

Role of N-Acylethanolamines in the Neuroinflammation: Ultramicronized Palmitoylethanolamide in the Relief of Chronic Pain and Neurodegenerative Diseases

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ABSTRACT

Pain and neuroinflammation are protective responses aimed at preventing and removing injurious stimuli. However, when prolonged, they can override the bounds of physiological control and become destructive. Chronic pain and neuroinflammation are critical components in the pathophysiology of neurodegenerative diseases, stroke, spinal cord injury, diabetes, and neuropsychiatric disorders. Natural mechanisms, including the production of lipid mediators, represent an endogenous protective process and a program of resolution stimulated and triggered by tissue injury or inflammation. Lipid mediators include N-acylethanolamines (NAEs) such as palmitoylethanolamide (PEA), an endocannabinoid anandamide congener which has shown to be endowed of neuroprotective and antiinflammatory properties activated under several pathological states. PEA does not bind the classical cannabinoid receptors but indirectly stimulates the effects of cannabinoids. Its antiinflammatory, analgesic and neuroprotective actions have been however associated with peroxisome proliferator-activated receptor- α (PPAR- α) activation. The administration of exogenous PEA requires parenteral routes owing to its lipid structure. The micronized and ultramicronized (m- and um-) formulation permits oral administration increasing the versatility, easiness and compliance of administrations in clinical studies. This review is intended to deal with the effects of m- and um-PEA on chronic pain and neuroinflammation in several animal models of chronic pain and neurodegenerative disorders and in clinical studies.

Keywords

Palmitoylethanolamide, Neuroinflammation, Chronic Pain, Neurodegenerative Disorders, Micronized and Ultramicronized Formulation, Peroxisome Proliferator-Activated Receptor- α

Introduction

Acute pain brings an alarm to the body of possible injuries and has normally a protective purpose. Conversely, chronic pain does not convey any useful information and has no any biological benefit. Chronic pain is a major

clinical problem that affects up to 30% of persons in the world. It includes neuropathic pain, caused by a dysfunction, damage or degeneration of the sensory nervous system. It gives a feeling of general discomfort and lowers the quality of life. Medications, massage

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therapy, acupuncture, electrical stimulation, nerve blocks, and surgery are some traditional therapies for chronic pain: all unsatisfactory. So far there are no drugs or treatments able to relieve chronic pain in an effective and definitive way. Increasing evidence suggest that neuroinflammation is a common mechanism of several central nervous system (CNS) diseases including chronic pain [1] but also Alzheimer's and Parkinson's diseases, lateral amyotrophic and multiple sclerosis, and psychiatric disorders [2-5]. A bidirectional signaling reciprocally connecting the immune system to the central nervous system promotes the development and maintenance of both, chronic pain and neurodegeneration. The principal cellular players in neuroinflammation are glial cells, whose activation has been shown to be involved in Alzheimer's disease, Parkinson's disease, cerebral ischemia, multiple and amyotrophic lateral sclerosis (MS and SLA), and mood disorders [6-9]. Among glial cells, microglia can either favor the recovery of injury in the CNS by scavenging dead cells and releasing factors promoting neuron survival or, under prolonged activation, induce autoimmune responses, neural death and brain injury [10-13]. Thus, microglia exerts a dual role in neurodegeneration, acting both, as instigators of damage and as guardians of brain homeostasis. In responses to signals generated by immune cells, neurodegeneration or the accumulation of folded proteins, microglia can multiply and assume the proinflammatory phenotype: the activated primed microglia [14]. Primed microglia responds more vigorously to inflammatory signals driving to deleterious consequences. Glia represents also the link between neuroinflammation and neuropathic pain [15]. Microglia in particular proved to be activated under peripheral injury-induced-neuropathic pain [15,16]. Under inflammatory conditions spinal microglia release interleukin-1 β (IL-1 β), which through the activation of its receptor phosphorylates NR1 subunit of N-methyl-D-aspartate (NMDA) receptors facilitating pain transmission [17]. IL-1 β , whose expression level proved too be increased at spinal and supraspinal level, acts as a neuromodulator increasing synaptic plasticity under inflammatory or neuropathic pain conditions [18,19]. Microglia at dorsal horn level can be also responsible of an up-regulation of purinergic receptors, whose genetic or pharmacological blockade has shown to relieve neuropathic pain [20-22].

