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Review

Palmitoylethanolamide (PEA)—'Promiscuous' anti-inflammatory and analgesic molecule at the interface between nutrition and pharma

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ABSTRACT

Palmitoylethanolamide (*N*-palmitoylethanolamine or PEA) is an endogenous fatty acid amide belonging to the N-acylethanolamine (NAE) class of signalling molecules. Earliest reports on the anti-inflammatory and immune modulating properties of PEA date back to 1957 when its isolation from soy lecithin, peanut meal, and egg yolk was reported. PEA is structurally related to anandamide and other endocannabinoids and possesses similar pathways for synthesis and breakdown. However, instead of being an endocannabinoid *per se*, PEA may be called a 'promiscuous' compound. It does not bind to cannabinoid receptors but interacts with several other receptors and non-receptor targets. This rather complex biology has indisputably contributed to the initially slow development of PEA, which witnessed a revival around 1993 with the seminal work of the late Rita Levi-Montalcini. Presently the compound is receiving increasing attention as a drug or nutraceutical against chronic pain, inflammation and degenerative diseases of the central nervous system. In this paper we review the development and pharmacology of this remarkable lipid mediator with its pleiotropic and 'promiscuous' character. The history of PEA exemplifies an evolving paradigm shift in pharma and nutrition from 'single-target' to 'multiple-target' approaches and provides new perspectives for future development in these fields.

1. Introduction

Palmitoylethanolamide (*N*-palmitoylethanolamine or PEA) (Fig. 1) is an endogenous fatty acid amide belonging to the *N*-acylethanolamine (NAE) class of signalling molecules. Earliest reports on its immune modulating properties date back to 1957 when scientists from Merck Sharp & Dome described its isolation from soy lecithin, peanut meal, and egg yolk and showed it to possess anti-inflammatory activities [1]. In the 1970s PEA has been temporary available as an approved medicinal product (Impulsin®) in former Czechoslovakia, especially used for the treatment and the prophylaxis of flu and respiratory infections [2]. However, the molecule remained largely unnoticed in the rest of the world until in the early 1990s Nobel Prize laureate Rita Levi-Montalcini proposed that PEA is an endogenously produced regulator of inflammation [3]. The revival of the molecule in the 1990s coincided with the discovery of the endocannabinoid system at that time. However, despite being a structural analogue of anandamide (arachidonoyl ethanolamide, AEA) [4,5] (Fig. 1) and some other NAE ligands of the cannabinoid receptors CB_1 and CB_2, PEA is not a typical endocannabinoids and has no significant affinity for these receptors [6–8]. Instead PEA possesses a broad spectrum of pharmacological activities, including interactions with G protein-coupled receptors GPR 55 and119 [9–11], nuclear receptors PPAR $\alpha/\gamma/\delta$ [6,12], ion channels TRPV1 [13,14], ATP-sensitive K^+ channels, and Ca^{2+}-activated K^+ channels [15,16]. Obviously, this "promiscuous" nature, which is more often seen with fatty acid amides [17] will have contributed to its initially slow development. It has now become clear that PEA is a highly abundant signalling molecule reaching concentrations in brain and peripheral tissues as high or even higher as those of anandamide and other known NAEs [18]. Next to its signalling properties, PEA appears to play a protective role in situations of biochemical stress, such as in ischaemia in vertebrates and invertebrates up to protection against ageing in plants [19,20]. An increasing number of non-clinical and clinical data from recent years are supporting its therapeutic potential, in particular in the field of pain and inflammation, in neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease, as well as in traumatic brain injury, brain ischaemia, multiple sclerosis and amyotrophic lateral sclerosis [21]. The history of PEA exemplifies the reversed pharmacology of a multi-target molecule, an example of a compound which previously might been referred to as

Abbreviations: n-3 LC-PUFA, (n-3) long chain polyunsaturated fatty acid; 2-AG, 2-arachidonoyl-glycerol; AEA, arachidonoylethanolamide (anandamide); CB (receptor), cannabinoid (receptor); GPCR, G-protein coupled receptor; FAAH, fatty acid amide hydrolase; PPAR, peroxisome proliferator-activated receptor; PEA-, palmitoylethanolamine; TRVP1, transient receptor potential channel type V1.

