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THEMED ISSUE REVIEW

The ongoing oleoylethanolamide story: Therapeutic implications in the control of obesity and its comorbidities

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The global burden of obesity continues to rise, demanding effective pharmacological strategies for individuals in whom prevention alone is insufficient. Recent incretin-based and multi-agonist therapies have delivered unprecedented weight loss, demonstrating that the simultaneous modulation of multiple metabolic pathways can optimize body weight control and improve obesity-related comorbidities. However, biological heterogeneity, interindividual variability in treatment response and uncertainties regarding long-term outcomes highlight the need to explore complementary regulatory mechanisms. Oleoylethanolamide (OEA) is an endogenous lipid mediator synthesized on demand in the small intestine in response to dietary lipid intake. Acting primarily through peroxisome proliferator-activated receptor-α (PPAR-α), OEA functions as a physiological satiety signal that promotes fatty acid oxidation and coordinates gut–brain communication. Preclinical evidence indicates that OEA reduces food intake without inducing malaise, enhances lipid utilization and improves metabolic dysfunction in models of diet-induced obesity, while engaging both homeostatic and reward-related neural circuits. Emerging clinical studies report modest but consistent effects on body weight and selected cardiometabolic parameters. In this review, we summarize the current evidence on OEA biosynthesis, molecular targets and mechanisms of action, with particular focus on its role in the regulation of feeding behaviour, metabolic homeostasis and obesity-related comorbidities, and discuss its potential positioning within the evolving landscape of anti-obesity pharmacotherapy.

KEYWORDS
cardiovascular dysfunction, feeding behaviour, gut-brain-microbiota axis, hepatic steatosis, obesity, oleoylethanolamide, PPAR-α

Abbreviations: 2-AG, 2-arachidonoylglycerol; ABHD4, α/β-hydrolase domain-containing protein 4; AEA, anandamide; AP, area postrema; eCBome, endocannabinoidome; FAAH, Fatty acid amide hydrolase; GDE, glycerophosphodiester phosphodiesterases; GLP-1, glucagon-like peptide-1; GPR119, G protein-coupled receptor 119; MAFLD, metabolic-associated fatty liver diseases; NAAA, N-acylethanolamine acid amidase; NAEs, *N*-acylethanolamines; NAFLD, non-alcoholic fatty liver disease; NAPE-PLD, NAPE-specific phospholipase D; NAPEs, *N*-acylphosphatidylethanolamines; NST, nucleus of the solitary tract; OEA, oleoylethanolamide; PEA, palmitoylethanolamide; PLA/AT, calcium-independent phospholipase A/acyltransferase; PPAR-α, peroxisome proliferator-activated receptor alpha; PVN, paraventricular nucleus; SON, supraoptic nucleus; TMN, tuberomammillary nucleus; TRPV1, transient receptor potential vanilloid-1channel; VTA, ventral tegmental area.

1 | INTRODUCTION

The regulation of body weight relies on adaptive mechanisms that continuously integrate nutritional cues, metabolic demands and neuroendocrine signals to preserve energy homeostasis (Morton et al., 2014). Under physiological conditions, energy homeostasis depends on flexible adjustments of energy intake and expenditure in response to nutrient availability and metabolic demands (Morton et al., 2014). Chronic energy surplus can progressively impair this flexibility, leading to maladaptive remodelling of regulatory systems (Levin et al., 2025). Consequently, compensatory mechanisms that initially support energy balance can paradoxically promote the persistent accumulation of adipose tissue, contributing to the development of obesity, a chronic disease driven by multifactorial processes (Levin et al., 2025; Młynarska et al., 2025).

Among the endogenous systems that participate in this adaptive control, a lipid-derived mediator generated in response to dietary fat has emerged as key regulator. It is **oleoylethanolamide** (OEA) that functions as an 'on demand' intestinal signal linking nutrient sensing to coordinated behavioural and metabolic adaptations (Piomelli, 2013).

Beyond excess fat accumulation, obesity is increasingly recognized as a systemic condition characterized by persistent low-grade inflammation, endocrine and metabolic dysfunction and impaired inter-organ communication (Blüher, 2019, 2025). In this context, insulin resistance and impaired glucose homeostasis represent early and central features of this condition, closely linked to alterations in lipid metabolism and inflammatory signalling (Hotamisligil, 2017). Among obesity-related comorbidities, hepatic involvement is particularly prominent. In most cases, obesity is associated with non-alcoholic fatty liver disease (NAFLD), reflecting the central role of the liver in lipid handling and metabolic integration (Fabbrini et al., 2010). Obesity is also strongly associated with cardiovascular complications, including endothelial dysfunction, hypertension and atherosclerotic disease, which are sustained by systemic inflammation, adverse lipid profiles and persistent metabolic stress (Powell-Wiley et al., 2021). In parallel, growing evidence highlights the contribution of gut-related alterations, such as changes in gut microbiota composition and intestinal barrier integrity, which may further exacerbate metabolic dysregulation through gut–brain signalling pathways (Asadi et al., 2022; Shen et al., 2025).

In this review, we will focus on those comorbidities for which OEA signalling shows the most coherent mechanistic and experimental support, particularly hepatic steatosis, cardiometabolic dysfunction and alterations of the gut–brain–microbiota axis.

In recent years, obesity pharmacotherapy has entered a transformative phase, driven by the development of incretin-based and multi-agonist therapies that have achieved unprecedented and clinically meaningful weight loss, together with well-documented glucoregulatory and cardioprotective benefits (Ben-Porat et al., 2025). These agents represent a breakthrough in obesity management and have rapidly expanded the therapeutic landscape. However, growing evidence indicates that even highly effective incretin-based therapies remain subject to fundamental biological and physiological mechanisms (Ben-Porat et al., 2025). Their sustained efficacy is challenged by the activation of compensatory responses at both peripheral and central levels, including metabolic adaptations, reductions in lean body mass and basal energy expenditure, gastrointestinal side effects and alterations in dietary intake and eating behaviours (Ben-Porat et al., 2025). Collectively, these factors may limit long-term weight maintenance, contribute to weight regain upon treatment suspension and introduce new clinical and nutritional vulnerabilities (Ben-Porat et al., 2025). These observations underscore that durable obesity management is unlikely to rely exclusively on pharmacological suppression of appetite or energy intake, even in the era of next-generation incretin mimetics. Moreover, they highlight the need to explore complementary regulatory pathways capable of modulating energy homeostasis in a more integrated and physiologically aligned manner.

In this context, OEA, by acting as a modulator of nutrient sensing and metabolic flexibility, might be useful, potentially complementing multi-target pharmacological approaches by restoring endogenous lipid-responsive signalling networks. OEA belongs to a group of naturally occurring bioactive lipids derived from saturated and unsaturated fatty acid precursors and acting as signalling molecules, the *N*-acylethanolamines (NAEs), which also include **anandamide** (AEA), **palmitoylethanolamide** (PEA), docosahexaenoylethanolamide, stearoylethanolamide and linoleoylethanolamide (Friuli et al., 2025; Romano et al., 2023). Although AEA has been mostly characterized for its role as an endogenous ligand of **cannabinoid receptors**, other NAEs exert biological actions independently of canonical endocannabinoid signalling, leading to the definition of the so-called paracannabinoid system, which comprises structurally related lipid mediators with distinct molecular targets and pharmacological profiles (Friuli et al., 2025). More recently, this broader lipid signalling network has been conceptualized as the 'endocannabinoidome' (eCBome), encompassing classical endocannabinoids, structurally related NAEs such as OEA and their diverse enzymatic pathways and molecular targets beyond CB_1 and CB_2 receptors (Iannotti & Di Marzo, 2021). Accumulating evidence highlights the involvement of NAEs in distinct biological activities with potential therapeutic relevance across different pathological contexts, spanning metabolic homeostasis, obesity-related dysfunctions and inflammatory and neurodegenerative conditions (Beggiato et al., 2019; Colizzi et al., 2022; Friuli et al., 2025; Keppel Hesselink et al., 2014; Maccarrone et al., 2002; Tovar et al., 2023).

Within this framework, OEA, a mono-unsaturated NAE derived from the omega-9 fatty acid, **oleic acid**, has emerged as one of the most extensively investigated unsaturated lipid mediators within the NAE family (Friuli et al., 2025; Romano et al., 2023). A large body of experimental evidence indicates that, when administered exogenously, OEA produces marked effects on food intake and lipid metabolism with a favourable safety profile (Bowen et al., 2017; Lo Verme et al., 2005; Thabuis et al., 2007, 2008). Based on these observations, OEA has attracted considerable interest as a pharmacological tool to explore lipid-responsive pathways involved in energy homeostasis.

Nevertheless, several key issues remain under active investigation. These include the relative contribution of direct central versus peripheral gut–brain mechanisms following systemic administration, the modest yet reproducible magnitude of clinical effects observed in

human studies and pharmacokinetic challenges related to formulation and bioavailability. Addressing these questions is essential for defining the translational potential of OEA-responsive pathways in obesity management.

In this review, we critically evaluate the current evidence on OEA, focusing on its biosynthesis, regulation and molecular targets, as well as its central and peripheral actions in the control of energy homeostasis. Specifically, we aim to (i) summarize the biochemical and molecular framework governing OEA synthesis and signalling within the eCBome; (ii) analyse the central and peripheral mechanisms, through which OEA modulates feeding behaviour and metabolic homeostasis; and (iii) discuss the evidence supporting its role in obesity-related comorbidities as well as its potential positioning within the current era of multi-target anti-obesity pharmacotherapy.

2 | BIOSYNTHESIS, DEGRADATION AND MOLECULAR TARGETS OF OEA

2.1 | Enzymatic mechanisms underlying OEA as a lipid sensor

OEA, a member of the family of NAEs, is a lipid mediator whose biological effects are critically dependent on the enzymatic processes governing its synthesis and degradation in peripheral tissues. As the other NAEs, OEA is not stored but generated on demand from membrane phospholipid precursors and rapidly inactivated by hydrolytic enzymes, resulting in tightly controlled and spatially restricted regulation of its tissue levels (Friuli et al., 2025).

At the biochemical level, OEA biosynthesis follows pathways common to NAEs and is primarily based on the generation of *N*-acylphosphatidylethanolamines (NAPEs) as immediate precursors (Friuli et al., 2025). In the classical route, NAPE formation is mediated by calcium-dependent *N*-acyltransferase activity, which transfers an oleoyl group from donor glycerophospholipids, such as phosphatidylcholine, to phosphatidylethanolamine (Romano et al., 2015). However, experimental evidence indicates that NAPEs can also be produced through calcium-independent phospholipase A/acyltransferase (PLA/AT) activities, suggesting that precursor generation can occur through multiple enzymatic mechanisms depending on the cellular context (Bowen et al., 2017). Following their formation, oleoyl-containing NAPEs are hydrolysed by NAPE-specific phospholipase D (**NAPE-PLD**), resulting in the release of OEA and phosphatidic acid (Romano et al., 2015). NAPE-PLD is broadly expressed in peripheral tissues and shows preferential expression within the enterocyte layer of the proximal small intestine, consistent with a role in locally coupling lipid absorption to the production of bioactive NAEs (Piomelli, 2013). In parallel with the NAPE-PLD-dependent pathway, OEA can also be generated through alternative biosynthetic routes that do not require NAPE-PLD activity (Bowen et al., 2017). In these pathways, NAPEs undergo stepwise deacylation to yield intermediate metabolites that are subsequently converted into NAEs. A key enzyme involved in this process is α/β-hydrolase domain-containing protein 4 (**ABHD4**), which catalyses the removal of acyl chains from NAPEs and related intermediates, generating lyso-NAPE and glycerophospho-NAE species (Bowen et al., 2017). These intermediates are further processed by glycerophosphodiester phosphodiesterases, including GDE1, GDE4 and GDE7, to yield NAEs such as OEA (Bowen et al., 2017). The coexistence of NAPE-PLD-dependent and -independent pathways provides biochemical redundancy and may allow tissue- and context-specific modulation of OEA production under different nutritional or metabolic conditions.

