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Behavioral Physiology

Oleoylethanolamide: The role of a bioactive lipid amide in modulating eating behaviour

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Summary

Fatty acid ethanolamides are lipid mediators that regulate a plethora of physiological functions. One such bioactive lipid mediator, oleoylethanolamide (OEA), is a potent agonist of the peroxisome proliferator-activated receptor-alpha (PPAR-α), which modulates increased expression of the fatty acid translocase CD36 that enables the regulation of feeding behaviour. Consumption of dietary fat rich in oleic acid activates taste receptors in the gut activating specific enzymes that lead to the formation of OEA. OEA further combines with PPAR-α to enable fat oxidation in the liver, resulting in enhanced energy production. Evidence suggests that sustained ingestion of a high-fat diet abolishes the anorexic signal of OEA. Additionally, malfunction of the enterocyte that transforms oleic acid produced during fat digestion into OEA might be responsible for reduced satiety and hyperphagia, resulting in overweight and obesity. Thus, OEA anorectic signalling may be an essential element of the physiology and metabolic system regulating dietary fat intake and obesity. The evidence reviewed in this article indicates that intake of oleic acid, and thereby the resulting OEA imparting anorexic properties, is dependent on CD36, PPAR-α, enterocyte fat sensory receptors, histamine, oxytocin and dopamine; leading to increased fat oxidation and enhanced energy expenditure to induce satiety and increase feeding latency; and that a disruption in any of these systems will cease/curb fat-induced satiety.

Keywords: Obesity, oleic acid, oleoylethanolamide, satiety.

Abbreviations: CCK, cholecystokinin; CNS, central nervous system; DIT, diet-induced thermogenesis; EE, energy expenditure; FA, fatty acid; FAAH, fatty-acid amide hydrolase; FAEs, fatty acid ethanolamides; FAs, fatty acids; GLP-1, glucagon-like peptide-1; HFD, high-fat diet; HOCO, high-oleic canola oil; i.p., intraperitoneally; MUFA, monounsaturated fatty acid; NAcS, nucleus accumbens shell; NAPE-PLD, N-acyl phosphatidylethanolamine phospholipase D; NAPEs, N-acyl phosphatidyl ethanolamines; NO, nitric oxide; NST, nucleus of the solitary tract; OEA, oleoylethanolamide; PE, phosphatidylethanolamine; PUFA, polyunsaturated fatty acids; PYY, peptide YY; SFA, saturated fatty acids; TEF, thermic effect of food.

Introduction

Obesity is a complex disorder that has reached epidemic proportions, particularly in industrialized/developed countries, and has been linked to an increased risk of non-communicable diseases. Despite the high prevalence of obesity, limited nutritional and pharmacological therapies are currently available. Therefore, the development of

efficacious and innocuous anti-obesity approaches is of primary importance for both patients and health systems. In this context, recent data have explored and generated interest in a class of N-acylethanolamides, also termed as fatty acid ethanolamides (FAEs), which are arachidonoylethanolamide and 2-arachidonoylglycerol analogues but appear to operate through independent mechanisms involving cannabinoid receptor type 1 (CB1) receptors (1). Other ethanolamides include a subclass of saturated, monounsaturated and polyunsaturated FAEs such as myristoylethanolamide, stearoylethanolamide, palmitoylethanolamide, linoleoylethanolamide, α-linoleoylethanolamide, eicosapentaenoylethanolamide and docosahexaenoylethanolamide. This family of FAEs also includes the monounsaturated fatty acid (MUFA) species oleoylethanolamide (OEA) (Fig. 1) (2).

Furthermore, DiPatrizio and Piomelli (1) have demonstrated that OEA and endocannabinoids act as key fat-dependent regulators of hunger as well as satiety. However, despite structural similarities, these substances interact with distinct molecular targets and elicit widely different biological responses. For example, OEA attenuates food intake by activating homeostatic brain circuits. On the other hand, endocannabinoids activate the hedonic cannabinoid receptors especially CB1. Stimulation and activation of CB1 lead to increased food intake (3).

OEA is a lipid amide that is released by enterocytes upon absorption of dietary fat and may engage in the initiation of satiety (4). Involvement of OEA in the process of food consumption and satiety has fuelled a new interest in the amide of fatty acids (FAs), particularly OEA. Therefore, the objective of the present review was to probe the effects of oral supplementation of OEA, either through the diet or supplements, on weight management by elucidating the physiological role of these lipid-signalling molecules in the modulation of food intake and energy expenditure (EE).

Metabolism of oleoylethanolamide

The pathway at a molecular level accounting for the anabolism and catabolism of OEA in mammalian cells involves a particular group of phospholipids, N-acylethanolamine phospholipids, termed N-acyl phosphatidylethanolamines (NAPEs), which have an additional FA bound to the amine group of phosphatidylethanolamine (PE) (5). These FAEs, including OEA, can be produced from NAPEs via two pathways that involve enzymatic activity: (i) N-acyl transferase and (ii) N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD) (Fig. 2). All FAEs emerge from the analogous NAPEs. Therefore, NAPE species consisting of oleic acid at the amine end (N-oleoyl-PE) produce OEA at the time of hydrolysis. The primary action of the principal enzymatic pathway is to exchange FA between two membrane phospholipids, with the transfer of an acyl group from the donor stereospecific numbering-1 (*sn*-1) position of phosphatidylcholine to the amine group of PE (6,7). Enterocytes thereby appropriate the diet-derived oleic acid, and synthesis of the membrane phospholipid, N-oleoyl-phosphatidylethanolamine, occurs utilizing it as a substrate. The reaction further leads to secondary activity by inducing the cleavage of NAPE by an NAPE-PLD to biosynthesize OEA (8–11). The hydrolysis of OEA terminates the physiological functions of this lipid mediator, resolving it into oleic acid and ethanolamine. Two intracellular amidases channel this reaction: fatty-acid amide hydrolase (FAAH), an intracellular membrane-bound serine hydrolase (12,13), and *N*-acylethanolamine-hydrolysing acid amidase, a lysosomal cysteine hydrolase (14). Higher intensities of FAAH expression are present in the liver, small intestine and central nervous system (CNS) (15). By contrast, *N*-acylethanolamine-hydrolyzing acid amidase activity in rats is highest in the lungs, whereas in humans, it is highest in the liver; thus, cross-species variability is observed in the selective activity of the enzyme (14).

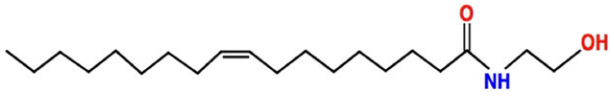

Figure 1 Structure of N-oleoylethanolamide.

Anorexic properties of oleoylethanolamide/food intake regulation by oleoylethanolamide

Anorectic potency of OEA has been proposed by Fu and colleagues (16) in an experiment performed in rats. They showed a transitory decrease in the overexpression of NAPE-PLD that further resulted in attenuated food ingestion, concomitant with elevated concentrations of intestinal OEA in adult male Wistar rats. The hypophagic action of OEA accompanies the action of proliferator-activated receptor type-alpha (PPAR-α) (9, 10, 17–19), to which OEA binds with high affinity; as in PPAR-α-null mice, controlled feeding behaviour was observed to be ablated (17,19). Additionally, in free-feeding mice or rats, systemic administration of OEA before dark escalated the feeding latency via the lipid-derived signal in dose dependent manner without affecting the meal size, whereas in food-deprived animals, OEA administration not only delayed feeding onset but also reduced the meal size (20), which is distinctive of satiety. To further substantiate its anorexic characteristics, OEA administration to mice or rats was observed to generate a time as well as dose-dependent effect on meal consumption, leading to reduced food intake at higher exogenous doses of OEA

