

# Roles of *N*-Acylethanolamines in Brain Functions and Neuropsychiatric Diseases

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**Abstract** *N*-acylethanolamines (NAEs) are bioactive lipids, structural analogues to the endocannabinoid arachidonylethanolamide (anandamide), whose functions and properties are being elucidated in recent years. By activating their receptors, specifically peroxisome proliferator-activated receptors (PPARs), these molecules exert a variety of physiological effects via genomic and rapid non-genomic mechanisms. Regulation of lipid metabolism, energy homeostasis, and anti-inflammation are among the best-characterized effects of PPAR activation. NAEs are abundant in the CNS and their receptors are widely expressed both in neurons and in glial cells, where they modulate brain functions and are involved in the pathophysiology of neurological and psychiatric disorders. In the brain, they participate in the regulation of feeding behavior, cognitive functions, mood, reward, and sleep-wake cycles, and evidence suggests that they might be therapeutically exploited as neuroprotective agents, “anti-addictive” medications, anticonvulsant, and antidepressant.

In this chapter, we will review the state of the art on these neuromodulators and their receptors in the brain and will discuss new hypotheses on their physiological and pathophysiological roles.

## 1 Introduction

Fatty acid ethanolamides, generally referred as *N*-acylethanolamines (NAEs), are a group of endogenous lipid molecules with long-chain fatty acids (Schmid et al. 1990; Hansen et al. 2000). It was long known that these molecules are ubiquitously found in animal tissues (Bachur et al. 1965), in both the periphery and the brain, and

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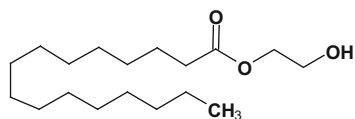
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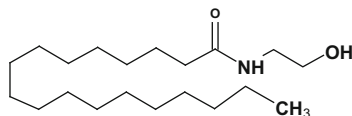
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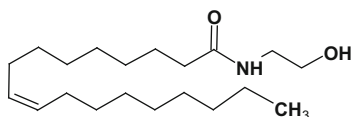
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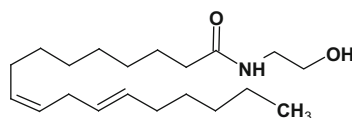
Palmitoylethanolamide (PEA)



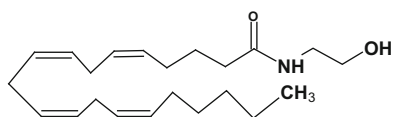
Stearoylethanolamide (SEA)



Oleoylethanolamide (OEA)



Linoleoylethanolamide (LEA)



Arachidonoylethanolamide (anandamide, AEA)

**Fig. 1** Chemical structures of representative NAEs

have attracted attention in recent years as they possess a variety of biological activities.

Among NAEs, the most studied are arachidonoylethanolamide (anandamide, AEA), palmitoylethanolamide (PEA), and oleoylethanolamide (OEA); other congeners are stearoylethanolamide (SEA) and linoleoylethanolamide (LEA) (Fig. 1) (Hansen 2010; Rahman et al. 2014). Anandamide is the first endocannabinoid to be discovered (Devane et al. 1992) and the only NAE to bind to cannabinoid type 1 (CB1) and type 2 (CB2) receptors. Quantitatively, anandamide is a minor component in most animal tissues when compared with other NAEs such as PEA, SEA, OEA, and LEA (Hansen and Diep 2009). NAEs, although belonging to the same extended endocannabinoid-like family as the cannabinoid agonist AEA, exert a variety of biological effects through several other receptors, in particular peroxisome proliferator-activated receptor- $\alpha$  (PPAR $\alpha$ ) (Hansen 2010; Lo Verme et al. 2005; Petrosino et al. 2010), but also G-protein-coupled receptors GPR55 (Baker et al. 2006) and GPR119 and transient receptor potential vanilloid type 1 (TRPV1) (Piomelli 2013).

Although these molecules were known from many years, the role of PEA and OEA, as well as of other NAEs, in the CNS has been elucidated only recently, when the discovery of AEA (Devane et al. 1992) fueled a renewed interest in these lipid messengers.

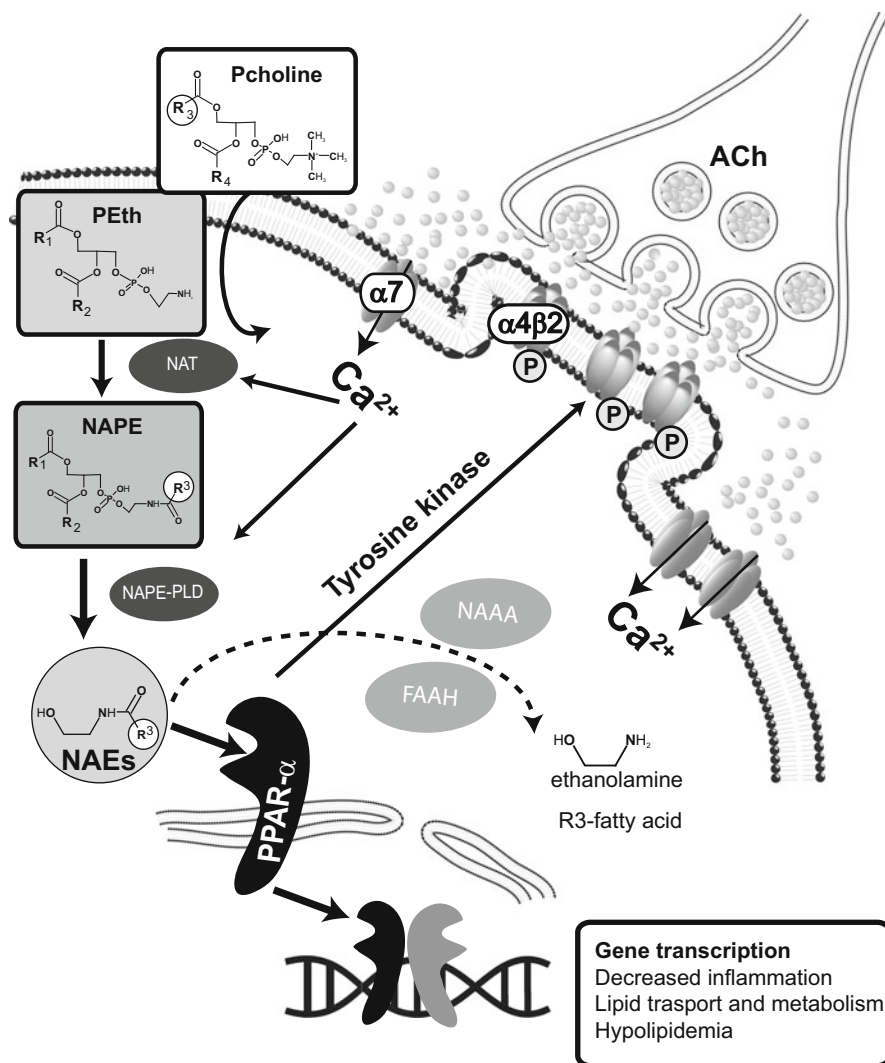
Specifically, functions and properties of PEA, a saturated fatty acid (palmitic acid) derivative, were discovered first in 1957, when this lipid (from soybeans, peanuts, and egg yolk) was found to exert anti-inflammatory activity in guinea pigs (Kuehl et al. 1957). High levels of PEA were measured in mammalian tissues, especially in the brain (Bachur et al. 1965). The finding that PEA is the most abundant NAE in the rat brain has been more recently substantiated by the use of lipidomics techniques (Kilaru et al. 2010).

