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Authors
DiPatrizio, NV
Piomelli, D

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Intestinal lipid–derived signals that sense dietary fat

Nicholas V. DiPatrizio and Daniele Piomelli

Departments of Anatomy and Neurobiology, Department of Pharmacology, and Department of Biological Chemistry, School of Medicine, University of California, Irvine, Irvine, California, USA.

Drug Discovery and Development, Istituto Italiano di Tecnologia, Genoa, Italy.

Fat is a vital macronutrient, and its intake is closely monitored by an array of molecular sensors distributed throughout the alimentary canal. In the mouth, dietary fat constituents such as mono- and diunsaturated fatty acids give rise to taste signals that stimulate food intake, in part by enhancing the production of lipid-derived endocannabinoid messengers in the gut. As fat-containing chyme enters the small intestine, it causes the formation of anorexic lipid mediators, such as oleoylethanolamide, which promote satiety. These anatomically and functionally distinct responses may contribute to the homeostatic control and, possibly, the pathological dysregulation of food intake.

Introduction

Dietary fat occupies a central place in the complex molecular web that controls energy homeostasis in animals (1, 2). Its fatty acid constituents are not only highly caloric — they pack more than twice the energy than do carbohydrates or proteins — but are also necessary to build cellular membranes and produce essential lipid-derived mediators such as prostaglandins, leukotrienes, and endocannabinoids (3). It is not surprising, therefore, that chemosensory and neural mechanisms have been selected for during evolution to closely monitor fat intake and optimize the seeking, sensing, and storage of this vital macronutrient (2, 4, 5). Indeed, the sharp seasonal and geographic fluctuations in availability of fat-rich foods, which are typical of natural environments and archaic human societies (6), are a likely source of the selective pressure that endowed these fat-sensing mechanisms with unusual saliency (7, 8). Our species’ hard-wired attraction to fat has lost much of its adaptive value in contemporary societies, where fatty foods are easily and continually available, and may contribute to the growing prevalence of overweight and obesity (2, 9).

An interacting network of peripheral and central circuits, which have been only partially mapped, governs the intake of palatable fat-containing foods: peripheral signals such as cholecystokinin and leptin (10), along with central neurotransmitters such as opioid peptides (8) and melanin-concentrating hormone (11), are known to be involved. The focus of this Review is on two classes of lipid-derived mediators produced in the gut that have recently emerged as important fat-dependent regulators of hunger and satiety. These are esters of long-chain unsaturated fatty acids (LCUFAs) with glycerol, such as 2-arachidonoyl-sn-glycerol (2-OG), and amides of LCUFA with ethanolamine, such as arachidonoylethanolamide (anandamide) and oleoylethanolamide (OEA) (Figure 1).

Despite their structural similarities, these substances interact with distinct molecular targets and elicit widely different biological responses.

Anandamide and 2-AG are high-affinity agonists for the G protein–coupled cannabinoid receptors CB₁ and CB₂ (12). Activation of the CB₁ receptor subtype — which is particularly abundant in the brain and spinal cord, but is also spread throughout the rest of the body (13) — increases food intake, enhances reward aspects of eating, and promotes energy conservation (4, 14). Conversely, pharmacological or genetic blockade of the receptor decreases feeding, sustains weight loss, heightens insulin sensitivity, and improves dysregulated lipid metabolism in both animal models and obese humans (14, 15). Central and peripheral mechanisms cooperate to produce these effects. Evidence for a central component includes, for example, the finding that microinjections of anandamide into hedonic “hot spots” in the rat nucleus accumbens enhance affective orofacial (“liking”) reactions (16) to a pleasant food taste (sucrose) (17) and, conversely, that genetic deletion of CB₁ receptors or of the 2-AG–deactivating enzyme monoacylglycerol lipase in mouse forebrain neurons causes leanness, accrued thermogenesis, and resistance to diet-induced obesity (18, 19).