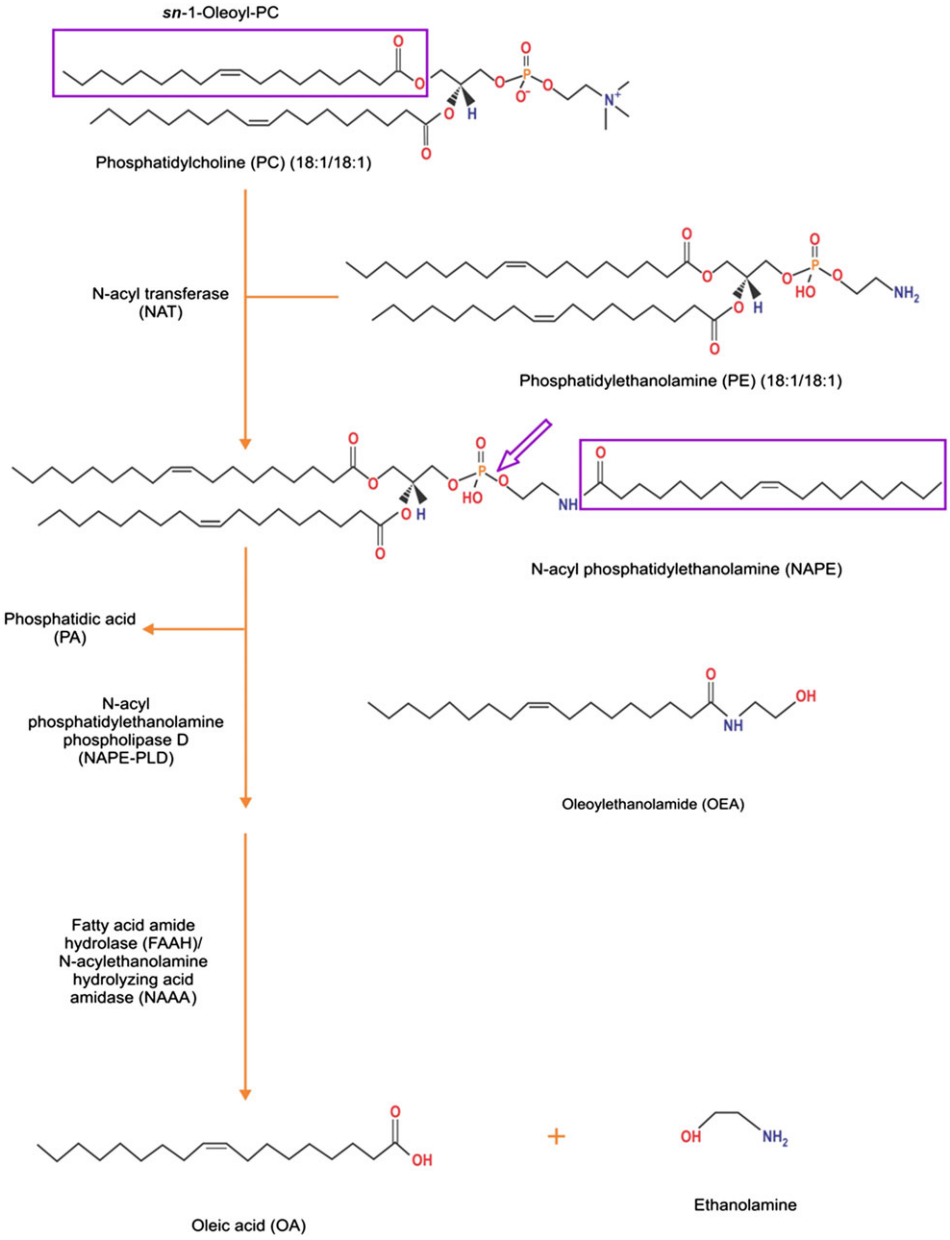

Figure 2 Metabolism of oleoylethanolamide (OEA) in mammalian cells (adapted) (9,27).

(20 mg.kg^{-1}, intraperitoneally [i.p.]) over the 24-h test period of OEA administration (17,19–26).

Previous studies have shown that the administration of OEA to fasting rats and mice either i.p. or by gavage curtails food consumption (10,18–20,22,24,25). Free-feeding rats fed standard chow pellets (Prolab RMH 2500) also exhibit unusual effects by persistently inhibiting food consumption, but only at selective doses of OEA administered i.p. at 5 mg.kg^{-1} i.p. and being most effective at 20 mg.kg^{-1} i.p. Therefore, the findings suggest that systemic administration of OEA to free-feeding rats leads to a dose-dependent delay in eating onset, which is not associated with changes in meal size or the postmeal interval (20,23). Altogether, OEA reduces meal frequency in free-feeding rats; however, OEA decreases both the rates of occurrence as well as the meal size in food-deprived rats (20). Additionally, fasting reduces and refeeding intensifies the OEA concentrations in the jejunum (25,27,28). To further confirm that OEA plays an important role in restricting the meal frequency, Fu and colleagues (27) observed NAPE-PLD activity in free-feeding and 24-h food deprived rats and concluded that the activity of NAPE-PLD remained low during fasting but increased in intensity promptly upon refeeding, comparable to the NAPE precursors for OEA (28). Overall, the study results

suggest that the synthesis of NAPE precursors and NAPE-PLD activity monitors the intestinal alterations in tissue OEA concentrations. By contrast, the OEA concentrations are not at all affected by the fluctuations involved in FAEs catabolism (9,16,27,28). Therefore, the research studies discussed above substantiate that the function of the NAPE-generating enzyme N-acyl transferase may provide a pivotal contribution to the modulation of the intestinal concentration of anorectic N-acylethanolamides. Furthermore, the studies assert that exogenously administered OEA has an extremely effective anorectic impact (18,25).

Additionally, regarding its anorexiant properties, when administered sub-chronically to lean (25) or obese rats (29) and mice (19), OEA decreased body weight gain in normal animals but not in PPAR-α-null mutants (19). Similar results were obtained in a clinical trial conducted by Jones and colleagues (30); during this human feeding trial, participants were provided with diets enriched with high-oleic canola oil (HOCO), HOCO blended with flaxseed oil or a Western diet for 29 d. Findings showed a negative correlation between the plasma OEA levels and body fat percentage. Another human trial conducted by Pu and colleagues (31) showed that dietary oleic acid enriched HOCO resulted in elevated plasma OEA levels that affected the regional and total fat mass, suggesting that the effect might be caused via lipid-signalling channels. Associations between OEA levels and improved body composition results are in agreement with another human trial performed with morbid obese patients (32). Barbour and colleagues (33) also conducted a human trial to examine energy intake; during the study, volunteers were offered high-oleic (oleic acid ~75% of total FAs) peanuts and regular peanuts (oleic acid ~50% and higher in polyunsaturated fatty acids [PUFAs]). The total energy intake was shown to be lower following the consumption of high-oleic and regular peanuts, suggesting that peanuts could be beneficial for maintaining a healthy weight. Moreover, a significant difference in energy intake was observed for the high-oleic peanuts with high levels of monounsaturated fat when compared with regular peanuts because of the high oleic acid content, which was readily oxidized and provided a more satiating effect. Recently, another human trial demonstrating the efficacy of oleic acid and circulating OEA levels leading to reduced energy intake was conducted by Mennella and colleagues (34). In this study, 30 mL of high levels of oleic sunflower oil and olive oil were offered to participants in a glass together with 30 g of white bread to be consumed within 15 min on different occasions as per the randomization in a bolus dose. The high oleic acid content of the oils increased the postprandial response of circulating OEA, resulting in diminished energy intake over 24 h following the experimental meal. Overall, the data from animal and human trials provide evidence of the practical involvement of the lipid mediator, OEA, in obesity.

Association between dietary oleic acid and oleoylethanolamide mobilization via molecular targets

The ingestion of food, particularly dietary fat that is high in oleic acid, triggers the formation of OEA, leading to satiety, enhancing lipid absorption via PPAR-α and consecutively promoting lipolysis, thereby helping to reduce body weight (35). The anorexic effects provided by OEA involve a series of actions that include (i) stimulation of the local nuclear receptor, PPAR-α; (ii) activation of afferent sensory nerve fibres, conceivably the vagus nerve; (iii) networking of the appetite-regulating circuits that recruit histamine and oxytocin as neurotransmitters in the brain; and (iv) restoration of dopamine release (19,36–38), the key neurotransmitter involved in the mediation of the reinforcing effects of foods and other reward-generating systems (Figs. 3 and 4) (39–43). Overall, studies indicate a stimulation of the 'food reward system' that triggers anorexic signalling. Two key molecular targets imparting anorexic signalling to OEA are PPAR-α and CD36.

Action of peroxisome proliferator activated receptor-alpha in imparting anorexic signalling

PPAR-α receptors, discovered in 1992, belong to a family of ligand-activated transcription factors (44). PPAR-α is a nuclear/transcription receptor/factor that regulates lipid and glucose metabolism (45). Stimulation of PPAR-α triggers uptake, utilization and catabolism of FAs via the up-regulation of genes associated with FA transport and peroxisomal and mitochondrial FA β-oxidation (44,45). Thus, provided it is associated with the modulation of FA-oxidation, PPAR-α may play a significant role in the regulation of obesity, specifically central obesity, which is associated with insulin resistance syndrome (46).