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'dirty' or 'promiscuous' drug, into a promising pharmacological and nutraceutical multi-target lead. The present review illustrates the development path of PEA from the early 1940s, when egg yolk was shown to contribute to the protection against rheumatic fever among poorly nourished children in New York, to the most recent studies on its activities.

2. 'Nutritional factor' in egg yolk becomes a multi-target signalling molecule

In 1943, Alvin F. Coburn and Lucile V. Moore discovered an association between egg consumption or supplementation of dried egg yolk and the incidence of rheumatic fever (caused by haemolytic streptococcal infection) in poor New York children [22]. In later studies Coburn and colleagues confirmed that supplementation of children's diets with egg yolk or fractions thereof not only contributed to a decreased susceptibility against rheumatic fever in children, but that yolk also contained an active fraction with anti-allergic activity in guinea pigs [23–25]. In parallel, Long et al. reported in a Lancet paper the finding of a 'factor' from peanut (arachis) oil that attenuated the response to tuberculin in B.C.G.-infected guinea pigs [26]. In 1957, these observations converged when Kuehl et al. were the first to demonstrate the isolation of PEA from egg yolk, soybean, and peanut meal [1]. It is now known that PEA and other NAEs as well as their N-acylphosphatidylethanolamine (NAPE) precursors are widely abundant in plants, in particular seeds [20,27,28]. In the next 40 years following its first isolation and characterization PEA did not receive much attention. LoVerme et al. [6] describe in 2005 how the compound became the active ingredient of a licensed medicine for the treatment of influenza and common cold in former Czechoslovakia during the 70s of the 20th century. During that period a number of clinical studies of apparently good quality underlined its activity as prophylactic against acute respiratory tract infections in adults and in children [2,29]. However, these findings remained largely unnoticed since it lasted until the 90s of last century before the compound started its revival. Following the cloning of the CB_1 [30] and CB_2 receptors [31] the first endogenous cannabinoid, anandamide was discovered [4]. Further search for structural analogues of the prototypical endocannabinoids revealed the existence of a large group of "endocannabinoid-related" compounds formed by conjugation of fatty acids with ethanolamine or other biological amines. Initially, PEA was referred to as 'ALIAmide' [5,32] based on findings from the lab of Levi-Montalcini that the compound reduced mast cell degranulation which was considered as part of a local autacoid regulatory effect ('ALIA' from 'autacoid local inflammation antagonist') [3]. Subsequent studies demonstrated that 'ALIAmide' displayed an activity pattern different from that of AEA and other endocannabinoids [33–35]. Since then several lines of research have shown that PEA behaves like a multi-target compound interacting with different receptors and other mechanisms [6,35–37].

3. Metabolism, targets and non-clinical pharmacology

3.1. PEA formation and breakdown

Palmitoylethanolamide belongs to the fatty (-acid) amides, conjugates of fatty acids with ethanolamine, amino acids or mono-amine neurotransmitters which are widely occurring in nature [38,39]. The biological and pharmacological properties of fatty (acid) amides do not follow their chemical classification (http://www.lipidmaps.org) and have shown to be very diverse. Anandamide, the conjugate of arachidonic acid with ethanolamine is a known ligand for both CB_1 and CB_2 receptors. However, it also binds to other receptors and interacts with non-receptor targets [40]. Furthermore, several other NAEs show different pharmacological profiles, including affinity for GPR55, GPR18, GPR119, TRPV1 (transient receptor potential channel type V1), PPARα, -γ, or -δ (peroxisome proliferator activated receptor), and some are possessing less or no affinity for CB_1 or CB_2 [17,41–43]. Examples of structural formulas of PEA and some related molecules are given in Fig. 1.