Important sites of endocannabinoid action outside the brain are the liver and the adipose organ, where CB₁ receptors act as positive regulators of lipogenesis (20), as well as the small intestine, where their activation slows down peristalsis (21, 22), suppresses mucosal inflammation (23), and increases food intake (24, 25). In the first two sections of this Review, we outline the molecular and neural pathways underlying fat taste and discuss the possible role of gut endocannabinoids as hunger signals triggered by fat ingestion.

OEA is a nanomolar agonist of PPARα, a member of the nuclear receptor superfamily (26, 27). PPARα is responsible for most of the biological actions of OEA, including its ability to curb food intake (26, 28, 29), enhance fatty acid absorption in small intestinal enterocytes (26, 30), and stimulate lipid usage (lipolysis or oxidation) in adipocytes, hepatocytes, and skeletal myocytes (31, 32). In addition to PPARα, OEA activates the GPCR GPR119 (33) and, by doing so, stimulates secretion of the insulin-releasing factor glucagon-like peptide 1 (GLP1) from enteroendocrine L

Conflict of interest: Daniele Piomelli is a cofounder of Thesan Pharmaceuticals and Anteana Therapeutics, two biopharmaceutical companies dedicated to the development of innovative therapies for skin diseases and pain, respectively. Daniele Piomelli owns equity in both companies.

sequences. For example, net diversification rates (the cumulative effect of speciation and extinction) are lower for omnivorous species than they are for herbivores and carnivores (42). While omnivory offers greater resistance to evolutionary pressures and adaptability in the face of shifting environmental forces (43), it also exacerbates the need to make frequent and complex dietary choices that are critical to the well-being of an animal. This unique decision-making task requires the integration of competing (Pavlovian, habitual, and goal-directed) behavioral controllers working in unison with homeostatic regulators such as ghrelin and leptin (44). Ultimately, however, dietary selection depends on the animal’s ability to monitor specific nutrient classes present in the diet and reliably gauge their intake against the changing needs of the organism. The chemical senses, smell and taste, as well as chemosensory responses to texture are all to varying degrees involved in the perception of fat (45, 46). However, studies in humans (47) and rodents (48, 49) have demonstrated that smell is not critical for fat detection, whereas taste is irreplaceable.

Foods are sensed in the oral cavity by receptors present on the surface of taste bud cells, which transduce chemical signals generated during feeding into electrical currents that are carried to the brain by fibers of the cranial nerve VII (CNVII, facial), CNIX (glossopharyngeal), and CNX (vagus) (50). These gustatory messages enter the nucleus of the solitary tract (NST) in the caudal brainstem, where they merge with information coming from the gut via the afferent vagus nerve. Neurotransmission continues onto the parabrachial nucleus of the pons, which communicates in a bidirectional manner with forebrain regions that control food reward and energy homeostasis (4, 51–54). In the last two sections of this article, we discuss evidence suggesting that OEA may act as a postingestive “stop” signal for dietary fat intake, and propose an integrated view of how this anorexic lipid-derived mediator might cooperate with orexigenic endocannabinoid-mediated signaling to modulate the ingestion of dietary fat (Figure 2).

Fat taste

Unlike obligatory herbivores and carnivores, which have inherently narrow boundaries of food choice, humans and other omnivores fulfill their energy requirements by consuming calories from a diversity of plant and animal sources (40, 41). This nutritional flexibility, which gives omnivores the distinctive capability of adapting their nutrient sources to seasonal and geographical changes in flora and fauna, has important evolutionary consequences. For example, net diversification rates (the cumulative effect of speciation and extinction) are lower for omnivorous species than they are for herbivores and carnivores (42). While omnivory offers greater resistance to evolutionary pressures and adaptability in the face of shifting environmental forces (43), it also exacerbates the need to make frequent and complex dietary choices that are critical to the well-being of an animal. This unique decision-making task requires the integration of competing (Pavlovian, habitual, and goal-directed) behavioral controllers working in unison with homeostatic regulators such as ghrelin and leptin (44). Ultimately, however, dietary selection depends on the animal’s ability to monitor specific nutrient classes present in the diet and reliably gauge their intake against the changing needs of the organism. The chemical senses, smell and taste, as well as chemosensory responses to texture are all to varying degrees involved in the perception of fat (45, 46). However, studies in humans (47) and rodents (48, 49) have demonstrated that smell is not critical for fat detection, whereas taste is irreplaceable.

