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Chapter 7

The Endocannabinoid-Like Derivative Oleoylethanolamide at the Gut–Brain Interface: A "Lipid Way" to Control Energy Intake and Body Weight

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Additional information is available at the end of the chapter

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Abstract

In the last three decades, we witnessed a concomitant major increase in lifespan and a worldwide increasing incidence of chronic diseases such as obesity and type 2 diabetes. Disruption of energy homeostasis and systemic inflammation appear as common traits of these epidemic human diseases. The conventional endocannabinoid (eCB) system encompasses two G-protein–coupled receptors (GPCRs), their endogenous ligands (anandamide and 2-AG), and the enzymes essential for eCB biosynthesis and hydrolytic inactivation. Nonetheless, the family of eCB-like derivatives is growing constantly including other *N*-acylethanolamines (NAEs) and 2-monoacylglycerols (2-MAGs) that do not bind canonical CB receptors rather other orphan G-protein–coupled receptors or peroxisome proliferator-activated nuclear receptors (PPARs). Here, we focus on the recent knowledge gathered on one such PPAR endocannabinoid ligand, oleoylethanolamide (OEA), from the identification of its synthesis in the small intestine to its anorexiant function with particular emphasis on our discovery of the main brain neurotransmitters system involved in its satiating effects.

Keywords: dietary fatty acids, histamine, PPARα, GPR119, oxytocin

Abbreviations:

2-arachidonoylglycerol (2-AG); 2-linoleoylglycerol (2-LG); 2-monoacylglycerols (2-MAGs); 2-oleoyl glycerol (2-OG); 2-palmitoyl glycerol (2-PG); α/β hydrolase domain 6 (ABHD6) and α/β hydrolase domain 12 (ABHD12); Alzheimer's disease (AD); amyotrophic lateral sclerosis (ALS); anandamide (AEA); calcium-dependent *N*-acyltransferase (Ca-NAT); carnitine palmi-

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toyltransferase-1 (CPT-1); docosahexaenoic acid (DHA); eicosapentaenoic acid (EPA); fatty acids (FAs); fatty acid amide hydrolase (FAAH); free fatty acids (FFAs); frontotemporal dementia (FTD); G-protein–coupled receptors (GPCRs); G-protein–coupled receptor 119 (GPR119); GIP (glucose-dependent insulinotropic peptide);glucagon-like peptide-1 (GLP-1); histidine decarboxylase (HDC); long-chain fatty acids (LCFAs); linoleoylethanolamide (LEA); lipoxygenase (LOX); monoacylglycerol lipase (MAGL); medium-chain fatty acids (MCFAs); monounsaturated fatty acids (MFAs); *N*-acylethanolamines (NAEs); *N*-acylethanolamine hydrolyzing acid amidase (NAAA); *N*-acyltransferase (NAT); *N*-arachidonoylethanolamine (AEA); *N*-acylphosphatidylethanolamine (NAPE); NAPE-hydrolyzing phospholipase D (NAPE-PLD); nucleus of the solitary tract (NST); *N*-oleoylethanolamide (OEA); obese (OB); obesity and type *2* diabetes (OBT2D); palmitoylethanolamide (PEA); paraventricular nucleus (PVN);peptide YY (PYY); peroxisome proliferator-activated receptors (PPARs); polyunsaturated fatty acids (PUFAs); pro-opiomelanocortin (POMC); protein kinase C (PKC); retinoid X receptor (RXR); saturated fatty acids (SFA); stearoylethanolamide (SEA); supraoptic nucleus (SON); transient receptor potential vanilloid type-1 (TRPV1); triacylglycerols (TAGs); type 2 diabetes (T2D); uncoupling protein 1 (Ucp1)

1. Introduction

Here the paradox, "although we are entering in the era of super-ageing population and the expected lifespan is increasing worldwide, overweight and obesity are growing global health threats in children and adult people." Western countries and their inhabitants largely contribute to the scenario. However, although in the United States 35% of the population is obese [1, 2], the rising economies are rapidly filling the gap [3, 4]. In this fatter world, obesity is the major health challenge that is accountable for multiple medical conditions. With a significant impact on morbidity and healthcare costs, obesity increases the risk of associated chronic diseases such as type 2 diabetes (T2D), stroke and heart diseases, hypertension and musculoskeletal disorders, and many types of cancer [5, 6]. In particular, the association between obesity and carcinogenesis as in colorectal, pancreatic, prostate, and breast cancer [7] is supported by the abnormal adipose tissue accumulation and systemic chronic inflammation that characterizes this condition. The concept of adiposopathy or "fat sickness" well translates the idea of adipocyte and adipose tissue dysfunction and chronic inflammation that is at the core of obesity-associated diseases.

Metabolic and neurological disorders have been traditionally viewed independently of one another and considered involving different etiologies and pathogenesis. However, obesity during midlife significantly increases the risk of dementias and Alzheimer's disease (AD) later in life [8, 9]. Thus, the detrimental accretion of "fat sickness" during aging and the problem of the defense of cognitive function are linked to unhealthy eating habits and changes in dietary composition of the current (Westernized) food environment. In the Western diet, not only complex carbohydrate and fibers, but also "good fat" (e.g., monounsaturated and polyunsaturated fats) are replaced in high proportions with easy affordable "bad fats" (e.g., saturated fats and vegetable oils) and refined sugars. The daily intake of saturated fat (SF) and simple

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sugars increases the risk of impairment of different cognitive functions and accelerate cognitive decline and AD incidence [10–13].

Unhealthy food can dysregulate the hypothalamic control of energy metabolism and affect hippocampal-dependent cognition, consequently every bit of knowledge about the mechanisms underlying the effects of nutrients on brain function becomes of primary importance.

In this chapter, we consider the role of endocannabinoid (eCB)-like derivatives as a particular class of lipids playing a key function in the control of energy intake, adipose tissue metabolism, management of body weight, and cognitive processing.

2. Obesity culprit of health life in Westernized societies: dietary fatty acids set the scenario for the lipid sensor oleoylethanolamide

Poor dietary habits (i.e., high-fat diet and refined carbohydrates) negatively contribute to excessive energy intake, energy accumulation, and consequent dyslipidemia and metabolic disorders such as obesity and type II diabetes (T2D). Poor dietary habits are considered a pathogenetic factor for the increasing incidence of cognitive dementias and primarily of AD [14, 15]. Deciphering the hidden symmetries underlying energy dysfunction in metabolic syndrome and cognitive decline is one of the main challenges of the next future. Despite the heterogeneity of its nutrients, the so-called Western diet is a dietary monopoly in which saturated fats and simple sugars (simple carbohydrates such as mono and disaccharides) are prevailing.

Indeed, the great convenience and affordability of energy-dense foods that are poor in dietary fiber and sucrose-rich are liable for the growing incidence of obesity. As a matter of fact, while dietary fatty acids (FAs) are essential substrates of oxidation and cell energy sources, the elevated concentration of circulating nonesterified fatty acids (NEFAs) or free fatty acids (FFAs) has been considered for a long time a marker of obesity and a pathogenetic factor in obesity, insulin resistance, and etiology of type 2 diabetes [16, 17]. Paradoxically, insulin-sensitive and highly trained athletes may show ectopic lipid deposition in skeletal muscle [18] proving that lipid accretion is not the only factor liable for deficient insulin signaling.

It is well known that the presence of double bonds determines the group to which FAs belong, from saturated fatty acids (SFA) lacking double bonds to one double-bond-containing monounsaturated fatty acids (MFAs), and polyunsaturated fatty acids (PUFAs) containing at least two double bonds. FFAs are signaling molecules capable to alter membrane fluidity, lipid raft, and therefore signal transduction [19]. Different G-protein–coupled receptors (GPCRs) have been identified to mediate FFA-dependent regulation of several metabolic functions as for instance by means of their anti- or proinflammatory effects [20]. The identification of several FFA receptors (FFARs) on the cell surface has allowed clarifying the existence of different classes of FFARs depending on the length of the carbon chain. Hence, FFA2 (GPR43) and FFA3 (GPR41) receptors are activated by short-chain fatty acids (SCFAs), and FFA1 (GPR40) and FFA4 (GPR120) receptors are activated by medium- and long-chain fatty acids (MCFAs and LCFAs, respectively) [21].

FFAs can also affect metabolism acting as ligands of nuclear hormone receptors such as the family of peroxisome proliferator-activated receptors (PPARs), which are ligand-activated transcription factors regulating key genes involved in lipid and nutrient homeostasis and glucose regulation [22]. PPARs are activated To different degrees by most of FFAs with long chain PUFAs showing great activation potency and *n*-3 PUFA eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as more effective than *n*-6 fatty acids. For this reason, PPARs are regarded as energy sensors, master regulators of energy homeostasis [23]. The PPARs family includes three isoforms, PPARα, PPARβ/δ, and PPARγ(NR1C1, NR1C2, and NR1C3, respectively), differing from one another because of their different tissue distribution, types of ligands, and physiological effects [23, 24]. Nevertheless, PPARs share a common mode of action, i.e., the formation of heterodimers with the nuclear receptor retinoid X receptor (RXR) followed by binding to specific DNA-response elements in target genes [23, 24]. Within this context, the involvement of PPAR-mediated signaling is critical in neural pathways that are essential for metabolic adaptivity to energy depletion, in which LCFAs represent the main energy source [25].

The eCBs are FA derivatives and from this point of view their high affinity for PPARs is not totally unexpected. The eCB signaling is terminated by specific lipases such as fatty acid amide hydrolase (FAAH) and *N*-acylethanolamine hydrolyzing acid amidase (NAAA) for anandamide (AEA) and monoacylglycerol lipase (MAGL), α/β hydrolase domain 6 (ABHD6) and domain 12 (ABHD12) for 2-arachidonyl glycerol (2-AG) [26, 27]. AEA and 2-AG are derivatives of *n*-6 PUFA arachidonic acid (AA) and are hydrolyzed into AA and ethanolamine or AA and glycerol, respectively [28, 29]. eCB also modulate functions that are independent of the stimulation of CB1 and CB2 receptors and transient receptor potential vanilloid type-1 (TRPV1) but are mediated by several "orphan" receptor candidates [30], among which the PPARγ that binds AEA, delta9-tetrahydrocannabinol, ajulemic acid, and 2-AG [31–34].