Preclinical observations suggest that among peripheral organs, the proximal small intestine represents the most nutritionally responsive site of OEA mobilization (Fu et al., 2007; Igarashi et al., 2021; Piomelli, 2013). OEA levels increase markedly in the duodenum and jejunum after feeding and decline during fasting, with these fluctuations largely confined to the intestinal mucosa (Fu et al., 2007; Igarashi et al., 2021; Piomelli, 2013). By contrast, comparable postprandial changes are not observed in distal intestinal regions or in extra-intestinal tissues (Fu et al., 2007; Igarashi et al., 2021; Piomelli, 2013). The increase in intestinal OEA observed after feeding reflects a coordinated modulation of its synthesis and degradation, resulting in a transient accumulation of OEA during nutrient absorption (Fu et al., 2007; Igarashi et al., 2021; Piomelli, 2013). These observations support the concept that intestinal OEA functions as a locally generated lipid messenger that links nutrient availability to adaptive metabolic responses.

A distinctive feature of intestinal OEA biosynthesis is its close dependence on dietary oleic acid availability (Igarashi et al., 2021). Experimental evidence indicates that OEA is synthesized upon the absorption of luminal oleic acid across the apical enterocyte membrane, rather than upon the uptake of circulating fatty acids (Schwartz et al., 2008). In this context, the cluster of differentiation 36 (**CD36**), a fatty acid translocase, plays a key upstream role by facilitating the uptake of long-chain unsaturated fatty acids in the proximal small intestine (Guijarro et al., 2010; Schwartz et al., 2008). Consistent with this function, genetic disruption of CD36 abolishes feeding-induced OEA mobilization and prevents the rise of NAPE and OEA pools, thereby identifying CD36 as a critical molecular link between dietary lipid uptake and intracellular OEA biosynthetic pathways (Guijarro et al., 2010). This tight dependence on dietary lipid sensing further reinforces the view of OEA as a nutrient-responsive signal rather than a constitutive metabolic regulator.

Termination of OEA signalling is primarily mediated by enzymatic hydrolysis. Fatty acid amide hydrolase **(FAAH)** represents the principal catabolic enzyme responsible for OEA degradation in metabolic tissues, including the small intestine and liver, and is predominantly localized to intracellular membranes such as the endoplasmic reticulum and mitochondria (Lo Verme et al., 2005). In the proximal small intestine, FAAH activity is dynamically regulated by nutritional status, with feeding reducing its activity and thereby contributing to postprandial OEA accumulation (Fu et al., 2007). In addition to FAAH, N-acylethanolamine acid amidase (**NAAA**) contributes to the degradation of NAEs in selected cellular contexts, particularly within immune cells, although this enzyme displays lower affinity for OEA and preferentially hydrolyses other NAEs, such as **PEA** (Piomelli, 2013; Ueda

et al., 2010). Although FAAH inhibition can increase OEA levels, its broad substrate specificity within the eCBome complicates selective pharmacological manipulation of OEA tone.

Chronic nutritional overload disrupts this regulatory framework. Both short- and long-term exposure to high-fat diets attenuate or abolish feeding-induced OEA mobilization in the proximal small intestine and reduce jejunal OEA levels (Igarashi et al., 2021). These alterations have been linked primarily to impaired upstream biosynthetic steps, including reduced NAPE formation (Igarashi et al., 2021), rather than to changes in degradative activity. Thus, sustained excess of dietary fat appears to blunt the adaptive intestinal OEA response, potentially contributing to the loss of postprandial satiety signalling observed in obesity. The enzymatic pathways governing the biosynthesis and degradation of OEA are schematically illustrated in Figure 1.

2.2 | PPAR-α and beyond: receptor targets and downstream signalling

OEA exerts its biological effects through interaction with multiple molecular targets, among which the nuclear **peroxisome proliferator-activated receptor alpha** (PPAR-α) represents the best-characterized and functionally dominant mediator (Fu et al., 2005). Quantitative binding studies indicate that OEA activates PPAR-α with nanomolar potency ($EC_{50} \approx 120$ nM), displaying greater efficacy than other natural ligands such as oleic acid and superior or comparable activity to synthetic PPAR-α agonists, including fibrates (Fu et al., 2005). Engagement of PPAR-α by exogenously administered OEA initiates a canonical ligand-dependent transcriptional program. Upon ligand binding, PPAR-α forms heterodimers with the **retinoid X receptor**s and binds to peroxisome proliferator response elements within the promoter regions of target genes, leading to the coordinated regulation of pathways involved in fatty acid uptake, intracellular trafficking and mitochondrial β-oxidation (Rakhshandehroo et al., 2010). This transcriptional shift promotes lipid utilization rather than storage, reinforcing the concept of OEA as a metabolic reprogramming signal rather than a direct lipolytic stimulus. Among the genes induced by OEA-driven PPAR-α activation are key regulators of lipid handling, such as CD36 and fatty acid transport proteins, as well as PPAR-α itself, suggesting the presence of autoregulatory amplification loops (Brown et al., 2017). In rodent models of obesity, chronic OEA administration reproduces the expected downstream consequences of sustained

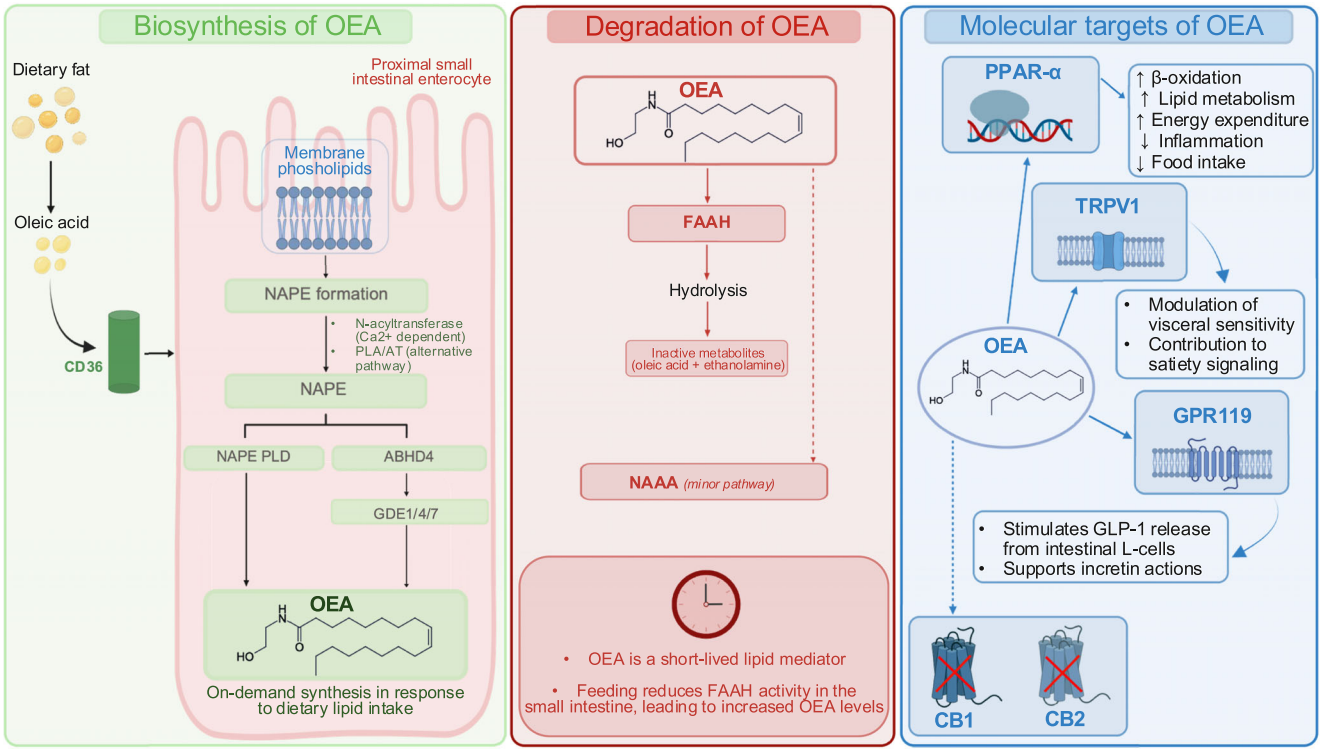

FIGURE 1 Enzymatic pathways and molecular targets underlying OEA signalling. OEA is synthesized on demand in enterocytes from membrane phospholipid precursors via N-acylphosphatidylethanolamine (NAPE)–dependent pathways, involving both NAPE-PLD and alternative enzymatic routes (ABHD4 and GDE 1/4/7). Its production is tightly linked to dietary oleic acid uptake through CD36. OEA signalling is terminated primarily by fatty acid amide hydrolase (FAAH). Functionally, OEA exerts its biological effects mainly through activation of PPAR-α, whereas additional targets such as TRPV1 and GPR119 contribute to context-dependent signalling. ABHD4, a/B-hydrolase domain 4; CD36, cluster of differentiation 36; FAAH, fatty acid amide hydrolase; GDE, glycerophosphodiesterase; GLP-1, glucagon-like peptide 1; GPR119, G-protein coupled receptor 119; NAAA, N-acylethanolamine acid amidase; NAPE, N-acy|phosphatidylethanolamine; NAPE-PLD, N-acylphosphatidylethanolamine-specific phospholipase D; OEA: Oleoylethanolamide; PLA/AT, phospholipase a/acyltransferase; PPAR-α, peroxisome proliferator-activated receptor alpha; TRPV1, transient receptor potential vanilloid 1.

PPAR-α activation, including enhanced fatty-acid catabolism, reductions in circulating lipid levels, attenuation of hepatic steatosis and decreased body-weight gain (Fu et al., 2003; Lo Verme et al., 2005). Importantly, these effects are largely abolished in PPAR-α–deficient mice, confirming that this receptor is required for the metabolic actions of exogenous OEA (Fu et al., 2003). Beyond metabolic regulation, PPAR-α activation is also essential for the hypophagic effects of OEA. Genetic ablation of PPAR-α abolished OEA-induced suppression of food intake, demonstrating that this receptor is an obligatory mediator of OEA-driven satiety (Fu et al., 2003). Notably, PPAR-α–deficient mice retain normal sensitivity to other anorexigenic agents, including **d-fenfluramine** and **cholecystokinin**, indicating that the loss of responsiveness is selective for OEA rather than reflecting a generalized impairment of feeding control mechanisms (Fu et al., 2003). These findings position PPAR-α as the central molecular hub linking peripheral lipid sensing to behavioural output regulated by OEA.