The PPAR family consists of additional members; however, all do not carry appetite-suppressing effects. Fu and colleagues conducted a study in rats to investigate overall PPAR family and confirmed that only PPAR-α is associated with a weight-reducing effect; PPAR-β and PPAR-δ agonists (GW501516) and a PPAR-γ agonist (ciglitazone) were inefficient for reducing food intake in rats (19,47). However, work performed by Wang and colleagues (48) verified that PPAR-δ has similar properties to PPAR-α and activates adipose tissue utilization and prevents diet-influenced obesity in animals. In general, PPAR-α is considered a metabolic sensor of dietary FAs (49,50), and its key function is to sense FA flux into cells. This leads to the assumption that all the FAs communicate with PPAR-α via a direct route and henceforth, all FAs will exert anorexic effects similar to OEA by activating PPAR-α in tissues containing this receptor. However, work done by Akbiyik and colleagues (51) demonstrated that the stimulation of PPAR-α by OEA is structurally discriminating against

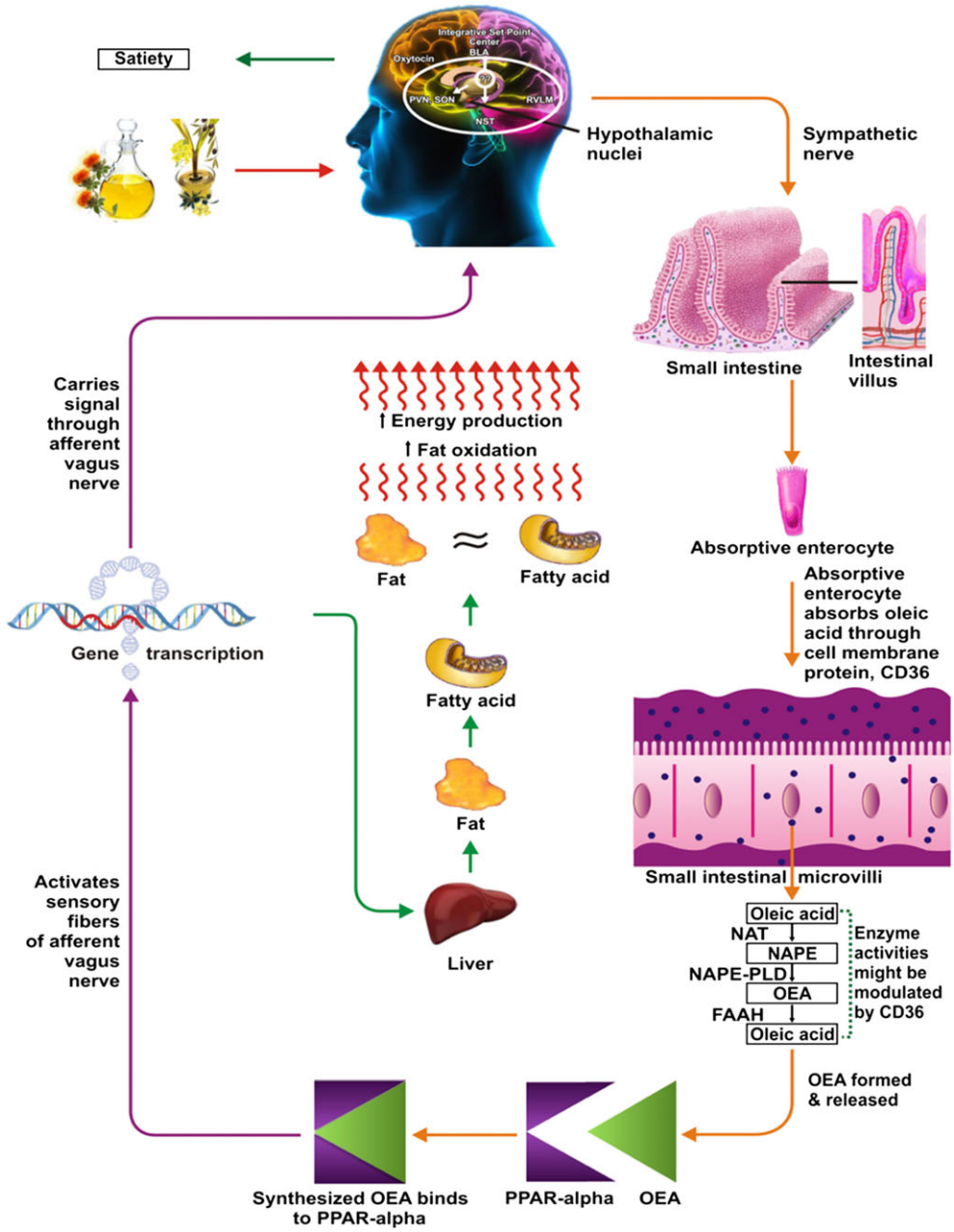

Figure 3 Gut and brain interrelationship and regulation of feeding behaviour (partly adapted) (9,27). BLA, basolateral complex of the amygdala; FAAH, fatty-acid amide hydrolase; NAPE, N-acyl phosphatidylethanolamine; NAPE-PLD, N-acyl phosphatidylethanolamine phospholipase D; NAT, N-acyl transferase; NST, nucleus of the solitary tract; OEA, oleoylethanolamide; PPAR, peroxisome proliferator activated receptor; PVN, para-ventricular nucleus; RVLM, rostral ventrolateral medulla; SON, supraoptic nuclei.

homologous FAEs, including myristoylethanolamide (14:0), stearoylethanolamide (18:0) and anandamide (20:4n6), because they have no impact on this receptor (35). Conversely, similar concentrations were observed of two downstream targets of PPAR-α, acyl-CoA-dehydrogenase, the rate-restricting enzyme of peroxisomal β-oxidation, and acyl-CoA-oxidase, a mitochondrial β-oxidation enzyme. This finding implies that abundant FAs in the liver, such as palmitic acid, oleic acid, linoleic acid and arachidonic acid, do not change the function of PPAR-α (51). However, these fatty acids do activate the expression of PPAR-α, which leads to FA-oxidation in the liver to regulate the increased FA load. This effect appears to be dependent on the function of the described FAs as endogenous ligands for PPAR-α (49,52–55). Similar studies performed by Schwartz and colleagues (10) showed that amongst various fats, duodenal infusion of only oleic acid prompted OEA synthesis and initiated satiety, leading to increased PPAR-α expression in liver.

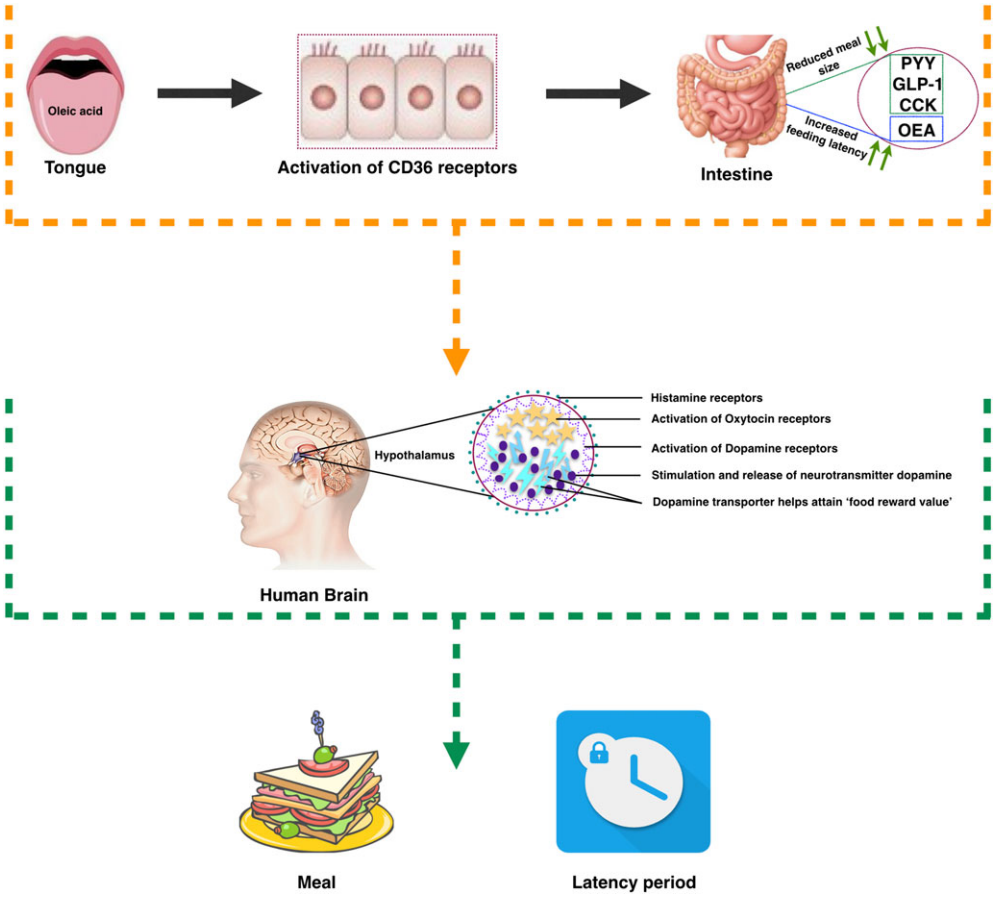

Figure 4 Consumption of oleic acid and action of neurotransmitters in the regulation of appetite and eating. PYY, peptide YY; GLP-1, glucagon-like peptide-1; CCK, cholecystokinin; OEA, oleoylethanolamide.

