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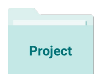

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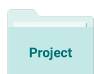

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Biochimie 92 (2010) 724–727

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Review

N-palmitoyl-ethanolamine: Biochemistry and new therapeutic opportunities

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ARTICLE INFO

Article history:
Received 30 October 2009
Accepted 12 January 2010
Available online 21 January 2010

Keywords:
N-Acylethanolamines
PEA
Inflammation
Allergy
Pain
FAAH
NAAA

ABSTRACT

Although its presence in mammalian tissues has been known since the 1960s, *N*-palmitoyl-ethanolamine (PEA) has emerged only recently among other bioactive *N*-acylethanolamines as an important local pro-homeostatic mediator which, due to its chemical stability, can be also administered exogenously as the active principle of current anti-inflammatory and analgesic preparations (e.g. Normast®, Pelvilen®). Much progress has been made towards the understanding of the mechanisms regulating both the tissue levels of PEA under physiological and pathological conditions, and its pharmacological actions. Here we review these new developments in PEA biochemistry and pharmacology, and discuss novel potential indications for the therapeutic use of this compound and of synthetic tools that selectively retard its catabolism, such as the inhibitors of the recently cloned *N*-acylethanolamine-hydrolyzing acid amidase.

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1. Introduction

N-palmitoyl-ethanolamine (PEA) is an endogenous fatty acid amide known since the 1950s as an anti-inflammatory component of egg yolk, and marketed for some time during the 1970s in Eastern Europe under the brand name of impulsin, for the prevention of virus infection of the respiratory tract [1]. More recently, PEA has been emerging as an important analgesic, anti-inflammatory and neuroprotective mediator, acting at several molecular targets in both central and sensory nervous systems as well as immune cells [2,3]. PEA belongs to the family of the *N*-acylethanolamines (NAEs) (Fig. 1A), which: 1) include the first endocannabinoid to be discovered, *N*-arachidonoyl-ethanolamine (anandamide, AEA) and the anorectic mediator *N*-oleoyl-ethanolamine (OEA); and 2) share with PEA similar anabolic and catabolic pathways. One of the enzymes responsible for the biosynthesis of NAEs from their direct biosynthetic precursor, the corresponding *N*-acyl-phosphatidyl-ethanolamines (NAPEs), is the NAPE-selective phospholipase D (NAPE-PLD) and has been cloned [4,5]. *N*-palmitoyl-phosphatidyl-ethanolamine is converted into PEA by this enzyme. However, other possible pathways are reported for the conversion of NAPEs into the corresponding NAEs [6], including: 1) a secretory phospholipase 2 ($sPLA_2$) that hydrolyzes NAPEs into *N*-acyl-lyso-phosphatidyl-ethanolamines (lyso-NAPE), which are then hydrolysed to NAEs by a lysophospholipase D [7]; 2) an alpha/beta-hydrolase 4 (Abh4) that acts as a lysophospholipase/phospholipase B for the formation of glycerol-phospho-NAEs, which are then converted to NAEs by the glycerophosphodiester phosphodiesterase GDE1 [8]; and 3) a PLC-dependent pathway for NAPE conversion to phospho-NAEs, followed by formation of NAEs via the protein tyrosine phosphatase N22 (PTPN22) [9,10].

Also the proteins involved in the degradation of NAEs have been identified and cloned. Fatty acid amide hydrolase (FAAH), an intracellular integral membrane protein of 597 amino acids belonging to the amidase family of enzymes and characterized by the optimal pH value of 8.5–10, catalyses the hydrolysis of NAEs into the corresponding fatty acids and ethanolamine [11,12]. Recently, another enzyme not related to FAAH, with structure homology to ceramidase and belonging to the family of choloylglycine hydrolases, has been cloned and found to hydrolyze preferentially PEA [13]. The enzyme, known as *N*-acylethanolamine-hydrolyzing acid amidase (NAAA), is highly expressed in macrophages and the lungs, as well as in various rat tissues including the brain [14,15]. It is characterized by an optimal pH of 5 (and, hence, localizes to lysosomes), is activated by self-catalysed proteolysis and is stabilized by *N*-glycosylation of Asn-37, Asn-107, Asn-309, and Asn-333 [16].