Alongside its well-established transcriptional activity, PPAR-α activation by OEA has also been associated with rapid non-genomic signalling mechanisms. In dopaminergic neurons of the ventral tegmental area (VTA), OEA can activate PPAR-α to rapidly suppress neuronal activity through negative modulation of **β_2-containing nicotinic acetylcholine receptors** (Melis et al., 2010, 2013). This effect occurs within minutes and does not involve gene transcription, but rather intracellular signalling processes probably involving tyrosine kinase–dependent phosphorylation mechanisms that alter receptor function (Melis et al., 2010). Through this pathway, OEA reduces the spontaneous firing of **dopamine** neurons and the number of active dopaminergic cells in the VTA, suggesting that PPAR-α signalling may rapidly modulate dopaminergic tone. However, the precise physiological relevance of these rapid effects remains less well defined than the canonical transcriptional program.

OEA can also engage additional molecular targets that contribute to its pleiotropic signalling profile, without being essential for its anorexigenic effects (Bowen et al., 2017).

At micromolar concentrations, OEA activates the **transient receptor potential vanilloid-1 (TRPV1)** channel, as demonstrated in heterologous expression systems and primary sensory neurons (Bowen et al., 2017; Lo Verme et al., 2005). Moreover, experiments on mice treated with a high dose of OEA (25 mg·kg^{-1}) showed that TRPV1 activation by OEA induces inward currents in capsaicin-sensitive nodose ganglion neurons and elicits nociceptive and visceral pain-related behaviours. Both effects are absent in TRPV1-null animals or following pharmacological blockade of the channel (Wang et al., 2005). Notably, the concentrations required for robust TRPV1 activation exceed those typically associated with endogenous OEA fluctuations. Similarly, the dose able to produce pain-related behaviours was double the dose producing hypophagia; this effect is still detectable in TRPV1-null animals, thus indicating that TRPV1 signalling is not essential for satiety mediation and that OEA's anorexiant effects are not caused by visceral pain (Wang et al., 2005).

OEA has also been identified as a medium-potency endogenous agonist of the G protein-coupled receptor **GPR119**, which is expressed predominantly in the gastrointestinal tract and pancreas (Lauffer et al., 2009). Through GPR119 activation, OEA can stimulate **glucagon-like peptide-1 (GLP-1)** secretion from intestinal L-cells, linking lipid sensing to enteroendocrine signalling (Lauffer et al., 2009). However, genetic ablation of GPR119 does not prevent OEA-induced suppression of food intake, demonstrating that this receptor is unnecessary for the hypophagic response (Lan et al., 2009). Thus, although GPR119 may contribute to metabolic modulation, it does not represent the primary mediator of OEA-driven satiety.

Importantly, OEA does not bind or activate cannabinoid **CB_1** or **CB_2** receptors, distinguishing its signalling profile from that of classical endocannabinoids (Friuli et al., 2025). Instead, OEA operates within the para-cannabinoid system, engaging non-cannabinoid receptors to counterbalance endocannabinoid-driven orexigenic signalling. Collectively, these findings identify PPAR-α as the central integrative hub mediating both transcriptional and behavioural effects of exogenously administered OEA, whereas additional targets such as TRPV1 and GPR119 provide context-dependent, ancillary contributions rather than obligatory mediators of satiety. The principal molecular targets and downstream signalling pathways engaged by OEA are schematically illustrated in Figure 1.

2.3 | Crosstalk with endocannabinoid tone and lipid metabolic pathways

OEA is part of a broader lipid-signalling framework, in which endocannabinoid and para-cannabinoid mediators cooperate to regulate energy homeostasis through dynamic interactions with lipid metabolic pathways. Within this network—now conceptualized as the eCBome (Iannotti & Di Marzo, 2025)—bioactive lipids derived from membrane phospholipids integrate nutritional status, lipid flux and metabolic demands, thereby shaping the balance between energy intake, storage and utilization. A fundamental basis for crosstalk between OEA, AEA and **2-arachidonoylglycerol (2-AG)** lies in their shared biochemical origin. These mediators are synthesized on demand from membrane phospholipids in response to metabolic cues and are not stored in preformed pools (Mock et al., 2023). OEA and AEA belong to the NAE family and originate from NAPE precursors embedded within the phospholipid bilayer, whereas 2-AG derives primarily from phospholipase C-dependent hydrolysis of membrane phospholipids via diacylglycerol intermediates (Mock et al., 2023). Despite these structural differences, the synthesis of all three mediators is tightly coupled to membrane lipid remodelling and fatty acid availability, placing their signalling activity under direct metabolic control (J. Liu et al., 2008; Mock et al., 2023; Silvestri & Di Marzo, 2013).

The interdependence of OEA and endocannabinoid signalling is further reinforced by shared enzymatic pathways. AEA and OEA can be generated through both canonical NAPE-PLD-dependent routes and alternative NAPE-PLD-independent pathways (Mock et al., 2023). At the level of degradation, FAAH represents a major point of convergence, as it hydrolyses multiple NAEs and plays a central role in determining local NAE tone. Although 2-AG is primarily degraded by **monoacylglycerol lipase**, FAAH may contribute to its turnover in

specific cellular contexts, further linking endocannabinoid and paracannabinoid metabolism (J. Liu et al., 2008; Mock et al., 2023; Silvestri & Di Marzo, 2013). Importantly, alterations in the expression or activity of these enzymes have been reported under conditions of high-fat feeding and obesity, suggesting that nutritional overload can reshape the enzymatic landscape governing lipid mediator balance (Mock et al., 2023).

Through these shared metabolic routes, OEA and endocannabinoids may influence each other's signalling efficacy. Although direct in vivo competition for FAAH remains context-dependent and difficult to quantify, changes in the availability of one mediator can theoretically modify the persistence and functional effects of others by altering substrate access and enzymatic capacity (Mock et al., 2023). In this framework, elevations in OEA could modulate endocannabinoid tone indirectly, whereas sustained increases in endocannabinoid levels may shift membrane lipid composition or enzyme activity in ways that attenuate OEA production. Such bidirectional modulation is likely to reflect metabolic interdependence, rather than direct receptor-level antagonism. Functionally, OEA and endocannabinoids exert largely opposing effects on lipid metabolism and energy balance. OEA acts primarily as a peripheral satiety signal that promotes fatty acid utilization and catabolic pathways (Silvestri & Di Marzo, 2013), whereas AEA and 2-AG, acting through cannabinoid receptor-dependent mechanisms, favour energy storage, lipogenesis and reduced energy expenditure (Silvestri & Di Marzo, 2013). In conditions of nutritional excess and obesity, hyperactivation of the endocannabinoid system is frequently observed, shifting this balance towards anabolic states (Silvestri & Di Marzo, 2013). Both experimental models and human studies indicate that obesity is associated with an increased AEA tone and altered circulating or tissue NAE ratios, including reduced OEA/AEA balance, consistent with enhanced appetite drive and impaired satiety signalling (Mock et al., 2023; Silvestri & Di Marzo, 2013).

Within this context, OEA signalling can be viewed as a counter-regulatory mechanism that opposes excessive endocannabinoid activity and contributes to metabolic restraint (Friuli et al., 2025; Silvestri & Di Marzo, 2013). These interactions are particularly relevant in metabolically active tissues such as the intestine, liver and adipose tissue, where dietary lipids continuously feed into membrane phospholipid pools (Silvestri & Di Marzo, 2013). In these compartments, fluctuations in fatty acid flux influence the synthesis and degradation of OEA, AEA and 2-AG, linking lipid metabolism to signalling pathways that regulate feeding behaviour, lipid storage and peripheral energy homeostasis (Mock et al., 2023). At the intestinal level, where lipid absorption, nutrient sensing and local lipid mediator mobilization converge, OEA may play a particularly prominent role in buffering endocannabinoid-driven responses associated with chronic high-fat feeding (Silvestri & Di Marzo, 2013; Vari et al., 2025).

Collectively, this evidence supports the view that OEA does not operate in isolation but functions within an integrated lipid signalling network that dynamically coordinates endocannabinoid tone and metabolic pathways. Through shared precursors, partially overlapping enzymatic systems and opposing functional outputs, the eCBome provides the flexibility required to shift between energy storage and energy utilization. Disruption of this balance in obesity may therefore reflect not only increased endocannabinoid signalling but also impaired OEA-mediated counter-regulation, reinforcing the translational relevance of restoring lipid mediator equilibrium.

3 | CENTRAL AND PERIPHERAL MECHANISMS MEDIATING THE ANTI-OBESITY EFFECTS OF OEA

3.1 | Central mechanisms mediating OEA's effects on feeding behaviour

Feeding behaviour results from the integration of homeostatic mechanisms that monitor energy needs and metabolic status with non-homeostatic processes encoding motivational, emotional and contextual aspects of food intake (C. M. Liu & Kanoski, 2018; Romano, Friuli, et al., 2020). Homeostatic control primarily relies on hypothalamic and brainstem circuits integrating peripheral metabolic signals, whereas non-homeostatic regulation involves corticolimbic networks governing reward processing and stress responsiveness (C. M. Liu & Kanoski, 2018; Romano, Friuli, et al., 2020). Dysregulation within or between these domains contributes to overeating and obesity (Brown et al., 2017; Friuli et al., 2025).

In this framework, OEA has emerged as a lipid mediator capable of influencing both homeostatic and reward-related circuits, rather than acting as a non-specific anorexigenic signal (Brown et al., 2017). Experimental evidence indicates that systemic administration of OEA recruits central pathways spanning these domains, providing a mechanistic basis for its anti-obesity effects observed in different preclinical models (Brown et al., 2017; Friuli et al., 2025). Early studies in rats under physiological feeding conditions showed that peripheral administration of OEA induced rapid and selective activation of discrete brainstem and hypothalamic nuclei, as assessed by Fos immunoreactivity (Brown et al., 2017; Friuli et al., 2025; Romano et al., 2015). These include the area postrema (AP) and the nucleus of the solitary tract (NST) in the brainstem, as well as hypothalamic nuclei such as the paraventricular (PVN), supraoptic (SON) and tuberomammillary nuclei (TMN) (Gaetani et al., 2010; Provensi et al., 2014; Rodríguez De Fonseca et al., 2001; Romano et al., 2013, 2014, 2015). Collectively, these regions represent major integrative hubs for visceral and metabolic information and coordinate neuroendocrine and behavioural responses to peripheral signals. Notably, OEA-induced hypophagia is characterized primarily by delayed meal initiation (Azari et al., 2014; Gaetani et al., 2003; Oveisi et al., 2004), without markers of visceral malaise or stress activation (Proulx et al., 2005; Rodríguez De Fonseca et al., 2001), consistent with engagement of physiological satiety pathways rather than aversive suppression of feeding (Proulx et al., 2005).