Endogenous PEA is formed from palmitic acid (C16:0), the most common fatty acid in animals and a product of normal fatty acid synthesis. It is a major component of palm tree oil and also present in meat, cheese, butter, and dairy products. Synthesis and degradation of PEA occur in various cell types, including those relevant for chronic pain and inflammation signalling, such as immune cells, neurons and microglia [7]. Its tissue concentrations vary to some extent between studies but are generally found to be similar to, or even higher than those found for AEA [18,44,45]. It has been suggested that differences found between studies could partly be caused by contamination resulting from the rather wide-spread technical use of PEA in detergents or other products, or the release of PEA from cells or tissues following their collection [44]. It is assumed that PEA is synthesized *via* similar routes as those of other NEAs, for which two pathways have so far been described. The classic 'N-acylation-phosphodiesterase pathway' goes *via* N-acylphosphatidylethanolamine (NAPE). NAEs are released by the action of NAPE-hydrolysing phospholipase D (NAPE-PLD), but recent studies also demonstrate the presence of NAPE-PLD-independent multi-step pathways to form NAEs from NAPE. The second pathway involves formation of NAEs from N-acylated plasmalogen-type ethanolamine phospholipid (N-acyl-plasmenylethanolamine) through both NAPE-PLD-dependent and -independent pathways [44,46]. For many fatty acids it has been found that their tissue patterns reflect the local availability of their precursor fatty acids and amines. Fatty acid availability and patterns in turn are amongst others determined by dietary intake and metabolic factors [47]. However, in case of PEA no association has been found so far between its tissue concentrations and dietary fatty acid intake. An exception might be the small intestine since mice studies showed that increased fat intake resulted in decreased levels of PEA and other NAEs [44,45]. The apparent stability of endogenous PEA could be caused by the fact that fatty acid synthesis will normally deliver a constant supply of palmitic acid. During inflammatory conditions increased plasma and tissue levels of free PEA are generally found, although in some animal models the opposite has been reported [45]. PEA is broken down by enzymatic hydrolysis, catalysed by fatty acid amide hydrolases (FAAH and FAAH2) and by NAE-hydrolysing acid amidase (NAAA) [48]. Inhibition of NAAH has been shown to increase PEA levels in activated leukocytes and to inhibit the effects of inflammatory stimuli *in vitro* and *in vivo*. These effects could be mimicked by exogenous PEA and were abolished by PPAR-α deletion [49]. At the same time, FAAH inhibitors including URB597, PF-3845 and the clinical candidate PF-04457845 are also able to cause markedly elevated plasma and tissue levels of PEA and other NAEs [50–52].

3.2. Molecular targets of PEA

PEA has been found to interact with different receptors and non-receptor targets and it seems conceivable that its ultimate biological effects are a consequence of these combined multiple-target actions. Clearly, PEA is not a 'classical' endocannabinoid according to the current pharmacological classification rules [40]. Although it was originally suggested that the compound also activated CB_2 receptors [6], these findings may probably have been related to an 'entourage effect'. This refers to a mechanism in which PEA reduces the enzymatic breakdown of AEA through competition for FAAH, resulting in higher AEA concentrations [7,53]. Anandamide (AEA) in turn can modulate inflammation and other immune functions *via* CB_2 [54] or TRPV1 (transient receptor potential channel type V1) receptors [7,40]. PEA itself also acts on the TRVP1 receptor [13]. This receptor, well-known to