Neuroinflammation in chronic pain

Chronic pain represents a substantial and growing therapeutic need. Among all types of chronic pain, neuropathic pain, resulting from damage, degeneration or dysfunction in the sensory system remains almost untreatable. Neuropathic pain is associated with spinal cord injury, multiple sclerosis, stroke, cancer, diabetes and other metabolic diseases. A bidirectional signaling between the immune system and the nervous system contributes to the development and maintenance of neuropathic pain [19,23]. Neuropathic pain development is strictly dependent on Schwann cells, spinal microglia, astrocytes and peripheral immune system elements [24]. Microglia plays a central role in the coordination between the immune system and brain. For example, following infections or nervous system injuries, microglia switch to the "activated" form acquiring an inflammatory cell phenotype. Activated microglia release cytokines such as TNF- α and IL-1 β and inflammatory chemokines [25-27] facilitating the recruitment of leukocytes in the brain [28]. Activated microglia undergoes cytoskeleton rearrangements altering the expression pattern of the receptors on the cell surface. These alterations allow microglia to reach the sites of lesions or infections [29] and increase their phagocyte efficiency [30]. If on one hand the activation of microglia and the release of cytokines are aimed to protect against injury, on the other hand the persistent activation of microglia drives to pathological changes such as pain-related affective and cognitive disorders [31]. Activated microglia represents also the convergence point between neuroinflammation and chronic pain. TNF- α and IL-1 β released from spinal microglia, act as neuromodulators following peripheral nerve injury and increase synaptic plasticity leading to peripheral and central sensitization, at the base of both, inflammatory and neuropathic pain. Indeed, increased IL-1 β /TNF- α released by microglial cells and astrocytes at the spinal cord level, as well as in the brain, were observed in neuropathic mice [18,19]. IL-1 β by engaging its own receptors induces phosphorylation of the NR1 subunit of N-methyl-D-aspartate receptors facilitating pain transmission [17]. A cytokines-mediated immune system imbalance has been shown to be associated with neuropathic pain development in both, human and animal studies [32,33]. Oligodendrocytes play also an important role in the induction of neuropathic pain. The over-expression of the oligodendrocyte-derived

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IL-33 at spinal levels contributes to a further release of proinflammatory cytokines such as TNF- α and IL-1 β [34]. Another important role in neuroinflammation at the base of chronic pain appears to be mediated by mast cells, which represent the signaling link between peripheral inflammation and the brain. Indeed mast cells move easily through the blood-brain barrier in normal and under pathological conditions [35]. Mast cells are the player of phagocytosis, antigen presentation, adaptive immune response regulation, IgE switching by B cells [36] and chemokines--induced eosinophil recruitment [37]. Mast cell proliferation and degranulation under pathological conditions involving autoimmune demyelination [38] produce algogenic mediators sensitizing nociceptors and contributing to neuropathic pain [39]. Infiltration and activation of mast cells have been found after spinal cord injury [40,41]. The role of glial and mast cells in neuroinflammation is strengthened by their reciprocal interaction [42,43]. A signal pathway activated by toll like receptors 2 and 4 (TLR2/TLR4) expressed on mast cell surface evokes microglia recruitment [44]. The activation of mast cells also up-regulates CCL5/RANTES signaling, which in turn induces the switch of microglia into the pro-inflammatory phenotype. Reciprocally microglial release of IL-6 and CCL5 induces the expression of TLR2 and TLR4 on mast cells. The cross-talk between mast cells and microglia involves also the complement system and in particular C5a, which appears to be up-regulated together with its cognate receptor [45] on mast cells, astrocytes and activated microglia. A cross-talk between mast cells and astrocytes and microglia and astrocytes has been also described throughout the involvement of CD40-CD40L and translocator protein, respectively [46,47].