Within the hypothalamus, OEA robustly engages **oxytocinergic** signalling pathways. In fact, studies in rats demonstrated that systemic administration of OEA increases oxytocin gene expression and release, also elevating circulating oxytocin levels (Gaetani et al., 2010). These effects are abolished in PPAR-α knockout mice and prevented

by central oxytocin receptor antagonism, which also blocks OEA's effects on food intake, thus demonstrating that activation of PVN and SON oxytocinergic neurons is required for OEA-induced hypophagia (Gaetani et al., 2010). These findings identify oxytocin as a critical downstream mediator of OEA actions on feeding and suggest that this system might represent a key effector linking peripheral lipid sensing to central satiety control.

Brainstem-hypothalamic connectivity is essential in mediating OEA's central effects. Using neurotoxic approaches in rats, it was shown that selective disruption of noradrenergic projections from the NST to the PVN prevented both oxytocinergic activation and food intake suppression following OEA administration (Romano et al., 2013). Consistent with these findings, peripheral OEA administration increased hypothalamic **noradrenaline** levels, further supporting a functional role for noradrenergic transmission in the central actions of OEA (Romano et al., 2013).

The **histaminergic** system provides an additional modulatory central component. In histamine-deficient mice or in rats subjected to pharmacological depletion of brain histamine, OEA fails to activate hypothalamic oxytocinergic neurons and does not suppress food intake (Provensi et al., 2014). These findings suggest that coordinated engagement of catecholaminergic and histaminergic pathways upstream of oxytocin is required for full expression of OEA's central effects.

Beyond these classical homeostatic pathways, OEA also modulates neural circuits involved in motivational and reward-related aspects of feeding (Melis et al., 2013; Murillo-Rodríguez et al., 2011; Romano et al., 2015; Romano, Micioni Di Bonaventura, et al., 2020; Serrano et al., 2011; Tellez et al., 2013). Direct modulation of mesolimbic dopamine signalling has been demonstrated in vivo. Microdialysis studies in freely feeding rats show that OEA administration into the lateral hypothalamus or the dorsal raphe nucleus increased extracellular dopamine levels in the nucleus accumbens (Murillo-Rodríguez et al., 2011). In addition, in adult rats, OEA modulates the excitability of midbrain dopaminergic neurons via activation of PPAR-α, which negatively regulates β_2-containing nicotinic acetylcholine receptors expressed on dopaminergic neurons of the VTA. This PPAR-α–dependent mechanism provides a cellular substrate through which OEA may constrain excessive dopaminergic activation, while preserving physiological dopamine signalling under basal conditions (Melis et al., 2010, 2013).

The functional relevance of OEA-dopamine interactions in the context of feeding behaviour has been demonstrated in dietary models of reward dysfunction. Sub-chronic OEA treatment restores normal reward responsiveness in rats exposed to chronic high-fat diet, a condition associated with dopaminergic hypofunction and reduced sensitivity to food reward (Tellez et al., 2013). Moreover, in a model of frustration stress-induced binge-like eating with female rats, acute OEA administration suppresses excessive intake of palatable food without affecting baseline feeding (Romano, Micioni Di Bonaventura, et al., 2020). This behavioural modulation is accompanied by reduced activation of stress- and reward-related brain regions, including the nucleus accumbens and the amygdala, and enhanced activation of hypothalamic and midbrain nuclei implicated in feeding control, such as the PVN and the VTA (Romano, Micioni Di Bonaventura, et al., 2020). In the same model, OEA dampens stress-induced dopamine release in the nucleus accumbens shell while enhancing serotonergic and noradrenergic tone and modulating central corticotropin-releasing factor and oxytocinergic systems (Romano, Micioni Di Bonaventura, et al., 2020).

Collectively, the available evidence indicates that OEA regulates feeding behaviour through coordinated engagement of homeostatic and non-homeostatic circuits. The central neural pathways through which OEA modulates feeding behaviour are schematically illustrated in Figure 2. Rather than acting solely as a satiety signal, OEA appears to rebalance interactions between metabolic needs and reward-driven motivation. This multimodal central profile distinguishes OEA from purely appetite-suppressing agents and supports its potential relevance in conditions characterized by reward dysregulation or stress-driven overeating. However, the extent to which these central effects translate into clinically meaningful outcomes in humans remains to be determined, underscoring the need for studies that directly assess neurobehavioural endpoints alongside metabolic efficacy.

3.2 | Peripheral mechanisms mediating OEA's effects and gut–brain communication

The ability of peripherally administered OEA to engage central circuits involved in the regulation of feeding behaviour has raised the question of how this lipid mediator communicates with the brain (Romano et al., 2023). Clarifying the relative contribution of neural versus humoral pathways is critical not only for understanding OEA physiology but also for defining its pharmacokinetic and translational potential as a therapeutic candidate (Romano et al., 2023; Tutunchi, Saghafi-Asl, & Ostadrahimi, 2020).

Initial studies implicated visceral vagal afferents, as OEA-induced hypophagia was attenuated in rats subjected to total subdiaphragmatic vagotomy or treated with neurotoxic doses of **capsaicin** (Fu et al., 2003; Rodríguez De Fonseca et al., 2001; Romano et al., 2023). However, subsequent analyses highlighted important methodological limitations of both experimental approaches. Total subdiaphragmatic vagotomy removes both afferent and efferent fibres, thereby disrupting the physiological bidirectional communication between the gastrointestinal tract and the brain. This produces profound alterations in digestive and metabolic function that may confound behavioural outcomes (Romano et al., 2023). Similarly, capsaicin treatment lacks selectivity for vagal afferents, as it induces neurotoxic damage to unmyelinated visceral sensory neurons of both vagal and spinal origin. Moreover, it has been shown to affect neurons within the AP and the NST, regions critically involved in the central processing of visceral signals (Romano et al., 2017, 2023). These limitations complicate interpretation of early findings.

More selective subdiaphragmatic vagal deafferentation in rats—a surgical procedure that can spare a substantial proportion of vagal efferent fibres (Azari et al., 2014)—demonstrated that OEA retains its hypophagic efficacy despite removal of abdominal vagal afferents (Azari et al., 2014; Romano et al., 2023). These data indicate that

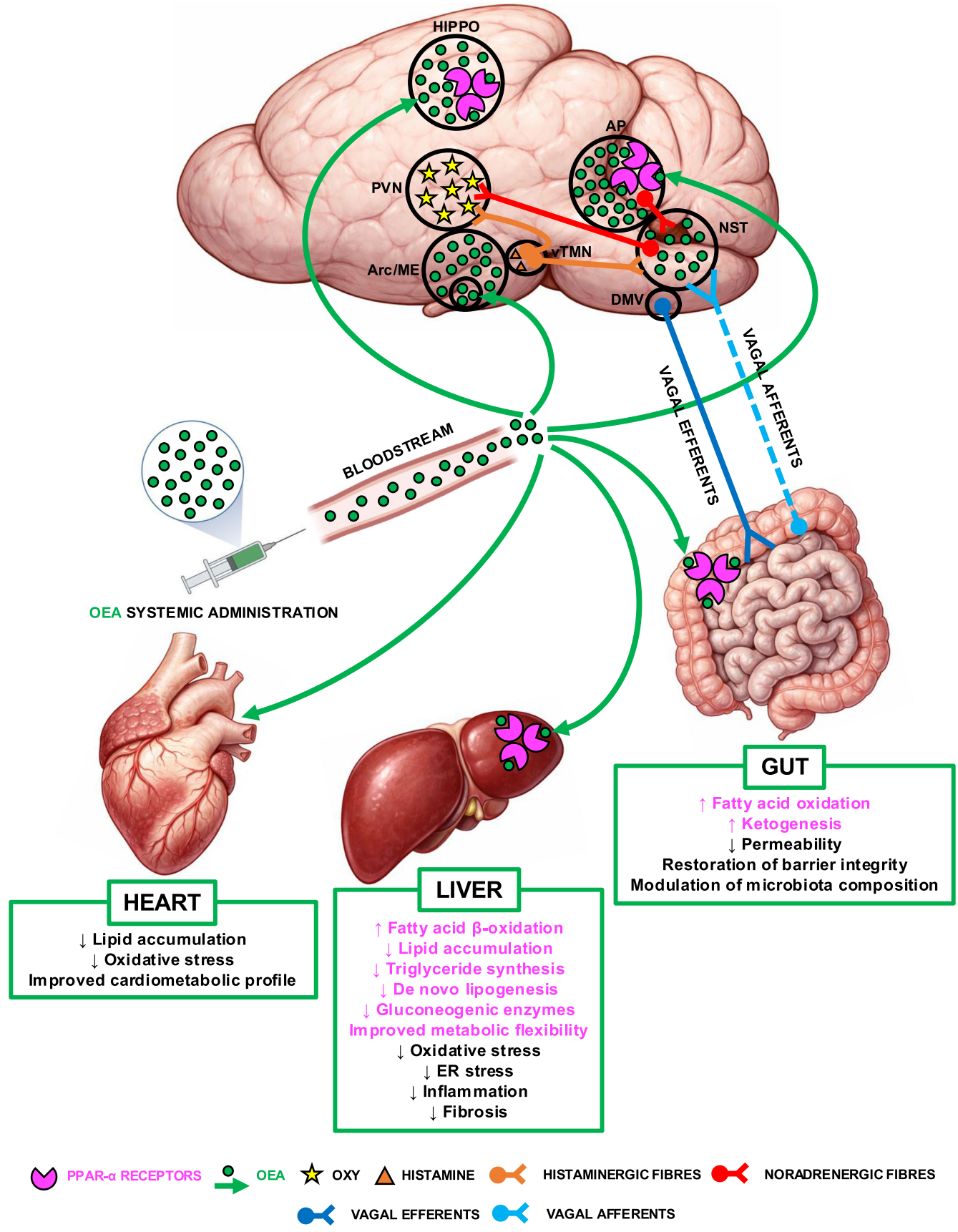

FIGURE 2 Legend on next page.

intact vagal sensory transmission is not required for the anorexigenic action of exogenous OEA and suggest the involvement of alternative signalling routes from the periphery to the brain.

The AP (area postrema) has emerged as a critical interface in this context (Romano et al., 2017, 2023). As a circumventricular organ devoid of a functional blood–brain barrier, the AP is uniquely positioned to detect circulating metabolic signals (Romano et al., 2017). Surgical ablation of the AP abolishes both OEA-induced hypophagia and associated neurochemical effects, suggesting that circulating OEA can access and activate central feeding circuits via AP-dependent mechanisms (Romano et al., 2023). Recent pharmacokinetic analyses further support this interpretation. Following systemic administration, intact OEA appears in the circulation and accumulates in discrete brain regions implicated in feeding regulation, including the AP, NST, arcuate nucleus/median eminence and hippocampus (Romano et al., 2023). Notably, the earliest and most pronounced increase occurs in the AP, reinforcing its role as a primary sensing site for circulating OEA (Romano et al., 2023). These findings substantially revise earlier models that exclusively emphasized vagal mediation. Moreover, the rapid detection of OEA in the adjacent NST further supports the functional coupling between these brainstem structures, consistent with sequential engagement of AP-NST circuits involved in the central integration of peripheral metabolic signals (Romano et al., 2023).