The monounsaturated OEA is a potent anorectic lipid mediator (Fu et al. 2003, 2005; Rodriguez de Fonseca et al. 2001; Piomelli 2013) and shares this property with PEA, LEA (Hansen 2014; Hansen and Diep 2009), and SEA (Terrazzino et al. 2004). As anorexiant, however, PEA is significantly less potent than OEA in reducing food intake, and LEA is similar in potency to OEA (Rodriguez de Fonseca et al. 2001; Diep et al. 2011).

Besides their anti-inflammatory activity and their physiological functions as modulators of feeding behavior, NAEs, and specifically PEA and OEA, have been recently involved in pathophysiology of neurological and psychiatric disorders, ranging from addiction, neurodegenerative diseases, epilepsy, and mood disorders (Pistis and Melis 2010; Scherma et al. 2016; Melis and Pistis 2014). In this review, we will focus on physiology of non-cannabinoid NAEs in the CNS and on their relevance in neuropsychiatric disorders.

## 2 Synthesis and Catabolism

NAEs including AEA and the non-cannabinoid PEA and OEA are not stored in vesicles but produced “on demand”. Their endogenous levels are strictly regulated by enzymes responsible for their formation and degradation (Ueda et al. 2010a; Rahman et al. 2014). In fact, they are synthesized from glycerophospholipids via their corresponding *N*-acylphosphatidylethanolamines (NAPEs) (Okamoto et al. 2004; Rahman et al. 2014; Ueda et al. 2010b; Hansen 2010; Hansen et al. 2000). The classical pathway for NAE synthesis is a two-step process (Fig. 2). The first step is the generation of NAPE by a  $\text{Ca}^{2+}$ -dependent *N*-acyltransferase (NAT), which transfers the Sn-1 fatty acid to phosphatidylethanolamine from a donor phospholipid (Hansen et al. 2000; Hansen and Diep 2009). *N*-Acyltransferase is not specific for any fatty acids, since it catalyzes the transfer of any acyl group from the Sn-1 position of donor phospholipids. NAPE is then hydrolyzed by NAPE-hydrolyzing PLD (NAPE-PLD) with the generation of NAEs (Rahman et al. 2014). Human, mouse, and rat NAPE-PLD cloning allowed the functional characterization of NAE biosynthetic pathways (Okamoto et al. 2004). NAPE-PLD $^{-/-}$  mice (Leung et al. 2006) show a highly reduced  $\text{Ca}^{2+}$ -dependent conversion of NAPE to long-chain saturated and unsaturated NAEs in brain tissue. These mice display decreased levels of OEA and PEA, but similar levels of AEA compared with wild-type littermates (Leung et al. 2006). This indicates that AEA is formed by other



**Fig. 2** Schematic diagram illustrating the canonical biosynthetic and catabolic pathways for NAE formation and their cellular mechanisms of actions through their receptor of PPAR $\alpha$ . Phosphatidylcholine (Pcholine) donates a fatty acid moiety from the sn-1 position (R<sub>3</sub>) to a phosphatidylethanolamine (PEth). This reaction is catalyzed by N-acyltransferase (NAT). The resulting N-acylphosphatidylethanolamine (NAPE) is hydrolyzed by NAPE-PLD to the corresponding N-acylethanolamine (NAE). Activation of PPAR $\alpha$  by NAEs results in genomic effects (gene transcription) and in non-genomic actions, such as activation of a tyrosine kinase and phosphorylation of  $\beta 2^*$ nAChRs (i.e.,  $\alpha 4\beta 2$ ). Ca<sup>2+</sup> entry mediated by  $\alpha 7$ -nAChRs activates NAE synthesis through the Ca<sup>2+</sup>-dependent NAT and NAPE-PLD. Fatty acid amide hydrolase (FAAH) and NAE-hydrolyzing acid amidase (NAAA) are the major inactivating enzymes for OEA, PEA, and AEA which convert them into ethanolamine and corresponding fatty acids (oleic, palmitic, and arachidonic acids, respectively)

parallel pathways (Hansen and Diep 2009) and strongly suggests the existence of other NAE-forming enzymes within NAPE-PLD-independent pathways (Tsuboi et al. 2011; Simon and Cravatt 2010; Leung et al. 2006; Rahman et al. 2014). No gross phenotype in NAPE-PLD-deficient mice has been reported, whereas in humans a polymorphism of NAPE-PLD was associated with obesity in a Norwegian population (Wangensteen et al. 2010).