Neuroinflammation in neurodegenerative disorders

Apart from common mechanisms, such as the activation of microglia, neuroinflammation occurring in neurodegenerative diseases is however different from that occurring under chronic pain conditions. Causative agents of neurodegeneration have yet to be identified. Neurodegeneration occurs after viral insult and mostly in various 'neurodegenerative diseases', generally observed in the elderly, such as Alzheimer's disease, multiple and amyotrophic lateral sclerosis, Parkinson's disease, all negatively associated with mental and physical

functioning. Viruses are able to injure neurons directly or by apoptosis induction [48] leading to neurodegeneration [49]. Neurodegeneration induced by viruses suggests an important role of immune responses in neuron degeneration [50]. Immune activation in the CNS involves microglia and astrocytes [51] which constitute the resident immune cells of the CNS and play an important role in the regulation of homeostasis of the brain during development, adulthood and aging [52]. Indeed microglia constantly survey the microenvironment surrounding astrocytes and neurons and in response to pathogen invasion or tissue damage promote an inflammatory response engaging the immune system [53]. Inflammation may result in the production of neurotoxic factors amplifying and increasing the persistence of the disease state. These neurotoxic mediators are mainly interleukins and other cytokines which throughout the activation of their own receptors trigger intracellular mechanisms conveying in protein degradation, mitochondria dysfunction, axonal transport impairments and apoptosis [54-56]. The chronic activation of pro-inflammatory signals increases also the vulnerability to neuropsychiatric disorders [57]. The putative mechanism linking the neuroinflammation and depression involves oxidative stress, elevated pro-inflammatory cytokines IL-6 and IL-8, endothelial nitric oxide synthase uncoupling and hyperglutamatergism. Indeed in major depressive disorder increased inflammatory markers are strictly associated with depressive symptoms and high risk of suicide [58].

From molecular mechanisms to putative therapeutic strategies: the lipid mediators

Targeting the specific processes and molecules involved in neuroinflammation may provide new therapeutic opportunities for treating chronic pain and neurodegenerative diseases. Consistently with the crucial role played by non-neuronal cells such as microglia in neuropathic pain, the inhibition of microglial activation by minocycline prevents/delays neuropathic pain development [59-61]. Intrathecal injection of astroglial toxin fluorocitrate [62,63] and L-alpha-aminoadipate [64] also reverses nerve injury- or nerve inflammation-induced mechanical allodynia. Another approach to treat neuroinflammatory mechanisms at the base of chronic pain and neurodegenerative diseases would consist in exploiting and eventually strengthen the endogenous mechanisms able to defend against inflammation. So far a

considerable number of “resolution players”, whose stimulation is triggered by tissue inflammation or damage have been identified. These mediators operate an endogenous protective process and their enhancement may represent a natural approach to switch off the neuroinflammatory mechanisms at the base of neurological and psychiatric diseases. Among the several resolution program players, lipid mediators have shown a protective role in inflammatory processes [65,66]. Increasing evidence have suggested that lipid molecules suppress the inflammatory process, rescue homeostasis in damaged tissues and reduce pain sensitivity by affecting neural pathways involved in the processing of nociceptive stimuli from the periphery to the CNS. Moreover, the level and/or the actions of these molecules have shown to be lower in chronic inflammatory disease [67]. Among lipid mediators the fatty acid amides, N-acylethanolamines, are natural compounds which are composed by a fatty acid and ethanolamine. N-acylethanolamines include the endocannabinoid N-arachidonylethanolamine, anandamide (AEA), and several congeners such as the N-stearoylethanolamine, N-oleylethanolamine (OEA) and N-palmitoylethanolamide (PEA). AEA, OEA and PEA share anabolic and catabolic pathways. They are formed from N-arachidonylphosphatidylethanolamine (NAPE) by several enzymatic pathways: that one involving the NAPE-phospholipase D is the principal one [68]. N-acylethanolamines are hydrolyzed mainly by the fatty acid amide hydrolase (FAAH), an intracellular integral membrane protein belonging to the amidase family of enzymes, which catalyses the hydrolysis of N-acylethanolamines into the corresponding fatty acids and ethanolamine [69]. Recently, another enzyme not related to FAAH, known as N-acylethanolamine-hydrolyzing acid amidase (NAAA) has been found to hydrolyze preferentially PEA [70]. PEA has been proposed to maintain cellular homeostasis during inflammatory and neurodegenerative conditions and to function as a protective endogenous mediator counteracting inflammation, neuronal damage and pain [71,72]. The role of PEA as a player in the inflammation resolution program is supported by several evidence: i) mast cells and microglia synthesize and metabolize PEA [73,74], ii) PEA negatively modulate mast cell degranulation and microglia activation [75,76] and iii) the concentration of PEA increases in brain areas and spinal cords following peripheral