In this chapter, our focus is on the PPARα isoform that is highly expressed in tissues undergoing oxidative stress and is characterized by an elevated metabolic activity as in cardiac muscle, skeletal muscle, intestine, liver, and brown adipose tissue. PPARα activates the expression of genes involved in fatty acid transport and β-oxidation, thus lowering lipid levels [35]. It is known that PPARα can be activated by synthetic ligands such as the hypolipidemic fibrates (e.g., bezafibrate, clofibrate, and fenofibrate) that are part of the treatment of dyslipidemia and T2D [36]. In fact, the PPARα is considered a key fatty acids sensor that mediates lipid metabolism and the effects of FAs and FAs derivatives on gene expression. PPARα is involved in nutrient metabolism, including the metabolism of lipoproteins, glucose, cholesterol, and amino acids. Besides FAs, among the endogenous ligands of PPARα there are FA-like compounds encompassing acyl-CoAs, eicosanoids, eCBs, and eCB-like derivatives [37, 38].

A pioneeristic evidence of the role of PPARα in the effects of eCB derivatives is represented by the demonstration that fatty acid oxygenases, and in particular the lipoxygenase (LOX) metabolism of 2-AG can increase the transcriptional activity of PPARα [39]. Soon after these discoveries, the structural analog of AEA oleoylethanolamide (OEA) appeared on the scene. OEA belongs to a family of lipid mediators known as fatty acyl ethanolamides or *N*-acylethanolamines (NAEs) that are FA derivatives possessing an amide bond linking an ethanolamine

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to an acyl group [40–42]. Besides AEA (i.e., *N*-arachidonoylethanolamine) and OEA (*N*-oleoylethanolamide), the NAEs family also includes palmitoylethanolamide (PEA), linoleoylethanolamide (LEA), and stearoylethanolamide (SEA) [43].

Briefly, the complex (and best known) biosynthetic pathways of NAEs initiates from the common precursor N-acylphosphatidylethanolamine (NAPE) and consists in a two-step reaction leading first to NAPE formation by transferring the *sn*-1 fatty acid from a donor phospholipid to phosphatidylethanolamine by a calcium-dependent *N*-acyltransferase (Ca-NAT) [44, 45]. Then, in the second-step, NAPE is hydrolyzed to NAEs via the NAPE-hydrolyzing phospholipase D (NAPE-PLD) [45–47]. Interestingly, each NAE is produced by a corresponding NAPE and those having oleic acid (a monounsatured*n*-9 FA) at the amine position (*N*-oleoyl-PE) generate OEA [45].

Thus, dietary FA intake directly affects and modulates endogenous OEA levels according to nutrient (fat) ingestion or food deprivation-induced restriction of OEA synthesis [48]. Dietary FAs modulate food ingestion in the small intestine (luminal layer) via the increased generation of oleic acid-containing NAPEs, mobilization of NAPE-PLD as well as via the reduction of OEA-degrading FAAH activity [49].

OEA is a well-established anorexiant factor, a lipid-based satiety signal whose increase in the lumen of the small intestine induces a persistent and selective inhibition of food intake without known adverse reactions [42, 48–52]. Anorexiant agents can curb food ingestion via distinct mode of action such as the reduction of meal size ingested. Basically, in nonfood deprived animals, OEA administration increases inter-meal latency (decreasing meal frequency), whereas it decreases also meal size in food deprived animals [42, 52]. Recently, it has also been shown that OEA administration induces a clear leftward shifting (an index of early occurrence) in the temporal development of satiety and the premature onset of satiety [53, 54].

According to the current model of functioning, OEA-mediated satiety signal achieves its anorexiant effects via a multistep process that (upon OEA formation) initiates in the small intestinal lumen via the binding to PPARα, of which OEA is a high affinity agonist [49]. This is further corroborated by the failure of OEA-induced decrease of food intake in mice carrying the deletion of PPARα [49, 52]. OEA is a nanomolar agonist of the PPARα [55], and this nuclear receptor is responsible for most of the actions of OEA described so far. In addition, OEA is also a natural ligand of the G-protein–coupled receptor 119 (GPR119), which is not actually a true FFAs receptor, such as FFA1, FFA2, and FFA3 (see above), rather a novel target for FAs derivatives. The orphan GPR119 has been deorphanized by recognizing in the OEA one of its endogenous high affinity ligands [56]. Besides appetite control, GPR119 is also highly expressed in pancreatic β cells and involved in glucose-dependent insulin secretion as well as secretion of gastrointestinal incretin hormone and peptides (glucagon-like peptide-1 (GLP-1) [57] and GIP (glucose-dependent insulinotropic peptide) from enteroendocrine cells [57] (**Figure 1**). GLP-1 has, among other properties, insulinotropic effects inhibition of gastric emptying, reduction of appetite and promotion of satiety in humans [58] and rodents [59]. Likewise other FAs and FFAs receptors such as GPR120 [60] and FFA1 [61], GPR119 is a lipid sensing receptor [62] that is activated by oleic acid-containing lipids (e.g., *N*-oleoyl-dopamine) and regarded as a potential drug target for the treatment of T2D. In this view, the antidiabetic

potential of OEA is still unexplored. The ability of OEA to bind the GPR119 is already demonstrated not to be required for appetite suppression [63]; indeed, deletion of the GPR119 in mice does not prevent the anorexigenic effects of OEA [63, 64]. OEA binding to GPR119 induces secretion of GLP-1 from enteroendocrine L-cells of the ileum [65, 66] and therefore OEA is an *in- vivo* GLP-1 secretagogue. Finally, the TRPV1 must be included [67] especially for its relevance in the "entourage effect" and therefore in the ability to interfere with the eCB system [68].

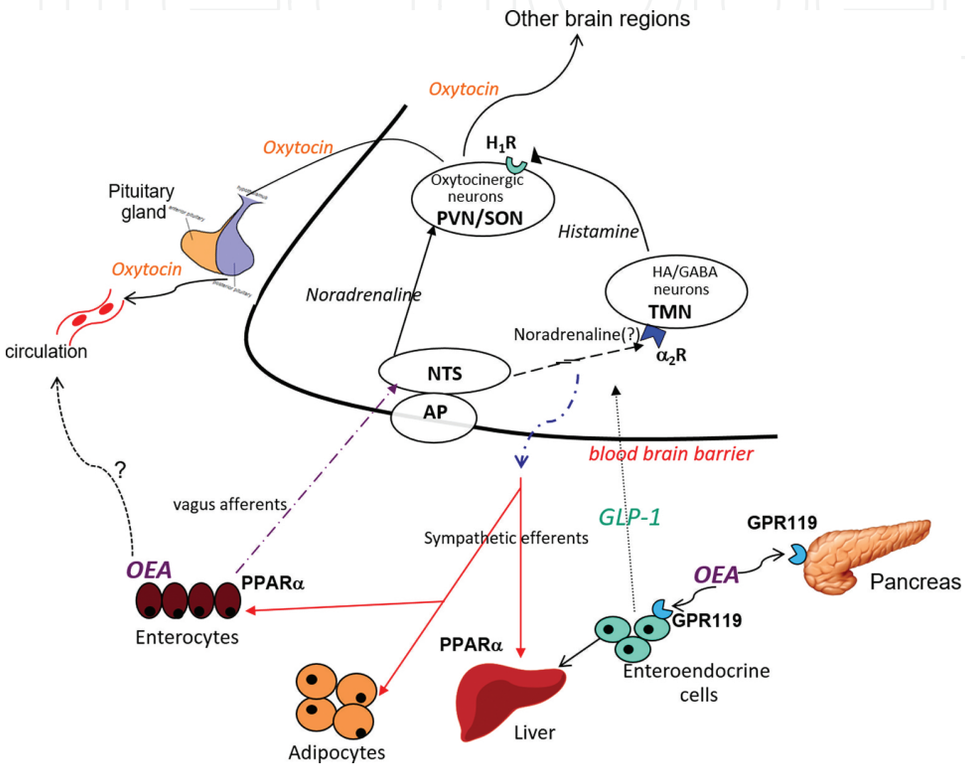


Figure 1. Schematic drawing illustrating the putative interactions between OEA, brain regions, and peripheral organs. OEA activates PPAR-α in the jejunum generating a signal that induces several transcriptional changes leading to increased fatty-acid catabolism, reduced blood lipid levels, and decreased appetite through the activation of brain centers. OEA signaling travels through vagal afferents to the nucleus of the solitary tract (NST). OEA may also reach the area postrema (AP; that lacks a tight blood brain barrier) through the circulation. From the NST noradrenergic afferents regulate oxytocin synthesis in the paraventricular (PVN) and supraoptic nucleus (SON) both directly and via the histaminergic tuberomammillary nucleus (TMN). Efferent neural pathways (for clarity only the sympathetic component is shown here) under the control of brain nuclei may alter energy expenditure and peripheral organs' function. OEA binds also to GPR119 that are expressed on pancreatic β-cells involved in glucose-dependent insulin secretion, as well as on enteroendocrine cells that secrete incretins such as glucagon-like peptide-1 (GLP-1).