NAPE-PLD is expressed in many tissues, including the brain (Egertova et al. 2008; Morishita et al. 2005; Cristino et al. 2008; Suarez et al. 2008). The cellular localization of NAPE-PLD in the brain is informative on the functional significance of NAEs in the CNS. NAPE-PLD mRNA and immunoreactivity are located both presynaptically and postsynaptically and are intense in axons of the vomeronasal nerve projecting to the accessory olfactory bulb (Egertova et al. 2008) and in the hippocampus (Cristino et al. 2008; Egertova et al. 2008; Nyilas et al. 2008). Other brain areas with NAPE-PLD immunoreactivity are the cortex, thalamus, hypothalamus (Reguero et al. 2014; Egertova et al. 2008), and cerebellum (Suarez et al. 2008). The postsynaptic localization of NAPE-PLD indicates that NAEs may act as an autocrine or paracrine signal at receptors expressed in the same or neighboring cells. On the other hand, the axonal localization suggests that synthesized NAEs may be released to target postsynaptic neurons and regulate synaptic signaling.

The generated NAEs are then degraded to their corresponding free fatty acids and ethanolamine (Cravatt et al. 1996; Deutsch et al. 2002) (Fig. 2). This hydrolysis is catalyzed mainly by fatty acid amide hydrolase (FAAH) (Cravatt et al. 1996) and NAE-hydrolyzing acid amidase (NAAA) (Tsuboi et al. 2005). FAAH hydrolyzes all NAEs with high efficiency, and it is expressed in many different tissues and cell types, including in the brain.

NAAA has no sequence homology with FAAH and is expressed in lysosomes. NAAA displays same specificity toward unsaturated NAEs such as PEA to much greater extent than AEA (Tsuboi et al. 2007a). In the rat, NAAA is highly expressed in the lung, spleen, thymus, and intestine (Tsuboi et al. 2007a), very high in alveolar macrophages (Tsuboi et al. 2007b), but low in the brain.

Alternatively, AEA and other polyunsaturated NAEs are oxygenated in their polyunsaturated fatty acyl moieties and converted to prostamides by cyclooxygenase-2 (COX-2) (Yu et al. 1997; Kozak et al. 2002) or to other oxygenated metabolites by lipoxygenases (Hampson et al. 1995; Ueda et al. 1995) or by cytochrome P-450 (Bornheim et al. 1993). In addition to these enzymes, more recent studies revealed the involvement of new players in NAE metabolism (see Rahman et al. 2014 for a comprehensive review).

### 3 Receptors for NAEs

#### 3.1 Peroxisome Proliferator-Activated Receptor- $\alpha$ (PPAR $\alpha$ )

PPARs belong to the large superfamily of transcription factors, accounting 48 members in the human genome (Germain et al. 2006). The PPAR subfamily, specifically, is composed of three isotypes: PPAR $\alpha$ , PPAR $\gamma$ , and PPAR $\beta/\delta$ .

The denomination of these receptors dates back to the 1960s, when the lipid-lowering drug clofibrate was found to induce proliferation of peroxisomes in the liver and hepatomegaly in rodents (Thorp and Waring 1962; Hess et al. 1965). The receptor activated by clofibrate, other fibrates, and synthetic ligands was cloned and denominated peroxisome proliferator-activated receptor- $\alpha$  (Issemann and Green 1990). Although the other members of this subfamily ( $\beta/\delta$  and  $\gamma$ ) are structural homologs of PPAR $\alpha$ , they do not induce peroxisome proliferation (Graves et al. 1992; Dreyer et al. 1992; Schmidt et al. 1992). Nevertheless, the name has remained.

PPARs, like other nuclear receptors, are composed of four domains (Fidaleo et al. 2014), among which the DNA-binding domain and the ligand-binding domain, which are the most conserved portions of the protein across the different isotypes (Desvergne and Wahli 1999; Escriva et al. 1998; Laudet et al. 1992). The ligand-binding domain, in particular, is strikingly large in comparison with other nuclear receptors (Desvergne and Wahli 1999). This explains why PPARs are activated by a large number of diverse endogenous ligands as well as by synthetic agonists: saturated and unsaturated fatty acids (palmitic acid, oleic acid, linoleic acid, and arachidonic acid), NAEs, and eicosanoids (Desvergne and Wahli 1999).

Considerable evidence suggests that NAEs display most of their CNS activity through PPAR $\alpha$ . In HeLa cells stably expressing a luciferase reporter gene together with the ligand-binding domain of human PPAR $\alpha$ , OEA activates PPAR $\alpha$  with an EC<sub>50</sub> of 120 nM, whereas PEA displays lower potency (EC<sub>50</sub> of 3.1  $\mu$ M) (Lo Verme et al. 2005; Fu et al. 2003). Under identical conditions, SEA was reported to be ineffective (Lo Verme et al. 2005).

PPAR $\alpha$  has been cloned and characterized in several species, including humans (Sher et al. 1993). PPAR $\alpha$  expression is enriched in tissues with high fatty acid oxidation rates such as the liver, heart, skeletal muscle, brown adipose tissue, and kidney. It is also expressed in other tissues and cells including the intestine, vascular endothelium, smooth muscle, and immune cells such as monocytes, macrophages, and lymphocytes (Lefebvre et al. 2006; Chinetti et al. 1998) and in the CNS (Mandard et al. 2004; Galan-Rodriguez et al. 2009; Moreno et al. 2004; Braissant et al. 1996; Auboeuf et al. 1997). The highest PPAR $\alpha$  expression was found in the basal ganglia; some thalamic, mesencephalic, and cranial motor nuclei; the reticular formation; and the large motoneurons of the spinal cord (Fidaleo et al. 2014; Moreno et al. 2004). Besides neuronal localization, a specific distribution of PPAR $\alpha$  in ependymal and astroglial cells, but not in oligodendrocytes, was reported (Moreno et al. 2004).

Several structurally different classes of compounds bind to PPAR $\alpha$ , including the hypolipidemic fibrates. Saturated or monounsaturated NAEs are high-affinity ligands for PPAR $\alpha$ , particularly OEA which may be considered an endogenous ligand at concentrations normally achieved under physiological conditions (Fu et al. 2003).

### 3.2 GPR119 and GPR55

NAEs bind also to G-protein-coupled receptors 119 (GPR119) and 55 (GPR55). GPR119 is involved in insulin secretion, and, for this reason, it is emerging as a potential therapeutic target for type 2 diabetes, with beneficial effects on glucose homeostasis (Moran et al. 2014). There is no evidence of GPR119 expression in the CNS, therefore a detailed discussion of its functions is not within the aims of this chapter.