The AP-centred model also reconciles previous inconsistencies across experimental models. The loss of OEA efficacy following capsaicin treatment may reflect collateral disruption of AP/NST circuitry rather than selective vagal blockade (Romano et al., 2023). Conversely, the lack of consistent hypophagic effects following intracerebroventricular administration of OEA may relate to rapid enzymatic degradation by FAAH at ventricular interfaces, whereas FAAH expression appears to be limited in the AP, potentially conferring increased sensitivity to circulating OEA (Piomelli, 2013; Romano et al., 2023).

In parallel with these direct access mechanisms, peripheral metabolic actions of OEA may contribute indirectly to gut–brain communication. Experimental studies have shown that peripheral OEA administration increases intestinal fatty acid oxidation and elevates circulating **β-hydroxybutyrate** levels (Azari et al., 2014), raising the possibility that OEA-induced humoral signals may participate in conveying metabolic information to the brain independently of direct neural pathways (Igarashi et al., 2021; Piomelli, 2013). Although the causal contribution of such metabolic intermediates to OEA's central effects remains to be fully elucidated, this humoral component is consistent with the persistence of OEA-induced hypophagia in the absence of intact vagal afferents.

Collectively, the available evidence indicates that exogenously administered OEA engages central feeding circuits through a combination of mechanisms, including direct access of circulating OEA to circumventricular brain regions—particularly the AP—and secondary metabolic signalling downstream of peripheral PPAR-α activation.

The peripheral mechanisms, through which OEA engages gut–brain communication, are schematically illustrated in Figure 2. From a pharmacological standpoint, these findings underscore the importance of systemic exposure profiles, route of administration and dose selection in determining central efficacy. They also suggest that OEA's mode of action differs fundamentally from gut hormone-based therapies that rely predominantly on receptor-mediated neural signalling, positioning OEA as a lipid-derived modulator of gut–brain communication rather than a classical peptide hormone analogue.

3.3 | Evidence for the anti-obesity effects of OEA

OEA was initially characterized as a lipid mediator involved in the regulation of energy intake and body weight and suppression of food intake remains the most consistently reported functional outcome following exogenous administration in experimental models (Azari et al., 2014; Fu et al., 2003, 2005; Payahoo, Khajebishak, & Ostadrahimi, 2019; Rodríguez De Fonseca et al., 2001; Tovar et al., 2021; Tutunchi, Saghafi-Asl, & Ostadrahimi, 2020). In rodents, peripheral OEA administration reduces feeding primarily by delaying meal initiation, without inducing behavioural signs of stress, visceral illness or alterations in locomotor activity or water intake (Azari et al., 2014; Fu et al., 2003; Rodríguez De Fonseca et al., 2001). Importantly, the magnitude and pattern of feeding suppression are influenced by metabolic context. In free-feeding animals, intraperitoneal OEA administration (1–20 $mg \cdot kg^{-1}$) produced a dose-dependent delay in feeding onset, with limited disruption of meal structure, whereas in food-deprived conditions, both feeding latency and meal size may be reduced (Azari et al., 2014; Gaetani et al., 2003; Romano et al., 2015). These observations indicate state-dependent modulation of energy intake rather than indiscriminate appetite suppression (Azari et al., 2014; Fu et al., 2003).

In models of diet-induced obesity, repeated OEA administration reduces cumulative caloric intake and attenuates body weight gain and adiposity (Fu et al., 2005; Tovar et al., 2021; Tutunchi, Saghafi-Asl, & Ostadrahimi, 2020). These effects are evident within days and persist throughout the treatment (Fu et al., 2005; Tovar et al., 2021; Tutunchi, Saghafi-Asl, & Ostadrahimi, 2020). Notably, these effects are markedly more pronounced in obese animals than in lean controls fed a standard diet, indicating that the anti-obesity efficacy of OEA may depend on metabolic state (Fu et al., 2005; Tovar et al., 2021; Tutunchi, Saghafi-Asl, & Ostadrahimi, 2020). Comparative investigations among structurally related NAEs further indicated that OEA produced more robust and reproducible reductions in food intake and

FIGURE 2 Central and peripheral mechanisms underlying OEA-mediated regulation of feeding behaviour and metabolic homeostasis. Schematic representation of the central and peripheral pathways through which oleoylethanolamide (OEA) regulates feeding behaviour and metabolic homeostasis. ↑ up-regulation; ↓ down-regulation; AP: area postrema; arc/ME: arcuate nucleus/median eminence; DMV: dorsal motor nucleus of the vagus; HIPPO: hippocampus; NST: nucleus of the solitary tract; OEA: oleoylethanolamide; OXY: oxytocin; PVN: paraventricular nucleus of the hypothalamus; vTMN: ventral tuberomammillary nucleus; pink colour indicates biological effects mediated by PPAR-α activation.

TABLE 1 Summary of preclinical and clinical evidence on the metabolic effects of OEA in obesity and related comorbidities.

Animal model/population	Condition	Dose	Duration	Group size	Key outcomes	Study
Anti-obesity effects of OEA						
Male C57BL/6J, wild-type and PPAR-α KO mice; male Wistar and Zucker rats	7-week diet (HFD)	5 $mg^{-1}kg^{-1}day^{-1}$	4-week treatment (mice); 2-week treatment (rats)	6–8/group (mice); 7–8/group (rats)	↓ body weight, ↓ food intake (PPAR-α–dependent); ↓ adiposity (OEA)	Fu et al., 2005
Male Sprague–Dawley rats	13 weeks (HFD)	10 $mg^{-1}kg^{-1}day^{-1}$	2-week treatment	8/group	↓ food intake (OEA ≈ POEA in HFD) ↓ body weight gain (OEA ≥ POEA) ↓ adiposity (OEA > POEA)	Tovar et al., 2021
Obese patients	Obesity	125 mg, twice daily	8-week treatment	60 total (56 completed; ∼27–29/group)	↓ body weight, ↓ BMI, ↓ waist circumference, ↓ fat mass, ↑ satiety (OEA)	Payahoo et al., 2018
OEA effects on metabolic homeostasis and insulin sensitivity						
Male Sprague–Dawley rats; 129S4/SvJae mice and PPAR-α knockout mice	6-week diet (HFD) + STZ-induced T2DM model	10, 30, 60 $mg^{-1}kg^{-1}day^{-1}$	6-week treatment	6–7/group	↓ fasting glucose, ↓ insulin resistance, ↑ hepatic glycogen synthesis, ↓ gluconeogenesis (PPAR-α–independent) (OEA)	Ren et al., 2020
Male C57Bl/6J mice	12-week diet (HFD)	2.5 $mg^{-1}kg^{-1}day^{-1}$	8-week treatment	10/group	↓ fasting glycaemia, ↑ glucose tolerance, ↓ body weight, ↓ fat mass, ↑ insulin signalling (OEA)	Comella et al., 2024
Obese patients	Obesity	125 mg, twice daily	8-week treatment	60 total (56 completed; 27 OEA/29 placebo)	↓ triglycerides, ↔ fasting glucose, ↔ dietary habits or physical activity (OEA)	Ostadrahimi et al., 2024
Obese patients	Obesity-related metabolic dysfunctions	125–600 $mg^{-1}day^{-1}$	1- to 12-week treatment	13 RCTs	↓ fasting glycaemia, ↓ triglycerides, ↓ waist circumference, ↓ inflammatory markers, ↑ total antioxidant capacity, variable insulin response (OEA)	Eslahi et al., 2025
OEA effects on hepatic steatosis and metabolic-associated fatty liver disease						
Male Wistar–Han rats	11-week diet (LFD)	10 $mg^{-1}kg^{-1}day^{-1}$	2-week treatment	12/group	↓ de novo lipogenesis, ↓ triglyceride synthesis (SREBP- and PPAR-dependent) (OEA)	Romano et al., 2021
Male Wistar–Han rats	11-week diet (HFD)	10 $mg^{-1}kg^{-1}day^{-1}$	2-week treatment	5/group	↓ steatosis, ↓ oxidative stress, ↓ ER stress, ↑ antioxidant defences (OEA)	Giudetti et al., 2021
Male C57Bl/6J mice	5-week diet (HFD)	5 $mg^{-1}kg^{-1}day^{-1}$	6-week treatment	4–8/group	↓ histamine-dependent OEA production (HFD), ↓ steatosis, ↓ inflammation, ↓ fibrosis (OEA)	Lin et al., 2022
Female C57Bl/6J mice	2-month diet (HFD-high cholesterol)	200 $mg^{-1}kg^{-1}day^{-1}$ (OEA-DS)	2 months	12/group	↓ cholesterol, ↓ inflammation, ↓ apoptosis, ↑ PPAR-α signalling, ↑ FA oxidation, ↓ steatosis (OEA-DS)	Ivashkevich, Ponomarenko, Manzhulo, Egoraeva, & Dyuizen, 2025
Obese patients with NAFLD	Calorie-restricted diet	125 mg twice daily	12-week treatment	76 total (∼38/group)	↓ triglycerides, ↓ alanine and aspartate aminotransferases, ↓ anthropometric indices, ↑ PPAR-α, ↑ uncoupling proteins (PBMCs) (OEA)	Tutunchi, Ostadrahimi, et al., 2020
		125 mg twice daily			↑ antioxidant capacity, ↓ oxidative stress (OEA)	

TABLE 1 (Continued)