Three mechanisms have been proposed so far to explain the anti-inflammatory and analgesic effects of PEA. The first mechanism, which does not exclude the other two, suggests that PEA acts by down-regulating mast-cell degranulation via an "Autacoid Local Inflammation Antagonism" (ALIA) effect [17]. The "entourage effect" [18,19], instead, postulates that PEA acts by enhancing the anti-inflammatory and anti-nociceptive effects exerted by AEA, which is

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doi:10.1016/j.biochi.2010.01.006

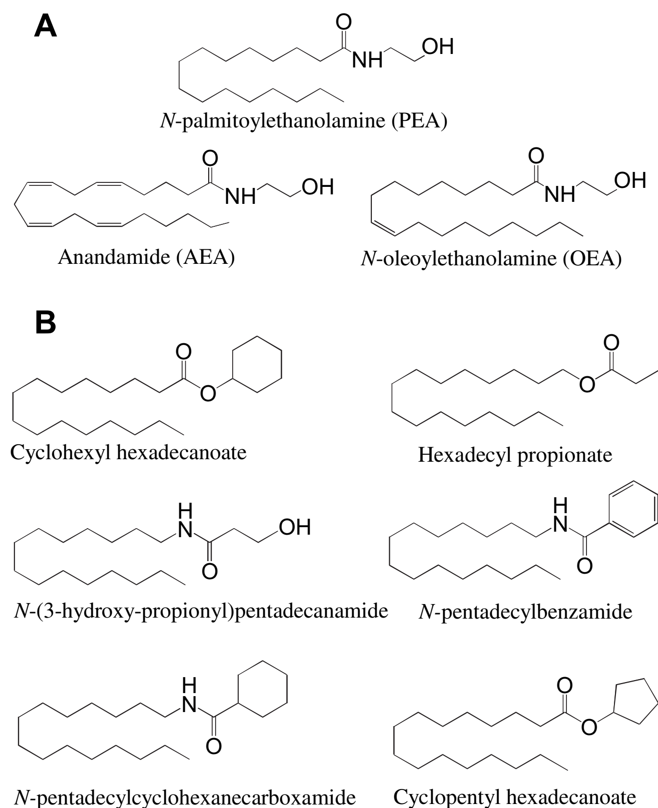

Fig. 1. (A) Chemical structures of some of the most studied bioactive *N*-acyl-ethanolamines. (B) Chemical structures of some specific inhibitors of *N*-acyl-ethanolamine-hydrolyzing acid amidase (NAAA).

often produced together with PEA, and activates cannabinoid CB_1 and CB_2 receptors or transient receptor potential vanilloid receptor type 1 (TRPV1) channels [20–24]. Finally, the "receptor mechanism" is based on the capability of PEA to directly stimulate either an as-yet uncharacterized cannabinoid CB_2 receptor-like target [25–27], or the nuclear peroxisome proliferator-activated receptor-α (PPAR-α), which clearly mediates many of the anti-inflammatory effects of this compound [2], or the orphan receptor G-protein coupling, GPR55, the functional activity of which some authors [28], but not others [29], found to be stimulated by PEA as well as AEA.

PEA has been proposed to act as a protective endogenous mediator produced "on demand" during inflammatory and neurodegenerative conditions to counteract inflammation, neuronal damage and pain. In fact, several studies demonstrate that, like with the endocannabinoids, AEA and 2-arachidonoylglycerol, also the tissue concentrations of PEA are altered during different pathological conditions [3,30]. However, unlike the endocannabinoids, the lack of pharmacological tools able to selectively modulate its tissue levels (such as specific inhibitors of its biosynthesis or degradation), has negated so far the definitive and convincing demonstration of such protective functions for endogenous PEA.

2. Towards the development of NAAA inhibitors

Whilst there are several examples of selective and potent FAAH inhibitors [6], to date there is almost no report of NAAA inhibitors. Vandevoorde et al. were the first to propose that different esters, retroesters and retroamides of palmitic acid could act as such inhibitors [31]. In fact, the screening of these compounds allowed to identify three compounds that weakly inhibit NAAA: cyclohexyl hexadecanoate, hexadecyl propionate and *N*-(3-hydroxy-propionyl)pentadecanamide, with IC_{50} values of 19 μM, 54 μM and 32 μM, respectively [31,32] (Fig. 1B). These compounds were selective for NAAA, with no inhibitory activity on FAAH [32]. Later, Tsuboi et al. synthesized two cyclohexyl hexadecanoate analogues: *N*-pentadecyl-cyclohexanecarboxamide and *N*-pentadecylbenzamide (Fig. 1B), which exhibited stronger inhibitory activity, with IC_{50} values of 4.5 μM and 8.3 μM, respectively [33].