Furthermore, the expression of PPAR-α is not only restricted to the liver, organs such as the brain also contains high levels of PPAR-α in selected locations/selected lobes that have limited ability to generate FAs (56). Additionally, the sequence of the molecular chain linking PPAR-α activation to vagal sensory fibre stimulation yielding to satiating properties remains to be elucidated. The message is assumed to be transmitted through nitric oxide (NO) production. Enterocytes release high quantities of this gaseous transmitter, which may function as a peripheral food craving/hunger-activating signal (57,58). Furthermore, PPAR-α suppresses the expression of enzymes responsible for NO intestinal release, including intestinal NO synthetase (19,59). Hence, the suppression of intestinal NO synthetase expression by PPAR-α may play an influential role in inducing the prolonged satiating actions of OEA, which extend for numerous hours after the injection of this compound (19,20), suggesting that NO can stimulate appetite (60) that can be suppressed by PPAR-α. Similarly, PPAR-α activation mediating the anorexic/anorexiant effects of OEA is yet to be accurately elucidated. Nevertheless, the finding that eating modulates OEA concentrations in the duodenum and jejunum (19,25) suggests that lipid-derived anorexic signalling potentially acts on the PPAR-α that remains confined within cells of the small intestine. Thus, OEA is known to be a PPAR-α agonist, which accounts for its appetite suppressing as well as its energy-enhancing effects.

Action of fatty acid translocase/CD36 in imparting anorexic signalling

CD36 is also known as fatty acid translocase because it binds to long-chain free FAs and facilitates their transport into cells (61). CD36 also binds to long-chain fatty acids and acts as a conveyor or modulator of FA carriage into the small intestine (62–64).

The apical membranes of taste bud cells in the tongue express CD36 (65–67), which contribute to the taste recognition of fats and to the initiation of the cephalic phase of digestion (66,68). These events of taste perception regulated by signalling pathways are prompted by long-chain fatty acids bound to CD36. Several *in vivo* studies, conducted in both rodents and humans, have documented that CD36 plays an essential function in FA up-regulation, eventually

resulting in FA-oxidation. Furthermore, numerous trials performed in CD-36 deficient mice (69,70) and humans (71–73) have demonstrated a malfunction in tissue FA uptake and regulation and therefore abnormalities in FA metabolism. Another study performed by Martin and colleagues (74) in mice heterozygous for CD36 deficiency, a 50% reduction in CD36 expression was observed that was associated with a significant decrease in fat perception, suggesting that the findings of Martin and colleagues (74) may be applicable in humans. Henceforth, the studies performed in humans (75–77) indicate that CD36 gene polymorphisms correlate to lipid level variations in plasma (78–80) due to diminished responsiveness to the taste perception of oleic acid (81). Therefore, human carriers of CD36 gene polymorphisms are unable to synthesize OEA and are more prone to developing metabolic syndrome such as obesity (82,83).

Dietary oleic acid and its association with oleoylethanolamide

The chemical composition of the ingested food is paramount in OEA formation. Schwartz and colleagues (10) showed that the infusion of glucose or proteins into the duodenum did not have any effect, whereas amongst several fats, only oleic acid elicited OEA production in animals. In humans, Joosten and colleagues (84) found that fasting and non-fasting plasma concentrations of OEA were positively correlated with both serum total free FAs and their particular FA precursor oleic acid. In fact, oleic acid may act as the precursor for OEA formation in the intestine, as previously demonstrated in animals (27,28,85), and engender some physiological mechanisms regulating its specific release from intestinal membrane phospholipids; thereby increasing the capacity to oxidize fatty acids by fat oxidation resulting in enhanced energy expenditure by means of utilizing oleic acid as precursor and chief FA.

Dietary oleic acid and the effects of oleoylethanolamide on fat oxidation

Fat distribution is directed by the composition of the diet (86–89), age or life stage (90–93) and the genetics of the individual (94–101), for either energy or storage (86,102–105). The degree of dietary fat unsaturation also plays a critical role in whether the fat will be stored or oxidized. Long-chain fatty acids unsaturation has been suggested to affect the regulation of dietary fat in the direction of either oxidation or storage. Numerous human and animal trials have provided evidence that the saturation of FAs affects rates of oxidation, with unsaturated FAs being more readily oxidized (106–108) and therefore potentially exerting improved body composition than saturated fatty acids (SFAs) (109) through the activation of uncoupling protein 1 mediated by sympathetic nervous system (SNS) (110). Furthermore, some animal studies (111–114), but not all (115,116), propose that oleic acid is taken up more swiftly for utilizable energy compared with linoleic acid. Likewise, some human studies (117–119), excluding one (120), have demonstrated an elevated oxidation rate of oleic acid compared with linoleic or linolenic acids.

Furthermore, studies using the labelled FA approach have demonstrated that oleic acid and other unsaturated FAs are oxidized promptly when compared with SFAs (103,112,119,121,122). However, the isotope tracer data do not indicate whether altering the arrangement of dietary FAs would influence the total FA-oxidation. Moreover, a few studies conducted in humans and animals have shown that the consumption of diets rich in PUFAs and MUFAs results in elevated total FA-oxidation, EE or both compared with diets enriched with higher levels of SFAs (86,116,123–125). Additionally, in another human study, canola and peanut oil muffins, which are rich in oleic acid-MUFAs, resulted in greater fullness, with reduced hunger ratings after 30, 60 and 120 min (126). Regarding fat oxidation, Kien and allies (104) have also reported differences between MUFAs and SFAs enriched diets. The researchers performed a study in humans showing that augmenting the ratio of MUFAs rich in oleic acid (78.4%) to SFAs in the diet escalated fat oxidation. Additionally, there was no apparent reduction in fasting FA-oxidation, which is consistent with similar findings reported by Jones and colleagues (86) as well as by Piers and colleagues (127). Furthermore, French and colleagues (128) performed another human trial with lean participants that showed that less food consumption and almost identical appetite ratings were noticed after infusion of an oil emulsion rich in linoleic acid, in contrast to an infusion rich in oleic acid and stearic acid. Therefore, due to inconsistent results, further randomized clinical trials are required to confirm the effect of different FAs on fat oxidation. However, the findings by Kien and colleagues (104) can be justified by the observation that oleic acid is an integral component of stored FAs in human physiology compared with palmitic acid (129) and support a high degree of oxidation similar to PUFAs due to the carbon–carbon double bond (86,130). Similar findings have also been reported by another human trial performed by Alves and partners (131), where high oleic peanut consumption increased fat oxidation and reduced body fat in overweight and obese men. These findings were presumably due to the effect of oleic acid, which stimulates the cyclic adenosine monophosphate/protein kinase A pathway, further activating the sirtuin 1-peroxisome proliferator-activated receptor gamma coactivator 1-α transcriptional complex to regulate the rates of FA-oxidation (132). In summary, these data indicate that following intake of MUFA enriched diet, specifically oleic acid, gets utilized readily for energy production than being stored. Also, the relationship between oleic acid

and OEA levels can be established from the fact that amount of circulating concentrations of oleic acid will correspond to the concentrations of OEA synthesized in the body (30,31) leading to higher fat oxidation rates following consumption of oleic acid (35).