3. Placing NAEs and 2-MAGs in the framework of the eCB system and lipid detection: satiety signals and fat sensors

Besides OEA, anorexiant effects have been ascribed also to other NAEs such as PEA and LEA [69]. This study elegantly demonstrates that high-fat feeding reduces intestinal NAEs levels in a dose-dependent fashion also supporting the previous idea that such reduction may also

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differently affect OEA, PEA and LEA depending on the type of fat (e.g., oleic Vs palmitic oil) ingested [70]. Another key point is the observation that orexigenic AEA and 2-AG levels in the jejunum are upregulated by the arachidonic acid-based diet [70] and that a diet reaching 38% of energy from fat reduces OEA, PEA, and LEA content, irrespective of dietary fat composition [70]. This finding demonstrates the critical importance of long-term exposure to high-fat-like Western diet, rich in saturated (e.g., palmitic acid) and *n*-6 PUFAs dietary fat. Indeed, protracted intake of high-fat diet has been hypothesized to increase the luminal content of FAs and 2-monoacylglycerol thus downregulating the NAT activity lowering the main anorectic NAEs OEA, PEA and LEA [46]. In turn, decreasing the endogenous levels of lipid signals conveying information on meal cessation and satiety removes the control brake on high-fat diet-induced hyperphagia.

The family of eCB-like derivatives includes the additional component of 2-monoacylglycerols (2-MAGs) among which 2-oleoyl glycerol (2-OG), 2-palmitoyl glycerol (2-PG), and 2-linoleoylglycerol (2-LG). Dietary triacylglycerols (TAGs) are the major lipids source for the stimulation of intestinal incretin hormones release. TAG hydrolysis by pancreas lipase produces FAs (two molecules) and 2-MAG (one molecule), with the portion of 2-MAG not degraded contributing to the total levels of 2-MAGs of the intestinal lumen after dietary fat intake [71, 72].

Although we have previously described the high affinity of OEA for GPR119, it is presently not clear the extent to which the low endogenous levels of this lipid-derived signal in the gastrointestinal cells can activate for instance GLP-1 release. Moreover, contrary to the cycles of feeding deprivation and refeeding [49] that produces opposite changes in OEA levels as function of NAPE-PLD activity, prolonged dietary fat intake can reduce intestinal NAEs levels. By contrast, direct effects of dietary fat on incretin secretion (plasma GLP-1 and GIP) have been shown to occur upon 2-OG administration in (fasting) humans volunteers [73]. More recently, it has been demonstrated that the GPR119 activation induced by 2-OG can explain the olive oil-elicited secretion of GLP-1 and peptide YY (PYY) [74]. Similarly, meal rich either in palmitic or linoleic acids will produce TAG deposit in adipose tissue mostly as 2-PG and 2-LG, respectively [75].

This opens a scenario where NAEs, and in particular OEA and 2-MAGs, can play together a concerted (though slightly different) action in fat sensing, lipid detection, and regulation of dietary fat ingestion via satiety signaling. Assuming GPR119 as a fat sensor [62], the high binding potency of full agonists such as OEA [56] is not sufficient to predict higher stimulatory effects on incretin secretion. Although 2-MAGs bind GPR119 less potently than OEA [73] their elevated intestinal levels will increase the probability of GLP-1 activation, especially for 2-OG. Moreover, GLP-1 stimulation is higher upon synthesis of 2-OG than 2-PG, further confirming how much healthier the olive oil-based diet (i.e., Mediterranean diet) can be in comparison with the saturated fat-rich (e.g., palmitic acid) Western diet. An increase of the intestinal levels of 2-MAGs has been described as one key factor underlying the insulin sensitizer effects and antiadipogenic activity of probiotic (*Akkermansia muciniphila*) treatment in high-fat-fed mice [76]. One hypothesis suggests that prolonged high-fat diet intake may downregulate the activity of the NAPE-synthetizing enzyme NAT, thus reducing NAEs levels via a still unknown

2-MAGs-dependent mechanism [46]. In our opinion, this supports the potential *dichotomous role of* 2-MAGs (mainly 2-OG) and NAEs (mainly OEA) that might function as fat sensors and satiety signaling, respectively.

Despite the important knowledge accumulated regarding the hypothalamic mechanisms underlying the control of energy homeostasis and the distinct populations of neurons responsible for appetite regulation [77], very little is known about the central pathways responsible for translating the peripheral information of nutritional status and in orchestrating neural adaptive responses. For instance, we know that different protein kinase C (PKC) isoforms (PKC-δ, PKC-ε, and PKC-θ) are required as dietary fat-associated (e.g., LCFA-CoA) signal transduction pathways and are involved in the development of insulin resistance [78]. In the following sections, we further examine the notion of brain–gut interface, where the OEA signaling originates, the role of OEA in energy homeostasis, and the discovery of the main brain anorexigenic neural pathways engaged by OEA.

4. The notion of brain–gut interface

Fatty acid components are the primary source of calories and constituents of cells and cell membrane-derived modulators such as eCBs and prostanoids. Evolution has endowed our species and other mammals of chemical sensors and neuronal machineries to monitor fat intake and direct foraging behavior to the optimization of fat-rich food collection and consumption. Therefore, a constant updating of the nutritional status and energy expenditure is required for the adequate behavioral responses and homeostatic adjustments. This network links not only peripheral intestinal functions via the production of a number of bioactive molecules with hypothalamic satiety and hunger centers, but also with brain areas devoted to emotional responses and cognitive processes. In modern days, though, fat rich food has lost its survival salience, as it is easily and often inexpensively available to a large part of the population in Western cultures. In fact, a fatty diet has become one of the major causes of obesity, one of today's most blatantly visible – yet most neglected – public health problems. The World Health Organization coined the term "globesity" [3] to pinpoint the escalating global epidemic of overweight and obesity, paradoxically coexisting with undernutrition and malnutrition.

How this "gut–brain axis" network works has only partially been elucidated, however some of the pathways, transmitters, and hormones involved are beginning to be mapped and discovered.

Sensing for dietary fat, begins in the mouth where taste bud cells of the lingual epithelium are activated and transmit an initial set of signals to the nucleus of the solitary tract (NST) in the brain stem [79, 80], and then to brain regions devoted to controlling satiety (e.g., hypothalamic paraventricular, tuberomamillary, arcuate nuclei) as well as to centers that coordinate reward related responses such as the nucleus accumbens [80, 81]. Taken together, all these observations suggest that mammals at least may indeed have a "taste" for fatty food. In the intestine, upon activation by lipids, specialized chemosensory cells release hormones, peptides, lipid-derived mediators that relay signals to the brain via hormonal or neuronal pathways [82, 83]. Among

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the membrane sensors expressed by these specialized neurons in the oral and intestinal epithelium are the CD36 proteins [79, 84], the G-protein–coupled receptors GPR40 and GPR120 [85]. A decade ago it was discovered that OEA and a subset of structurally similar FAEs are key components of the molecular machinery responsible for monitoring fat intake in the small intestine [48]. Fatty acid ethanolamides provide afferent signals from the digestive tract that travel mostly via vagal afferents [48] to the NST in the brain stem, and activate hypothalamic brain centers that promote satiety, therefore controlling eating behavior (**Figure 1**). It appears then, that the NST serves as a relay station where gustatory information carried by autonomic cephalic nerves, and postingestive information via the vagus nerve converge, filtering out pleasurable sensations (the cephalic phase that assigns rewarding value to food) and metabolic responses (reviewed in [80]).

The concept of brain lipid sensing is not new and is related to the problem of brain detection of body's nutritional status. In addition to fat sensing hypothalamic nuclei, midbrain, and hindbrain circuitry can detect glucose levels (glucose sensing neurons), as in pro-opiomelanocortin (POMC) neurons of high-fat-fed mice that developed insensitivity to glucose load and impaired glucose-elicited ATP production [86]. Glucose and lipid sensing are the two main brain systems for nutrients detection corresponding to insulin and fatty acids signaling acting to preserve energy homeostasis. Moreover, insulin and fat sensing may act either cooperatively or independently of each other to inhibit glucose production and appetite, respectively. The brain lipid sensing system relies on long-chain fatty acids (LCFAs), as lipid signals and oleic acid infusion within the brain inhibits hepatic glucose production, food intake and elicits satiety [87, 88]. In the neurons LCFAs are esterified to LCFA-CoA by acyl-CoA synthetase. In turn, the entry of LCFA-CoA into mitochondria for β-oxidation is regulated by carnitine palmitoyltransferase-1 (CPT-1). The experimental inhibition of hypothalamic CPT-1 increases LCFA-CoA neuronal levels and this event is able to reduce glucose production and to promote premature satiety occurrence [88, 89]. These studies provide evidence that lipid sensing through the gut–brain axis links together different macromolecules involved in nutrients sensing and is critical for glucose homeostasis and appetite control. These reports also indicate that in parallel with the duodenum, LCFA-CoA accumulation is a key event for the inhibition of energy intake and glucose production. Yet again, in case of prolonged intake of high-fat diet, LCFA-CoA fails to accumulate and oleic acid does not reduce hepatic glucose production [90, 91], possibly because of the increase in hypothalamic CPT-1 activity. Remarkably, besides gut nutrient sensing (e.g., intestinal lipid metabolism and cholecystokinin signaling), the brain is able to detect afferent nutrients and peripheral nutritional status to regulate whole-body glucose metabolism and energy homeostasis [86, 92–94].

Efferent neural pathways, i.e., the autonomic nervous system and the hypothalamic-pituitary adrenal axis, under the regulation of the brain may alter energy expenditure and intestinal function [95]. One such pathway originates in the NST toward the digestive tract facilitating fat digestion and absorption (**Figure 1**). Another example of central control of peripheral functions is provided by the influence exerted by the hypothalamic histaminergic neurons, one of the key brain systems regulating eating behavior [96, 97] on peripheral homeostatic responses. Preclinical studies showed that the administration of histamine or of an agonist of

the histamine H_1 receptor in the ventricle or the hypothalamic paraventricular nucleus, where activation of these receptors induces satiety, increases mRNA expression levels of uncoupling protein 1 (Ucp1), a marker of energy expenditure, in brown adipose tissue and increases the electrophysiological activity of sympathetic nerves that innervate it [98, 99]. Also, the central administration of histamine augments the lipolytic response in white adipose tissue, whereas pretreatment with a beta adrenergic receptor antagonist blocks the histamine-induced response, suggesting that the effect is mediated by sympathetic nerves that innervate the white adipose tissue [100]. Furthermore, it has been recently proposed [101] that neuronal histamine by activating H_1 receptors downregulates hepatic gluconeogenic gene expression. Interestingly, several of these effects are shared by gut-derived OEA. Another efferent pathway was demonstrated by direct intracerebroventricular infusion of palmitic acid that reduced insulin-mediated suppression of hepatic insulin production. Furthermore, palmitic acid-enriched diet activates PKC-θ in the arcuate nucleus and impairs insulin and leptin signaling [102]. This study elegantly demonstrates the role of PKC-θ activation as one of the pathogenetic mechanisms involved in the genesis of insulin resistance during prolonged high-fat diet intake.