nerve or spinal nerve injury as well as following stroke [77-79]. Being the role of PEA as mediator of resolution of inflammatory process already ascertained, three mechanisms have been proposed for its anti-inflammatory and analgesic effect. The first mechanism, which does not exclude the other two, suggests that PEA acts via an autacoid local inflammation antagonism by down-regulating mast cell degranulation [75]. PEA also acts by enhancing the anti-inflammatory and anti-nociceptive effects exerted by AEA, which is often produced together with PEA, and indirectly activates cannabinoid CB1 and CB2 receptors or transient receptor potential vanilloid receptor type 1 (TRPV1) channels, an effect known as the “entourage effect” [80,81]. Moreover PEA directly stimulates the nuclear peroxisome proliferator-activated receptor- α (PPAR- α), which clearly mediates many of the anti-inflammatory effects of this compound [82]. However, a yet uncharacterized cannabinoid CB2 receptor-like target [83,84], or the orphan receptor G-protein coupling, GPR55 [85], have been also proposed as target of PEA. A recent study has also suggested a new mechanism of action, through which PEA may affect cannabinoid signaling by upregulating CB2 receptor expression in mononuclear phagocytic cells [86].

The effect of um-PEA on chronic pain

The analgesic property of PEA has emerged in several models of inflammatory pain conditions induced by formalin [83,87], prostaglandins [88], magnesium sulfate [83], kaolin [83,87], carrageenan [76,80,89,90], nerve growth factor [91], and turpentine [92,93]. The anti-inflammatory and analgesic effects of PEA were initially attributed to peripheral CB2 receptors [83,87,93]. Later on PPAR α was proposed to mediate the effect of PEA in inflammatory pain conditions since GW7647, a PPAR α selective agonist, mimic, the effect of PEA and since the anti-hyperalgesic effect of PEA was absent in PPAR α null mice [90,94]. The action of PEA in inflammation-induced hyperalgesia proved to be also dose dependent [88,95], and to be associated with the suppression of pro-inflammatory enzymes such as cyclooxygenase and endothelial and inducible nitroxide synthases [96]. PEA indeed plays an important role in maintaining cellular homeostasis in inflammatory states. It is produced by microglia and mast cells and, in turn, down-modulates mast cell and microglia activation [77,97,98]. The analgesic properties of PEA have been confirmed in neuropathic pain

