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Review

Role of anorectic *N*-acylethanolamines in intestinal physiology and satiety control with respect to dietary fat

Harald S. Hansen*

Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen, Universitetsparken 2, 2100 Copenhagen, Denmark

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ABSTRACT

Anandamide is a well-known agonist for the cannabinoid receptors. Along with endogenous anandamide other non-endocannabinoid *N*-acylethanolamines are also formed, apparently in higher amounts. These include mainly oleoylethanolamide (OEA), palmitoyelethanolamide (PEA) and linoleoylethanolamide (LEA), and they have biological activity by themselves being anorectic and anti-inflammatory. It appears that the major effect of dietary fat on the level of these molecules is in the gastrointestinal system, where OEA, PEA and LEA in the enterocytes may function as homeostatic signals, which are decreased by prolonged consumption of a high-fat diet. These lipid amides appear to mediate their signaling activity via activation of PPARα in the enterocyte followed by activation of afferent vagal fibers leading to the brain. Through this mechanism OEA, PEA and LEA may both reduce the consumption of a meal as well as increase the reward value of the food. Thus, they may function as homeostatic intestinal signals involving hedonic aspects that contribute to the regulation of the amounts of dietary fat to be ingested.

Contents

1. Introduction

Satiation and/or satiety is primarily controlled by the hypothalamus, which receives many different signals from the mouth, the stomach, the intestine and the organs participating in energy metabolism. From the gastrointestinal tract these signals can be neuronal via the vagus nerve and hormonal via the gastrointestinal hormones like ghrelin, cholescystokinin (CCK), and glucagon-like polypeptide-1 (GLP-1) [1]. Several of the hormones may in fact transmit their signal to the brain through the vagus nerve, e.g. CCK [2]. Within the gastrointestinal system, there exist several sensors for various dietary components and many of these sensors belong to the G-protein-coupled receptor family although metabolic sensing mechanisms may also be involved [3–6]. Sensing of dietary fat intake in the gastrointestinal system is thought to be mediated by the fatty acid receptors GPR40 [7,8], and GPR120 [9–11], the fatty acid transporter CD36 [12,13], intestinal beta-oxidation of fatty acids [6,14], protein kinase C-zeta or protein kinase C-delta [15,16], and the 2-monoacylglycerol receptor GPR119 [17,18]. Dietary fat may also be sensed on the tongue [19]. Generally it is known that infusion of free fatty acids or

Abbreviations: AEA, anandamide; 2-AG, 2-arachidonoyl glycerol; CCK, cholescystokinin; EPEA, eicosapentaenoylethanolamide; DHEA, docosahexaenoylethanolamide; FAAH, fatty acid amide hydrolase; GLP-1, glucagon-like peptide-1; LEA, linoleoylethanolamide; NAAA, *N*-acylethanolamine acid amidase; NAE, *N*-acylethanolamine; NAPE, *N*-acylphosphatidylethanolamine; NAPE-PLD, *N*-acylphosphatidylethanolamine-hydrolyzing phospholipase D; NAT, *N*-acyltransferase; PE, phosphatidylethanolamine; PEA, palmitoylethanolamide; SEA, stearoylethanolamide.

* Tel.: +45 35336332; fax: +45 35336020.
E-mail address: hsh@sund.ku.dk

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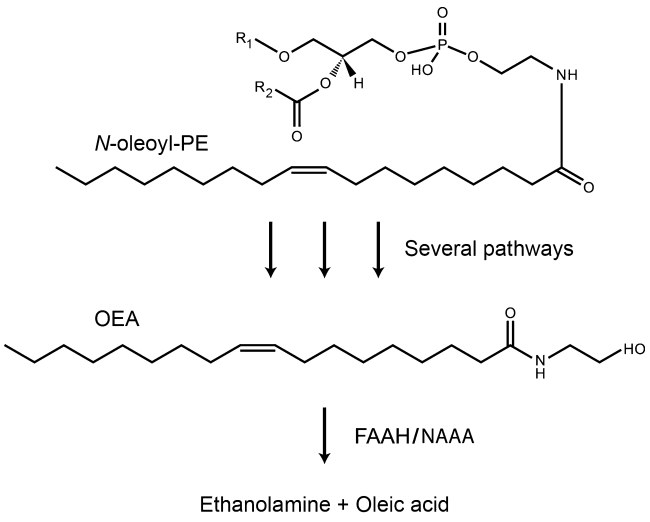

Fig. 1. Formation and degradation of oleoylethanolamide (OEA). OEA is generated from its phospholipid precursor *N*-oleoylphosphatidylethanolamine (*N*-oleoyl-PE) by several enzymatic pathways. OEA can be hydrolyzed to oleic acid and ethanolamine by two enzymes: fatty acid amide hydrolase (FAAH) and to a lesser degree by *N*-acylethanolamine acidic amidase (NAAA). Palmitoylethanolamide and linoleoylethanolamide are formed by the same pathways as are OEA.

triacylglycerol into the intestinal lumen induce a satiation effect [20–23], but on the other hand prolonged intake of dietary fat is known to promote obesity in humans and in laboratory animals [24–26].