Animal model/population	Condition	Dose	Duration	Group size	Key outcomes	Study
Obese patients with NAFLD	Calorie-restricted diet		12-week treatment	60 total (30/group)		Tutunchi, Zolrahim, et al. 2023
Obese patients with NAFLD	Calorie-restricted diet	125 mg twice daily	12-week treatment	76 total (38/group)	↓ atherogenic indices, ↓ RDW (OEA)	Tutunchi, Naeini, et al., 2020
Obese patients with NAFLD	Calorie-restricted diet	125 mg twice daily	12-week treatment	60 total (30/group)	↑ lipid metabolism (PBMCs), ↑ NRG4 (OEA)	Tutunchi, Ebrahimi-Mameghani, et al., 2023
OEA effects on cardiovascular dysfunction						
Female C57Bl/6J mice	2-month diet (HFD-high cholesterol)	200 $mg^{-1}kg^{-1}day^{-1}$ (OEA-DS)	2 months	12/group	↓ cholesterol, ↓ PCSK9, ↑ LDLR-related pathways (OEA-DS)	Ivashkevich, Ponomarenko, Manzhulo, Egoraeva, & Dyuizen, 2025
Male C57Bl/6J mice	12-week diet (HFD)	2.5 $mg^{-1}kg^{-1}day^{-1}$	8-week treatment	10/group	↓ lipid accumulation, ↓ inflammation, ↓ oxidative stress and fibrosis markers, ↑ insulin signalling, ↓ heart weight, ↓ cardiac damage markers (OEA)	Comella et al., 2024
Obese patients with NAFLD	Calorie-restricted diet	125 mg twice daily	12-week treatment	76 total (38/group)	↓ atherogenic indices, ↓ RDW (OEA)	Tutunchi, Naeini, et al., 2020
Overweight/obese patients	Obesity-related metabolic dysfunctions	125-600 $mg^{-1}kg^{-1}day^{-1}$	1–12-week treatment	10 RCTs	↓ fasting glycaemia, ↓ insulin levels and resistance, ↓ triglycerides, ↓ body weight, BMI, waist circumference, fat mass, ↑ total antioxidant capacity, ↓ oxidative stress (OEA)	Bahari et al., 2025
Obese patients	Obesity-related metabolic dysfunctions	125–600 $mg^{-1}day^{-1}$	1–12-week treatment	13 RCTs	↓ fasting glycaemia, ↓ triglycerides, ↓ waist circumference (OEA)	Eslahi et al., 2025
OEA effects on intestinal dysfunction and gut–brain–microbiota axis alterations						
Male C57BL/6J mice	12-week diet (HFD)	OEA-producing *Lactobacillus paracasei* + oleate (precursor)	8-week treatment	10/group	↓ body weight, ↓ metabolic dysfunction, ↑ gut barrier integrity, ↓ intestinal permeability, restoration of microbiota composition, improved gut–brain axis signalling (OEA)	Seguella et al., 2025
Male C57Bl/6J mice	18-week diet (HFD)	2.5 $mg^{-1}kg^{-1}day^{-1}$ (first 2 w) and then 3 $mg^{-1}kg^{-1}day^{-1}$ (next 2 w)	4-week treatment	7/group	↓ body weight, ↓ food intake, ↓ inflammation, modulation of eCBome, ↑ *Akkermansia muciniphila*, improved microbiota composition (OEA)	Cimmino et al., 2025
Obese patients	Ipocaloric diet	125 mg twice daily	8-week treatment	60 total (56 completed; 27 OEA/29 placebo)	↑ *Akkermansia muciniphila* abundance, ↓ energy intake, ↓ carbohydrate intake (OEA)	Payahoo, Khajebishak, Alivand, et al., 2019

Abbreviations: ↑: increase; ↓: decrease; ↔: no significant changes; BMI: body mass index; ER: endoplasmic reticulum; FA: fatty acid; HFD: high-fat diet; KO: knock-out; LDLR: low-density lipoprotein receptor; LFD: low-fat diet; NAFLD: non-alcoholic fatty liver disease; NRG4: neuregulin 4; OEA: oleoylethanolamide; OEA-DS: oleoylethanolamide-based dietary supplement; PBMCs: peripheral blood mononuclear cells; PCSK9: proprotein convertase subtilisin/kexin type 9; POEA: palmitoleoylethanolamide; PPAR: peroxisome proliferator-activated receptor; RCTs: randomized controlled trials; RDW: red cell distribution width; SREBP: sterol regulatory element-binding protein; STZ: streptozotocin; T2DM: type 2 diabetes mellitus.

body weight than other lipid congeners, supporting a degree of functional specificity within the NAE family (Tovar et al., 2021). Across experimental paradigms, reductions in body weight induced by OEA were closely associated with decreased energy intake rather than aversive or nonspecific behavioural effects. Systematic evaluation of the preclinical literature confirmed that suppression of food intake represents the primary driver of OEA-induced attenuation of body weight gain, with consistent effects observed across species, dietary paradigms and treatment regimens (Tutunchi, Saghafi-Asl, & Ostadrahimi, 2020).

Clinical evidence, although more limited, is congruent with preclinical observations (Payahoo, Khajebishak, & Ostadrahimi, 2019). Randomized controlled trials in overweight and obese individuals report that oral OEA supplementation is associated with reductions in body weight, body mass index and waist circumference, often accompanied by decreased appetite ratings and improved adherence to dietary interventions (Payahoo et al., 2018). Although the magnitude of weight loss remains modest, these findings support a translational relevance of OEA-mediated control of energy intake.

Collectively, these data identify OEA as an endogenous lipid-derived regulator with reproducible anti-obesity effects primarily driven by modulation of food intake. The consistency of this phenotype across species and metabolic contexts supports the positioning of OEA among physiologically grounded lipid-derived modulators of energy balance with potential relevance for obesity management, particularly in strategies aimed at complementing, rather than replacing, existing pharmacological approaches. The main preclinical and clinical evidence supporting the anti-obesity effects of OEA is summarized in Table 1.

4 | OEA AND METABOLIC COMORBIDITIES ASSOCIATED WITH OBESITY

4.1 | Metabolic homeostasis and insulin sensitivity

Beyond its well-established role in the control of feeding behaviour, OEA has emerged as a relevant modulator of metabolic homeostasis in experimental models of obesity (Bowen et al., 2017). Acute OEA administration does not consistently or directly alter circulating **glucose**, insulin or **glucagon** levels across rodent studies, and available evidence does not support a robust insulinotropic profile (Piomelli, 2013). Nevertheless, depending on dose, nutritional state and metabolic context, OEA can influence glucose handling through indirect mechanisms, and more reproducible metabolic benefits are generally reported following repeated administration, in parallel with changes in substrate utilization and lipid metabolism.

In preclinical settings, OEA modulated energy metabolism in rodent models of diet-induced obesity, thereby influencing pathways that are tightly linked to insulin responsiveness (Ivashkevich, Ponomarenko, Manzhulo, & Dyuizen, 2025). In the obese state, dysregulation of hepatic lipid handling and gluconeogenic activity represents a major driver of systemic metabolic imbalance (Ivashkevich, Ponomarenko, Manzhulo, & Dyuizen, 2025). In this context, OEA administration has been associated with reduced metabolic stress and improved substrate utilization (Ivashkevich, Ponomarenko, Manzhulo, & Dyuizen, 2025). Mechanistic evidence from high-fat diet-fed rats indicates that these effects involve, among others, PPAR-α–dependent hepatic pathways, including reduced lipid accumulation, enhanced fatty-acid oxidation and downregulation of key gluconeogenic enzymes, collectively reflecting improved hepatic metabolic flexibility (Ivashkevich, Ponomarenko, Manzhulo, & Dyuizen, 2025). Notably, additional signalling routes have also been implicated in selected models, supporting the view that OEA may affect hepatic glucose metabolism through multiple, context-dependent mechanisms (Ren et al., 2020; Tutunchi et al., 2019).

The relevance of PPAR-α–dependent mechanisms for the regulation of insulin responsiveness in obesity is further supported by experimental studies in which PPAR-α activity is selectively enhanced in peripheral tissues (Araki et al., 2018; Takahashi et al., 2017). In mice with diet-induced obesity, adipose tissue-specific overexpression of PPAR-α was associated with improved insulin responsiveness, as evidenced by insulin tolerance tests, and reduced insulin levels during oral glucose challenge (Araki et al., 2018; Takahashi et al., 2017). These changes occurred alongside decreased adipocyte hypertrophy, attenuation of obesity-associated inflammatory markers in white adipose tissue and marked alterations in lipid handling, including reduced levels of saturated fatty acids and arachidonic acids (Araki et al., 2018; Takahashi et al., 2017). Modulation of branched-chain amino acid metabolism was also observed, consistent with an overall improvement in metabolic efficiency in the obese state (Araki et al., 2018; Takahashi et al., 2017).

In line with these observations, pharmacological activation of PPAR-α using selective agonists has been shown to protect against diet-induced obesity and to improve systemic metabolic homeostasis in mice (Araki et al., 2018; Takahashi et al., 2017). Treatment with the PPAR-α agonist pemafibrate attenuated weight gain and improved lipid and energy metabolism in high-fat diet-fed animals, further supporting the contribution of sustained PPAR-α activation to the modulation of obesity-associated metabolic dysfunction (Araki et al., 2018; Takahashi et al., 2017).

Within this framework, chronic OEA treatment has also been reported to be associated with improved glucose handling in an experimental model of diet-induced obesity, as reflected by reduced fasting glycaemia and improved glucose tolerance, in parallel with attenuation of body weight gain and adiposity (Comella et al., 2024).

Importantly, when present, these changes are generally interpreted as secondary to improved metabolic efficiency, reduced lipotoxic stress and tissue-level reprogramming of substrate partitioning, rather than to direct modulation of insulin secretion.

Physiological evidence further supports a role for endogenous OEA signalling in the regulation of metabolic homeostasis. OEA is synthesized in the small intestine upon the intake of dietary oleic acid and has been proposed to act as a lipid-derived signal linking fat ingestion to postprandial metabolic responses (Fu et al., 2007; Piomelli, 2013). In experimental studies, endogenous OEA production has been

associated with the coordination of satiety signalling and peripheral metabolic responses, contributing to the maintenance of energy and glucose homeostasis primarily through lipid metabolic pathways rather than direct modulation of circulating glucose or insulin levels (Brown et al., 2017; Fu et al., 2007; Piomelli, 2013). In line with this view, broader analyses of endocannabinoid-like lipid mediators identify OEA as part of a nutrient-sensitive signalling network involved in metabolic flexibility and the fine regulation of insulin responsiveness (Rahman et al., 2021).

Translational evidence in humans, although still limited, is broadly consistent with these preclinical observations. In a randomized, double-blind, placebo-controlled trial conducted in obese but otherwise healthy individuals, oral supplementation with OEA (125 mg twice daily for 8 weeks) resulted in a significant reduction in circulating triglyceride levels, whereas fasting blood glucose remained unchanged and no major modifications in reported dietary habits or physical activity were observed (Ostadrahimi et al., 2024). Similarly, reductions in body weight, body mass index and waist circumference have been reported following OEA supplementation, together with increased expression of PPAR-α–related metabolic markers, supporting an improvement in metabolic efficiency rather than a direct modulation of glycaemic control (Payahoo et al., 2018).

Consistent with these findings, systematic evaluations of the available preclinical and clinical publications conclude that OEA treatment is associated with modest but reproducible improvements in metabolic parameters in overweight and obese conditions, particularly with respect to lipid handling and energy balance, whereas effects on glucose homeostasis appear limited and context-dependent (Tutunchi, Saghafi-Asl, & Ostadrahimi, 2020).

A recent systematic review and meta-analysis of randomized controlled trials similarly indicated that OEA supplementation was associated with context-dependent changes in parameters linked to insulin sensitivity, rather than with uniform effects on insulin secretion (Eslahi et al., 2025). Across clinical studies, OEA treatment was consistently associated with improvements in fasting glycaemia, triglyceride levels, waist circumference and inflammatory and oxidative stress markers, whereas effects on circulating insulin levels appeared variable and dependent on baseline metabolic status and study design (Eslahi et al., 2025). This pattern supports the view that OEA influences glucose handling and insulin responsiveness primarily through improvements in metabolic efficiency and tissue lipid utilization, rather than through direct insulinotropic actions (Eslahi et al., 2025).