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demonstrated the critical role played by gustatory neurotransmission in fat detection and preference. For example, surgical resection of the chorda tympani (branch of CNVII) or CNIX in rodents decreases both intake of and preference for a high-fat liquid meal (55–59). Conversely, oral exposure to fat increases the activity of taste-sensitive neurons of the NST (57) and excites forebrain circuits involved in food reward (60, 61).

The exact chemical source of fat taste is still debated (62, 63). Nevertheless, the available data indicate that release of nonesterified fatty acids (FFAs) from triacylglycerols — the main quantitative component of dietary fat — is required to detect this macronutrient in both humans (64, 65) and rodents (66). Humans readily distinguish low intraoral concentrations of triacylglycerols (67, 68), which catalyzes the hydrolysis of these composite lipids into individual FFAs, impairs this ability (65). Similar to our species, rodents prefer liquid diets containing triacylglycerols, but this preference disappears when the animals are treated with the lipase inhibitor tetrahydrolipstatin (66). These findings strongly implicate the release of FFAs by oral lipolytic activity as a key determinant of fat taste.

There is also convincing evidence that the sensory experience associated with the eating of fatty foods is initiated by gustatory signals that require selective receptors on taste bud cells to be engaged by FFAs (62, 63). Deletion of genes encoding four distinct candidate receptors has yielded results that support this conclusion. Mice lacking the multifunctional membrane glycoprotein CD36 the cation-selective transient receptor potential type M5 (TRPM5), or the GPCRs GPR40 and GPR120 all display significant reductions in preference for LCUFAs (69–72). Furthermore, application of LCUFAs elevates intracellular Ca¨2+ levels in isolated mouse taste cells, an effect that is blunt in cells lacking CD36 (73) or TRPM5 (72). Adding clinical relevance to these findings, a single nucleotide polymorphism in the CD36 gene of obese African-American women has been associated with an increase in the detection threshold for fat (64). In addition, a study in obese men found increased detection threshold for fat compared with lean controls (74). Thus, the information currently available allows us to identify CD36, TRPM5, GPR40, and GPR120 as candidate fat-taste receptors. As an evolutionary test of this idea, it would be interesting to determine whether expression of these proteins is conserved in marine mammals that have lost all other taste receptors (e.g., sea lions and whales) (41, 75) or terrestrial mammals that are insensitive to the taste of sweet (e.g., obligatory carnivores such as cats) (41) or umami (e.g., highly specialized herbivores such as the panda) (76).

Gut endocannabinoids as hunger signals

The orosensory qualities of fat are a major contributor to the hedonic properties of this macronutrient (63). For example, rats avidly consume corn oil emulsions even under sham feeding conditions, when postdigestive feedbacks are absent (see below) (77). This is due, at least in part, to a direct activation of reward centers in the brain. Microdialysis experiments in sham-feeding rats have shown, indeed, that oral presentation of fat triggers the release of dopamine in the nucleus accumbens (60, 61), a critical controller of value learning (78–82). In addition to these central processes, oral fat also deploys multiple regulatory responses in the periphery of the body. For example, building...
on pioneering experiments by the laboratory of Gerard P. Smith (77), Philippe Besnard, and coworkers have demonstrated that lingual application of linoleic acid rapidly elevates pancreatic and biliary secretions in anesthetized mice whose esophagus was clamped to prevent access of the fatty acid to the stomach (69). This finding links the cephalic response to fat to a peripheral physiological event that is probably mediated by effenter vagal neurotransmission.