Dietary oleic acid, diet-induced thermogenesis and effects on energy expenditure

The dietary proportion of unsaturated to saturated fat alters EE in humans due to the high PUFA:SFA ratio, resulting in elevated resting metabolic rates and increased fat oxidation compared with a low PUFA:SFA fat ratio (86,119,130,133). Additionally, one more component termed as diet-induced thermogenesis (DIT) plays a critical role in increasing the resting metabolic rates. Takeuchi and companions (116) conducted a study in rats showing that FAs have various effects on the thermic effect of food (TEF), also termed DIT. Furthermore, the postprandial data from the study performed by Jones *et al.* (130), illustrate that lean individuals oxidized fat more rapidly than their obese equivalents when fed a low PUFA:SFA diet because obese individuals were observed to have reduced fat oxidation towards TEF compared with their lean counterparts. Moreover, the trial demonstrated that postprandially, overweight individuals contribute less dietary saturated fat for oxidation compared with individuals with a normal body weight because in obese participants, malfunctioning gene transcription associated with PPAR-α renders FA transport and peroxisomal and mitochondrial FA β-oxidation ineffective, leading to blunted TEF and EE.

Evidence of MUFA-enriched diets on DIT has been supported by Piers and colleagues (127); the researchers conducted a human study including participants with a high waist circumference and observed that olive oil enriched in MUFAs considerably intensified postprandial thermogenesis as well as the rate of fat oxidation compared with the administration of a cream rich in SFAs. Moreover, the total daily EE was significantly higher in individuals fed a high oleic acid diet (104). These results have been confirmed by studies performed in rats demonstrating that different fatty acids have a different thermic potency of food (116).

The findings of reduced EE after SFA diets feeding are supported by several studies (116,123,124), excluding one (134) performed in rodents fed varying dietary FA compositions, that suggest that the fractional elevation in SFAs in the diet increases susceptibility to reduced EE. Mechanistic explanations leading to this outcome could involve a diminished thermogenic response in brown adipose tissue (116,123). Numerous studies (135–139) indicate that dietary and endogenous FAs along with their genes, chiefly PPAR-α, monitor FA-oxidation and energy uptake pathways and hence enable energy utilization. Therefore, the various oxidation rates of dietary FAs via peroxisomal β-oxidation or by enhanced activation of PPAR-α mechanisms could also lead to alterations in daily EE (140,141), also enhancing utilization of oleic acid. These results imply that PPAR-α has a centrally coordinated role in the regulation of FA-oxidation (46). Henceforth, the upregulated oleic acid acts as precursor to OEA, activating PPAR-α and yields higher fat oxidation rates, thereby improving total energy expenditure. The action of OEA leading to enhanced EE is also supported by a pharmacological animal trial conducted by Suárez and affiliates (142); the study showed that co-administration of OEA (5 $mg.kg^{-1}$) and CL316243 (1 $mg.kg^{-1}$), a β3-adrenergic agonist, i.p. for 6 d, amplified both the reduction of food intake and body weight gain; with increase in EE and reduction in the respiratory quotient (VCO_2/VO_2). Overall, the data demonstrate that the vital component for the maintenance of weight over the long term is the quality as well as the quantity of fat consumed that further activates the lipid transport pathways.

In summary, the evidence indicates that lipid transport appears to be the eventual effect of oral OEA to reduce adiposity that is also supported by data from the trial performed by Thabuis *et al.* (143) in mice via a minimum of seven different pathways including (i) lipid transport; (ii) energy intake; (iii) regulation of EE; (iv) endocannabinoid signalling; (v) lipogenesis; (vi) glucose metabolism; and (vii) faecal fat excretion. Consequently, oleic acid may function in triggering a negative feedback signal to handle an overflow of FAs and thus maintain lipid homeostasis. Moreover, the findings suggest that diets rich in oleic acid derived from MUFAs result in the synthesis of OEA, which may offer increased oxidation that translates into increased EE in the presence of CD36 and PPAR-α. Bowen *et al.* (144) have proposed a potential mechanism for the physiological effects of oleic acid-derived OEA on lipid metabolism in humans. Altogether, these findings indicate that oleic acid resulting in OEA may have a prospective relevance and clinical utility in the prevention of obesity.

Relationship between oleoylethanolamide and feeding regulating hormones

A complex interaction of central neurotransmitter systems and peripheral stimuli manages eating behaviour, including hunger and satiety. Satiation is fundamentally regulated by the hypothalamus, which is a key site for receiving different signals from the organs engaged in energy metabolism, including the mouth, duodenum, jejunum and ileum. Furthermore, various channels modify feeding behaviour either by (i) pharmacological intervention with anorexigenic drugs or (ii) food-regulating hormones. However, the action of OEA imparting anorexic properties is different from other satiety-inducing hormones.

Difference between satiety effect exerted by oleoylethanolamide and feeding regulating hormones

In response to nutrient intake, the gastrointestinal tract plays a vital role and monitors energy homeostasis by releasing appetite-regulating lipid mediators and peptides. Energy homeostasis is regulated downstream by producing signals that can either be hormonal or neuronal, neuronal via the vagus nerve or hormonal by producing hunger and satiety-inducing peptide hormones such as ghrelin, cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) (145,146). Together with these peptides, foods rich in oleic acid boost the synthesis of the lipid-derived mediator, OEA, which induces satiety, intensifies lipid absorption, ameliorates lipolysis and attenuates body weight, consequently imparting anorexic results (9,25). These anorexiant properties are disparate from those elicited by traditional satiety regulators, as observed for CCK, which decreases the meal size without affecting the latency period between meals (147). By contrast, OEA reduces the meal frequency, thereby mediating the well-known satiety effect (148). Furthermore, the hypophagic functions of OEA also vary from those implemented by GLP-1 (149) and corticotropin-producing factors (150). Therefore, the best property of OEA in increasing the feeding latency in contrast to reducing the meal size makes it a potential novel compound to control appetite.

Similarities between oleoylethanolamide and the feeding regulating hormones in imparting satiety

Although the above results demonstrate that the satiating action of OEA is distinct from the regular peptide hormones, some similarities exist between both as well. Mobilization of OEA is initiated by fat intake, specifically by oleic acid-enriched fat intake. However, animal data illustrate that prolonged subjection to a diet enriched in fat reduces intestinal concentrations of OEA in rodents (18,38,85,151), consistent with the attenuated action of the gut peptide hormone GLP-1 (152,153). Similarly, the reaction of GLP-1 receptor agonists was also altered in obesity leading to increased appetite (154). Additionally, when obese individuals and rodents were provided with moderate to high-fat diets, this peptide signalling is impaired along with diminished postprandial levels of CCK and PYY (155–158). Moreover, CCK, PYY and GLP-1 expression levels were attenuated in the jejunum in diet-induced obese rats, leading to reduced satiation due to the lower levels of endogenous satiety peptides (155); similar effect in reduced intestinal OEA levels after high-fat diet (HFD) fed animals has been reported by Igarashi *et al.* (151). Additionally, GLP-1 is classified as a potent insulin-releasing and satiety-inducing gut hormone (159). The activation of G protein-coupled receptors, especially GPR119 stimulates the release of GLP-1 from the intestine (160). Furthermore, Overton *et al.* (161) illustrated that OEA acts as an agonist of GPR119 enabling satiating effects. On the contrary, another animal study performed by Lan and co-workers (162) demonstrated that OEA when administered to GPR119 knock-out mice-induced satiety, explaining that the role of GPR119 is important for insulin secretion but not for appetite suppression. Therefore, the clinical utility of activation of GPR119, stimulating the release of GLP-1 and hypophagic interactions with OEA, is yet to be explored. Henceforth, further investigation regarding molecular pharmacology of GPR119 is warranted in understanding its role in metabolic homeostasis.

Overall, from the cumulative evidence in humans and rodents and work done by Tinoco and colleagues (163), it is worth noting that a strong association between OEA and other feeding regulators exists imparting the satiating/anorexic properties. Therefore, future studies are required to clarify the satiating efficacy of OEA alone by performing studies using knock-out animal models for specific receptors involved in inducing satiation.