models [84,98-104]. The levels of PEA proved to be increased in pain-controlling brain areas and in the spinal cord following neuropathic pain development [78]. PEA beneficial actions in neuropathic pain conditions depend always on PPAR α activation since they were either absent in PPAR α null mice or blocked by PPAR α antagonists [100,105]. The analgesic properties of PEA depend also on the modulation of non-neuronal cells in a chronic constriction injury- (CCI) and formalin-induced models of neuropathic pain [98,101]. Moreover, PEA restores the glutamatergic synapse proteins and the changes in amino acid release, the levels of which were deeply altered in the spared nerve injury model of neuropathic pain [103]. PEA also relieved hyperalgesia and allodynia in a model of oxaliplatin-induced neuropathy, either following acute or repeated treatment. In this model of neuropathic pain PEA also produced an improvement in motor coordination [106]. In another study PEA reverted thermal hyperalgesia and mechanical allodynia that developed 14 day after a mild traumatic brain injury model in mice [107]. PEA and anandamide share the activation and desensitization of TRPV1, a non-selective cation channel activated by noxious heat, low pH and capsaicin, the major active constituent of chilli, whose role in pain transmission has been widely reported [108-114]. PEA has shown to enhance the action of AEA on human TRPV1 [115] in a way inhibited by CB2 receptor antagonist [87,93]. Microglia and mast cells have shown to express both, TRPV1 and CB2 receptors, whose activation/desensitization may inhibit their activation [86,116]. CB1, PPAR- α and TRPV1 receptors proved to be involved in the anti-hyperalgesic and anti-allodynic effect of PEA in neuropathic pain conditions [84]. Other proposed mechanisms for PEA in counteracting pain include ATP-sensitive K⁺ channels [88], transient receptor potential (TRP) channels [117], NF- κ B [90], Ca²⁺-activated potassium channels [105] and NR2b subunit of NMDA receptor [103]. Most of the studies about PEA efficacy on pain have been carried out with parenteral administration. The lipid structure of PEA limits the solubility and the oral bioavailability of PEA. The micronization and ultramicronization is a technology often used in the pharmaceutical field to reduce large drug crystals under the micron range (<10 μ m). The micronized and ultra-micronized formulation of PEA (m-PEA and um-PEA) facilitates the dissolution and reduces the absorption variability of PEA after oral administration. The analgesic

effect of orally administered m-PEA and um-PEA was firstly demonstrated in a carrageenan-model of inflammatory pain by Impellizzeri et al. [118].

The effects of PEA have been tested in several clinical studies under several different pain conditions. Differently from preclinical studies in which PEA has been administered via parenteral route, in humans the oral administration is the most popular and accepted administration route for its easiness, versatility and the high compliance of the patients. Accordingly, the administration form of PEA was in most case through oral tablets and rarely sachets (sublingual preparations). The first clinical study using m-PEA or um-PEA revealed an analgesic effect in a diabetic patients suffering of peripheral neuropathy [119]. The effectiveness of um-PEA was also demonstrated in patients suffering from lumbosciatalgia or neuropathic pain of different etiologies [120,121]. The study has demonstrated that PEA either alleviated pain scores or potentiated the effect of other concomitant analgesic therapies [121,122]. The analgesic efficacy of PEA was also demonstrated in patients suffering from traumatic neuropathic pain or diabetes [123]. Two recent meta-analysis studies reported that not only PEA was effective in inducing analgesia in several chronic pain conditions but it did not produce adverse reactions worthy of notes [124,125]. Contrariwise, Andresen and colleagues reported that um-PEA did not alleviate pain in patients with spinal cord injury-induced neuropathic pain, compared to placebo-treated patients [126]. The efficacy of PEA in clinical trials and meta-analysis is however reviewed [127,128]. The actions of PEA on the neuroinflammation processes underlying chronic pain are summarized in **Figure 1**.

The effect of um-PEA on neurodegenerative diseases

Neurodegeneration, such as that observed in Alzheimer's and Parkinson's diseases (AD and PD) and multiple and amyotrophic lateral sclerosis (MS and ALS), consists of a gradual neuronal cell death affecting a specific cellular population of the CNS causing a progressive disability such as cognitive impairments, behavioural and motor dysfunctions up to paralysis. PEA has demonstrated to play a neuroprotective role in several experimental models of neurodegenerative diseases. In animal model of Parkinson's disease induced by