On the base of this background, we recently designed and synthesized new PEA analogues by substituting either the ethanolamine or the alkyl function of PEA, and established a specific enzymatic assay of NAAA activity, using human embryonic kidney (HEK)-293 cells in which the cDNA encoding the human enzyme was stably overexpressed (HEK-NAAA cells) [33]. In agreement with the findings previously obtained by Tsuboi et al. in various cells [14] and by Ueda et al. in mammalian tissues [34], we found that significant NAAA enzymatic activity was present in HEK-NAAA cells as compared to wild type HEK-293 cells. Moreover, NAAA activity was predominantly observed in the membranes (submitted to two cycles of freezing and thawing) and lysosome fractions of HEK-NAAA cells, as previously described by Tsuboi et al. [14]. Consequently, we concluded that HEK-NAAA cells were functionally useful for subsequent experiments. To validate the assay, we next tested *N*-pentadecyl-cyclohexanecarboxamide and found that the inhibition was concentration-dependent with an IC_{50} value under our conditions (17 ± 1.4 μM) higher than that previously reported by Tsuboi et al. for the rat lung [32]. On the other hand, the screening of our novel analogues of palmitic acid led us to identify a compound more potent than *N*-pentadecyl-cyclohexanecarboxamide, in which the amide bond and the cyclohexyl group of were exchanged to an ester bond and a cyclopentyl group, respectively. This new compound, cyclopentyl hexadecanoate, inhibited NAAA by 85% at 50 μM and with an IC_{50} value of 10.0 ± 2.1 μM. Moreover, cyclopentyl hexadecanoate showed no inhibitory activity on FAAH, nor any binding capability to CB_1 and CB_2 receptors, nor any functional activity at TRPV1 receptors, at concentrations as high as 50 μM. The type of inhibition of NAAA by cyclopentyl hexadecanoate, evaluated by using Lineweaver–Burk plots (Fig. 2A), appeared to be of a competitive nature, since, in the presence of the compound, the apparent K_m value for PEA was significantly enhanced from to 118 ± 2.0 μM to 198 ± 1.0 μM, with no significant change in the V_{max} value (11.1 ± 3.6 $nmol^{-1}$ min mg proteins and 14.1 ± 3.4 $nmol^{-1}$ min mg proteins, respectively). Cyclopentyl hexadecanoate also inhibited NAAA in intact HEK-NAAA cells since it increased the levels of PEA without influencing the levels of two other *N*-acyl-ethanolamines, AEA and OEA, nor of the endocannabinoid 2-arachidonoylglycerol (Fig. 2B).

Cyclopentyl hexadecanoate may be useful both as a template to design new and more potent NAAA inhibitors and as a pharmacological tool to investigate the consequences of pharmacological elevation of endogenous PEA levels in cells and tissues. For example, in a model of chronic inflammation in rats, in which PEA levels are significantly reduced during carrageenan-induced granuloma, and PEA exerts anti-inflammatory and anti-angiogenic effects [35], also cyclopentyl hexadecanoate reduces inflammation at a dose similar to that of PEA (800 μg, local injection) (Fig. 2C), thus strongly supporting the hypothesis that the inflammatory reaction in this model is sustained by reduction of the local levels of anti-inflammatory PEA. Importantly, during the revision process of the present article, Solorzano and colleagues [36] reported the development of another selective NAAA inhibitor, *N*-[(3S)-2-oxo-3-oxetanyl]-3-phenylpropanamide (IC_{50} = 0.42 μM against the rat enzyme), and found that this compound blunts responses induced by inflammatory stimuli both in vitro and in vivo, while elevating PEA levels in vitro.