The fascinating aspects of this complex interplay between the intestinal and the central nervous system is that bioactive molecules generated in the digestive tract signal to the brain not only the nutritional status, but may affect also cognitive and emotional responses. As a matter of fact, diet containing balanced PUFAs has become the object of intense research in relation to cognitive aging and neurodegenerative diseases. In this scenario the potential role of gut microbiota in influencing brain function, behavior, in the development of the central nervous system and mental health has recently attracted the attention of neuroscientists and psychiatrists [103–105]. The relevance of the gut–brain axis in health and disease is becoming manifest as preclinical and clinical studies are providing new evidence. In a recent report [106], metabolic changes incorporating fluctuations in weight, insulin resistance, and cholesterol concentrations in several neurodegenerative disorders, such as amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) have been observed. The authors raise the intriguing possibility of a dysregulated homeostatic balance between peripheral and central signals as partly accountable for the different phenotypes of ALS and FTD patients. In other words, the authors' hypothesis is that neurodegenerative processes affecting brain regions necessary for metabolic regulation concur to the onset of the observed metabolic changes. The gut and the brain, then, use a plethora of signals to communicate, to monitor and integrate gut functions as well as to link emotional and cognitive centers of the brain with peripheral intestinal activity.

It is clear then, that gaining insight into this bidirectional communication network on the one hand poses truly great challenges to the scientific community, on the other it is indispensable to understand the potential for targeting modifiable risk factors in disease development and progression.

5. OEA and the control of energy homeostasis

As previously mentioned, OEA signaling is a biosensor for dietary fat that is generated from oleic acid and conveys a message that translates into a state of satiety characterized by

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prolonged inter-meal intervals and reduced feeding frequency [48]. OEA is also found in several other organs such as liver, adipose tissue, and brain and its levels can be affected by short-term feeding of nutrients reminiscent of human diets [70]. However, protein and carbohydrates do not stimulate OEA mobilization [52]. OEA biological effects are not limited to moderating food intake, but include stimulation of fat utilization in adipocytes and hepatocytes [107], of fatty acid absorption in the jejunum [108], of incretins secretion from the ileum [65]. The effects of OEA on peripheral organs will be dealt in this paragraph, whereas a separate section will be dedicated to the central actions of OEA.

Digestion of complex dietary lipids in the small-intestinal lumen releases free oleic acid, which is internalized presumably by the transporter CD36 on the luminal membrane of enterocytes in the jejunum [109]. Oleic acid is then directed either toward the formation of chylomicrons or toward the production of OEA through the NAT/NAPE-PLD pathway [109]. Palmitic acid and linoleic acid as well are taken up presumably by the same transporter CD36 into the enterocyte and incorporated into NAPE increasing intestinal levels of PEA and LEA, respectively [46]. Surprisingly, diet-induced obese rats and mice, or rats fed with a diet high in NAEs precursors' content for over 1 week, had decreased intestinal (not hepatic, nor central) levels of the three NAEs [110] independently of the type of dietary fatty acid fed to the rats [70]. This effect is reversible as switching the high-fat diet back to low-fat chow restores the intestinal levels of OEA, LEA, and PEA to normal within 3 days [111]. Therefore, it appears that excessive fat intake may render the mechanism dysfunctional, suggesting that suppressing the satiating effects of gut-derived OEA with a diet rich in fat might contribute to overeating [112].

Food intake and food deprivation also regulate the content of OEA in the jejunum as OEA levels decrease during food deprivation and increase upon refeeding through a concerted regulation of OEA biosynthesis and degradation [49]. However, other visceral organs, such as the liver and pancreas, respond to food deprivation with an increase rather than a decrease in OEA levels, whereas plasma OEA concentrations is modestly affected, implying that nutrients regulate OEA mobilization in a tissue-specific manner [49]. The mechanisms by which nutrients and food deprivation regulate OEA levels in the liver and pancreas is not known, and the biological significance of such a control is not fully explained. Nonetheless, OEA appears to have potential therapeutic effects in liver dysfunctions. A direct comparison of the effect of OEA and fenofibrate (a PPARα agonist used in clinical practice to regulate plasma lipid disorders) on a rat model of nonalcoholic fatty liver disease showed an improved protective effect of OEA and a safer profile with respect to the fibrate [113]. OEA reduces liver triacylglycerol levels and enhances fatty acid oxidation in hepatocytes and these effects are maintained in mice fed a high-fat diet [107]. The authors suggest that changes in lipid metabolism induced by PPARα activation contribute to the weight-reducing action of OEA in obese mice. Furthermore, in rats OEA regulates several hepatic enzymes including liver fatty acid binding protein (responsible for uptake and intracellular trafficking of fatty acids) [113] and the thermogenic uncoupling protein-1 [114]. Also, subchronic administration of a recently synthesized analog of OEA that binds PPARα receptors, elaidyl-sulfamide, was found to lower plasma cholesterol and improve the hepatic function of obese rats [115]. Clearly, these

observations warrant further investigation to fully understand the potential therapeutic of OEA and congeners in hepatic function.

The available data on the effects of OEA on the adipose tissue suggest that OEA may work in concert with the sympathetic system to control fat metabolism. The incubation of dissociated rat and mouse adipocytes with OEA increased the release of nonesterified fatty acids and glycerol into the extracellular medium in a dose-dependent manner [107]. Of note, a significant fatty acid mobilization occurred also *in vivo* after systemic administration of OEA to lean rats. Conversely, OEA did not change the plasma levels of glucose, insulin, or glucagon, but markedly increased the transcription of several adipose-tissue genes involved in lipid transport, including CD36 and fatty acid-binding protein [107]. More recently it was reported that administration of OEA caused a significant fat mass reduction and enhanced energy expenditure in rats [114].

One of the first studies in humans showed the potential role of OEA as a regulator of adipose tissue metabolism in obesity and type II diabetes [116]. The study evaluated the levels of endocannabinoids such as AEA, 2-AG, OEA and PEA in the subcutaneous adipose tissue of subjects with both obesity and type II diabetes (OBT2D) and nondiabetic obese (OB) vs normal subjects. All participants in the study showed similar adiposity and whole-body insulin resistance and lower plasma leptin levels when compared with normal controls. However, the levels of OEA, PEA, 2-AG, and AEA were all altered only in OBT2D, but not in OB as compared with normal subjects [116]. The authors suggest that such alterations might contribute to a redistribution of fat accumulation in the subcutaneous adipose tissue relative to visceral adipose tissue and to metabolic dysfunctions that, along with impaired insulin release and sensitivity, are typical of OBT2D patients [116].

6. From gut to the brain: OEA signaling engages the anorexigenic neural pathways

The extensive body of preclinical literature presented so far provides undisputable evidence that OEA functions as a homeostatic signal that regulates metabolic functions, and causes a long-lasting inhibition of food intake in rats, mice, and humans as well [48, 55, 117, 118].

OEA produces its anorexic effects through a mechanism mediated by the vagus nerve, as the hypophagic effect is prevented after vagotomy or reversible blockade of the NST a brain stem area that receives vagal inputs, and it is ineffective when infused directly in the cerebral ventricles [48]. A recent study, though, challenged this suggestion as it reported that in rats that received a subdiaphragmatic vagotomy, OEA maintained its hypophagic effect [119]. Clearly, these inconsistencies require further elucidations. In addition to the vagus nerve, a descending sympathetic pathway originating in the rostral ventrolateral medulla that sends noradrenergic projections to the intestine and other visceral organs, contributes to OEA signaling. Surgical disconnection of this pathway impairs the ability of intraduodenal fat infusions to reduce food intake and inhibits the food-induced OEA synthesis in the jejunum [120].

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The central neurotransmitter systems recruited by peripheral OEA to inhibit food intake is beginning to be unraveled. Exogenous administration of OEA increases transcription of the early gene c-Fos, a marker of neuronal activation, in the NST [48], it increases c-Fos mRNA and protein expression in oxytocin-immunoreactive neurons in the paraventricular (PVN) and supraoptic nucleus (SON) [42, 53] in the histaminergic tuberomammillary nucleus [53] and in the area postrema [121], a circumventricular organ that lacks a functional blood brain barrier (**Figure 1**). This latter observation suggests a direct action of OEA in the brain stem by reaching the area postrema from the blood stream [42].

The activation of PVN and SON is paralleled by increased oxytocin mRNA levels, increased peptide neurosecretion, and elevated circulating oxytocin levels [42, 53] (**Figure 1**).In addition, pharmacological blockade of central oxytocin receptors abolishes the hypophagic effects of OEA [42], implying that release of oxytocin in the hypothalamus and/or other brain regions is an obligatory effector of OEA-induced satiety. A noradrenergic pathway from the NST to the hypothalamus seems to mediate OEA effects on feeding behavior and on hypothalamic oxytocin increase, as demonstrated in rats with chemical lesions of hindbrain noradrenergic neurons [122]. Accordingly, in rats, peripheral administration of OEA increases noradrenaline concentrations in the hypothalamus [123]. Recently, we reported that OEA requires the integrity of the central histaminergic system to fully exert its hypophagic effect [53]. Brain histamine has long been known as a mediator of satiety through activation of hypothalamic histamine H_1 receptors [95–97]. In our study [53] we report that mice deficient of the histamine synthesizing enzyme histidine decarboxylase ($HDC^{-/-}$ mice), or pharmacologically deprived of releasable brain histamine did not respond to the hypophagic effect of exogenously administered OEA as normal mice did. We also found that OEA increased c-Fos protein expression in oxytocin neurons of the PVN of wild type, but not $HDC^{-/-}$ mice, suggesting that oxytocin rich nuclei are the likely brain region where histaminergic and OEA indirect signaling converge (**Figure 1**). In this context, it is important to note that OEA does not induce conditioned taste aversion in rats and does not produce behaviors that are indicative of a state of fear or anxiety as it does not change plasma corticosterone levels [124]. Hence, we may exclude that OEA hypophagic actions are attributable to stress or malaise. In fact, the exogenous subchronic oral administration of OEA in rats was shown to have an antidepressant-like action, an effect that is attributed to OEA-induced changes in cerebral noradrenaline and serotonin contents [125].