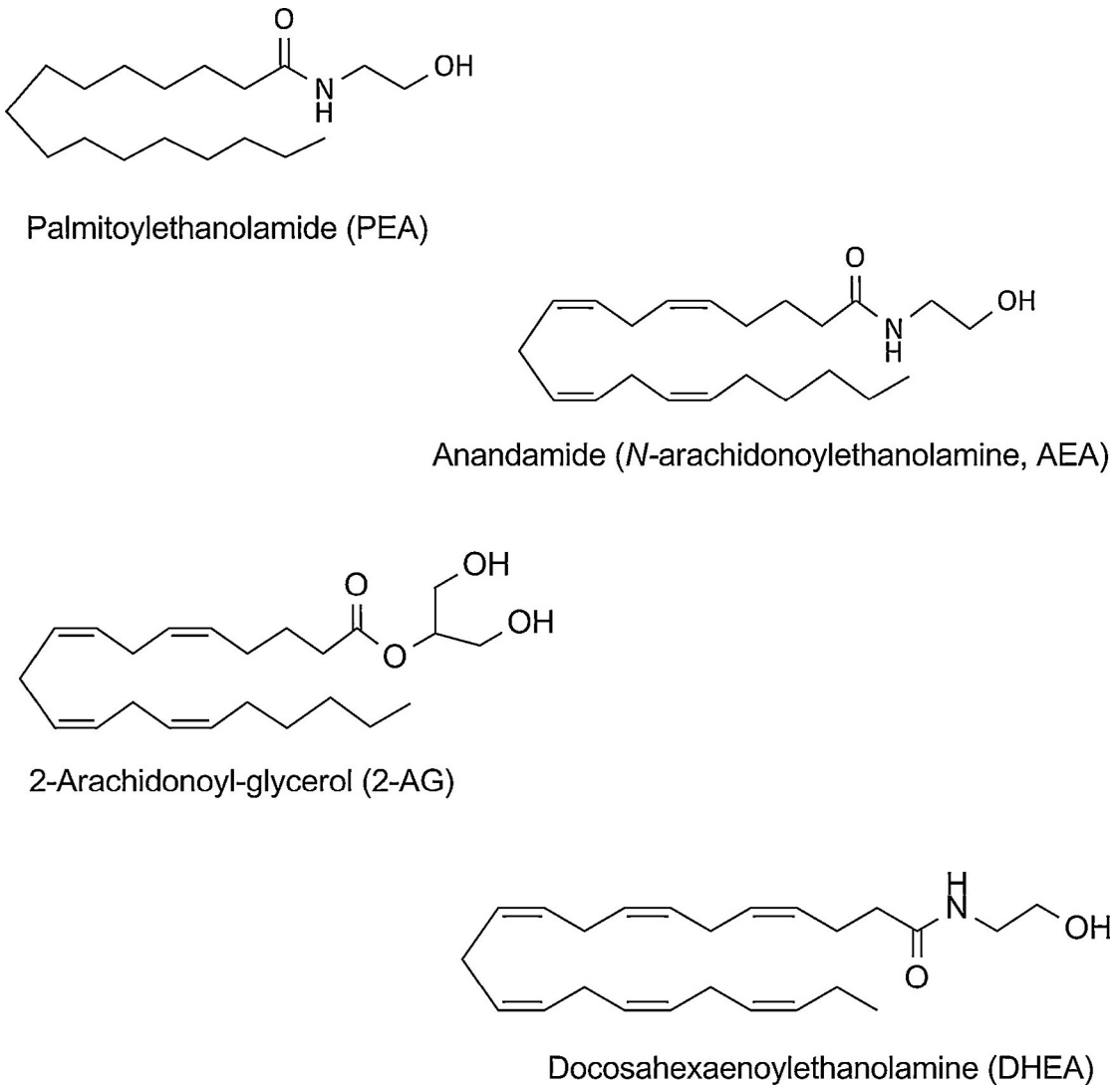

Fig. 1. Chemical structures of palmitoylethanolamide (PEA) and three of its congeners: *N*-arachidonoylethanolamine (AEA), also known as anandamide, 2-arachidonoylethanolamine (2-AG) and docosahexaenoylethanolamine (DHEA). Anandamide and 2-AG are derived from arachidonic acid (20:4n-6) and belong to the classical endocannabinoids, although also acting on other targets. DHEA is derived from docosahexaenoic acid (22:6n-3) and is a ligand for CB_1 and CB_2 while also acting on other targets.

bind the red pepper ingredient capsaicin, has been considered a pro-inflammatory receptor in several conditions, including neuropathic pain, joint inflammation and inflammatory bowel disease. However, recent evidence also demonstrates paradoxical, protective functions *in vivo* [7,8,55]. The best-documented mechanism of PEA is its agonist activity for PPARα receptors, which is supported by several *in vitro* and *in vivo* studies [6–8,37]. The role of the PPARα receptor as a pivotal switch in different inflammatory and pain signalling pathways in the CNS and periphery is widely acknowledged [37,56,57]. In addition, PPARα plays a role in fatty acid metabolism, the synthesis of NAEs including PEA itself and in the regulation of the dynamic balance between dopamine and acetylcholine circuits in brain [58]. As described in the next section a recent study [12] also suggests an interaction of PEA with other (γ, δ) PPARs, although this seems in contrast with previous findings [6]. In addition, PEA has shown agonist activity towards GPR55 [9]. This orphan GPCR is particularly expressed in the gut and also found in cells of the immune system. Initially considered a "third" endocannabinoid receptor despite sharing little homology with CB receptors it has been linked to inflammatory processes as well [59]. Another GPCR receptor to which PEA can bind is GPR119 [10]. This receptor is particularly known for its involvement in GLP-1 secretion from entero-endocrine cells in the gut. Other potential molecular mechanisms of PEA include the inhibition of ceramidases and inhibition of K^+ channels Kv4.3 and Kv1.5 [15,60,61]. Animal studies (Section 3.3) sometimes suggest further candidate targets including NF-κB and COX. However, although direct interactions with enzymes and transcription factors are possible and have been demonstrated with other NAEs, these findings could also be explained from interactions with receptors previously described.