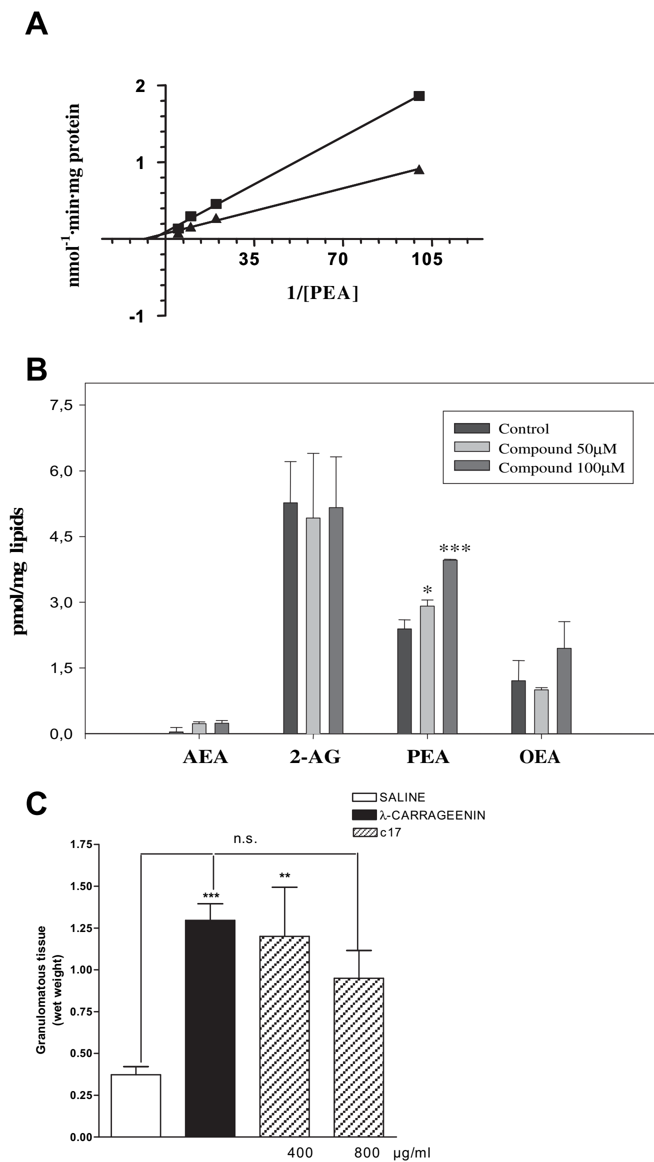

Fig. 2. Pharmacological activity of the selective inhibitor of *N*-acyl-ethanolamine-hydrolyzing acid amidase (NAAA), cyclopentyl hexadecanoate. (A) Lineweaver Burk plots for the inhibition of human recombinant NAAA by cyclopentyl hexadecanoate [32]. HEK-NAAA cells were suspended and homogenized in TRIS-HCl 20 mM (pH 7.4). The 12,000 × g pellet (membranes) was suspended in PBS (pH 7.4), subjected to two cycles of freezing and thawing and used in the assay. The enzyme preparation (50 μg/sample) was allowed to react at 37 °C for 30 min with varying concentrations of [$^{1,2-14}$C]PEA in citrate/sodium phosphate 50 mM (pH 5.2) and 0.1% Triton X-100, and in the presence of 20 μM cyclopentyl hexadecanoate (■) or in its absence (▲). The reaction was terminated by the addition of chloroform/methanol (1:1 by vol.) and quantification of [$^{1,2-14}$C]Ethanolamine was carried out by using Liquid Scintillation Analyzer [32]. (B) Effect of cyclopentyl hexadecanoate (denoted here as "compound") on *N*-acyl-ethanolamine levels in HEK-293 cells overexpressing the human recombinant NAAA [32]. Cells and supernatants were homogenized in a solution of chloroform/methanol/Tris–HCl 50 mM pH 7.4 (2:1:1 by vol.) containing 10 pmol of [^{2}H]$_8$-AEA, and 50 pmol of [^{2}H]$_5$-2-AG, [^{2}H]$_4$-PEA and [^{2}H]$_2$-OEA as internal standards. The lipid-containing organic phase was pre-purified by chromatography on silica gel and analyzed by liquid chromatography–atmospheric pressure chemical ionization–mass spectrometry (LC–APCI–MS). Measurement of AEA, 2-AG, PEA and OEA were carried out by isotope dilution and using the selected ion monitoring (SIM) mode [25,34]. *, $P < 0.05$; ***, $P < 0.005$ vs. control, using one way-ANOVA followed by Bonferroni's test. (C) Effect of cyclopentyl hexadecanoate (denoted here as "c17") on granuloma weight in the chronic inflammation granuloma model [34]. Briefly, two polyether sponges (0.5 × 1.5 × 2.0 cm) were implanted subcutaneously on the back of Male Wistar rats ($n = 4$ for each group) under general anesthesia with pentobarbital (60 mg/kg). Carrageenin (1% w/v) (Sigma) was dissolved in pyrogen-free saline and injected into each sponge in presence or absence of 100 μl of different concentrations of the NAAA inhibitor (400; 800 μg/ml) in a final volume of 0.5 ml/sponge; saline (0.5 ml/sponge) was used as control. Ninety-six hours after sponge implantation, rats were sacrificed in atmosphere of CO_2. The granulomatous tissue around the sponge was dissected by using a surgical blade, weighted, quickly frozen in liquid nitrogen, and stored at −80 °C. Animal care as well as all experiments were in accordance with European Community Council Directive 86/609/EEC and efforts were made to minimize animal suffering and to reduce the number of animals used. **, $P < 0.01$; ***, $P < 0.005$ vs. vehicle; n.s., not significant, using one way-ANOVA followed by Bonferroni's test.