GPR55 is expressed in the CNS (Sawzdargo et al. 1999; Ryberg et al. 2007), as well as in peripheral tissues (intestine, bone marrow, immune and endothelial cells, spleen, and platelets) (Pietr et al. 2009; Balenga et al. 2011; Rowley et al. 2011; Cherif et al. 2015). GPR55 is a 319-amino acid protein that was cloned in 1999 and mapped to chromosome 2q37 in humans (Sawzdargo et al. 1999). GPR55 shows low amino acid homology with CB1 (13.5%) or CB2 (14.4%) (Ryberg et al. 2007; Kapur et al. 2009; Baker et al. 2006). Similarly to PPAR $\alpha$ , GPR55 is a receptor for small lipid mediators, and it is also activated by some synthetic cannabinoids and related molecules. The lipid lysophosphatidylinositol (LPI), which activates GPR55 but has no affinity for CB1 or CB2 receptors, was the first endogenous ligand identified for this receptor (Oka et al. 2007). Among lipids and NAEs, PEA binds with high affinity at GPR55 ( $EC_{50} = 1\text{--}20$  nM), whereas OEA is less potent ( $EC_{50} = 440$  nM) (Baker et al. 2006; Ryberg et al. 2007). Recent evidence suggests that GPR55 is involved in the regulation of axonal growth during development (Cherif et al. 2015). GPR55 participates also in central processing of neuropathic and inflammatory pain (Deliu et al. 2015) as it has been reported to play a pronociceptive role in the periaqueductal gray. Consistently, GPR55<sup>-/-</sup> (knockout) mice have been shown to be protected in models of inflammatory and neuropathic pain. This suggests that GPR55 antagonists may have therapeutic potential as analgesics for both these pain types (Staton et al. 2008). It is not clear how the anti-inflammatory and anti-neuropathic effects of PEA can be reconciled with the functional role of GPR55 in pain and inflammation. As little is known on the physiological roles of GPR55, particularly in the CNS, further studies are needed to shed some lights into this receptor and its endogenous agonists.

## 4 Physiological Role of NAEs and PPAR

PPAR $\alpha$  is a transcriptional regulator of genes involved in peroxisomal and mitochondrial  $\beta$ -oxidation, fatty acid transport, and, in rodents, hepatic glucose production (Xu et al. 2002). PPAR $\alpha$  negatively regulates pro-inflammatory and acute phase response signaling pathways, as seen in rodent models of systemic inflammation (Gervois et al. 2004; Bensinger and Tontonoz 2008; Glass and Ogawa 2006). Consistently, PPAR $\alpha^{-/-}$  mice display longer inflammatory responses (Devchand et al. 1996), increased susceptibility to experimental colitis, and experimental autoimmune encephalitis (an experimental model of multiple sclerosis) (Straus and Glass 2007). PPAR $\alpha$  agonists reduce peripheral inflammation in a PPAR $\alpha$ -dependent manner (Sheu et al. 2002; Lo Verme et al. 2005).

The canonical mechanism of action downstream to PPAR $\alpha$  activation is regulation of gene transcription (Ferre 2004; Berger and Moller 2002; Moreno et al. 2004). Specifically, ligand binding promotes dissociation of corepressor proteins, association of coactivators, and coactivator proteins and heterodimerization with the retinoid X receptor (RXR). This dimer is then translocated into the nucleus and binds to specific regions on DNA termed peroxisome proliferator response elements (PPRE). The result is either an increase or a decrease of gene transcription, depending on the target gene. Besides this typical transduction mechanism, non-transcriptional actions by PPAR $\alpha$  have also been observed (Melis et al. 2008; Ropero et al. 2009; Gardner et al. 2005). These effects are rapid in onset (2–5 min). This short onset time rules out the possibility of a genomic mechanism of action and involves signaling pathways similar to those described for many other nuclear receptor ligands (Losel and Wehling 2003; Losel et al. 2003; Moraes et al. 2007; Ropero et al. 2009). Consistent with this scenario, PPAR $\alpha$  activation induced production of cytosolic effectors, such as reactive oxygen species (Ropero et al. 2009; Melis et al. 2008).

These non-transcriptional effects take place also in the CNS and have the potential to regulate neuronal functions on a short timescale. In fact, our recent studies show that in ventral tegmental area (VTA), dopamine neurons OEA and PEA bind to PPAR $\alpha$  within the cytosol and trigger a rapid non-genomic mechanism leading to increased endogenous hydrogen peroxide and consequent activation of tyrosine kinase(s) (Melis et al. 2008, 2010). In turn, these tyrosine kinases phosphorylate the  $\beta$ 2 subunits of the nicotinic acetylcholine receptors (nAChRs) (Melis et al. 2013b). Phosphorylation of nAChRs is an efficient mechanism to control receptor functions and results in a faster desensitization rate or a downregulation (Huganir and Greengard 1990). As cholinergic afferents control firing rate and burst firing of midbrain dopamine cells, the functional regulation of  $\beta$ 2-containing nAChRs ( $\beta$ 2\*nAChR, the asterisk indicates the presence of other subunits) alters dopaminergic activity. Thus, NAEs as PPAR $\alpha$  ligands act as intrinsic modulators of cholinergic transmission and modify dopamine cell excitability, contributing to acetylcholine effects on dopamine system. Moreover, our studies revealed that PPAR $\alpha$ -induced regulation of  $\beta$ 2\*nAChR abolished electrophysiological,



neurochemical, and behavioral effects of nicotine (Scherma et al. 2008; Melis and Pistis 2014; Melis et al. 2013a, b; Panlilio et al. 2012). Therefore, enhancing brain levels of PPAR $\alpha$  endogenous agonists or activating this receptor with synthetic ligands represents a novel strategy for anti-smoking medications (Melis and Pistis 2014) (see next section).

Noteworthy, this cellular mechanism of action explains why the effects of PPAR $\alpha$  activation are specific to nicotine, as it does not attenuate cocaine or cannabinoid-induced electrophysiological or behavioral effects (Justinova et al. 2008, 2015; Luchicchi et al. 2010).