3.3. Studies in animal models

Following the first studies with PEA in Guinea pigs published almost 60 years ago [24–26] which demonstrated its ability to modulate immune functions, several animal studies have confirmed its role as endogenous mediator as well as its therapeutic potential. An attempt to discuss all animal studies on PEA published falls outside the scope of this paper and readers are referred to a number of reviews on this topic [6,8,37,44,45,62,63]. Instead studies relevant to this review published during the last 5 years will be highlighted here. In relation to pain management there have been a number of recent investigations aiming to elucidate the mechanisms of action of PEA in chronic pain. For example, Costa et al. [14] demonstrated that PEA, given by i.p. injection inhibited both thermal hyperalgesia and mechanical allodynia

in a mouse model for persistent pain, induced by chronic constriction injury of the sciatic nerve. Receptor antagonists were used to investigate the relative contribution of the CB_1, TRVP1 and PPARγ receptors to these effects. Findings suggest that these receptors are indeed playing a role in mediating the anti-nociception induced by PEA and that this can be attributed to an "entourage effect". In addition, results from this study further support the concept that modulation of local mast cell degranulation (see also Section 3.4) is an important effect of PEA. Further support for a central PPARα-mediated effect of PEA on hyperalgesia comes from the study of D'Agostino et al. [64]. These authors described that intra-cerebroventricular administration of PEA effectively reduced hyperalgesia in a carrageenan-induced paw model in mice. Interestingly, the effects involved a reduction of the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) in sciatic nerves. Furthermore, IkB-α degradation and p65 NF-κB nuclear translocation were prevented by PEA. Naderi et al. [65] studied the effects of intrathecal administration of PEA on pain-related scores and IL1-β expression in the spinal cord using a formalin-induced pain rat model. Their results not only confirm the common view that CB_1 receptors are not directly involved in the activity of PEA, but also suggest the possible involvement of GPR55 in spinal pain pathways. Results from a recent study of Paterniti et al. [12] in a mouse model for spinal cord injury direct towards the involvement of PPARδ and PPARγ next to that of PPARα in the anti-inflammatory and neuroprotective activities of PEA.

In addition to its effects in chronic pain, accumulating data indicate that PEA exerts neuroprotective effects in brain and spinal cord following trauma or stroke, or resulting from ageing-related pathological processes. These include a reduction of cerebral oedema, down-regulation of inflammatory processes and a limitation of cellular necrosis and apoptosis [66]. Recent evidence for these effects, most likely involving non-neuronal cells (Section 3.4) comes from a number of animal studies. For example, in a mouse model for spinal cord injury (SCI), induced by applying an aneurysm clip to the spinal cord, repeated PEA administration (10 mg/kg i.p., 6 and 12 h after SCI) reduced the degree of the trauma severity [67]. This was associated with a reduction of mast cell infiltration and activation, and a reduced activation of microglia and astrocytes expressing cannabinoid CB_2 receptors. In a rat model for traumatic brain injury induced by occlusion of the middle cerebral artery, PEA (given by i.p. injection) was found to reduce lesion size, to decrease the induction of several inflammatory markers (including JNK and NF-κB) and decrease astrocyte infiltration [19]. Neurobehavioral parameters in the model were improved in PEA-treated animals compared to controls. In mice injected intra-cerebroventricularly with amyloid-ß 25–35 peptide as a model for Alzheimer's disease, PEA (given subcutaneously) reduced or prevented behavioural impairments. Interestingly, these effects could be mimicked by a PPARα agonist and could not be induced in PPARα knock-out mice [68]. Neuroprotective effects of PEA (10 mg/kg, i.p.) were also reported in an MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahyropyridine) mouse for Parkinson's disease by Esposito et al. [69]. Effects of PEA included a reduction of MPTP-induced microglial activation, in the number of GFAP-positive astrocytes and of S100b overexpression. PEA also reversed MPTP-associated motor deficits. Interestingly, MPTP systemic toxicity was exacerbated in PPARα knock-out mice and PEA-associated neuroprotection was partially PPARα-dependent. In a genetic rat model for generalized absence epilepsy (WAG/Rij) Citraro et al. [70] showed that both PEA and AEA administration significantly decreased absence seizures. The authors interpreted their findings from a direct PEA effect on PPARα and an 'entourage' effect *via* CB_1 receptors. Interestingly, they also reported that PEA concentrations in thalamus and cortex were lower in WAG/Rij rats compared to controls. Interesting effects of PEA on sleep/wake were reported by Murillo-Rodriguez et al. [71]. The investigators injected PEA (and OEA) as well as the FAAH inhibitor URB597 into the wake-related brain areas lateral hypothalamus or dorsal raphe nuclei of rats. The compounds promoted waking which could be linked with the enhancement in levels of DA and indirectly mediated with anandamide.