Despite no data are available indicating that OEA may subserve a neuromodulatory role in the brain, it has been reported that PPARα activity modulates the firing rate of dopaminergic neurons in the rat midbrain through a fast effect on nicotinic receptors [126]. These observations are suggestive of a role of OEA in the modulation of reward and hedonic, nonhomeostatic functions related to the salience of food-related stimuli.

It is well established that stress hormones activated by emotional arousal enhance memories associated with emotional events [127]. Hormonal and neural signaling elicited by feeding as well enhance the consolidation of recent experiences [128]. In this elegant work, the authors used two distinct experimental paradigms in rats to test consolidation of aversive and spatial memories, namely the inhibitory avoidance and the Morris water maze, and found that

systemic administration of OEA after training strongly improved the retention of these tasks. The memory-enhancing signal generated by OEA apparently activates the brain **via** the noradrenergic pathway that generates from NST and provides innervation of the basolateral amygdala, being this a pathway crucially implicated in the consolidation of recent emotional memories [129]. It is conceivable, then, that OEA mobilized in the gut after a fat-rich meal initiates an integrated response that prompts enhanced encoding of information about the spatial and emotional context in which the meal was consumed [130]. Synthetic PPARα agonists and inhibitor of FAAHs as well seem to ameliorate memory acquisition in a passive avoidance task in rats [131].

7. Conclusions

The evidence accumulated over the past years strongly support the notion that OEA mediates nutrient- and lipid-specific satiety, fatty acids absorption in enterocytes, lipolysis in adipose tissue, liver and skeletal myocytes, and thermogenic responses [48, 107, 108, 114]. Furthermore, we recently established that the eCB-derivative OEA engages the brain histaminergic [53] and oxytocinergic [42, 53] system to induce satiety and suppression of food intake (**Figure 1**). This study uncovers previously unidentified neural signaling mechanisms involved in the anorectic action of OEA and offers new perspectives for the development of more effective and safer pharmacotherapies to treat obesity and ameliorate the profile of centrally acting drugs [53].

OEA is an ethanolamide of long-chain unsaturated FAs that appears to fulfill most of the criteria used to classify the antiobesity medications, among which safety is of primary importance. Moreover, OEA is an anorexigenic factor that can curb energy intake, stimulate sympathetic activity, and control body weight. Thus, the possibility to investigate the role of OEA in obese patients might not be speculative anymore. A meal rich in oleic acid increases OEA plasma levels in healthy volunteers also reducing the total energy intake 3 hours after oleic acid ingestion [118]. In a recent study [132] on obese patients, it was found that plasma OEA levels positively correlated with body mass index (BMI) whereas an inverse correlation was observed between obesity andbrain areas activity (e.g., insula) associated with reward-signaling. Chronic consumption of "obesogenic" high-fat food can dampen dopamine-mediated signaling of reward and disrupt the relationship between palatable food-associated hedonic eating and neural correlates of reward processing [133–135]. The negative correlation between insular activity and OEA plasma levels in obese subjects raises the possibility that OEA may be involved in the suppression of food-associated liking reaction and that obesity might disturb this function. OEA synthesis is disrupted after prolonged high-fat intake but OEA administration can restore striatal dopamine release and lipid signaling in the gut and increase the hedonic value of less caloric food [136]. Collectively, these data broaden the potential of OEA as dietary fat-derived satiety signal involved in homeostatic feeding as well as in the regulation of hedonic eating.

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References

[1] Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999–2008. JAMA. 2010;303:235–241. DOI: 10.1001/jama.2009.2014

[2] Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. JAMA. 2014;311:806–814. DOI: 10.1001/jama.2014.732

[3] Prentice AM. The emerging epidemic of obesity in developing countries. Int J Epidemiol. 2006;35:93–99. DOI: 10.1093/ije/dyi272

[4] Arnold M, Pandeya N, Byrnes G, Renehan AG, Stevens GA, Ezzati M, et al. Global burden of cancer attributable to high body-mass index in 2012: a population-based study. Lancet Oncol. 2014;16:36–46. DOI: 10.1016/S1470-2045(14)71123-4

[5] Haslam DW, James WPT. Obesity. Lancet. 2005;366:1197–1209. DOI: 10.1016/S0140-6736(05)67483-1

[6] Wiseman M. The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Proc Nutr Soc. 2008;67:253–256.DOI: 10.1017/S002966510800712X

[7] Renehan AG, Tyson M, Egger M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet.2008;371:569–578. DOI: 10.1016/S0140-6736(08)60269-X

[8] Tolppanen AM, Ngandu T, Kåreholt I, Laatikainen T, Rusanen M, Soininen H, et al. Midlife and late-life body mass index and late-life dementia: results from a prospective population-based cohort. J Alzheimer's Dis. 2014;38:201–209. DOI: 10.3233/JAD-130698

[9] Emmerzaal TL, Kiliaan AJ, Gustafson DR. 2003–2013: A decade of body mass index, Alzheimer's disease, and dementia. J Alzheimer's Dis. 2015; 43:739–755. DOI: 10.3233/JAD-141086

[10] Winocur G, Greenwood CE. Studies of the effects of high fat diets on cognitive function in a rat model. Neurobiol Aging. 2005;26:46–49. DOI: 10.1016/j.neurobiolaging.2005.09.003

[11] Beydoun MA, Beydoun HA, Wang Y. Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis. Obes Rev. 2008;9:204–218. DOI: 10.1111/j.1467-789X.2008.00473.x

[12] De Felice FG, Lourenco M V. Brain metabolic stress and neuroinflammation at the basis of cognitive impairment in Alzheimer's disease. Front Aging Neurosci. 2015;7:94. DOI: 10.3389/fnagi.2015.00094

[13] Prickett C, Brennan L, Stolwyk R. Examining the relationship between obesity and cognitive function: a systematic literature review. Obes Res Clin Pract. 2015;9:93–113. DOI: 10.1016/j.orcp.2014.05.001

[14] Hsu TM, Kanoski SE. Blood-brain barrier disruption: mechanistic links between Western diet consumption and dementia. Front Aging Neurosci. 2014;9:88. DOI: 10.3389/fnagi.2014.00088

[15] Pasinetti GM, Eberstein JA. Metabolic syndrome and the role of dietary lifestyles in Alzheimer's disease. J Neurochem. 2008;106:1503–1514. DOI: 10.1111/j.1471-4159.2008.05454.x

[16] Boden G. Free fatty acids-the link between obesity and insulin resistance. Endocr Pract. 2001;7:44–51. DOI: 10.4158/EP.7.1.44

[17] Karpe F, Dickmann JR, Frayn KN. Fatty acids, obesity, and insulin resistance: Time for a reevaluation. Diabetes. 2011;60:2441–2449. DOI: 10.2337/db11-0425

[18] Goodpaster BH, He J, Watkins S, Kelley DE. Skeletal muscle lipid content and insulin resistance: Evidence for a paradox in endurance-trained athletes. J Clin Endocrinol Metab. 2001;86:5755–5761. http://dx.doi.org/10.1210/jcem.86.12.8075

[19] Ma DWL, Seo J, Switzer KC, Fan YY, McMurray DN, Lupton JR, et al. n-3 PUFA and membrane microdomains: a new frontier in bioactive lipid research. J Nutr Biochem. 2004;15:700–706. DOI: 10.1016/j.jnutbio.2004.08.002

[20] Ichimura A, Hasegawa S, Kasubuchi M, Kimura I. Free fatty acid receptors as therapeutic targets for the treatment of diabetes. Front Pharmacol. 2014;5:236. DOI: 10.3389/fphar.2014.00236

[21] Brown AJ, Goldsworthy SM, Barnes AA, Eilert MM, Tcheang L, Daniels D, et al. The orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. J Biol Chem. 2003;278:11312–11319. DOI: 10.1074/jbc.M211609200

[22] Evans RM. PPARs and the complex journey to obesity. Keio J Med.2004;53:53–58. http://doi.org/10.2302/kjm.53.53

[23] Berger J, Moller DE. The mechanisms of action of PPARs. Annu Rev Med. 2002;53:409–435. DOI: 10.1146/annurev.med.53.082901.104018

[24] Schmitz G, Ecker J. The opposing effects of n-3 and n-6 fatty acids. Prog Lipid Res. 2008;47:147–155. DOI: 10.1016/j.plipres.2007.12.004

[25] Nakamura MT, Yudell BE, Loor JJ. Regulation of energy metabolism by long-chain fatty acids. Prog Lipid Res. 2014;53:124–144. DOI: 10.1016/j.plipres.2013.12.001

[26] Sun Y, Alexander SP, Garle MJ, Gibson CL, Hewitt K, Murphy SP, et al. Cannabinoid activation of PPAR alpha; a novel neuroprotective mechanism. Br J Pharmacol. 2007;152:734–743. DOI: 10.1038/sj.bjp.0707478

[27] Blankman JL, Cravatt BF. Chemical probes of endocannabinoid metabolism. Pharmacol Rev. 2013;65:849–871. DOI: 10.1124/pr.112.006387