Impact of high fat diets on levels of oleoylethanolamide and satiety

Fat enriched in oleic acid is required to synthesize OEA, meaning that the higher the oleic acid content in fat, the higher is the OEA level inducing satiety mechanisms. This may lead to consumption of more dietary fat, hypothetically leading to the assumption of generating increased OEA content. However, increased fat intake may suppress the OEA mobilization leading to obesity. Furthermore, Diep and colleagues (164) conducted a study in mice in which animals administered a HFD showed decreased jejunal levels of OEA. Recent work by Igarashi and colleagues (151) suggests that in the gut of obese rodents, feeding-dependent OEA regulation is suppressed, revealing that short-term exposure to a HFD, as well as a low-fat high-sucrose diet, may also contribute to hyperphagia, thereby leading to reduced satiety. However, research conducted by Tellez and colleagues (38) in mice subjected to a HFD, which rendered the mice obese, yielded data demonstrating the restoration of suppressed OEA levels in the gut by treating obese mice with exogenous OEA. Taken together, these processes could all be components of various molecular pathways advancing the renowned 'obesogenic sequel' of a HFD (83,165,166), impacting the satiating potency of OEA as well as peptide hormones involved in regulating energy homeostasis. Moreover, in an experimental arrangement in which animals were trained to lick a dry spout to self-administer gastric infusions (167) of fat emulsions, lack of motivation to consume food via the gastric route was observed after OEA infusion in low-fat fed mice (38).

Additionally, the OEA injections showed anorectic effects in both low-fat and HFD fed mice during oral intake of a high-calorie emulsion; however, OEA administration was observed to increase the 'reward value' of the lower-calorie emulsion by stimulating low-fat intake during oral tests in HFD fed mice. These findings could be due to a restoration of 'gut-stimulated dopaminergic activity', which enhanced the 'reward value' of low-calorie foods. By contrast, HFD fed rodents demonstrated reduced oral acceptance of low-calorie fats without OEA (168–170). These results could also be a consequence of an increased detection threshold for fat in obesity (171).

Altogether, these studies suggest that in addition to contributing to the regulation of the quality of dietary fat for consumption, OEA may also function as a homeostatic intestinal stimulus that involves hedonic components (172) that has also been suggested in one human trial (173). However, future research is needed by conducting acute as well as long term full feeding trials. Additionally, trials performed with free living participants enabling participants to opt for self-selected dietary fat may shed more light on the impact of fat quality and quantity. Addressing these knowledge gaps will further enhance the understanding on the impact of desirable quantity of fat required to generate anorexic efficacy of OEA; along with thorough investigation of feeding regulating hormones on appetite, satiety by visual analogue scale, fat oxidation, energy expenditure and overall body composition to ascertain the safe efficacy and usage of OEA in curbing obesity.

The gut lipid messenger oleoylethanolamide recruits the food reward system to regulate feeding behaviour in the brain

The preceding segment provides evidence that OEA induces satiety. Overall, OEA is a nanomolar agonist of PPAR-α, a key element of the large superfamily of nuclear receptors (9,19). The biological actions of OEA are predominantly modulated by PPAR-α, including its ability to restrict food consumption (19,25,174), increase FA absorption in small intestinal enterocytes (19,175) and intensify lipid lipolysis and oxidation in adipocytes, hepatocytes and skeletal myocytes (29,142). However, this significant modulation of meal patterns in rats administered OEA is not observed in mice lacking PPAR-α. This effect has been attributed to the high affinity binding of OEA to PPAR-α and also its imitation by synthetic exogenous PPAR-α agonists, implying that the nuclear receptor is both vital as well as adequate for OEA-evoked hypophagia (17,19).

Research has shown that various intestinal sensory receptors detect the amount of dietary fat in the lumen; the absence of these fat sensory receptors leads to reduced intestinal OEA concentrations and contributes to a hyperphagic prolongation of dietary fat ingestion (18,159,176). Based on the above findings, there is a large interest in obtaining a better understanding of how OEA signalling in the gut initiates a feedback reaction that initiates satiety via the food reward system to modulate feeding behaviour.

Impact of oleoylethanolamide on satiety inducing targets

Following the consumption of dietary fat, particularly oleic acid, OEA levels increase in the duodenum and jejunum but not in the bloodstream (27). Possibly OEA is produced in various peripheral tissues and the CNS (177). The presence of OEA in the CNS suggests that the anorexic properties of OEA are mediated in an analogous fashion to CCK by paracrine stimulation of vagal afferent nerve fibres (178). This theory is supported by three discoveries. First, animals treated with capsaicin, which deprives them of peripheral vagal and non-vagal sensory fibres, show abolished hypophagic activity of OEA (25). Second, OEA administered at 10 $mg.kg^{-1}$ i.p. does not penetrate the brain and, hence, has been found to instantly stimulate the transcription of the c-Fos gene, a marker of neuronal activation, in the brainstem nucleus of the solitary tract (NST) (19,25,36,174). Third, surgical resection of the vagus nerve or blockage of NST activity either by infusion of the local anaesthetic lidocaine into the NST or the β-adrenergic antagonist propranolol into the basolateral complex of the amygdala impedes various functions of OEA, including strengthening memory retention (179) and activation of dopamine production (38). However, a recent animal study demonstrated that total subdiaphragmatic vagotomy, termed subdiaphragmatic vagal deafferentation, a type of surgery that removes all abdominal vagal afferents, leaving roughly half of the efferents (180,181), does not block OEA-induced hypophagia (182). The surgical side effects and/or small procedural differences might have contributed to the antagonism of the eating-inhibitory effect of OEA. In summary, evidence indicates that association of gut and brain interrelationship leads to the hypophagic actions of OEA as several signals generated in the gut activate vagal afferent nerves to promote meal termination.

The key involvement of vagal afferent nerves as well as SNS in promotion of meal termination and satiety induction is supported by another animal study conducted in rats. Sclafani and associates (183) revealed that gut vagal afferents and splanchnic nerves are not responsible for flavour-nutrient-liking adaptability, but both vagal afferents and splanchnic nerves are accountable for carbohydrate as well as fat-induced satiation following consumption of oleic acid, precursor for OEA. The group performed an experiment in which celiac-superior mesenteric ganglia were removed, following which the anorexic effects exerted by intraduodenal fat infusion were immediately extinguished (183). Similar findings have also been reported by Fu and colleagues (184)

that proposed the potential mechanism for the results of work performed by Sclafani and coworkers (183). In addition, Fu and associates (184) demonstrated that the surgical resection of the celiac-superior mesenteric ganglia abolished biosynthesis of OEA in fasting-refeeding rats. These finding demonstrates that the SNS emerges equally to play a critical role along with the vagus nerve in the induction of oleic acid-generated satiation signalling through OEA.

Furthermore, Sabatier *et al.* (185) demonstrated that gastrointestinal vago-vagal reflex modulates the feeding behaviour via the activation of parvocellular neurons of the paraventricular nucleus. Conversely, oxytocin released by magnocellular neurons diffuses to the hypothalamus targets involved in satiety after OEA release (185). Additionally, Romano and colleagues (174) demonstrated that OEA triggered an intense signal in the area postrema and NST, sites involved in regulating food intake. Interestingly, within the central part of the NST, c-Fos mRNA expression was highly apparent at the most rostral level, where this nucleus is in greater proximity to the area postrema. In summary, research findings suggest that magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus are closely intertwined to regulate feeding and energy homeostasis inducing satiety by the action of OEA (185,186). Therefore, these studies suggest a direct effect of OEA in the CNS by extension of circumventricular organs via the bloodstream.

Functional interaction between oleoylethanolamide and neurotransmitter histamine

OEA imparts satiety through combined action of gastrointestinal tract and brain interrelationship. Additionally, OEA requires the integrity of the brain histamine system to fully exert its hypophagic effect (37). Evidence illustrate that OEA affects the CNS by the activation and release of neurotransmitters and hormones at various 'food rewarding sites'. To further confirm the effects of OEA on the CNS, many researchers have conducted numerous experiments and robust trials. Different neurotransmitters together with OEA have also been shown to play important roles. One such neurotransmitter is histamine, which modulates fundamental homeostasis and vital functions in the brain, including feeding patterns, cognition, stimulation and circadian rhythms (187,188). However, little is known about the interactions between OEA and histamine. To elucidate the association, Provensi and colleagues (37) recently reported that the anorectic effects of OEA were reduced after intracerebroventricular infusion of a histamine-synthesizing enzyme inhibitor. The histamine-synthesizing enzyme 'histidine decarboxylase inhibitor', α-fluoromethylhistidine, either affects the histamine-producing enzyme histidine decarboxylase or dramatically deprives the brain of histamine. Additionally, the administration of OEA and ABT-239, the H_3R antagonist, obstructs both auto-receptors and hetero-receptors in the CNS and also aids in increasing transitory histamine production (189). Furthermore, Masaki *et al.* (190) also support the notion that histamine influences the anorexic potency of OEA; the co-administration of OEA and ABT-239 led to significantly increased brain histamine levels that boosted OEA-initiated anorexic signalling, further triggering a reduced sensation of food ingestion. Conversely, histamine receptor antagonists or pharmacological manipulation of H_1R markedly affect food intake in various mammalian species (190,191). H_3R antagonists and OEA have also been observed to modulate the release of several other neurotransmitters other than histamine (192,193), thereby contributing to their hypophagic but independent actions.