Several studies confirm that PEA also modulates inflammatory processes in peripheral tissues. For example, in an isolated perfused eye model obtained from pigs, Kumar et al. [72] showed that PEA increased aqueous humour outflow which involved GPR55 and PPARα receptors and activation of p42/44 MAPK. Very recently, Mattace Raso et al. [73] demonstrated that PEA significantly reduced blood pressure in spontaneously hypertensive rats and that it limited kidney damage secondary to high perfusion pressure. The latter apparently involved a reduction of oxidative stress. Also recently an interesting study on the effects of PEA in ulcerative colitis (UC) was published [74]. The authors used 3 different models to specifically study the role of enteric glial cells (EGCs); a dextran sodium sulphate (DSS)-induced colitis model in mice, colonic biopsies deriving from UC patients and primary cultures of mouse and human EGCs. In the mouse model PEA improved macroscopic signs of UC and decreased the expression and release of all pro-inflammatory markers tested. Enteric glia cells, TLR4 receptors and NF-κB-pathways were probably involved in this effect as concluded from the experiments in the ECG models. Antagonists for PPARα, but not for PPARγ abolished the effects of PEA in mice and in human material.

3.4. The role of non-neural cells in the effects of PEA

Increasing evidence indicates that non-neuronal cells within the CNS are crucially involved in mediating the effects of PEA [7,8,67]. These non-neuronal cells regulate inflammatory processes in the CNS and are key players in the communication between the immune system and the CNS during neurodegenerative disorders and in neuropathic pain. Activation of microglia and astroglia is also part of the pathology of most diseases and traumata of the CNS as well as certain processes occurring during ageing [7,8]. Glia cells respond to pro-inflammatory signals released from different immune cells, including mast cells. Mast cells are among the first cells triggered by environmental factors and there is increasing evidence for intensive communication between mast cells and microglia [75,76]. Therefore, mast cells are increasingly viewed as key players in orchestrating several disorders including both acute and chronic inflammatory processes, hyperalgesia and angiogenesis. Controlling, rather than blocking of mast cell degranulation is therefore considered an important target in immunopharmacology [76]. The ability of PEA to act as autacoid capable of downregulating mast cell activation (the 'ALIAmide' concept, see Section 2) was already described 20 years ago by the group of Rita Levi-Montalcini [3]. Since then, several animal studies have demonstrated the ability of PEA to reduce activation and infiltration of mast cells, microglia and astrocytes [19,67,77,78]. Another cell type shown to be influenced by PEA is the adipocyte [79]. It was found that PEA inhibited LPS-induced secretion of TNF-α by human adipocytes, an effect which did not seem to involve PPARα. These findings may be of relevance in relation to the chronic low-grade inflammatory process associated with obesity.

4. Clinical applications and developments

4.1. Administration, kinetics and safety

Between 1972 and 1977, the period that PEA was available in former Czechoslovakia as an approved drug for oral administration, 6 different placebo-controlled trials involving in total 3627 individuals were carried out with the compound. The aim of these studies was to investigate the prophylactic and therapeutic efficacy of PEA against influenza and the common cold [2,29,80]. Relevant side-effects were not seen at oral doses up to 1800 mg/day [81]. Later studies (see