As mentioned above, PPAR $\alpha$  activation can be achieved by preventing degradation of endogenous ligands or by promoting their synthesis (Melis et al. 2013a, b). NAE's synthesis is increased by elevating intracellular Ca<sup>2+</sup>, as NAPE-PLD is a Ca<sup>2+</sup>-dependent enzyme (Ueda et al. 2001). In fact, activation of  $\alpha$ 7-nAChRs, a low-affinity Ca<sup>2+</sup>-permeable nAChR subunit combination, enhanced midbrain OEA and PEA levels and prevented nicotine-induced excitation of dopamine neurons both in vitro and in vivo (Melis et al. 2013b). Thus, these observations indicate that  $\alpha$ 7-nAChRs function as sensors in dopamine neurons for excessive cholinergic transmission, which is attenuated by subsequent PPAR $\alpha$  activation by endogenous agonists and phosphorylation of  $\beta$ 2\*nAChRs.

## 5 Role of NAEs and PPAR $\alpha$ in Neuropsychiatric Diseases

### 5.1 Addiction

In the past two decades, research advances have progressively sustained the idea of addiction as a brain disease (Volkow et al. 2016). In particular, addiction can be defined as a chronic, relapsing disorder of brain reward, motivation, cognition, affective functioning, memory, and related circuitry (American Society of Addiction Medicine, ASAM, 2011). Dysfunction in these pathways leads to a behavioral pathology characterized by compulsive drug seeking and use with progressive loss of control over consumption despite the emergence of significant negative or disadvantageous consequences (see Volkow et al. 2016 and references therein). In the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (2013), the term addiction is synonymous with the most severe stage of substance use disorder (see Volkow et al. 2016). Drug addiction represents the most prevalent neuropsychiatric disorder affecting modern society (United Nations Office on Drugs and Crime, 2015). The global health burden attributable to alcohol and illicit drug use amounts to 5.4% of the total burden of diseases (WHO 2003).

A better knowledge of the neurobiological basis underlying addiction is certainly crucial for developing more effective pharmacological and behavioral interventions to counteract harmful consequences of drug use disorders. In this respect, the evidence that NAEs such as OEA and PEA block nicotine-induced excitation of

midbrain dopamine neurons by acting on PPAR $\alpha$  (Melis et al. 2008) pinpointed their key role in the modulation of the brain reward system and, therefore, in the pathophysiology of nicotine addiction ((Melis et al.2010); reviewed in (Pistis and Melis 2010)). In fact, since dopamine neurons projecting from the VTA to the nucleus accumbens (NAc) act as “reward sensors,” these results offered new perspectives in both understanding and treating tobacco dependence. Accordingly, a study by Scherma et al. (2008) unveiled that boosting brain levels of NAEs reverses abuse-related behavioral and neurochemical effects of nicotine in rats, including those predictive of relapse liability (Scherma et al. 2008). But how does URB597 exert its anti-addictive and anti-rewarding actions? Both the receptor and the mechanism responsible for the effect played by enhanced NAE levels against nicotine were identified soon after (Melis et al. 2008). In particular, it was demonstrated that URB597 counteracts nicotine-induced stimulation of the dopamine system by selectively enhancing intracellular levels of OEA and/or PEA within this circuit and by activating PPAR $\alpha$  (Luchicchi et al. 2010; Melis et al. 2008; Mascia et al. 2011). However, even though PPAR $\alpha$  was recognized as the receptor accounting for the “anti-nicotine” effect played by NAEs (Melis et al. 2008), a contribution of CB1 receptors activated by anandamide cannot be completely ruled out (Luchicchi et al. 2010; Melis et al. 2008; Mascia et al. 2011).

This wealth of experimental data revealed a novel property of endocannabinoid-like NAEs and suggested that increasing brain levels of OEA and PEA, or activating their receptors (PPAR $\alpha$ ) with synthetic ligands, might represent a novel and effective approach for achieving smoking cessation (Melis et al. 2013a, b; Melis and Pistis 2014; Scherma et al. 2008). Hence, a new frontier for the treatment of tobacco addiction, the number one preventable cause of death in the developed world, was opened. In keeping with these observations, synthetic PPAR $\alpha$  ligands such as fibrates, long-standing clinically available hypolipidemic drugs, were found to suppress (i) nicotine-induced stimulation of dopamine neurons and increased extracellular dopamine levels in the shell of the NAc, which are key features of its acute rewarding properties (Panlilio et al. 2012), and (ii) nicotine intake and reinstatement of nicotine-seeking behavior after a period of prolonged abstinence (Panlilio et al. 2012). Thus, all this evidence has prompted the idea that targeting PPAR $\alpha$  represents a promising therapeutic strategy in nicotine relapse prevention in humans and, in the end, for quitting smoking.

So far, anti-addictive actions of PPAR $\alpha$  agonists seem to be almost exclusively limited to nicotine in laboratory animals (Justinova et al. 2008, 2015; Luchicchi et al. 2010). The fact that in dopamine neurons PPAR $\alpha$  affects the phosphorylation status of  $\beta$ 2\*nAChRs by activating tyrosine kinase(s) (Melis et al. 2010, 2013b), therefore leading to a reduced excitation of dopamine neurons by nicotinic agonists, might provide a possible explanation for this specificity. Hence, it is not surprising that URB597 does not influence either self-administration of the main psychoactive ingredient of cannabis (i.e.,  $\Delta$ 9-tetrahydrocannabinol,  $\Delta$ 9-THC) or cocaine in nonhuman primates (Justinova et al. 2008). Moreover, URB597 is unable to prevent dopamine neuronal responses to morphine or cocaine in rats (Luchicchi et al. 2010). Accordingly, in humans, it has been reported that a natural genetic variation in

FAAH, +385 A/A (P129T), is associated with an increased risk of illicit, but not licit (i.e., nicotine, alcohol), drug use problems (Sipe et al. 2002; Tyndale et al. 2007). Notably, this FAAH variant displays a reduced expression and activity in humans, thereby supporting a potential link between enhanced NAE circulating levels and illicit drug abuse and dependence (Chiang et al. 2004).