Another such event may be the activation of endocannabinoid signaling in the upper gut (Figure 2). This idea is supported by studies in which a sham feeding protocol was utilized to test whether tasting carbohydrates, proteins, or fats stimulates endocannabinoid mobilization. In this protocol, a surgical intervention prevented food from accumulating in the stomach and small intestine, allowing the investigation of orosensory feeding controls in the absence of postingestive influences (77). Sham-feeding rats were offered a nutritionally complete liquid diet or liquid meals containing individual macronutrients (corn oil, sucrose, or a protein lysate) (83). After sham feeding, brain and peripheral organs were harvested and their endocannabinoid content was measured by liquid chromatography/mass spectrometry. Oral exposure to corn oil increased the levels of 2-AG and anandamide in the proximal small intestine (jejunum), but not elsewhere in the body, including brain regions involved in the control of food intake or reward (83). Importantly, this effect (a) was nutrient-specific, because sham feeding sugar or protein did not change jejunal endocannabinoid levels; and (b) was not attributable to the texture of corn oil, because mineral oil failed to mimic it (83). In another set of experiments in which rats were sham fed suspensions of pure FFAs, oleic acid (short-hand designation 18:1 Δ9), which denotes a fatty acid with 18 carbon atoms and one double bond between carbons 9 and 10) and linoleic acid (18:2 Δ9,12) both increased gut endocannabinoid levels in a manner similar to corn oil, whereas the saturated fatty acid, stearic acid (18:0), or the polyunsaturated fatty acid, linolenic acid (18:3 Δ9,12,15), had no such effect (84). This unexpected structural selectivity reveals an important role for fatty acid composition in the detection of dietary fat and is consistent with the idea that receptor-dependent mechanisms are at play in the oral perception of this nutrient.

To elucidate the neural pathway through which oral exposure to fat drives small intestinal endocannabinoid mobilization, rats were subjected to subdiaphragmatic resection of the vagus nerve, which completely interrupted this major two-way route connecting the brain to the gut (85). The procedure abolished the spike in endocannabinoid levels elicited by fat sham feeding (83), suggesting that the presence of fat in the mouth stimulates gut endocannabinoid signaling by engaging effenter vagal neurotransmission.

Why are endocannabinoids produced in response to fat taste? And why are they produced in the gut? The fact that fasting exerts an effect similar to oral fat exposure (24, 86) points to the possibility that small-intestinal endocannabinoids may act as hunger signals. Consistent with this idea, intraduodenal infusion of the CB1 inverse agonist, rimonabant, or systemic injection of the brain-impermeant neutral CB1 antagonist, UR8447, each attenuates sham feeding of corn oil (83). Additionally, peripheral blockade of CB1 receptors suppresses the intake of linoleic acid in a two-bottle choice test conducted on sham-feeding rats. In this test, the animals were shown to strongly prefer linoleic acid, which increases gut endocannabinoid levels over mineral oil, which has no such effect (84).

To sum up, the studies outlined above suggest that small-intestinal endocannabinoid signaling — started by oral exposure to select LCUFAs and transmitted to the gut by the vagus nerve — mediates the orexigenic response caused by the tasting of fat-containing foods. More work is needed to understand how gut endocannabinoids communicate with the brain. If CB1 receptors on terminals of the vagus nerve are involved, they are probably replaceable because mice in which such receptors have been selectively deleted show no change in food intake or body weight (however, these mice do have altered gut motility) (87). On the other hand, the presence of CB1 receptors in ghrelin cells of the stomach (88) and cholecystokinin-secreting enteroendocrine I cells of the duodenum (89) is suggestive of an indirect action mediated by these gut peptide hormones. In addition to testing this idea, future experiments should also aim at providing a more integrated picture of the physiological functions served by the endocannabinoid system in the gut. In particular, it is important to assess whether the known ability of these lipid mediators to delay peristalsis (86, 87, 90, 91) and attenuate mucosal innate immune responses (23) is part of a broader adaptive strategy aimed at optimizing the absorption of dietary fat, which is slower than the absorption of other nutrients and is accompanied by activation of local mast cells (92). It would be also interesting to examine in greater detail the role of CB1 receptors located on sympathetic nerve terminals, which have been implicated in the anti-obesity effects of the CB1 inverse agonist, rimonabant (93).