[28] Freund TF, Katona I, Piomelli D. Role of endogenous cannabinoids in synaptic signaling. Physiol Rev. 2003;83:1017–1066. DOI: 10.1152/physrev.00004.2003

[29] Turcotte C, Chouinard F, Lefebvre JS, Flamand N. Regulation of inflammation by cannabinoids, the endocannabinoids 2-arachidonoyl-glycerol and arachidonoyl-ethanolamide, and their metabolites. J Leukoc Biol. 2015;97:1049–1070. DOI: 10.1189/jlb.3RU0115-021R

[30] Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, Devane WA, et al. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol Rev. 2002;54:161–202. DOI: 10.1124/pr.54.2.161

[31] Liu J, Li H, Burstein SH, Zurier RB, Chen JD. Activation and binding of peroxisome proliferator-activated receptor gamma by synthetic cannabinoid ajulemic acid. Mol Pharmacol. 2003;63:983–992. DOI: 10.1124/mol.63.5.983

[32] O'Sullivan SE, Tarling EJ, Bennett AJ, Kendall DA, Randall MD. Novel time-dependent vascular actions of Delta9-tetrahydrocannabinol mediated by peroxisome proliferator-activated receptor gamma. Biochem Biophys Res Commun. 2005;337:824–831. DOI: 10.1016/j.bbrc.2005.09.121

[33] Bouaboula M, Hilairet S, Marchand J, Fajas L, Le Fur G, Casellas P. Anandamide induced PPAR gamma transcriptional activation and 3T3-L1 preadipocyte differentiation. Eur J Pharmacol. 2005;517:174–181. DOI: 10.1016/j.ejphar.2005.05.032

[34] Rockwell CE, Snider NT, Thompson JT, Vanden Heuvel JP, Kaminski NE. Interleukin-2 suppression by 2-arachidonyl glycerol is mediated through peroxisome proliferator-activated receptor gamma independently of cannabinoid receptors 1 and 2. Mol Pharmacol. 2006;70:101–111. DOI: 10.1124/mol.105.019117

[35] Dreyer C, Keller H, Mahfoudi A, Laudet V, Krey G, Wahli W. Positive regulation of the peroxisomal beta-oxidation pathway by fatty acids through activation of peroxisome proliferator-activated receptors (PPAR). Biol Cell. 1993;77:67–76. DOI: 10.1016/S0248-4900(05)80176-5

[36] Rakhshandehroo M, Knoch B, Müller M, Kersten S. Peroxisome proliferator-activated receptor alpha target genes. PPAR Res. vol. 2010, Article ID 612089, 20 pages, 2010. DOI: 10.1155/2010/612089

[37] Kliewer SA, Sundseth SS, Jones SA, Brown PJ, Wisely GB, Koble CS, et al. Fatty acids and eicosanoids regulate gene expression through direct interactions with peroxisome proliferator-activated receptors alpha and gamma. Proc Natl Acad Sci U S A. 1997;94:4318–4323

[38] Blankman JL, Simon GM, Cravatt BF. A comprehensive profile of brain enzymes that hydrolyze the endocannabinoid 2-arachidonoylglycerol. Chem Biol. 2007;14:1347–1356. DOI: 10.1016/j.chembiol.2007.11.006

[39] Kozak KR, Gupta RA, Moody JS, Ji C, Boeglin WE, Dubois RN, et al. 15-Lipoxygenase metabolism of 2-arachidonylglycerol: generation of a peroxisome proliferator-activated receptor α agonist. J Biol Chem. 2002;277:23278–23286. DOI: 10.1074/jbc.M201084200

[40] Schmid HHO, Berdyshev EV. Cannabinoid receptor-inactive N-acylethanolamines and other fatty acid amides: metabolism and function. Prostaglandins Leukot Essent Fat Acids. 2002;66:363–376. DOI: 10.1054/plef.2001.0348

[41] Romano A, Karimian Azari E, Tempesta B, Mansouri A, Micioni Di Bonaventura M V., Ramachandran D, et al. High dietary fat intake influences the activation of specific hindbrain and hypothalamic nuclei by the satiety factor oleoylethanolamide. Physiol Behav. 2014;136:55–62. DOI: 10.1016/j.physbeh.2014.04.039

[42] Gaetani S, Fu J, Cassano T, Dipasquale P, Romano A, Righetti L, et al. The fat-induced satiety factor oleoylethanolamide suppresses feeding through central release of oxytocin. J Neurosci. 2010;30:8096–8101. DOI: 10.1523/JNEUROSCI.0036-10.2010

[43] Hansen HS. Palmitoylethanolamide and other anandamide congeners. Proposed role in the diseased brain. Exp Neurol. 2010;224:48–55. DOI: 10.1016/j.expneurol.2010.03.022

[44] Hansen HS, Moesgaard B, Hansen HH, Petersen G. N-acylethanolamines and precursor phospholipids -– relation to cell injury. Chem Phys Lipids. 2000;108:135–150. DOI: 10.1016/S0009-3084(00)00192-4

[45] Ueda N, Tsuboi K, Uyama T. Enzymological studies on the biosynthesis of N-acylethanolamines. Biochim Biophys Acta. 2010;1801:1274–1285. DOI: 10.1016/j.bbalip.2010.08.010

[46] Hansen HS. Role of anorectic N-acylethanolamines in intestinal physiology and satiety control with respect to dietary fat. Pharmacol Res. 2014;86:18–25. DOI: 10.1016/j.phrs.2014.03.006

[47] Okamoto Y, Morishita J, Tsuboi K, Tonai T, Ueda N. Molecular Characterization of a phospholipase D generating anandamide and its congeners. J Biol Chem. 2004;279:5298–5305. DOI: 10.1074/jbc.M306642200

[48] Rodríguez de Fonseca F, Navarro M, Gómez R, Escuredo L, Nava F, Fu J, et al. An anorexic lipid mediator regulated by feeding. Nature. 2001;414:209–212. DOI: 10.1038/35102582

[49] Fu J, Astarita G, Gaetani S, Kim J, Cravatt BF, Mackie K, et al. Food intake regulates oleoylethanolamide formation and degradation in the proximal small intestine. J Biol Chem. 2007;282:1518–1528. DOI: 10.1074/jbc.M607809200

[50] Oveisi F, Gaetani S, Eng KTP, Piomelli D. Oleoylethanolamide inhibits food intake in free-feeding rats after oral administration. Pharmacol Res. 2004;49:461–466. DOI: 10.1016/j.phrs.2003.12.006

[51] Nielsen MJ, Petersen G, Astrup A, Hansen HS. Food intake is inhibited by oral oleoylethanolamide. J Lipid Res. 2004;45:1027–1029. DOI: 10.1194/jlr.C300008-JLR200

[52] Schwartz GJ, Fu J, Astarita G, Li X, Gaetani S, Campolongo P, et al. The lipid messenger OEA links dietary fat intake to satiety. Cell Metab. 2008;8:281–288. DOI: 10.1016/j.cmet.2008.08.005

[53] Provensi G, Coccurello R, Umehara H, Munari L, Giacovazzo G, Galeotti N, et al. Satiety factor oleoylethanolamide recruits the brain histaminergic system to inhibit food intake. Proc Natl Acad Sci U S A. 2014;111:11527–11532. DOI: 10.1073/pnas.1322016111

[54] Romano A, Coccurello R, Giacovazzo G, Bedse G, Moles A, Gaetani S. Oleoylethanolamide: a novel potential pharmacological alternative to cannabinoid antagonists for the control of appetite. Biomed Res Int. 2014;2014:203425. DOI: 10.1155/2014/203425

[55] Fu J, Gaetani S, Oveisi F, Lo Verme J, Serrano A, Rodriguez De Fonseca F, et al. Oleoylethanolamide regulates feeding and body weight through activation of the nuclear receptor PPAR-alpha. Nature. 2003;425:90–93. DOI: 10.1038/nature01921

[56] Overton HA, Babbs AJ, Doel SM, Fyfe MCT, Gardner LS, Griffin G, et al. Deorphanization of a G protein-coupled receptor for oleoylethanolamide and its use in the

discovery of small-molecule hypophagic agents. Cell Metab. 2006;3:167–175. DOI: 10.1016/j.cmet.2006.02.004

[57] Flock G, Holland D, Seino Y, Drucker DJ. GPR119 regulates murine glucose homeostasis through incretin receptor-dependent and independent mechanisms. Endocrinology. 2011;152:374–383. DOI: 10.1210/en.2010-1047

[58] Verdich C, Flint A, Gutzwiller JP, Näslund E, Beglinger C, Hellström PM, et al. A meta-analysis of the effect of glucagon-like peptide-1 (7–36) amide on Ad Libitum energy intake in humans. J Clin Endocrinol Metab. 2001;86:4382–4389. DOI: http://dx.doi.org/10.1210/jcem.86.9.7877

[59] Tang-Christensen M, Larsen PJ, Göke R, Fink-Jensen A, Jessop DS, Møller M, et al. Central administration of GLP-1-(7–36) amide inhibits food and water intake in rats. Am J Physiol. 1996;271:R848–R856

[60] Hirasawa A, Tsumaya K, Awaji T, Katsuma S, Adachi T, Yamada M, et al. Free fatty acids regulate gut incretin glucagon-like peptide-1 secretion through GPR120. Nat Med. 2005;11:90–94. DOI: 10.1038/nm1168

[61] Edfalk S, Steneberg P, Edlund H. Gpr40 is expressed in enteroendocrine cells and mediates free fatty acid stimulation of incretin secretion. Diabetes. 2008;57:2280–2287. DOI: 10.2337/db08-0307

[62] Hansen HS, Rosenkilde MM, Holst JJ, Schwartz TW. GPR119 as a fat sensor. Trends Pharmacol Sci. 2012;33:374–381. DOI: 10.1016/j.tips.2012.03.014

[63] Lan H, Vassileva G, Corona A, Liu L, Baker H, Golovko A, et al. GPR119 is required for physiological regulation of glucagon-like peptide-1 secretion but not for metabolic homeostasis. J Endocrinol. 2009;201:219–230. DOI: 10.1677/JOE-08-0453