Taken together, these data indicate that OEA contributes to the regulation of metabolic homeostasis in obesity primarily by modulating lipid metabolism, energy utilization and inflammatory tone in peripheral tissues, processes that are functionally linked to insulin sensitivity. Where improvements in glucose handling are observed, they most probably reflect indirect consequences of enhanced metabolic flexibility and reduced lipotoxic stress, rather than consistent, primary insulinotropic actions. This mode of action is consistent with the role of OEA as a nutrient-responsive lipid signal operating within a broader metabolic network coordinating energy balance and insulin responsiveness under obese conditions. The available preclinical and clinical evidence on the effects of OEA on metabolic homeostasis and insulin sensitivity is summarized in Table 1.

4.2 | Hepatic steatosis and metabolic-associated fatty liver disease (MAFLD)

Obesity is closely linked to hepatic steatosis and the broader spectrum of MAFLDs (Eslam et al., 2020). Excess adiposity and insulin resistance enhance the flux of free fatty acids to the liver, stimulate de novo lipogenesis, impair mitochondrial fatty acid oxidation and promote intrahepatic triglyceride accumulation (Samuel & Shulman, 2018). These alterations lead to hepatic steatosis, which represents the earliest and most prevalent manifestation of obesity-related liver disease (Fabbrini et al., 2010). In a substantial proportion of individuals, steatosis may progress towards inflammatory liver injury, oxidative and endoplasmic reticulum stress and fibrotic remodelling, thereby contributing to the development of more advanced liver dysfunction (Karin & Kim, 2025). Given the central role of the liver in systemic lipid and glucose metabolism, modulation of hepatic metabolic pathways represents a key therapeutic target in obesity-associated metabolic complications (Dukewich et al., 2025).

Within this framework, a growing body of evidence indicates that OEA exerts direct hepatoprotective actions in the context of obesity-associated hepatic steatosis and MAFLD, through coordinated effects on lipid metabolism, oxidative stress, endoplasmic reticulum stress and transcriptional regulation of metabolic pathways (Giudetti et al., 2021; Ivashkevich, Ponomarenko, Manzhulo, & Dyuizen, 2025; Lin et al., 2022; Romano et al., 2021; Tutunchi et al., 2019; Tutunchi, Ebrahimi-Mameghani, et al., 2023; Tutunchi, Naeini, et al., 2020; Tutunchi, Ostadrahimi, et al., 2020). Mechanistically, these effects are associated with suppression of de novo lipogenesis and triglyceride synthesis through transcriptional mechanisms involving sterol regulatory element-binding proteins and PPAR-dependent pathways (Romano et al., 2021), as demonstrated in rat models. In high-fat diet-fed rats, 2-week OEA treatment has additionally been shown to attenuate oxidative stress and endoplasmic reticulum stress, decreasing hepatic malondialdehyde and protein carbonylation, restoring antioxidant enzyme activities (superoxide dismutase, **catalase** and **glutathione peroxidase**) and improving markers of endoplasmic reticulum homeostasis (Giudetti et al., 2021).

Evidence from murine models further suggests that obesity may disrupt endogenous hepatic OEA signalling. Long-term exposure to a high-fat diet suppressed fasting-induced histamine release into portal circulation and the consequent histamine-dependent synthesis of OEA in the liver (Lin et al., 2022). Restoration of OEA signalling through exogenous administration reduced hepatic lipid accumulation, inflammatory responses and fibrosis in obese mice. Together, these findings highlight the relevance of impaired OEA production in the pathophysiology of obesity-associated liver disease (Lin et al., 2022).

More recent studies using dietary-induced obesity models further support a broad hepatoprotective profile of OEA. In mice fed a high-fat, high-cholesterol diet, supplementation with an OEA-based

formulation normalized serum cholesterol levels, reduced hepatic inflammation and apoptosis, increased expression of PPAR-α and genes involved in fatty acid oxidation (including *Acox1* and ***Cpt1a***) and improved markers of lipid and cholesterol handling, collectively indicating a coordinated improvement of MAFLD-related hepatic alterations (Ivashkevich, Ponomarenko, Manzhulo, Egoraeva, & Dyuizen, 2025).

Translational relevance is supported by several randomized controlled trials in obese patients with NAFLD. In these subjects, undergoing calorie-restricted diets, OEA supplementation for 12 weeks significantly improved metabolic and hepatic parameters, including reductions in serum triglycerides, alanine and aspartate aminotransferases and improvements in anthropometric indices (Tutunchi, Ostadrahimi, et al., 2020). At the molecular level, OEA increased the expression of PPAR-α and uncoupling proteins (**UCP1** and **UCP2**) in peripheral blood mononuclear cells, suggesting enhanced systemic fatty acid oxidation and energy dissipation (Tutunchi, Ostadrahimi, et al., 2020).

Additional clinical trials in obese patients with NAFLD reported that OEA supplementation improves atherogenic indices and lipid profiles when administered alongside dietary interventions, further supporting its beneficial impact on hepatic and metabolic risk factors (Tutunchi, Naeini, et al., 2020; Tutunchi, Zolrahim, et al., 2023). Moreover, OEA treatment has been associated with modulation of lipid metabolism-related gene expression and increased circulating levels of **neuregulin-4**, a hepatokine implicated in lipid homeostasis (Tutunchi, Ebrahimi-Mameghani, et al., 2023).

Taken together, current evidence supports a multifaceted hepato-metabolic action of OEA in obesity, characterized by modulation of lipid metabolism, activation of fatty acid oxidation pathways and attenuation of oxidative and endoplasmic reticulum stress, all direct effects, rather than secondary to reduced food intake.

The hepato-metabolic mechanisms through which OEA modulates lipid metabolism and protects against obesity-associated hepatic steatosis are schematically illustrated in Figure 2, whereas the available preclinical and clinical evidence on the effects of OEA on hepatic steatosis and MAFLD is summarized in Table 1. Overall, the convergence of robust preclinical mechanistic observations and early translational evidence positions OEA as a biologically plausible modulator of obesity-associated hepatic steatosis within the broader landscape of metabolic-targeted therapies.

4.3 | Cardiovascular dysfunction associated with obesity

Obesity is strongly associated with cardiac and vascular dysfunctions that substantially contribute to increased morbidity and mortality (Powell-Wiley et al., 2021). Beyond the haemodynamic burden imposed by excess body weight, obesity induces profound metabolic alterations that impair myocardial energy metabolism, promote ectopic lipid accumulation and alter vascular homeostasis, thereby predisposing to cardiometabolic remodelling and increased atherogenic risk (Powell-Wiley et al., 2021). Within this context, metabolic regulators that influence lipid handling, oxidative balance and tissue-specific energy utilization may critically influence cardiovascular outcomes in obese conditions (Khan et al., 2022).

Preclinical evidence supports a cardioprotective action of OEA in obesity-related cardiometabolic dysfunction (Comella et al., 2024; Ivashkevich, Ponomarenko, Manzhulo, Egoraeva, & Dyuizen, 2025). In murine models of diet-induced obesity, chronic supplementation with an OEA-based dietary formulation normalized circulating cholesterol levels and modulated key molecular determinants of atherogenesis, including down-regulation of the pro-atherogenic factor **PCSK9** and restoration of LDL receptor-related pathways (Ivashkevich, Ponomarenko, Manzhulo, Egoraeva, & Dyuizen, 2025). These effects were paralleled by a marked reduction in systemic and hepatic inflammation, oxidative stress and hepatocellular lipid accumulation, indicating that dietary supplementation of OEA exerts cardiometabolic protection primarily by targeting metabolic and inflammatory mechanisms that link obesity, dyslipidaemia and cardiovascular dysfunction (Ivashkevich, Ponomarenko, Manzhulo, Egoraeva, & Dyuizen, 2025).

Evidence of direct myocardial effects remains more limited. In high-fat diet–fed mice, OEA administration has been associated with reduced cardiac lipid accumulation, attenuation of oxidative stress and preservation of selected cardiac functional parameters. These findings suggest that modulation of myocardial lipid utilization may contribute to improved cardiac resilience under metabolic stress. However, detailed assessments of cardiac structure, long-term functional outcomes and dose–response relationships remain scarce (Comella et al., 2024).

Clinical data are preliminary and primarily focus on surrogate cardiometabolic risk markers (Tutunchi, Naeini, et al., 2020). In a randomized, placebo-controlled trial in obese patients with NAFLD, OEA supplementation (250 $mg \cdot day^{-1}$ for 12 weeks), in combination with caloric restriction, significantly improved several atherogenic lipid ratios, including those reflecting the balance between LDL-cholesterol and HDL-cholesterol (Tutunchi, Naeini, et al., 2020). These effects occurred without major changes in blood pressure, pointing to a selective effect on lipid-driven cardiovascular risk rather than on haemodynamic parameters (Tutunchi, Naeini, et al., 2020).

Meta-analyses of randomized controlled trials report significant reductions in fasting glucose, insulin levels, triglycerides and waist circumference following OEA administration, parameters that are known to contribute to myocardial metabolic stress and cardiometabolic burden (Bahari et al., 2025; Eslahi et al., 2025). In contrast, effects on total cholesterol and low-density lipoprotein-cholesterol appear less consistent across studies, underscoring a limited effect on classical lipid fractions (Bahari et al., 2025; Eslahi et al., 2025). Taken together, current evidence suggests that OEA influences cardiovascular risk in obesity predominantly through modulation of lipid metabolism, inflammatory status and systemic metabolic control, processes that critically influence myocardial and vascular vulnerability under obese conditions.

The cardiometabolic mechanisms through which OEA may influence cardiovascular risk in obesity are schematically illustrated in Figure 2, whereas the available evidence on its effects on obesity-

associated cardiovascular dysfunction is summarized in Table 1. Although preclinical data indicate potential benefits at the myocardial level, clinical evidence is limited to improvements in surrogate risk markers. At present, OEA should be regarded as a modulator of cardiometabolic determinants rather than as a direct cardioprotective agent. Further studies incorporating functional and imaging-based cardiovascular endpoints will be required to define its true effects on obesity-associated cardiovascular remodelling.

4.4 | Intestinal dysfunction and gut–brain–microbiota axis alterations

Obesity is increasingly recognized as a condition characterized by altered gut–brain communication and disruption of intestinal homeostasis, with relevant consequences for systemic metabolic regulation (Asadi et al., 2022). Impairments of epithelial barrier integrity, dysregulated nutrient sensing and gut microbiota dysbiosis contribute to defective signalling between the gastrointestinal tract, the CNS and peripheral metabolic organs. These alterations promote metabolic inflexibility and low-grade inflammation characteristic of obese states (Shen et al., 2025).

Within this framework, intestinal lipid-derived mediators, such as OEA, represent critical components of nutrient-responsive signalling networks linking luminal fat sensing to central and peripheral metabolic adaptation (DiPatrizio & Piomelli, 2015). Under physiological conditions, OEA is synthesized in the proximal small intestine in response to dietary fat intake and acts as a lipid sensor within the gut–brain axis (Schwartz et al., 2008). Beyond its established role in the control of feeding behaviour, OEA has been implicated in the modulation of epithelial integrity, immune-metabolic signalling and local lipid handling processes that contribute to intestinal homeostasis. Under physiological conditions, this system supports coordinated communication between the gastrointestinal tract, central feeding circuits and peripheral metabolic organs (De Filippo et al., 2023).