Most recently, a link of PPAR $\alpha$  (and  $\gamma$ ) with both alcohol consumption in rodents and withdrawal and dependence in humans emerged (Haile and Kosten 2017; Blednov et al. 2015). Specifically, Blednov et al. (2015) investigated the effects of different classes of PPAR agonists on chronic alcohol intake and preference in mice with a genetic predisposition for high alcohol consumption and then examined human genome-wide association data for polymorphisms in PPAR genes in alcohol-dependent subjects. According to the authors, the observed reduction of alcohol intake in mice and the genetic association between alcohol dependence and withdrawal (according to DSM-5 criteria) in humans underscore the potential for reconsidering clinically approved PPAR $\alpha$  or PPAR $\gamma$  agonists for the treatment of alcohol use disorders and alcoholism (Blednov et al. 2015). Consistently, administration of either OEA or synthetic PPAR $\alpha$  agonists was lately shown to block cue-induced reinstatement of alcohol-seeking behavior and reduce the severity of somatic withdrawal symptoms in alcohol-dependent rats (Bilbao et al. 2015; Haile and Kosten 2017; Blednov et al. 2016), thus supporting the intriguing possibility of using PPAR $\alpha$  as novel therapeutic tool also for alcoholism.

## 5.2 *Epilepsy and Other Neurological Disorders*

Epilepsy is a common and prevalent neurological disorder affecting 1–2% of the population worldwide (Thurman et al. 2011). As of 2015, nearly 50 million of people suffer from this disease, characterized by recurrent spontaneous seizures which negatively impact quality of life and respond to medication in about 70% of cases (see for a recent review Varvel et al. 2015). In addition, currently available antiepileptic drugs are mainly symptomatic and have numerous side effects. Thus, an urgent need exists to identify and exploit new, effective therapies. Unraveling the neurobiological mechanisms that subserve the generation of epilepsy will help the development of drugs to modify the disease outcome and, potentially, to prevent epileptogenesis. Intriguingly, the interplay between PPAR $\alpha$  and nAChRs shows relevance also for epilepsy and can be exploited as an innovative therapeutic target. Indeed, nAChRs are involved in the pathogenetic mechanisms underlying seizures and epilepsy. In particular, converging evidence from genetic studies in epileptic patients and animal models of seizures demonstrated that nAChR activity is increased in some types of epilepsy, including nocturnal frontal lobe epilepsy (De Fusco et al. 2000; Steinlein et al. 1997; Steinlein 2004; Sutor and Zolles 2001). From this standpoint, negative modulation of nAChRs exerted by endogenous NAEs, or by exogenous ligands of their receptors (PPAR $\alpha$ ), might represent a potential disease-modifying strategy for epilepsies where nAChRs contribute to

neuronal excitation and synchronization. This is particularly relevant considering that, as above mentioned, current therapies, besides from being ineffective in the 30% of patients, are mainly symptomatic and do not necessarily affect the epileptogenic process or the disease progression.

Accordingly, several preclinical studies have shown that selective agonists of PPAR $\alpha$  raise seizure thresholds, thus supporting PPARs as potential drug targets for seizure control (Auvin 2012). PEA, for example, proved to have antiepileptic effects in kindled rats (Sheerin et al. 2004) and showed anticonvulsant activity in mice (Lambert et al. 2001). Similarly, fenofibrate, a synthetic PPAR $\alpha$  ligand long used as hypolipidemic agent in clinical practice, has been reported to be effective as anticonvulsant in pentylenetetrazole (PTZ)-induced seizures and on latencies to the onset of status epilepticus induced by lithium-pilocarpine in adult rats (Porta et al. 2009). Likewise, acute and chronic PPAR $\alpha$  agonists (e.g., fenofibrate) are protective against nicotine-induced seizures and abolished nicotine-induced generation of ictal activity and synchronization in the frontal cortex (Puligheddu et al. 2013). Remarkably, these latter results were paralleled by an increased ratio of phosphorylated/dephosphorylated  $\beta$ 2 nAChR subunits in the frontal cortex following acute PPAR $\alpha$  ligand treatment, whereas the chronic regimen induced a threefold augment in OEA levels in the same brain region (Puligheddu et al., 2013).

Notably, these observations can also be applied to other models of epilepsy, since PEA was shown to display antiepileptic actions, though via direct PPAR $\alpha$  and indirect CB1 activation, in a rat genetic model of absence epilepsy (Citraro et al. 2013) and in DBA/2 mice (Citraro et al. 2016). In addition, a recent study by Saha et al. (2014) reported the anti-kindling effect of the PPAR $\alpha$  agonist bezafibrate in PTZ-induced kindling seizure model. Importantly, and not surprisingly, bezafibrate also reduced the neuronal damage and apoptosis in hippocampal areas of the rat brain (Saha et al. 2014).

In this scenario, it is worth to mention that ketogenic diet (KD) proved as efficacious as fenofibrate in exerting anticonvulsive properties in animal models of epilepsy (Porta et al. 2009). The KD is a high-fat, adequate-protein, and low-carbohydrate diet long used as beneficial therapy for refractory epilepsy, especially in children (Bough and Rho 2007). It has been proposed that KD, by increasing fast inhibition in the rat hippocampus dentate gyrus, might protect these neurons from excitotoxicity and, consequently, caused anticonvulsant and anti-epileptogenic effects (Bough et al. 2003). However, even though the KD mechanism of action is still unclear and under investigation (Porta et al. 2009; Bough and Rho 2007), it is tempting to hypothesize the existence of a direct, causal relationship between augmented levels of NAEs and activation of PPAR $\alpha$  following KD. In fact, both brain and peripheral tissue levels of NAEs change with high-fat diets (see Pistis and Melis, 2010 and references therein), thus suggesting that these lipid molecules would behave like PPAR $\alpha$  agonists (Cullingford 2008) and dampen hippocampal neuronal excitability (Bough et al. 2003). Moreover, circulating levels of different PPAR $\alpha$  endogenous ligands (e.g., fatty acids, oxysterols, hormones) might increase following KD and exert themselves the anticonvulsive properties ascribed to this diet (Pistis and Melis 2010).