[64] Lo Verme J, Gaetani S, Fu J, Oveisi F, Burton K, Piomelli D. Regulation of food intake by oleoylethanolamide. Cell Mol Life Sci. 2005;62:708–716. DOI: 10.1007/s00018-004-4494-0

[65] Lauffer LM, Iakoubov R, Brubaker PL. GPR119 is essential for oleoylethanolamide-induced glucagon-like peptide-1 secretion from the intestinal enteroendocrine L-cell. Diabetes. 2009;58:1058–1066. DOI: 10.2337/db08-1237

[66] Chu Z-L, Carroll C, Chen R, Alfonso J, Gutierrez V, He H, et al. N-Oleoyldopamine enhances glucose homeostasis through the activation of GPR119. Mol Endocrinol. 2010;24:161–170. DOI: 10.1210/me.2009-0239

[67] Ahern GP. Activation of TRPV1 by the satiety factor oleoylethanolamide. J Biol Chem. 2003;278:30429–30434. DOI: 10.1074/jbc.M305051200

[68] Ho W-S V, Barrett DA, Randall MD. "Entourage" effects of N-palmitoylethanolamide and N-oleoylethanolamide on vasorelaxation to anandamide occur through TRPV1 receptors. Br J Pharmacol. 2008;155:837–846. DOI: 10.1038/bjp.2008.324

[69] Diep TA, Madsen AN, Holst B, Kristiansen MM, Wellner N, Hansen SH, et al. Dietary fat decreases intestinal levels of the anorectic lipids through a fat sensor. FASEB J. 2011;25:765–774. DOI: 10.1096/fj.10-166595

[70] Artmann A, Petersen G, Hellgren LI, Boberg J, Skonberg C, Nellemann C, et al. Influence of dietary fatty acids on endocannabinoid and N-acylethanolamine levels in rat brain, liver and small intestine. Biochim Biophys Acta. 2008;1781:200–212. DOI: 10.1016/j.bbalip.2008.01.006

[71] Mu H, Høy CE. The digestion of dietary triacylglycerols. Prog Lipid Res. 2004; 43:105–133. DOI: 10.1016/S0163-7827(03)00050-X

[72] Mu H, Porsgaard T. The metabolism of structured triacylglycerols. Prog Lipid Res. 2005;44:430–448. DOI: 10.1016/j.plipres.2005.09.002

[73] Hansen KB, Rosenkilde MM, Knop FK, Wellner N, Diep TA, Rehfeld JF, et al. 2-Oleoyl glycerol is a GPR119 agonist and signals GLP-1 release in humans. J Clin Endocrinol Metab. 2011;96:e1409–1417. DOI: 10.1210/jc.2011-0647

[74] Mandøe MJ, Hansen KB, Hartmann B, Rehfeld JF, Holst JJ, Hansen HS. The 2-monoacylglycerol moiety of dietary fat appears to be responsible for the fat-induced release of GLP-1 in humans1. Am J Clin Nutr. 2015;102:548–55. DOI: 10.3945/ajcn.115.106799

[75] Perona JS, Portillo MP, Teresa Macarulla M, Tueros AI, Ruiz-Gutiérrez V. Influence of different dietary fats on triacylglycerol deposition in rat adipose tissue. Br J Nutr. 2000;84:765–74. DOI: 10.1017/S0007114500002130

[76] Everard A, Belzer C, Geurts L, Ouwerkerk JP, Druart C, Bindels LB, et al. Cross-talk between *Akkermansiamuciniph*ila and intestinal epithelium controls diet-induced obesity. Proc Natl Acad Sci U S A. 2013;110:9066–9071. DOI: 10.1073/pnas.1219451110/-/DCSupplemental

[77] Coll AP, Yeo GSH. The hypothalamus and metabolism: integrating signals to control energy and glucose homeostasis. Curr Opin Pharmacol. 2013;13:970–976. DOI: 10.1016/j.coph.2013.09.010

[78] Turban S, Hajduch E. Protein kinase C isoforms: mediators of reactive lipid metabolites in the development of insulin resistance. FEBS Lett. 2011;585:269–274. DOI: 10.1016/j.febslet.2010.12.022

[79] Gaillard D, Laugerette F, Darcel N, El-Yassimi A, Passilly-Degrace P, Hichami A, et al. The gustatory pathway is involved in CD36-mediated orosensory perception of long-chain fatty acids in the mouse. FASEB J. 2008;22:1458–1468. DOI: 10.1096/fj.07-8415com

[80] Gaillard D, Passilly-Degrace P, Besnard P. Molecular mechanisms of fat preference and overeating. Ann NY Acad Sci. 2008;1141:163–175. DOI: 10.1196/annals

[81] Liang N-C, Hajnal A, Norgren R. Sham feeding corn oil increases accumbens dopamine in the rat. Am J Physiol Regul Integr Comp Physiol. 2006;291:R1236–R1239. DOI: 10.1196/annals.1441.028

[82] DiPatrizio N V., Piomelli D. Intestinal lipid-derived signals that sense dietary fat. J Clin Invest. 2015;125:891–898. DOI: 10.1172/JCI76302

[83] Côté CD, Zadeh-Tahmasebi M, Rasmussen BA, Duca FA, Lam TKT. Hormonal signaling in the gut. J Biol Chem. 2014;289:11642–11649. DOI: 10.1074/jbc.O114.556068

[84] Laugerette F, Passilly-Degrace P, Patris B, Niot I, Febbraio M, Montmayeur JP, et al. CD36 involvement in orosensory detection of dietary lipids, spontaneous fat preference, and digestive secretions. J Clin Invest. 2005;115:3177–3184. DOI: 10.1172/JCI25299

[85] Cartoni C, Yasumatsu K, Ohkuri T, Shigemura N, Yoshida R, Godinot N, et al. Taste preference for fatty acids is mediated by GPR40 and GPR120. J Neurosci. 2010;30:8376–8382. DOI: 10.1523/JNEUROSCI.0496-10.2010

[86] Parton LE, Ye CP, Coppari R, Enriori PJ, Choi B, Zhang C-Y, et al. Glucose sensing by POMC neurons regulates glucose homeostasis and is impaired in obesity. Nature. 2007;449:228–232. DOI: 10.1038/nature06098

[87] Obici S, Feng Z, Morgan K, Stein D, Karkanias G, Rossetti L. Central administration of oleic acid inhibits glucose production and food intake. Diabetes. 2002;51:271–275. DOI: 10.2337/diabetes.51.2.271

[88] Coccurello R, Caprioli A, Bellantuono S, D'Amato FR, Conti R, Giannessi F, et al. Effects of the increase in neuronal fatty acids availability on food intake and satiety in mice. Psychopharmacology. 2010;210:85–95. DOI: 10.1007/s00213-010-1820-0

[89] Obici S, Feng Z, Arduini A, Conti R, Rossetti L. Inhibition of hypothalamic carnitine palmitoyltransferase-1 decreases food intake and glucose production. Nat Med. 2003;9:756–761. DOI: 10.1038/nm873

[90] Morgan K, Obici S, Rossetti L. Hypothalamic responses to long-chain fatty acids are nutritionally regulated. J Biol Chem. 2004;279:31139–31148. DOI: 10.1074/jbc.M400458200

[91] Pocai A, Lam TKT, Obici S, Gutierrez-Juarez R, Muse ED, Arduini A, et al. Restoration of hypothalamic lipid sensing normalizes energy and glucose homeostasis in overfed rats. J Clin Invest. 2006;116:1081–1091. DOI: 10.1172/JCI26640

[92] Lam TKT, Gutierrez-Juarez R, Pocai A, Rossetti L. Regulation of blood glucose by hypothalamic pyruvate metabolism. Science. 2005;309:943–947. DOI: 10.1126/science.1112085

[93] Plum L, Belgardt BF, Brüning JC. Central insulin action in energy and glucose homeostasis. J Clin Invest. 2006;116:1761–1766. DOI: 10.1172/JCI29063

[94] Chari M, Lam CKL, Wang PYT, Lam TKT. Activation of central lactate metabolism lowers glucose production in uncontrolled diabetes and diet-induced insulin resistance. Diabetes. 2008;57:836–840. DOI: 10.2337/db07-1464

[95] Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol. 2015;28:203–209. DOI: 10.1172/JCI76304

[96] Passani MB, Blandina P, Torrealba F. The histamine H3 receptor and eating behavior. J Pharmacol Exp Ther. 2011;336:24–29. DOI: 10.1124/jpet.110.171306

[97] Provensi G, Blandina P, Passani MB. The histaminergic system as a target for the prevention of obesity and metabolic syndrome. Neuropharmacology. 2015; http://dx.doi.org/10.1016/j.neuropharm.2015.07.002

[98] Masaki T, Chiba S, Yasuda T, Noguchi H, Kakuma T, Watanabe T, et al. Involvement of hypothalamic histamine H1 receptor in the regulation of feeding rhythm and obesity. Diabetes. 2004;53:2250–2260. DOI: 10.2337/diabetes.53.9.2250

[99] Yasuda T, Masaki T, Sakata T, Yoshimatsu H. Hypothalamic neuronal histamine regulates sympathetic nerve activity and expression of uncoupling protein 1 mRNA in brown adipose tissue in rats. Neuroscience. 2004;125:535–540. DOI: 10.2337/diabetes.53.9.2250

[100] Masaki T, Yoshimatsu H, Chiba S, Watanabe T, Sakata T. Central infusion of histamine reduces fat accumulation and upregulates UCP family in leptin-resistant obese mice. Diabetes. 2001;50:376–384. DOI: 10.2337/diabetes.50.2.376

[101] Kimura K, Nakamura Y, Inaba Y, Matsumoto M, Kido Y, Asahara SI, et al. Histidine augments the suppression of hepatic glucose production by central insulin action. Diabetes. 2013;62:2266–2277. DOI: 10.2337/db12-1701