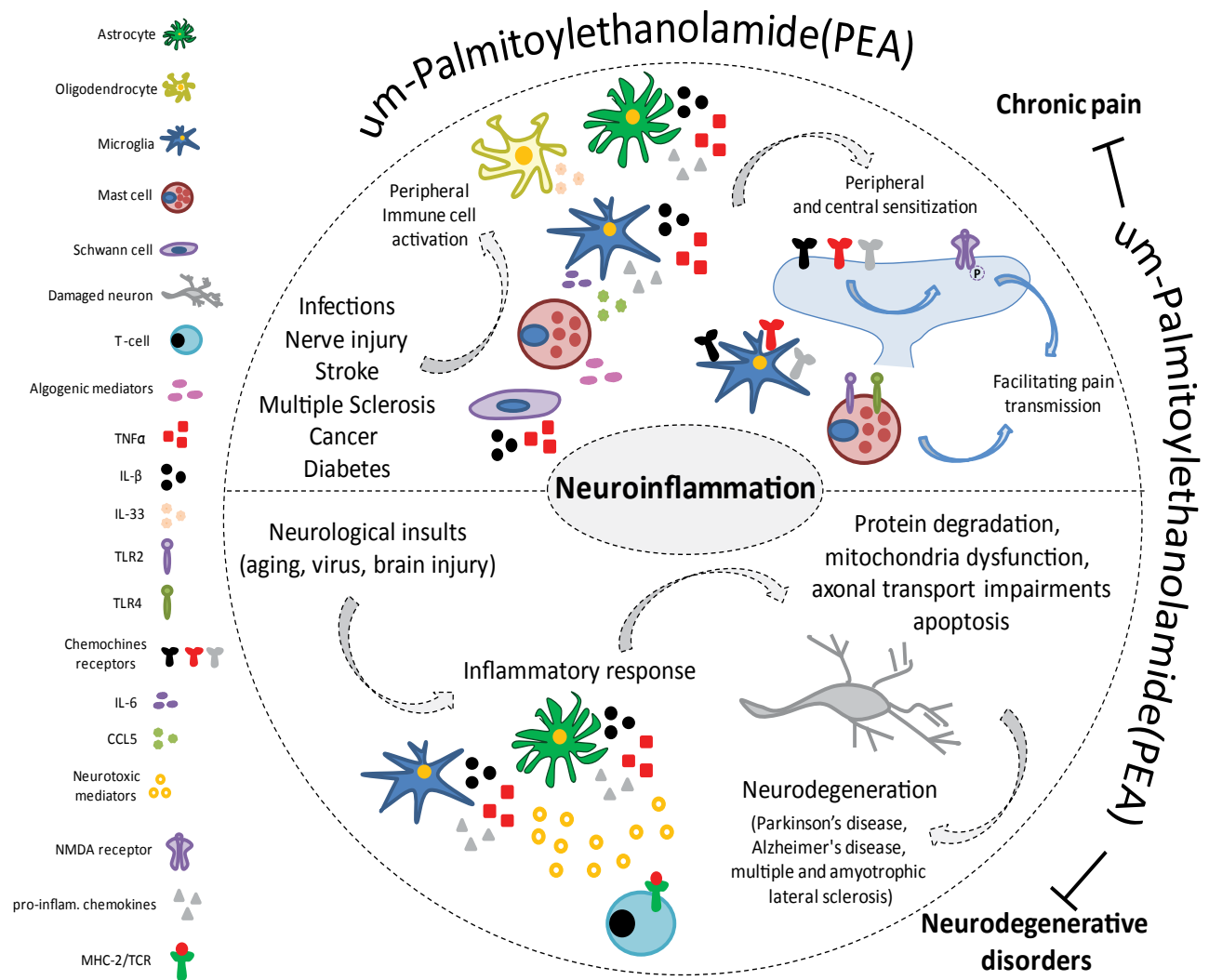


Figure 1: Schematic representation of inhibitory effect of ultramicronized palmitoylethanolamide (PEA) on neuroinflammation-driven immune cell activation. (Upper) Spinal cord injury, multiple sclerosis, stroke, cancer, diabetes and other metabolic diseases induce peripheral immune cell activation, including Schwann cells, spinal microglia, astrocytes, oligodendrocytes and mast cells that in turn release cytokines such as TNF- α and IL-1 β and inflammatory chemokines inducing peripheral and central sensitization associated with pain facilitation. (Lower) Neurological insults such as aging, virus or brain injury induce immune cell activation in the CNS including microglia and astrocytes with consequent release of neurotoxic mediators mainly interleukins and other cytokines. These latter throughout the activation of their own receptors trigger intracellular mechanisms conveying in protein degradation, mitochondria dysfunction, axonal transport impairments and apoptosis, with consequent neurodegeneration at the basis of diseases like Parkinson, Alzheimer, multiple and amyotrophic lateral sclerosis. Lateral dotted lines indicate the neuroprotective role of umPEA in neuroinflammation underlying chronic pain and neurodegenerative disorders.

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) the chronic treatment with PEA counteracted behavioral impairments, motor dysfunction, the loss of nigrostriatal neurons, astrocytes activation, altered expression of iNOS and microtubule-associated proteins. Such effects were PPAR α -dependent [129]. A co-um-PEA/luteolin composite proved to be neuroprotective in the same Parkinson's model. It indeed protects against inflammation and increased autophagy [130]. In an AD model produced by i.c.v. injection of amyloid- β 25-35 (A β 25-

35) peptide PEA ameliorated the behavioral impairments and reduced lipid peroxidation, inducible NO synthase (iNOS) and caspase-3 activation [131]. This effect was reproduced by the GW7647, a PPAR- α agonist, [131]. PEA counteracted the increased expression of glial fibrillary acidic protein (GFAP) and S100 β , two typical proteins of astrocytes activation, and that of amyloidogenic proteins BACE1 and APP and phosphorylated τ in a different AD model, consisting of the injection of amyloid- β 1-42 (A β 1-42) peptide into the hippocampus [132].

