data provide evidence that an interaction between GLP1 and OEA can modulate signaling patterns downstream from the GLP1R. Within GLP1R signaling, distinct potency of various signaling events downstream from GLP1R activation are dependent on the specific ligand binding the receptor (*i.e.*, biased signaling). This phenomenon could explain why GLP1R agonists such as GLP1 and Exendin-4 bind the GLP1R with similar affinity [160,161], yet induce different anorectic potencies [162]. Past drug development focused on identifying small molecules that bind to allosteric sites on the GLP1R and stimulate canonical GLP1R signaling (*i.e.*, cAMP production) [163–165]. These new observations suggest that binding lipid moieties, such as OEA, to GLP1R agonists or potentially other peptides, has consequences beyond an originally intended purpose of increasing binding to albumin and extending the half-life of the peptide [154,158] and provide an alternate strategy for the development of novel GLP1R based therapies. Furthermore, enhancing specific GLP1R downstream signaling events associated with desired phenotypes (*i.e.*, increased insulin secretion and decreased food intake) is an attractive strategy for developing more effective diabetes and obesity therapeutics. Further exploration is needed to determine whether an endogenous interaction between OEA and GLP1 occurs and if this enhances the hypophagic effects of GLP1.

7. Summary

More effective obesity therapies are vital to prevent and reverse the global escalation of obesity and obesity-related disorders. The development of safe, effective drugs that reduce food intake and lower body weight will be necessary in this effort. Almost two decades of research show the important role OEA plays in reducing food intake via homeostatic and, more recently, hedonic mechanisms. Rodent and human studies support OEA as a prime starting point to determine physiological mechanisms underlying reductions in eating behaviors that can be leveraged for the development of more effective obesity therapies.

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