Whether or not NAEs, as well as KD, have anticonvulsants and anti-epileptogenic effects via activation of PPAR $\alpha$ , it is undeniable the physiological role played by these receptors in neuroinflammation and protection from excitotoxicity and, therefore, a link between these phenomena (Pistis and Melis 2010; Melis and Pistis 2014). Hence, considering their multifaceted pharmacological properties (neurotrophic/neuroprotective and anti-inflammatory), PPAR pathways are under evaluation as potential therapeutic targets as well as vulnerability factors in Parkinson's disease (PD), Alzheimer's disease (AD), and multiple sclerosis (MS) (Pistis and Melis 2010; Fidaleo et al. 2014). For example, NAEs seem to be directly implicated in the pathogenesis of AD (Pazos et al. 2004), the most common cause of dementia and one of the leading sources of morbidity and mortality in the aging population (Reitz et al. 2011). Accordingly, OEA, PEA, and the NAE-enhancing FAAH inhibitor URB597 increase memory acquisition and consolidation in naïve rats in a PPAR $\alpha$ -dependent manner (Mazzola et al. 2009; Campolongo et al. 2009), while PPAR $\gamma$  improve both learning and memory not only in an experimental model of AD (Heneka et al. 2005) but also in AD patients (Risner et al. 2006; Watson et al. 2005; Landreth et al. 2008; Jiang et al. 2008). Importantly, activation of PPAR $\gamma$  is also able to ameliorate AD-related signs by reducing both microglial activation and A $\beta$  plaques (Heneka et al. 2005). In line with these observations, Scuderi et al. (2011, 2012) demonstrated that PEA anti-inflammatory properties are responsible for counteracting A $\beta$ -induced astrogliosis and helped to identify the molecular apparatus by which PEA, via PPAR $\alpha$  activation, contributes to downregulate astroglial reaction, pro-inflammatory signal overproduction, and neuronal loss. Next, an elegant *in vivo* study by D'Agostino et al. (2012) substantiated the fundamental role of PPAR $\alpha$  for the neuroprotective and memory-rescuing effects of PEA in an AD animal model (see (Scuderi and Steardo 2013; Mattace Raso et al. 2014) for recent reviews).

On the other hand, MS subjects show reduced levels of NAEs (Di Filippo et al. 2008), thus suggesting the involvement of endocannabinoid system imbalances also in the pathogenesis of MS (Shohami and Mechoulam 2006), the most widespread disabling neurological condition of young adults around the world (see for a recent review Ascherio and Munger 2016). However, it should be pointed out that during MS clinical exacerbations, levels of OEA, PEA, and AEA increased, although being still lower than in controls. This evidence consolidates the hypothesis that NAEs can have a significant impact in reducing inflammation and, therefore, act as endogenous neuroprotective molecules (Di Filippo et al. 2008). In accordance with this, an increase of CNS PEA levels has been observed in a mouse chronic model of MS (Loria et al. 2008), which might be interpreted as an adaptive mechanism to preserve function and integrity during the development of neurodegenerative damage (Mattace Raso et al. 2014). Noteworthy, in the same MS chronic model, PEA administration induced, together with an anti-inflammatory effect, a reduction of motor disability (Loria et al. 2008). Concerning PD, which is among the most prevalent neurodegenerative conditions (Pringsheim et al. 2014), a protective/neurotrophic (and, therefore, potentially therapeutic) role of NAEs has also been demonstrated. In particular, it has been shown that OEA significantly decreased

behavioral PD symptoms and exerted neuroprotective effects on the nigrostriatal circuit in an experimental model of the disease through a PPAR $\alpha$ -dependent mechanism (Galan-Rodriguez et al. 2009; Gonzalez-Aparicio and Moratalla 2014; Avagliano et al. 2016). Similarly, systemic administration of PEA reduced 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced glial cell activation and protected against MPTP-related loss of tyrosine hydroxylase-positive neurons in the substantia nigra pars compacta, two effects that were blunted in PPAR $\alpha$ -/- mice. Moreover, chronic administration of PEA reversed MPTP-associated motor deficits, as revealed by the analysis of forepaw step width and percentage of faults (Esposito et al. 2012). The fact that PEA proved to be neuroprotective even when administered after the insult is of particular importance, as the lack of PD biomarkers and the difficulties of early diagnosis make the pharmacotherapy of PD possible only when dopamine neuronal loss is advanced and the first symptoms have appeared (Esposito et al. 2012). Likewise, PPAR $\gamma$  ligands have been reported to arrest PD progression in preclinical settings (Randy and Guoying 2007; Carta 2013; Schintu et al. 2009; Pinto et al. 2016). However, it should be mentioned that a recent study published in *The Lancet Neurology* (NINDS Exploratory Trials in Parkinson Disease (NET-PD) FS-ZONE Investigators, 2015), which assessed the PPAR $\gamma$  agonist pioglitazone for its disease-modifying potential in early-stage PD, does not support initiation of further trials with this drug (see also Brundin and Wyse 2015).

### 5.3 *Mood Disorders and Schizophrenia*

The magnitude, suffering, and burden of mental health disorders in terms of disability and costs for individuals, families, and societies are astonishing. According to WHO's Global Burden of Disease reports, four of the six primary causes of years lived with disability are due to neuropsychiatric disorders (depression, alcohol use disorders, schizophrenia, and bipolar disorder). In particular, unipolar depression alone leads to 12.15% of years lived with disability and ranks as the third most important contributor to the global burden of diseases (Whiteford et al. 2013 and references therein). Depression is indeed a very common illness worldwide, with an estimated 350 million people affected, and is one of the priority conditions covered by WHO's Mental Health Gap Action Programme (Reed et al. 2015). Current therapies for this disorder are ineffective in many patients or cause intolerable side effects, thus highlighting the importance of novel, improved therapeutic options. Mesolimbic dopamine system dysfunctions have been implicated in numerous brain disorders, including depression (reviewed in Nestler and Carlezon 2006; Russo and Nestler 2013). Apart from specific anti-inflammatory and neuroprotective mechanisms, it has been proposed that PPARs may affect mood by interfering with its neurobiological bases (Rolland et al. 2013). Thus, NAEs, as endogenous PPAR $\alpha$  ligands and modulators of midbrain dopamine neuronal activity, are well suited to regulate several dopamine-dependent brain