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The treatment with PEA also restored the cognitive behavior and the altered expression of microtubule-associated protein (MAP-2) in a PPAR α -dependent way [132]. The co-umPEA/luteolin composite was also effective in reverting the altered expression of iNOS, GFAP and brain-derived neurotrophic factor (BDNF) expression in hippocampal slice culture exposed to A β 1-42 peptide [133]. Thus, the neuroprotective effect of PEA is based on its capability to revert the altered expression of proteins strictly associated with AD or PD and to down-regulated the activation of pro-inflammatory/pro-apoptotic factors leading to neural loss. PEA has also shown to improve the clinical conditions of a patient suffering from ALS, in particular the respiration and the electromyography [134]. In a more recent clinical study um-PEA counteracted the respiratory worsening and delayed the tracheotomy and death in ALS patients when compared with untreated patients [135]. The neuroprotective effects of PEA have also been shown in several animal models of MS. The levels of PEA proved to be increased in the spinal cord of mice with chronic relapsing experimental autoimmune encephalomyelitis (CREAE), Theiler's murine encephalomyelitis, virus-induced demyelinating disease (TMEV-IDD) and myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis (MOG-EAE) [136,137]. The plasma levels of PEA were also increased in remitting and secondary progressive MS patients [138]. The more relevant aspect of these studies was that PEA treatment ameliorated motor impairment and spasticity [136,137]. Importantly, the behavioural effect of PEA treatment was associated with a reduced expression of inflammatory cytokines, demyelination and axonal damages [137,139]. Thus, PEA seems to enhance or compensate endogenous defense mechanisms counteracting neuroinflammation and neurodegeneration development. The molecular target through which PEA ameliorates MS and ALS symptoms and slows the progression of the diseases has not been investigated yet. **Figure 1** summarizes the different mechanisms through which um-PEA inhibits neuroinflammation processes underlying neurodegenerative diseases.

PEA and Sirtuin-1, sharing a common target or a direct interaction?