N-Acylethanolamines (NAEs) is a group of endogenous lipid molecules that can be considered to have a second messenger-like function within the cells [27] more or less comparable to that of diacylglycerol. Although NAEs can be found in extracellular fluids [28,29], where they may be bound to albumin [30,31], it is not clear whether these low levels serve any physiological function. NAEs are evolutionarily conserved being found in plants, yeast, slime molds, insects, and mammals [32–36]. The most well-known NAE is anandamide (=*N*-arachidonoylethanolamine) [37,38], which is an agonist for the cannabinoid receptors [39]. However, exogenous administered *N*-palmitoylethanolamine (PEA), *N*-oleoylethanolamine (OEA) and *N*-linoleoylethanolamine (LEA), which do not activate the cannabinoid receptors, also have various biological activities via activation of PPARα [40–42], activation of vanilloid receptor [43,44], activation of GPR119 [18,45], inhibition of various ion channels [46–48] and for OEA inhibition of ceramidase [49]. Furthermore, exogenously administered NAEs may inhibit degradation of endogenous NAEs including anandamide, thereby causing an increase in their tissue levels [50].

2. Formation and degradation

N-Acylethanolamine phospholipids (NAPEs) are a special group of phospholipids, which have an extra fatty acid attached to the amino group of phosphatidylethanolamine (or plasmalogen). NAPEs are present in all tissues in very small levels, amounting to less than 0.05% of tissue phospholipids [51], being in the same order of magnitude as the signaling phosphoinositides. All NAEs appear to be generated from the corresponding NAPEs. Thus, NAPE species having oleic acid at the amine position (*N*-oleoyl-PE) generate OEA upon hydrolysis (see Fig. 1) [34,52,53]. The NAEs can be generated from NAPEs by several enzymatic pathways, where the best known is via NAPE-hydrolyzing phospholipase D (NAPE-PLD) [54]. In mice having targeted disruption of the gene for NAPE-PLD, the tissue levels of the various NAEs are decreased but not totally suppressed [55,56], underscoring the existence of alternative biosynthetic pathways. These pathways are described in detail in the other reviews in this issue, but until now there is no consensus about whether one specific enzymatic pathway is responsible for formation of one specific NAE, e.g. OEA or anandamide. On the contrary, it seems as if it is the levels of the different NAPE species that determines the amount of the different NAEs formed, at least in the small intestine. Thus, during fasting of rats a decrease in the intestinal level of OEA and an concomitant increase in the level of anandamide [57] was found to be paralleled with a decrease in the level of *N*-oleoyl-PE (i.e. a NAPE with oleic acid in the *N*-acyl position) and an increase in the level of *N*-arachidonoyl-PE (i.e. a NAPE with arachidonic acid in the *N*-acyl position) [58]. Upon feeding, OEA levels increased and anandamide levels decreased and this was again paralleled by an increased level of *N*-oleoyl-PE and a decreased level of *N*-aracidonoyl-PE [58]. LEA and PEA and their two NAPE-precursors, *N*-linoleoyl-PE and *N*-palmitoyl-PE, respectively, followed the same pattern as did OEA and its NAPE-precursor, while *N*-stearoylethanolamine and its NAPE-precursor, *N*-stearoyl-PE, did not change [58]. NAPEs are generated from ethanolamine phospholipid and an acyl-donor phospholipid by a *N*-acyltransferase (NAT) of which two enzymatic activities are known in rats: a membrane-associated calcium-stimulated NAT, which has not yet been cloned, that are found in most tissues and especially in the brain [51,53,59], and a group of enzymes called PLA/AT family, which can be found in both soluble and particulate fractions of tissue homogenates [60–64]. These PLA/AT enzymes are poorly characterized and their activities appear not to be stimulated by calcium ions [60,62]. It is not clear which enzyme activities are responsible for NAPE formation in the small intestine. Neither is it known in which type of cells NAEs are formed in response to food intake, but it is generally believed to occur in the enterocyte [27,65].

NAEs are mainly hydrolyzed by two enzymes: fatty acid amide hydrolase (FAAH), which is located in the endoplasmic reticulum [66,67], and *N*-acylethanolamine-hydrolyzing acid amidase (NAAA) located primarily in lysosomes [68]. FAAH has highest hydrolytic activity for anandamide and other unsaturated NAEs while NAAA has highest activity for PEA and other saturated NAEs. FAAH is present in the small intestine but administration of well-known FAAH inhibitors, URB 597 and AM 3506, do not increase NAE levels in the small intestine [65,69–71] and URB 597 does not affect food intake [71], so other hydrolase activities beside FAAH may contribute to feeding-regulated NAE hydrolysis [65]. It is possible that most intestinal FAAH activity is associated with the enteric nervous system and not with the enterocytes [69], thereby explaining the lack of effect of FAAH-inhibitors on bulk NAE levels in the small intestine. High-fat food consumption was enhanced during the dark hours and decreased during the light hours in FAAH knockout mice as compared to wild type mice, and the reinforcing and motivational effects of food were also enhanced in FAAH knockout mice as revealed by operant behavioral paradigms [72]. However, these effects were mediated by cannabinoid receptors and may thus be due to increased levels of anandamide and not due to the non-endocannaboid NAEs like OEA, PEA and LEA [72]. In these FAAH knockout mice, the intestinal level of OEA was 1.6-fold higher than in wild type mice suggesting that FAAH may have a small contributing effect on the level of OEA, PEA and LEA in intestinal tissue. In other tissues (hypothalamus and liver) of the same mice, OEA levels were 6-fold and 9-fold higher [72]. In FAAH knockout mice and in mice receiving FAAH inhibitors, the tissue levels (e.g. in liver, brain, testis and plasma [73]) of both anandamide and the non-endocannabinoid NAEs are increased and this hampers the interpretations of behavioral data since anandamide seems to have important functions in the intestine, including contributing to regulating dietary fat intake [74], and intestinal motility [75].

NAAA is highly expressed in the small intestine but this enzyme has low activity for unsaturated NAEs like OEA and LEA [76]. NAAA