Lipid-derived signals of satiety

Postingestive processes are critical to the control of fat intake (27, 94). This point is well illustrated by experiments showing that the local infusion of fat into the duodenum of humans or rodents exerts potent inhibitory effects on feeding by both enhancing satiation (i.e., reducing meal size) and maintaining satiety (i.e., increasing inter-meal intervals) (27, 77, 95–97). The anorexic effects of intraduodenal fat require afferent vagal fibers (98, 99) and are partly due to the release of cholecystokinin from enteroendocrine I cells in the proximal gut (98, 100, 101). These cells express various cell surface receptors that bind FFAs, including GPR120, TRPM5, and FFA receptors 1–3 (102). Gilbertson and collaborators have shown that polyunsaturated FFAs stimulate STC-1 enteroendocrine cells to secrete cholecystokinin by direct activation of GPR120 and downstream recruitment of TRPM5 (103).

In addition to cholecystokinin, two distinct lipid-derived signaling molecules — 2-OG and OEA (Figure 1) — may contribute in complementary ways to the postingestive control of satiety. The action of pancreatic lipase on dietary triacylglycerols generates 2-OG and other 2-monoacylglycerols. It is likely to reach millimolar concentrations in the lumen of the upper gut during fat digestion and may act as a local regulator of GLP1 release by virtue of its ability to activate GPR119 receptors localized to the apical surface of enteroendocrine L cells of the ileum (104). The administration of exogenous 2-OG through a duodenal catheter increases circulating GLP1 levels in human volunteers (36). It is still unclear, however, whether 2-OG released following the hydrolysis of triacyl-
glycerols by pancreatic lipase is capable of eliciting a similar effect. Interestingly, a recent study showed that dietary lipids directly induce GLP1 release from taste bud cells, which might contribute to the reinforcing properties of fats (105).

While many questions about 2-OG remain unanswered, a great deal more is known about the formation and physiological implications of OEA (27). Duodenal and jejunal enterocytes produce this bioactive lipid substance in three consecutive steps. They first internalize oleic acid released during fat digestion, through a mechanism that requires the membrane glycoprotein CD36 (37); they then use the newly absorbed fatty acid as substrate for the biosynthesis of NOPE, a member of the N-acylphosphatidylethanolamine (NAPE) family of membrane phospholipids, and finally cleave NOPE to generate OEA (37). These reactions are accompanied by accrued activity in the biochemical pathway that generates OEA (26). The long evolutionary history of feeding-dependent OEA mobilization is indicated by its occurrence in the upper gut of mammals (mice and rats) (28, 106), reptiles (Burmese pythons, Python molurus Linnaeus) (107), and fish (goldfish, Carassius auratus Linnaeus) (108).

When administered as a drug to free-feeding mice or rats, OEA modifies meal patterns in a manner that is characteristic of a satiety signal, i.e., primarily by increasing post-meal intervals rather than reducing meal size (38). This effect is absent in mice lacking PPARα, to which OEA binds with high affinity (dissociation constant \([K_D] \approx 40 \, \text{nM}\)), and is mimicked by synthetic α-sympathetic denervation (i.e., increased meal frequency and decreased post-meal intervals) (120). A plausible interpretation of these findings is that sympathetic outflow to the small intestine enables fat-induced OEA satiety signaling, possibly by regulating the expression and/or post-translational regulation of enzymes in the pathway of OEA biosynthesis.