Accumulating experimental evidence indicates that obesity is associated with a disruption of endogenous intestinal OEA signalling (De Filippo et al., 2023). Diet-induced obesity impairs postprandial OEA mobilization in the proximal intestine, blunting the normal coupling between dietary lipid sensing and downstream appropriate metabolic and neuroendocrine responses (De Filippo et al., 2023). Alterations in gut microbiota composition and intestinal inflammatory tone further contribute to this dysfunction, positioning defective OEA signalling as a component of the broader dysregulation of the microbiota–gut–brain axis observed in obese states (De Filippo et al., 2023). Within this pathological context, the administration of exogenous OEA has been widely employed in preclinical studies and more recently explored in clinical settings, as a strategy to compensate for defective endogenous lipid-mediated signalling (De Filippo et al., 2023).

Preclinical studies suggest that restoration of OEA tone may partially counteract obesity-associated intestinal dysfunction (Cimmino et al., 2025; Igarashi et al., 2023; Payahoo, Khajebishak, Alivand, et al., 2019; Seguella et al., 2025; Vari et al., 2025). In high-fat diet-fed mice, administration of an OEA-producing strain of *Lactobacillus paracasei* improved epithelial barrier integrity, reduced intestinal permeability, normalized microbiota composition, alongside improvements in metabolic and behavioural alterations associated with obesity (Seguella et al., 2025). These findings support a functional interaction between microbiota-derived OEA and host metabolic regulation, although the relative contribution of bacterial versus host-derived OEA requires further clarification. Complementary experimental studies further indicate that OEA contributes to the preservation of intestinal structure and metabolic homeostasis under high-fat dietary conditions (Vari et al., 2025). Pharmacological modulation of endocannabinoid-like lipid signalling, including OEA, limits diet-induced alterations in epithelial integrity, intestinal permeability and metabolic signalling pathways, highlighting a protective role against obesity-associated intestinal dysfunction (Vari et al., 2025). Additional mechanistic insight is provided by studies showing that OEA interacts with the eCBome and influences mitochondrial bioenergetics, lipid signalling networks and gut microbiota composition in models of diet-induced obesity, collectively contributing to improved metabolic flexibility and energy homeostasis (Cimmino et al., 2025).

Emerging clinical evidence supports translational relevance, albeit indirectly. In randomized controlled trials conducted in obese individuals, OEA supplementation has been associated with increased relative abundance of *Akkermansia muciniphila*, a bacterial species linked to improved metabolic health and intestinal barrier function (Payahoo, Khajebishak, Alivand, et al., 2019). These microbiota changes were accompanied by modifications in dietary intake, suggesting that OEA supplementation may influence host-microbiota interactions and feeding-related behaviours in obese subjects. However, causal relationships between microbiota shifts and metabolic improvements remain to be established, and most studies rely on compositional rather than functional microbiome analyses.

At the molecular level, convergence between microbial metabolites and host lipid mediators may further influence gut–brain communication (Igarashi et al., 2023). Microbiota-derived metabolites can activate intestinal receptors involved in metabolic regulation, including GPR119, a recognized molecular target of OEA (Igarashi et al., 2023). Although direct causal links between microbiota-derived metabolites, OEA signalling and GPR119 activation remain to be fully established, available evidence supports the existence of overlapping signalling pathways through which intestinal lipid mediators and microbial products jointly modulate metabolic and neurobehavioural outcomes in obesity (Igarashi et al., 2023).

Taken together, available evidence indicates that OEA contributes to the modulation of gut–brain–microbiota interactions in obesity through effects on intestinal lipid sensing, barrier integrity and metabolic signalling.

The mechanisms through which OEA modulates intestinal homeostasis and microbiota–gut–brain communication are schematically illustrated in Figure 2, whereas the available evidence on its effects on intestinal dysfunction and alterations of the microbiota–gut–brain axis is summarized in Table 1. Although mechanistic links

remain incompletely defined, restoration of OEA signalling in obesogenic conditions may represent a biologically plausible strategy to improve intestinal metabolic communication. Further studies integrating microbiome function, host lipid mediator dynamics and neurobehavioural endpoints will be required to clarify the extent of OEA's role within the complex microbiota–gut–brain network.

5 | OEA IN THE TIME OF INCRETIN-BASED THERAPIES

OEA and incretin-based therapies regulate energy homeostasis through fundamentally distinct molecular targets, yet converge on partly overlapping physiological outcomes, including reduced energy intake and remodelling of systemic metabolic balance (Moiz et al., 2025). Although both systems ultimately influence satiety, metabolic efficiency and body weight regulation, they operate through divergent receptor architectures, signalling dynamics and regulatory hierarchies, reflecting distinct levels of metabolic control (Zheng et al., 2024).

Consistent with this framework, OEA-driven activation of PPAR-α promotes transcriptional programs that enhance fatty acid transport and mitochondrial β-oxidation, thereby supporting lipid utilization and metabolic flexibility (Tutunchi et al., 2019). Through this transcriptional reprogramming, OEA coordinates nutrient handling and energy balance in a manner that secondarily influences feeding behaviour. Its effects on appetite suppression seem to arise within a broader metabolic framework, rather than from direct, rapid receptor-mediated inhibition of hunger signals (Schwartz et al., 2008). In contrast, incretin receptor agonists act through high-affinity receptor activation that directly modulates glucose-dependent insulin secretion, suppress glucagon release, delay gastric emptying and exert potent anorectic effects through direct and indirect actions on central nervous system circuits controlling appetite, reward processing and satiety. These receptor-driven mechanisms translate into robust reductions in caloric intake and reproducible weight loss, with a magnitude and consistency that currently exceed those observed with OEA supplementation (Moiz et al., 2025). The temporal profile of incretin-based therapies is also distinct, characterized by rapid pharmacodynamic effects tightly linked to receptor occupancy (Sfairopoulos et al., 2018).

Despite these differences, a relevant point of interaction between OEA and incretin signalling emerges at the level of the gut. Although OEA's hypophagic actions are largely independent of classical incretin pathways, OEA can activate GPR119 in enteroendocrine L-cells, leading to stimulation of GLP-1 secretion in vitro and in vivo (Lauffer et al., 2009). This mechanism represents the main well-established contribution of GPR119 to OEA signalling and suggests that OEA may indirectly engage incretin pathways under specific physiological contexts, without relying on GLP-1 receptor activation as its primary mode of action (Lauffer et al., 2009).

Beyond indirect GLP-1 release, preclinical evidence also indicates that OEA can modulate GLP-1 receptor agonist signalling in a context-dependent manner (Brown et al., 2018). In diet-induced obese mice, combined administration of OEA and **exendin-4** (a long-acting GLP-1 receptor agonist) resulted in greater short-term weight loss, as compared to either compound alone, an effect attributed to parallel and partially additive actions on feeding behaviour and energy expenditure, rather than true pharmacological synergy (Brown et al., 2018). These findings suggest that OEA and GLP-1 receptor agonists operate on complementary metabolic axes: one primarily transcriptional and lipid-centred, the other receptor-driven and neuroendocrine (Brown et al., 2018).

Emerging translational observations indicate that the eCBome signalling may influence individual responsiveness to GLP-1 receptor agonists (Matias et al., 2024). Associations between circulating endocannabinoid-related molecules and variability in treatment outcomes raise the possibility that baseline lipid signalling states could shape incretin efficacy, although causal relationships remain to be established (Matias et al., 2024).

Taken together, current evidence supports a conceptual framework in which OEA and incretin-mimetics should not be viewed as competing interventions, but as complementary therapies acting at distinct regulatory tiers of energy homeostasis. GLP-1 agonists provide potent receptor-mediated control of appetite and glycaemia, whereas OEA modulates nutrient-responsive lipid-signalling and metabolic flexibility through transcriptional mechanisms. Understanding how these distinct signalling systems intersect may help refine future combination or sequential strategies aimed at improving metabolic health and long-term regulation of energy balance beyond weight loss alone.

6 | CONCLUSIONS AND FUTURE DIRECTIONS

The evidence reviewed here positions OEA as a biologically coherent lipid mediator linking intestinal nutrient sensing to the regulation of energy balance through coordinated peripheral and central mechanisms. By engaging PPAR-α–dependent metabolic pathways and recruiting neural circuits involved in both homeostatic and reward-related aspects of feeding, OEA operates as a modulator of metabolic flexibility rather than as a classical anorectic agent.

This integrative mode of action distinguishes OEA from current receptor-targeted anti-obesity therapies. Although incretin-based and multi-agonist drugs achieve robust weight loss through potent receptor-mediated effects, OEA appears to promote more physiologically aligned adaptations, influencing food intake, lipid metabolism, inflammatory tone and gut–brain communication within a broader regulatory framework. In this sense, OEA may contribute to restoring endogenous lipid-responsive signalling pathways that are disrupted in obesity, rather than simply overriding them pharmacologically.

From a translational perspective, this profile is both a strength and a limitation. On one hand, the endogenous origin of OEA and its coordinated metabolic effects suggest potential compatibility with long-term strategies aimed at improving metabolic flexibility and sustaining adaptive responses. On the other hand, the currently available

clinical evidence remains limited, with modest effects on body weight and insufficient data on long-term efficacy and clinically relevant outcomes. In addition, key aspects such as pharmacokinetics, brain exposure, optimal dosing strategies and identification of responder phenotypes remain to be fully elucidated.

Within the current therapeutic landscape, dominated by incretin-based and multi-target pharmacological approaches, OEA should therefore not be viewed as a competing intervention. Rather, its mechanism of action supports a complementary role, potentially targeting dimensions of obesity pathophysiology that are only partly addressed by receptor-driven therapies, including metabolic flexibility, lipid partitioning and reward-related feeding processes.

Future research should prioritize rigorous clinical validation, deeper mechanistic characterization and the development of rational combination strategies. Clarifying these aspects will be essential to determine whether modulation of OEA signalling can translate into meaningful and sustained clinical benefits in obesity and its associated comorbidities.

6.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY (http://www.guidetopharmacology.org) and are permanently archived in the Concise Guide to PHARMACOLOGY 2025/26 (Alexander, Cidlowski et al., 2025; Alexander, Davenport et al., 2025; Alexander, Fabbro et al., 2025; Alexander, Striessnig et al., 2025).

AUTHOR CONTRIBUTIONS

Marzia Friuli: Conceptualization (equal); investigation (equal); methodology (equal); writing—original draft (equal). **Alessia Campagna:** Investigation (equal); methodology (equal); writing—original draft (equal). **Barbara Eramo:** Investigation; methodology. **Christian Sepe:** Investigation (equal); methodology (equal). **Annarita Zuena:** resources; visualization; writing—review and editing. **Silvana Gaetani:** Conceptualization (equal); project administration (equal); supervision (equal); writing—review and editing (equal). **Adele Romano:** Conceptualization (equal); supervision (equal); writing—review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article because no new data were created or analysed in this study.

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