3. New therapeutic opportunities from PEA

In the last two years, there have been numerous reports of pharmacological effects suggesting the therapeutic use of PEA (or of compounds inhibiting its degradation), and supporting most of the mechanisms of action proposed so far for this mediator. In particular, in an experimental model of spinal cord injury in mice [37], the intraperitoneal administration of PEA significantly reduced the degree of spinal cord inflammation and tissue injury, neutrophil infiltration, nitrotyrosine formation, proinflammatory cytokine expression, nuclear transcription factor activation-kappaB activation, inducible nitric-oxide synthase expression and apoptosis. Moreover, PEA treatment ameliorated the recovery of motor limb function [37]. All these effects were absent in PPAR-α null mice [37]. A PPAR-alpha-dependent mechanism was also proposed to underlie the effect of the intracerebroventricular administration of PEA in mice following carrageenan injection. PEA markedly reduced mechanical hyperalgesia through inhibition IkB-alpha degradation and p65 NF-kappaB nuclear translocation [38].

On the contrary, a mechanism potentially dependent on indirect cannabinoid receptor activation by PEA was proposed in a chronic model of multiple sclerosis in mice, where the exogenous administration of PEA resulted in a reduction of motor disability, accompanied by an anti-inflammatory effect through the reduced expression of typical proinflammatory cytokines [39]. Indeed, many papers demonstrate an "entourage mechanism" of PEA. In particular, the intraperitoneal administration of PEA in mice with chronic constriction injury of sciatic nerve evoked a relief of both thermal hyperalgesia and mechanical allodynia in neuropathic mice [25]. Several selective receptor antagonists were used in order to clarify the relative contribution of cannabinoid, vanilloid and peroxisome proliferator-activated receptor to PEA-induced effects. The results indicated that CB_1, PPARγ and TRPV1 receptors mediate the anti-nociceptive effect of PEA, suggesting an "entourage" action due to the enhancement of AEA effects at these receptors [25]. More recently, it was also reported that, in the spinal cord, PEA acts as an entourage compound for the hypotensive effects of intrathecally administered endocannabinoids [40]. However, the neuroprotective effect of PEA in a rat model of stroke was recently suggested to occur via a non-CB_1, non-TRPV1-dependent intracellular mechanism [41].

Finally, we recently reported the protective effect of PEA in an experimental model of contact allergic dermatitis (CAD) and demonstrated that this effect occurs via an "entourage" mechanism in keratinocytes [42]. In fact, we found that following induction of CAD with 2,4-dinitrofluorobenzene (DNFB), ear skin PEA levels were increased and the expression of TRPV1 and PPAR-α, as well as of NAPE-PLD, were up-regulated in ear keratinocytes [42]. In addition, in human keratinocytes (HaCaT cells), the stimulation with poly-inosinic–polycitidilic acid (poly-(I:C)) elevated the levels of both PEA and AEA, and exogenous PEA (10 μM) inhibited poly-(I:C)-induced expression and release of monocyte chemotactic protein-2 (MCP-2) in a way reversed by antagonism of TRPV1, but not PPAR-α or CB_2 receptors [42]. PEA (5–10 mg/kg, i.p.) also inhibited DNFB-induced ear inflammation in mice *in vivo*, in a way again attenuated by TRPV1 antagonism, thus suggesting an "entourage" effect of PEA at TRPV1 receptors [42].

In conclusion, PEA, its analogues, and agents that inhibit specifically its degradation are likely to result in the development of new therapeutic strategies for the treatment of pathological conditions also different from pain and inflammation. In support of this possible future outcome, it is important to point out that a PEA preparation is already on the market in Italy under the brand name Normast® (www.normast.com), a dietary component for special medical purposes, advised for pathological conditions that are sustained by mast cell-mediated tissue hyper-reactivity.

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