Silent information regulator 1 (Sirt1), a NAD-dependent deacetylase, through deacetylating

acetylated histone and other specific substrates plays a relevant role in many physiopathological conditions such as diabetes, cardiovascular disorders, cancer, neurodegeneration and neuropathic pain [140,141]. Abnormal histone acetylation is suggested to be a characteristic gene modification and a transcription factor-mediated epigenetic mechanism underlying neuropathic pain [143-144]. The role of Sirt1 and Sirt1 activator (resveratrol) in alleviating neuropathic pain is more and more emerging [140,142,146]. There are not at the moment clear evidence suggesting that the effects of PEA are mediated through a PPAR- α -Sirt1 complex. Rather, PEA and Sirt1 share a common mechanism, consisting in the activation of PPAR- α [146-148]. Sirt1 potentiates the effect of PPAR- α , the main target of PEA involved in the anti-inflammatory, analgesic and neuroprotective effects [82,90,94,100]. Pertinent to this, PEA and Sirt1 could play a PPAR- α mediated synergic action. Resveratrol as well plays anti-inflammatory and neuroprotective actions with beneficial effects in neurological disorders including neuropathic pain [140,146,149,150]. Reciprocally, inhibitors of Sirt1 either worsen symptoms of neuropathic pain (and other neurological diseases) or block the effect of Sirt1 or Sirt1 activators [140]. Sirt1, such as PEA, has multitarget-mediated effects which altogether contribute to its protective effects in the nervous system. Studies investigating the neuroprotective effects of PEA in Sirt1 $-/-$ mice or in combination with Sirt1 inhibitors, would certainly clarify whether the neuroprotective effect of PEA involves Sirt1 or a Sirt1/PPAR- α complex. The possible interaction of PEA with Sirt1 is also relevant considering the role of the latter in mitophagy [151]. Mitophagy assures the turnover of defective mitochondria associated with the pathogenesis of several neurological disorders and constitutes a protective mechanism avoiding detrimental consequences on neuron function and plasticity [152,153, 154]. Sirt1 controls also the proapoptotic gene p53, whose dysregulation is associated with autoimmune diseases [155]. Thus Sirt1 beneficial effect in neuropathic pain is also likely associated with its important role on immune response. Due to its important role in pathological processes including those associated with neurological disease and neuropathic pain development, novel therapeutic strategies aimed at enhancing Sirt1 action may have an unlimited potential [156]. PEA and Sirt1, playing similar effects and sharing a common

target, could be exploited (either in combined therapies) to counteract the detrimental processes associated with in neurological disorders including neuropathic pain.

Conclusions

The capability of PEA to modulate protective response in inflammatory, neurodegenerative and chronic pain conditions suggests that endogenous PEA may be a component of the homeostatic system involved in the resolution program of neuroinflammation. Consequently, the administration of exogenous PEA, or the inhibition of PEA degradation may be a therapeutic strategy to counteract the neuroinflammation at the base of several neurological disorders. Alternatively, the discovery of the targets and mechanisms underlying the neuroprotective effects of PEA may drive to the development of novel effective treatment for neurodegenerative and chronic pain diseases. The molecular target

through which PEA plays its anti-inflammatory, analgesic and neuroprotective role is PPAR α [82,158], even if several indirect mechanisms, known as the “entourage effect” have been demonstrated. The entourage effect includes the endocannabinoid-mediated activation of CB1, CB2 and TRPV1 receptors [114,159] or PPAR α -mediated TRPV1 desensitization [60,161]. Moreover, the PPAR α direct activation by PEA does not exclude the contribution of the entourage effects thus justifying the multiple and the large spectrum effects of PEA. The development of novel formulations such as m- or um-PEA or the combination with the flavonoid luteolin with antioxidant property has improved the clinical efficacy of PEA. Moreover, PEA was avoided of adverse reactions worthy of notes in clinical studies. Preclinical and clinical studies about PEA efficacy in neurological disease report encouraging outcomes and are considerably multiplying in these last years, which is already a clear sign of its enormous therapeutic potential.

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