physiological and pathological processes. Specifically, NAEs regulate cholinergic input onto dopamine cells and dampen hypercholinergic drive (Fig. 2) and the consequent aberrant excitation of dopamine neurons. This intrinsic negative feedback mechanism might be exploited as a therapeutic strategy in depression, which is characterized also by an unbalance between dopamine and acetylcholine systems (Melis et al. 2013b). Accordingly, experimental evidence suggests that abnormal nicotinic signaling may contribute to depressive symptoms (Mineur and Picciotto 2010; Tizabi et al. 2000) and raises the possibility that  $\beta_2^*$ nAChR availability could be a biomarker of depression, correlated with severity of the symptoms (see for a review Picciotto et al. 2015). Consistently, a recent human imaging study has revealed that ACh levels are elevated in patients who are actively depressed, as measured by occupancy of nAChRs throughout the brain, and remain high in patients who have a history of depression (Saricicek et al. 2012). In this context, the PPAR $\alpha$  agonist fenofibrate (Jiang et al. 2017; Scheggi et al. 2016) or WY-14643 (Yang et al. 2017), PEA (Yu et al. 2011), and FAAH inhibitors show antidepressant-like activity in rodents (Gobbi et al. 2005; Bortolato et al. 2007; Adamczyk et al. 2008; Umathe et al. 2011). In addition, OEA was also lately proven to be effective in ameliorating animal depression-like behaviors, even though through complex mechanisms (Yu et al. 2015; Jin et al. 2015). Similarly, PPAR $\gamma$  agonists (i.e., pioglitazone, rosiglitazone) have displayed some antidepressant-like properties in preclinical settings (Eissa Ahmed and Al-Rasheed 2009; Sadaghiani et al. 2011). Even though it is still unclear whether the PPAR $\gamma$  beneficial effect lays on the NO pathways (Sadaghiani et al. 2011) or whether it is NMDAR-related (Salehi-Sadaghiani et al. 2012), these results encouraged clinical research. In humans, few studies have been carried out so far, the first of which reporting a moderate improvement in two different depression scales in depressed (and insulin-resistant) patients treated with rosiglitazone (Rasgon et al. 2010). Subsequently, randomized controlled trials tested pioglitazone as adjunctive therapy (Sepanjnia et al. 2012) or as monotherapy (Colle et al. 2017) on subjects with a major depressive disorder and demonstrated a significant amelioration in early response, remission, and symptom attenuation for the pioglitazone-treated group. More recently, open-label administration of this PPAR $\gamma$  agonist was found to be associated with improvement of depressive symptoms in bipolar disorder patients (Kemp et al. 2014). Remarkably, a positive correlation has been observed between depressive symptomatology score and change in interleukin (IL)-6, thus indicating that reduction in inflammation might contribute to the mechanism by which pioglitazone modulates mood (Kemp et al. 2014).

Noteworthy, NAEs can also play a role in the etiopathogenesis of schizophrenia (see for a review Rolland et al. 2013), in which substantial dopamine transmission dysfunctions are strongly involved. Briefly, schizophrenia is a severe mental disorder afflicting approximately 1% of the population around the world (which corresponds to more than 21 million people) (see for a recent review Owen et al. 2016). Clinically, schizophrenia is characterized by profound disruptions in thinking that affect language, perception, and the sense of self. The so-called psychotic experiences (or positive symptoms), such as hearing voices or delusions, are the



main target of current antipsychotic drugs which all block dopamine D2 receptors (Leucht et al. 2009). In line with this, and with the above discussed observations, PPAR $\alpha$  may exert antipsychotic effects by dampening dopamine neuron activity. Data from preclinical and clinical studies seem to support this hypothesis. For example, the PPAR $\alpha$  agonist fenofibrate reduces prepulse inhibition disruption in a neurodevelopmental model of schizophrenia, an effect that might be explained by a direct action of fenofibrate on dopaminergic transmission (Rolland et al. 2012). Consistently, PPAR $\alpha$  or  $\alpha$ 7-nAChRs agonists have been demonstrated to be beneficial in animal models of schizophrenia (Zanaletti et al. 2012; Rolland et al. 2012; Kucinski et al. 2012; Pichat et al. 2007; Thomsen et al. 2012). Moreover, since the idea is emerging that schizophrenia displays a pro-inflammatory phenotype (e.g., pro-inflammatory cytokines IL-6 and TNF- $\alpha$  are upregulated in obesity, inflammation, and schizophrenia), a recent human genetic study measured expression of prototypic obesogenic and immunogenic genes in peripheral blood cells from controls and schizophrenic patients (Chase et al. 2015). Intriguingly, Chase et al. reported a profound dysregulation of genes relating to metabolic inflammation, including a significant decrease in PPAR $\alpha$  mRNA levels and increases in IL-6 and TNF- $\alpha$ , with additional BMI interactions. Finally, a recent (Croatian) population study aimed at determining whether a functional L162V polymorphism in PPAR $\alpha$  gene, extensively investigated in the etiology of abnormal lipid and glucose metabolism, was also linked to schizophrenia risk (Nadalin et al. 2014). While the PPAR $\alpha$ -L162V polymorphism did not show an association with schizophrenia risk, it impacts clinical expression of the illness and plasma lipid concentrations in female patients (Nadalin et al. 2014). According to the authors, these polymorphisms could have a possible protective effect toward negative symptom severity in female schizophrenic patients.

## 6 Concluding Remarks

The explosion of research in the field of the endocannabinoid system in the last two decades has fueled an increased interest in lipid messengers. NAEs have many similarities with endocannabinoids: they share synthetic and catabolic pathways but also the logic in signaling mechanism, as they are produced “on demand” and their diffusion and targets are not restricted to the prototypical anterograde signaling that characterizes classical neurotransmitters. Yet, peculiarities are emerging that might render NAEs and their receptors a new Pandora’s box for pharmacologists. NAE signaling in the CNS is engaged under physiological conditions but, more importantly, under several pathological circumstances. Thus, exploiting these targets with novel pharmacological tools will help us to better understand pathophysiological mechanisms in neuropsychiatric disorders and will pave new roads to therapeutic intervention.



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