Moreover, Torrealba and colleagues (194) demonstrated that histamine is distinctively associated with two-key features of eating behaviour: (i) appetitive phase (searching for food) and (ii) consummatory phase. Valdés and colleagues (188,195) have also indicated that histamine is more vital for the temptation to eat. Therefore, histamine contributes to varying functions in the brain concerning feeding behaviour (196). On the whole, these reports suggest that functional interactions occur between peripherally functioning hypophagic stimuli, such as OEA and brain histamine neurotransmission. Additionally, these studies also propose that in addition to affecting the homeostatic systems that modulate hunger and satiety in the brain, the regulation of food consumption induced by OEA also affects hedonic as well as non-homeostatic domains that modulate hunger and satiety.

Functional interaction between oleoylethanolamide and oxytocin receptors

The central effects of OEA, influenced by brain histamine, activate the oxytocin neuron-rich nuclei, the hypothalamic area involved in inducing satiety (37). Intestinal OEA, which reduces feeding by activating the vagus nerve (197), has also been observed to stimulate oxytocin mRNA expression in the paraventricular and supraoptic nuclei of the hypothalamus (25,36). Moreover, Gaetani *et al.* (36) illustrated the use of the synthetic blockade of central oxytocin receptors that instantly hampered the anorexiant efficacy of OEA. In another study, rats fed extra virgin olive oil showed increased levels of hypothalamic oxytocin mRNA expression, indicating that oxytocin may be modulated by dietary lipids, especially oleic acid (198). Additionally, previous studies have documented that OEA's capabilities to enhance the expression of the neuropeptide oxytocin were obstructed when the oxytocin receptor antagonist L-368,899 was administered intracerebroventricularly, which further prevented its ability to decrease food consumption (36,199). Serrano *et al.* (193), in compliance with this observation, reported that when administered to rats peripherally (5–20 $mg.kg^{-1}$), OEA caused an increase in noradrenaline levels in the hypothalamus in a dose-dependent

manner. This demonstrates the crucial involvement of noradrenaline which enhances production and release of the neurotransmitter, histamine. Histamine then exerts its hypophagic actions to completely inhibit food intake (37), via facilitated increased oxytocin mRNA expression.

Functional interaction between oleoylethanolamide and brain dopamine

The ingestion of dietary fat is recognized to have a hedonic impact, triggering dopamine stimulation in the reward regions of the brain to activate the 'reward circuit' (200,201). However, Tellez *et al.* (38) demonstrated that excessive intake of dietary fats leads to diminished brain dopaminergic function leading to overeating and eventually obesity. Dopamine release in the dorsal striatum (DS) of mice is also evident after gastric infusions of a fat emulsion (38,167). Another finding reported that intra-gastric infusions of a low-calorie diluted fat emulsion (7.5% and 15% IntraLipid®) triggered dopamine release (38). By contrast, intra-gastric infusions of a high-calorie concentrated fat emulsion (30% IntraLipid®) failed to induce any effect (38). Additionally, Tellez and colleagues (38) performed an animal experiment showing that in HFD-fed mice, in which the diet comprised 60 kcal% fat, 20 kcal% protein and 20 kcal% carbohydrate, intestinal infusion of a concentrated triacylglycerol emulsion comprising 30% soybean oil, 1.2% egg yolk phospholipids, 1.7% glycerine and water decreased the dopamine response in mice, confirming a blunted 'reward response' making mice obese. The researchers also demonstrated, in the same rats, that before intra-gastric infusion of the concentrated fat emulsion, injected OEA i.p. instantly restored the weak dopamine response in the brain, whereas this re-established response was altered following injection of the PPAR-α-specific antagonist (GW6471) (38). These findings suggest that improved dopamine responses in the mice brain after intestinal OEA injection stimulated the 'reward circuit' because OEA injection improved the dopamine response in response to diluted fat emulsions in both controls and HFD fed mice (38) that further triggered the 'reward value' of food that induced satiety and less food consumption. Furthermore, the study also reported the ability of OEA to potentiate dopamine efflux was abolished in sub-diaphragmatic bilaterally vagotomised mice compared with unilaterally vagotomised mice (38). This finding confirms that OEA participates in modulating the hedonic actions of dietary fat via vagal afferent nerves suggesting the role of jejunum in sensing fatty acid oxidation sensors that can influence eating (202).

Moreover, in another experiment conducted by Murillo-Rodríguez and colleagues in rats (203), local administration of the FAAH inhibitor URB597, which increases the levels of OEA in the brain and OEA in the lateral hypothalamus and the dorsal raphe nuclei showed increased levels of dopamine in nucleus accumbens shell (NAcS). Subsequent investigations in the rat midbrain demonstrated a modulation of dopaminergic function due to the peculiar capability of OEA to regulate nicotinic receptors containing β2 subunits, a nicotinic acetylcholine receptor symbolized as β2*-nAChRs expressed by dopamine neurons that enhance the reward system from a brain stimulus (204). Furthermore, the limbic forebrain comprising of the endocannabinoids CB1 and CB2, (205) is also known to regulate and modulate the reward properties of food as well as drugs and these endocannabinoids are impacted by OEA (206–217). The anorexic properties of OEA are also facilitated via the blockade of CB1 receptors, which, when administered systemically in combined therapies with the cannabinoid CB1 receptor antagonist Rimonabant and the PPAR-α agonists OEA, reduces food intake and body weight to supply a synergistic effect (218). Furthermore, evidence based on microdialysis techniques illustrate that gut endocannabinoids also act as hunger signals. During these experiments, rats, when subjected to fat (1% corn oil and 1% linoleic acid), showed a significant stimulation of dopamine release in the NAcS despite a very low calorie content (219,220). Moreover, the opioidergic system in NAcS is considered a predominant mediator of the hedonic sensation triggered by food (221), thereby validating that NAcS is a central controller of value learning (222–226) that enables animals to retain memory and ingest a low caloric emulsion.

In summary, these findings confirm that vital function of OEA in the regulation of reward actions occurs via activated release of dopamine. Tellez and colleagues (38) successfully demonstrated that exogenous OEA administration in subchronic treatments restored a normal and functional reward system in obese rats wherein obesity was generated by chronic exposure to a diet rich in fat. After the OEA administration, dopamine diffusion was activated in the DS, a brain section that connects and combines hedonic responses to habit learning (227); enabling mice to consume low fat emulsions. The findings are supported by Ferreira and colleagues (167) by demonstrating a similar increase in striatal dopamine flux after gastric fat infusions in lean mice and hence, regulating fat intake.

Additionally, L'hirondel and colleagues (228) reported that oleic acid did not affect dopamine release. By contrast, Heller and colleagues (229) ruled out this possibility by demonstrating that oleic acid affected dopaminergic function in primary neurons of mesencephalic origin and, therefore, increased the dopamine content. Henceforth, because of inconsistencies amongst the reported findings, further investigation is warranted to understand the potential ability of oleic acid-OEA to increase dopamine levels to regulate feeding behaviour. Therefore, human trials focussing exclusively on dopaminergic system after bolus doses of oleic acid may enhance the understanding of modulating feeding behaviour that may carry therapeutic relevance and may contribute to the development of efficient strategies for treating obesity.

Summary of gut and brain interrelationship and regulation of feeding behaviour

The hypothalamus plays a pivotal role in the modulation of nutrient segregation, energy metabolism and feeding behaviours. The functions of the hypothalamus–pituitary–adrenal axis and the gastrointestinal tract have deep-seated interconnections via the following: (i) the stimulation and release of peptides; (ii) neuroendocrine hormones; and (iii) anorexigenic (appetite suppressing) or orexigenic (appetite stimulating) signals through endogenous compounds from the gut. The previous section demonstrates evidence that combined action of feeding regulating hormones, histamine, oxytocin and dopamine modulates feeding behaviour and regulates appetite inducing satiety. Oxytocin is one such hormone released from the hypothalamus that plays a crucial role in inducing the satiating properties of OEA via inducing oxytocin neurotransmission in the CNS. In addition, OEA triggers the dopamine stimulation in the reward regions of the brain postconsumption of dietary fat enriched in oleic acid, to activate the 'reward circuit' in the brain via gut generated lipid signalling; enhancing sensitivity and motivation towards less palatable, yet healthier, foods, that will reduce increasing obesity.