As seen with gut peptide hormones such as GLP1 (122, 123), continued exposure to a high-fat diet lowers OEA levels in the small intestine of rodents (112, 124, 125). Does this effect influence OEA-mediated satiety signaling? We cannot answer this question yet, but recent work by Tellez and collaborators (112) provides data suggesting that dampened OEA availability in the gut may affect dopamine transmission in the dorsal striatum, a brain structure that links hedonic responses to habit learning (44). Using brain microdialysis, these researchers found that gastric infusions of fat increase striatal dopamine outflow in lean mice (94, 112). This response — which is prevented by pharmacological blockade of PPARα or surgical resection of the vagus nerve — is absent in mice rendered obese by exposure to a high-fat diet, but could be reinstated by treating obese mice with exogenous OEA (112).

In summary, the available data indicate that OEA, generated by small-intestinal enterocytes during the digestion of fat-containing foods, causes satiety through a paracrine PPARα-mediated mechanism that requires the recruitment of afferent sensory fibers. This response also depends on the presence of an intact sympathetic nervous system — which may function to facilitate fat-induced OEA production in the gut — and engages oxytocin, histamine, and dopamine transmission in the CNS. The intriguing but as yet unexplained observation that prolonged exposure to dietary fat lowers small intestinal OEA levels (124, 125) raises questions about the mechanism regulating OEA signaling in the gut and the possible role it might play in overeating and obesity.
An integrated view

Gut peptide hormones are differentially distributed along the longitudinal axis of the alimentary canal and serve complementary functions in the control of feeding behavior. For example, ghrelin released from specialized cells in the stomach stimulates food intake during fasting, whereas cholecystokinin and GLP1 secreted from enteroendocrine cells in the small intestine inhibit intake after feeding (126, 127). The evidence summarized in this article suggests that two chemically distinct classes of lipid-derived mediators — glycerol esters and etherlipolamides of LCFUs — may act in parallel and presumably in concert with peptide hormones to regulate the ingestion of fat-containing foods (Figure 2). As discussed above, select chemical components of dietary fat (e.g., mono- and diunsaturated fatty acids) trigger gustatory signals that drive feeding, in part by stimulating the accumulation of orexigenic endocannabinoid messengers in the jejunum. Vagal neurotransmission bridges the tasting of fat in the mouth to endocannabinoid mobilization in the gut. As fat-containing chyme travels through the small intestine, its triacylglycerol constituents undergo chemical changes that convert these diet-derived nutrients into signaling molecules: they are absorbed by enterocytes to be used as precursors for anorexigenic mediators such as OEA and are hydrolyzed in the gut lumen to form GPR119 agonists such as 2-OG. The sympathetic nervous system is necessary for at least one of these processes — the conversion of fat-derived oleic acid into OEA. The ability shown by both endocannabinoids (128) and OEA (22, 129) to slow gastrointestinal transit likely contributes to the overall effects of these lipid mediators on food intake. Though still incomplete, this body of evidence allows us to conjecture that the ingestion of fat-rich foods initiates two temporally distinct events that require a coordinated interaction between the parasympathetic and sympathetic nervous systems: a cephalically driven induction of endocannabinoid activity in the gut, which acts as a “go” signal to maximize consumption of fat-rich foods, and a post-oral phase that includes the formation of OEA, which serves as a “stop” signal on feeding (Figure 2). This model underscores the close integration between gut and brain, likely a product of the co-evolution of these two metabolically expensive organs (130), and predicts that imbalances between opposing lipid-derived signaling systems and dysfunctions in their interactions with peptide hormones may lead to overweight and obesity.

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Address correspondence to: Daniele Piomelli, 3216 Gillespie Neuroscience Research Facility, Irvine, California 92697, USA. Phone: 949.824.7080; E-mail: piomelli@uci.edu.

Nicholas V. DiPatrizio’s present address is: Division of Biomedical Sciences, School of Medicine, University of California, Riverside, Riverside, California, USA.

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