[102] Benoit SC, Kemp CJ, Elias CF, Abplanalp W, Herman JP, Migrenne S, et al. Palmitic acid mediates hypothalamic insulin resistance by altering PKC-theta subcellular localization in rodents. J Clin Invest. 2009;119:2577–2589. DOI: 10.1172/JCI36714

[103] Foster JA, Lyte M, Meyer E, Cryan JF. Gut microbiota and brain function: an evolving field in neuroscience. Int J Neuropsychopharmacol. 2015;pyv114. DOI: 10.1093/ijnp/pyv114

[104] Dinan TG, Cryan JF. Regulation of the stress response by the gut microbiota: implications for psychoneuroendocrinology. Psychoneuroendocrinology. 2012;37:1369–1378. DOI: 10.1016/j.psyneuen.2012.03.007

[105] Erny D, Hrabě de Angelis AL, Jaitin D, Wieghofer P, Staszewski O, David E, et al. Host microbiota constantly control maturation and function of microglia in the CNS. Nat Neurosci. 2015;18:965–977. DOI: 10.1038/nn.4030

[106] Ahmed RM, Irish M, Piguet O, Halliday GM, Ittner LM, Farooqi S, et al. Amyotrophic lateral sclerosis and frontotemporal dementia: distinct and overlapping changes in

eating behaviour and metabolism. Lancet Neurol. 2016;15:332–342. DOI: 10.1016/S1474-4422(15)00380-4

[107] Guzmán M, Lo Verme J, Fu J, Oveisi F, Blázquez C, Piomelli D. Oleoylethanolamide stimulates lipolysis by activating the nuclear receptor peroxisome proliferator-activated receptor◎alpha (PPAR-alpha). J Biol Chem. 2004;279:27849–27854. DOI: 10.1074/jbc.M404087200

[108] Yang Y, Chen M, Georgeson KE, Harmon CM. Mechanism of oleoylethanolamide on fatty acid uptake in small intestine after food intake and body weight reduction. Am J Physiol Regul Integr Comp Physiol. 2007;292:R235–R241. DOI: 10.1152/ajpregu.00270.2006

[109] Piomelli D.A fatty gut feeling. Trends Endocrinol Metab.2013;24:332–341. DOI: 10.1016/j.tem.2013.03.001

[110] Igarashi M, DiPatrizio N V, Narayanaswami V, Piomelli D. Feeding-induced oleoylethanolamide mobilization is disrupted in the gut of diet-induced obese rodents. Biochim Biophys Acta. 2015;1851:1218–1226. DOI: 10.1016/j.bbalip.2015.05.006

[111] Diep TA, Madsen AN, Krogh-Hansen S, Al-Shahwani M, Al-Sabagh L, Holst B, et al. Dietary non-esterified oleic acid decreases the jejunal levels of anorectic N-acylethanolamines. PLoS One. 2014;9: e100365DOI: 10.1371/journal.pone.0100365

[112] Hansen HS, Diep TA. N-acylethanolamines, anandamide and food intake. Biochem Pharmacol. 2009;78:553–560. DOI: 10.1016/j.bcp.2009.04.024

[113] Li L, Li L, Chen L, Lin X, Xu Y, Ren J, et al. Effect of oleoylethanolamide on diet-induced nonalcoholic fatty liver in rats. J Pharmacol Sci. 2015;127:244–250. DOI: 10.1016/j.jphs.2014.12.001

[114] Suárez J, Rivera P, Arrabal S, Crespillo A, Serrano A, Baixeras E, et al. Oleoylethanolamide enhances β-adrenergic-mediated thermogenesis and white-to-brown adipocyte phenotype in epididymal white adipose tissue in rat. Dis Model Mech. 2014;7:129–141. DOI: 10.1242/dmm.013110

[115] Decara JM, Romero-Cuevas M, Rivera P, Macias-González M, Vida M, Pavón FJ, et al. Elaidyl-sulfamide, an oleoylethanolamide-modelled PPARα agonist, reduces body weight gain and plasma cholesterol in rats. Dis Model Mech. 2012;5:660–670. DOI: 10.1242/dmm.009233

[116] Annuzzi G, Piscitelli F, Di Marino L, Patti L, Giacco R, Costabile G, et al. Differential alterations of the concentrations of endocannabinoids and related lipids in the subcutaneous adipose tissue of obese diabetic patients. Lipids Heal Dis. 2010;9:43. DOI: 10.1186/1476-511X-9-43

[117] Gaetani S, Oveisi F, Piomelli D. Modulation of meal pattern in the rat by the anorexic lipid mediator oleoylethanolamide. Neuropsychopharmacology. 2003;28:1311–1316. DOI: 10.1038/sj.npp.1300166

[118] Mennella I, Savarese M, Ferracane R, Sacchi R, Vitaglione P. Oleic acid content of a meal promotes oleoylethanolamide response and reduces subsequent energy intake in humans. Food Funct. 2015;6:204–210. DOI: 10.1039/c4fo00697f

[119] Azari EK, Ramachandran D, Weibel S, Arnold M, Romano A, Gaetani S, et al. Vagal afferents are not necessary for the satiety effect of the gut lipid messenger oleoylethanolamide (OEA). Am J Physiol Regul Integr Comp Physiol. 2014;307:R167–R178. DOI: 10.1152/ajpregu.00067.2014

[120] Sclafani A, Ackroff K, Schwartz GJ. Selective effects of vagal deafferentation and celiac-superior mesenteric ganglionectomy on the reinforcing and satiating action of intestinal nutrients. Physiol Behav. 2003;78:285–294. DOI: 10.1016/S0031-9384(02)00968-X

[121] Romano a., Karimian Azari E, Tempesta B, Mansouri a., Micioni Di Bonaventura M V., Ramachandran D, et al. High dietary fat intake influences the activation of specific hindbrain and hypothalamic nuclei by the satiety factor oleoylethanolamide. Physiol Behav. 2014;136:55–62. DOI: 10.1016/j.physbeh.2014.04.039

[122] Romano A, Cassano T, Tempesta B, Cianci S, Dipasquale P, Coccurello R, et al. The satiety signal oleoylethanolamide stimulates oxytocin neurosecretion from rat hypothalamic neurons. Peptides. 2013;49:21–26. DOI: 10.1016/j.peptides.2013.08.006

[123] Serrano A, Pavón FJ, Tovar S, Casanueva F, Señarís R, Diéguez C, et al. Oleoylethanolamide: Effects on hypothalamic transmitters and gut peptides regulating food intake. Neuropharmacology. 2011;60:593–601. DOI: 10.1016/j.neuropharm.2010.12.007

[124] Proulx K, Cota D, Castaneda TR, Tschop MH, D'Alessio DA, Tso P, et al. Mechanisms of oleoylethanolamide-induced changes in feeding behavior and motor activity. Am J Physiol Regul Integr Comp Physiol. 2005;289:R729–R737. DOI: 10.1152/ajpregu.00029.2005

[125] Yu H-L, Sun L-P, Li M-M, Quan Z-S. Involvement of norepinephrine and serotonin system in antidepressant-like effects of oleoylethanolamide in the mice models of behavior despair. Neurosci Lett. 2015;593:24–28. DOI: 10.1016/j.neulet.2015.03.019

[126] Melis M, Carta S, Fattore L, Tolu S, Yasar S, Goldberg SR, et al. Peroxisome proliferator-activated receptors-alpha modulate dopamine cell activity through nicotinic receptors. Biol Psychiatry. 2010;68:256–264. DOI: 10.1016/j.biopsych.2010.04.016

[127] McGaugh JL, Roozendaal B. Role of adrenal stress hormones in forming lasting memories in the brain. Curr Opin Neurobiol. 2002;12:205–210. DOI: 10.1016/S0959-4388(02)00306-9

[128] Campolongo P, Roozendaal B, Trezza V, Hauer D, Schelling G, McGaugh JL, et al. Endocannabinoids in the rat basolateral amygdala enhance memory consolidation and enable glucocorticoid modulation of memory. Proc Natl Acad Sci U S A. 2009;106:4888–4893. DOI: 10.1073/pnas.0900835106

[129] McGaugh JL. Memory—a century of consolidation. Science. 2000;287:248–251. DOI: 10.1126/science.287.5451.248

[130] Campolongo P, Roozendaal B, Trezza V, Cuomo V, Astarita G, Fu J, et al. Fat-induced satiety factor oleoylethanolamide enhances memory consolidation. Proc Natl Acad Sci U S A. 2009;106:8027–8031. DOI: 10.1073/pnas.0903038106

[131] Mazzola C, Medalie J, Scherma M, Panlilio L V, Solinas M, Tanda G, et al. Fatty acid amide hydrolase (FAAH) inhibition enhances memory acquisition through activation of PPAR-alpha nuclear receptors. Learn Mem. 2009;16:332–337. DOI: 10.1101/lm.1145209

[132] Grosshans M, Schwarz E, Bumb JM, Schaefer C, Rohleder C, Vollmert C, et al. Oleoylethanolamide and human neural responses to food stimuli in obesity. JAMA Psychiatry. 2014;71:1254–1261. DOI: 10.1001/jamapsychiatry.2014.1215

[133] Kenny PJ. Common cellular and molecular mechanisms in obesity and drug addiction. Nat Rev Neurosci. 2011;12:638–651. DOI: 10.1038/nrn3105

[134] Volkow ND, Wang GJ, Baler RD. Reward, dopamine and the control of food intake: implications for obesity. Trends Cogn Sci. 2011;15:37–46. DOI: 10.1016/j.tics.2010.11.001

[135] Berthoud H-R. The neurobiology of food intake in an obesogenic environment. Proc Nutr Soc. 2012;71:478–487. DOI: 10.1017/S0029665112000602

[136] Tellez LA, Medina S, Han W, Ferreira JG, Licona-Limón P, Ren X, et al. A gut lipid messenger links excess dietary fat to dopamine deficiency. Science. 2013;341:800–802. DOI: 10.1126/science.1239275

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