Furthermore, regulation of the appetite is fundamentally oriented in the three core nuclei of the hypothalamus and the brain stem located mainly in the tuberal medial area: (i) the arcuate nucleus of the hypothalamus; (ii) the dorsomedial hypothalamic nucleus; and (iii) the ventromedial hypothalamic nucleus. These nuclei are predominantly associated with feeding behaviours and satiety signals. Salient features of the arcuate nucleus of the hypothalamus, along with the regulation of feeding behaviour, involve the release of various pituitary hormones. Dorsomedial hypothalamic nucleus functions to stimulate gastrointestinal activity, and ventromedial hypothalamic nucleus primarily participates in inducing satiety. The rostral ventrolateral medulla in the medulla is another site in the brain that functions as a key regulator of the SNS. Orexinergic and anorexic neurons from the lateral hypothalamus open up in the rostral ventrolateral medulla. This site further activates the β-adrenergic receptor signals carried by sympathetic nerve fibres to the gut, enabling OEA production (184). Furthermore, to commence meal termination, satiating signals from the liver and gastrointestinal tract are initiated through the vagus nerve to the NST. These signals are integrated and assessed by the hypothalamus together with the NST to determine the feeding response.

The preceding section suggests that the sympathetic cascade exerts fat-induced OEA satiety signalling to the small intestine either by (i) modulation of expression or (ii) management of enzymes in the OEA synthesis cascade. Although a complete understanding of OEA-induced satiety signalling remains to be elucidated, this detailed review enables the investigation and provides a summary showing that the consumption of fat-enriched food items particularly in oleic acid and the biosynthesis of OEA requires a synchronized association between the parasympathetic and sympathetic nervous systems. Therefore, synchronization between these two systems influences feeding as well as feeding-stimulated satiety signals by regulating the vagal-nigro-striatal pathway.

Oleoylethanolamide as safe anti-obesity alternative to drugs

Numerous anti-obesity pharmacological drugs have reached clinical use; however, these drugs still lack safety and efficacy because most of these drugs are centrally acting drugs which bear the adverse-effects. Therefore, it is vital to find an effective yet safe alternative to drugs that can induce satiety without burden of side effects. OEA has been observed to be a safe satiety-inducing compound, as demonstrated by Romano and associates (230), who monitored the behavioural satiety sequence involving the eating, grooming, rearing, locomotion and resting over the course of the initiation of satiety in mice. This study substantiated the hypothesis that OEA, a functional antagonist of anandamide, suppresses appetite by stimulating satiety without altering total motor activity. By contrast, mice treated with the CB1 antagonist rimonabant, in addition to demonstrating decreased eating activity, showed an apparent increase in time spent grooming and reduced horizontal motor activity (230). Therefore, the reported alterations might be indicative of aversive non-motivational effects on feeding. These findings are analogous to a recent innovative study performed by Provensi and colleagues (37), thus providing a basis for the safe and efficient usage of OEA as an anti-obesity treatment. In summary, from nutritional, behavioural and psychological perspective, the anorexiant properties of OEA do not include any signs of anxiety or any other after-effects with changes in circulating corticosterone concentrations, which is a crucial biochemical indicator that regulates the overall energy balance (24,25), proving it to be a potentially safe anti-obesity alternative.

Future directions

Overall, to understand the safe and efficient therapeutic usage of OEA in humans, future Phases I and II clinical trials are required with careful insight on the data provided by these trials obtained from neurobiologists, nutritionists, pharmacologists, physiologists and psychiatrists. Trial parameters could include neuroimaging by functional magnetic resonance imaging as well as motor, cognition and behaviour assessment. Additionally, single nucleotide polymorphisms in genes may influence an individual's response to a specific nutritional intervention. Therefore, research is needed to confirm the therapeutic potential of OEA in suppressing food intake to curb obesity by conducting human clinical trials wherein participants should be recruited based

on selected single nucleotide polymorphism-related genotypes. These trials should investigate the short as well as long-term effects of oleic acid consumption and their resulting impact on food intake, food regulating hormones, satiety, energy expenditure, fat distribution and body composition. The inclusion of invasive techniques such as fat pad biopsy of the abdominal fat pad and brown adipose tissue should enable a deeper mechanistic understanding of OEA stimulating gene expression. Addressing these points will further clarify the role for OEA in the context of the outcomes discussed. Henceforth, an amalgamated approach of conducting human clinical trials wherein motor, cognitive, behavioural, and regulation of appetite, as well as eating, will be monitored in comparison with the existing anti-obesity drugs would merit OEA in developing as an effective anti-obesity approach.

Summary and conclusion

A suggested mechanism for the uptake of OEA by dietary fat has been proposed in a study demonstrating that the upregulation of oleic acid from dietary fat via the membrane protein CD36 results in higher levels of N-oleoyl-PE in enterocytes (9,27). The resultant N-oleoyl-PE is further broken down by NAPE-PLD to produce OEA. Newly generated OEA activates PPAR-α, which initiates the anorexic signalling through the afferent vagal fibre (9). Although the evidence regarding anorectic properties of OEA exist, a knowledge gap exists as well regarding both the conversion of FAs to their respective FAEs, e.g., the progression following the ingestion of oleic acid to the biosynthesis of OEA, as well as the factors that contribute to the rate of transformation/conversion. The evidence reviewed in this article indicates that intake of oleic acid, and thereby the resulting OEA, is dependent on CD36, PPAR-α, enterocyte fat sensory receptors, histamine, oxytocin and dopamine; leading to increased fat oxidation and enhanced energy expenditure to induce satiety and increase feeding latency; and that a disruption in any of these systems will cease/curb fat-induced satiety.

In conclusion, the evidence reveals that small intestinal enterocytes synthesize OEA during the digestion of fat-containing foods, rich in oleic acid that leads to satiety and involves a series of molecular events in the paracrine PPAR-α mediated pathway that also necessitate the involvement of afferent sensory nerve fibres. Conversely, HFD induces gastrointestinal dysfunction attenuating dopamine levels and hampering the 'reward sensitivity circuit.' This deficiency of dopamine exacerbates obesity by provoking hyperphagia to restore the 'food reward value.' Although the mechanism of OEA's anorexic signalling to induce satiety remains the same in every individual, *in vivo* evidence conducted in animals and humans demonstrates an immense variability in FA intake perception by individuals due to the distinct activity of receptors in each individual's gut, which plays a critical role in food consumption and obesity (231). Therefore, amongst obese subjects, significant amounts of fat ingestion for prolonged durations could result in a decreased sensitivity to FAs, encouraging excessive fat ingestion to attain an adequate taste perception and thus lead to obesity. Furthermore, prolonged exposure to HFDs may induce a feedback mechanism that ultimately attenuates OEA levels due to diminished brain dopaminergic function (148). Hence, future studies should clarify the overall molecular cascade by extending knowledge to understand the molecular mechanisms involved in the ingestion of FAs and their further perception and conversion to FAEs, which eventually leads to fat oxidation and EE. Research is needed to understand the in-depth mechanisms carrying out intestinal anorexic OEA signalling in the obese gut. In particular, identification of FA intake receptors will enable the elucidation of how fat perception works from a molecular standpoint, leading to a greater understanding of the influence of fat perception in humans. Future studies should also address the association between genetic polymorphisms associated with CD36 and consumption of oleic acid.

The studies reviewed in this article show that appetite regulation is multifactorial, and therefore, sophisticated clinical approaches must be developed. Overall, the studies reviewed propose that the lipid-amide OEA acts as a fat sensor that is regulated by the synchronization between two divisions of the autonomic nervous system. First, is the SNS, by triggering the activation of OEA through efferent nerve fibres in the gut. Second, the parasympathetic nervous system, which conveys the anorectic signalling through the afferent fibres to the brain. The evidence reviewed herein also indicates that oleic acid increases EE, but whether this effect can be developed into a fruitful weight maintenance strategy will require further research. Therefore, future robust human randomized clinical trials are required focussing on the consumption of oleic acid, leading to the synthesis of OEA and associated satiety signals in gut and brain receptors along with the positron emission tomography technique to successfully capture the neuronal activities in humans. Results from such trials will facilitate the development of apposite nutritional and pharmacological strategies to check appetite in obesity.

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Conflict of interest statement

No conflict of interest was declared.

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