[82] for review) all confirm that PEA is a very safe drug. In 2005 PEA was re-introduced, first as veterinary drug (Redonyl®) against allergic dermatitis in dogs. Since 2007 PEA is available in oral formulations (tablets and microgranules for sublingual administration, 300 mg or 600 mg) in a number of countries, regulated as food supplement (Normast®, Pelvilen® and Peapure®). Dermal application of PEA, alone or combined with ketamine, may present an interesting alternative [83] but data are scarce. Unfortunately, figures on oral bioavailability, dermal penetration, bio-equivalence of the preparations used and general pharmacokinetic (PK) data on PEA are lacking in the literature. As a consequence there is also no insight in the relationship between the pharmacokinetics (PK) and pharmacodynamics (PD) of the compound. In addition it would be of interest to investigate the effects of PEA given in pharmacological doses on the concentrations of other NAEs, including those belonging with endocannabinoid activity. Another relevant issue would be to further explore the effects of FAAH inhibitors, of which a number are in clinical development (PF-04457845, JNJ-42165279 and URB 597, see ClinicalTrials.gov) on the PK of PEA and other NAEs.

4.2. Clinical efficacy

Following the trials with PEA as therapeutic/prophylactic against viral infections in Czechoslovakia during the 70s [2,29,80,81] the focus has now completely shifted to chronic pain syndromes and to damage (*e.g.* by stroke or trauma) and degenerative diseases of the CNS. Since the 90s and especially since 2008 a number of clinical studies, ranging from small observational studies with limited numbers to randomized controlled trials in various chronic pain syndromes have been reported, in a total of 2000 patients [82].

Positive or at least promising results are particularly reported for peripheral neuropathic pain (*e.g.* sciatic pain, diabetic pain, low back pain, carpal tunnel syndrome), central neuropathic pain (post stroke, MS-related) and pelvic pain. For specific data readers are referred to recent reviews [81,82]. In the ClinicalTrials.gov database (http://clinicaltrials.gov) there are currently 3 referrals to running studies. Main indications are neuropathic pain from spinal cord injury (ClinicalTrials.gov Identifier: NCT01851499), dietary treatment for intestinal Inflammation and visceral hyperalgesia in IBS (NCT01370720) and the prevention of post-operative pain (NCT01491191).

5. Conclusion and future developments

Palmitoylethanolamide is a typical example of a compound belonging to what may be called the 'endocannabinoidome', a complex system including several endocannabinoid-like mediators with pharmacological profiles that are often much broader than those of the classical endocannabinoids [84]. Since the discovery of the 'promiscuous' mediator PEA almost 70 years ago, the number of new studies reported on this compound is greater than ever before. Next to its complicated biology and pharmacology, the limited possibilities to generate intellectual property and hence its poor commercial prospects will have contributed to the initial slow development. The revival of PEA coincides with a paradigm shift currently taking place in the discovery and development process of drugs and nutritional products. It is clear that many chronic diseases involve tissue degeneration and remodelling, inflammation and pain, which are orchestrated by different interacting processes. These disorders demand for alternatives to the one disease-one target-one drug concept. Development in 'omics' technologies, bio-statistics and ICT enable the evolution in pharma and nutrition from 'single-target' to 'multiple-target' approaches and narrow the gap between these fields [85]. In the areas of chronic disease and pain management, much of the low hanging fruit has been picked. Indications for PEA are of complicated character and clinical endpoints for efficacy are often not without controversy. Future studies on PEA should not only include RCTs of proper design with well-documented outcomes but also studies on its PK-PD relationships and its molecular interactions with other signalling systems.

Layperson's summary

Palmitoylethanolamide (PEA) is a fat-derived signalling compound normally made in the body. In addition, PEA is present in soy lecithin, peanut meal, egg yolk and other foodstuffs. The compound has quite a long history, with its effects on the immune system and (to a lesser extent) pain already known for over half a century. Our review describes the development of PEA, which showed a revival around the 90's of last century. In particular during the last decade, the compound is receiving more and more attention as a drug and dietary supplement. It is particularly used against chronic pain, inflammation and certain brain diseases. PEA shows a rather complex biological and pharmacological profile. It is not a classical endocannabinoid, despite some structural and metabolic similarities with these signalling molecules. Instead, PEA may is sometimes called a 'promiscuous' molecule as it interacts with several receptors and non-receptor targets. However, this apparent lack of selectivity is increasingly regarded as a potential plus in certain diseases, where 'multiple-target' molecules may have advantages over classical 'single-target' medicines.

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