A mini review: Palmitoylethanolamide a cannabimimetic compound with pleiotrophic effects.

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Abstract

Palmitoylethanolamide (PEA) is a compound that the body produces naturally to combat pain and inflammation. It's also being researched as a supplement, though large-scale data are still lacking. Here a brief introduction will be given on PEA and its medical capacity for diverse diseases. PEA is a fatty acid amid like anandamide, the main cannabinoid bliss molecule the body makes. Unlike regular fats, amide-containing fatty acids like PEA and the cannabinoids are directly involved in nerve communication. These molecules are called "neuroactive lipids". PEA activates the energy-boosting, fat-burning, and anti-inflammatory PPAR alpha. By activating this key protein, PEA stops the activity of pro-inflammatory genes and the production of many inflammatory substances. PEA reduces the activity of the bliss gene FAAH that breaks down natural cannabinoid anandamide. This increases the levels of calming anandamide in the body, helping to combat pain and increase relaxation. It may also activate cannabinoid receptors CB2 and CB1. PEA contains palmitic acid in its structure. The starting point for making PEA in the body is precisely this saturated fatty acid. Many animals and plants also produce PEA. The highest amounts can be found in soy lecithin, soybeans, egg yolk, peanuts, and alfalfa. As a supplement PEA's co-micronized and ultra-pure forms are available and some co-mixed with luteolin and polydatin.

Keywords: Polydatin, Neuroinflammatory, Palmitoylethanolamide.

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Introduction

PEA is a lipid mediator utilized within the clinic for its neuroprotective, anti-neuroinflammatory and pain relieving properties and in recent years too in psychiatric illnesses and indeed in oncology. Palmitoylethanolamide (PEA) is an endogenous saturated fatty acid derivative. Within the body, PEA is synthesized from palmitic acid (C16:0), the foremost common fatty acid. Synthesis of PEA takes put in films of different cell sorts, is delivered on request and acts locally. When cells are subjected to possibly hurtful stimuli, they express a specific protein that discharges PEA from the membrane.

Palmitoylethanolamide (PEA) is a cannabimimetic compound and lipid courier. PEA does not tie the classical cannabinoid receptors but may indirectly invigorate the impacts of both phyto- or endocannabinoids, either by its part as an agonist of the transient receptor potential vanilloid type 1 (TRPV1), peroxisome proliferator-activated receptor-α (PPAR-α) and the cannabinoid receptors. Palmitoylethanolamide (PEA) is a cannabimimetic compound which decreases neuropathic pain. It is a special food for therapeutic reason within the treatment of chronic pain and chronic depression etc. PEA is considered an endogenous Peroxisome Proliferator Activated Receptors (PPAR) agonist or activator, association with this receptor to repress inflammatory pathways and oxidative stress.During neuropathic pain and any kind of stress and inflammation, PEA can modulate the PPAR pathway that is able to attenuate Nuclear Factor Kappa B cells (NFKB) induced inflammatory factors or tumor necrosis factor (IL-1 or TNF), inhibit infiltration and activation of mast cells MC, reduce mesangial matrix proliferation induced by reactive oxidative stress (ROS) which then results in albuminuria [1].

Literature Review

Among anti-inflammatory and pro-resolving lipid arbiters, PEA has been detailed to down-modulate mast cell activation and to control glial cell behavior. PEA is an acylethanolamide broadly dispersed completely different tissues, counting nervous tissues, and is synthesized on demand. Endogenous levels of PEA are altered following stress or injury, pain and stress. Systemic or local alterations of PEA levels have been reported in clinical conditions associated with them. Numerous preclinical studies demonstrate the ability of PEA to reduce inflammation, pain and stress induced by various acute stimuli.

The impact of PEA administration is dose-dependent. The anti-inflammatory and pain relieving impacts of PEA have been affirmed in models of chronic inflammation and incessant or neuropathic pain. In these models, chronic treatment with PEA not only diminished pain but moreover protected peripheral nerve morphology, diminished endoneural edema, the enrollment and activation of mast cells, and the generation of pro-inflammatory mediators at the damage location. PEA, via direction of persistent inflammatory processes, can straightforwardly mediate in apprehensive tissue modifications responsible for pain, i.e., to act as a disease-modifying operator.

Current analgesics are primarily based on molecules that diminish pain perception, transduction, and transmission, and balance in neurons and/or decrease peripheral aggravation. The

nature of these pharmacological targets is likely to be the foremost cause of their constrained victory in controlling malady progression. Mounting prove focuses to neuroinflammation intervened by safe cell activation, in specific mast cells and microglia, and the generation of inflammatory mediators, as having a vital part within the pathogenesis of inveterate pain. Neuroinflammation drives persistent torment through neuron-immune cell intuitive. Focusing on the processes/molecules included in neuroinflammation may in this way lead to more successful treatment of unremitting pain. The comes about detailed in this pooled meta-analysis represent an vital support to this presumption. PEA, a pro-resolving lipid signaling molecule which controls the action of mast cells and glia, when included to continuous standard treatments for persistent pain and stress [2].

Over the last two decades, increasing data has demonstrated that immuno-inflammatory biomarkers, including interleukin (IL)−1, IL-6, and tumor necrosis factor (TNF)-α, are present and involved in the pathogenesis of major depression (Anisman, H et al). The interaction between these pro-inflammatory cytokines, prostaglandin(PG)-E2 production, and depressive symptoms have led to the hypothesis of anti-inflammatory agent utilization in the treatment of patients with MDD.

Moreover, a growing body of evidence indicates that deficits in endocannabinoid system (ECS) signaling may result in neuropsychiatric disorders, mainly mood disturbances, while the augmentative therapeutic use of endocannabinoids is suggested to produce convincing results in affective disorders. The N-methyl-D-aspartate (NMDA) receptors are also indicated to be involved in the circuits affecting mood disturbances, and targeting of NMDA receptors are becoming of interest in the treatment of depressive symptoms.

PEA is an N-acylethanolamine (NAE), an endogenous fatty acid amide with different targets ranging from peroxisome proliferator-activated receptor alpha (PPAR-α) and cannabinoid-like Gcoupled receptors to less discussed targets like NMDA receptors.

PEA affects endocannabinoid (eCB) signaling through PPAR-α activation and affects indirect regulation of microglial cannabinoid (CB) type2 receptor (CB2R) expression. It's suggested that PPAR-α agonists might have therapeutic efficacy in treatment of mood disorders through regulation of dopamine (and possibly serotonin) neuron activity via nicotinic acetylcholine receptors.

Glutamate transmission and its dysregulation are included in depressive disorders. PEA reestablishes the glutamatergic neural connection proteins and changes amino acid discharge (homeostasis) . PEA actuates and desensitizes TRPV1 (transitory receptor potential cation channel subfamily V part 1) channels. This impact runs at slightest in portion by PPARα activation. TRPV1, known as the capsaicin receptor, is communicated at high levels within the central nervous system and is included in pain transmission and modulation. It has been recommended as a target for treatment of neuropsychiatric conditions such as anxiety aside from pain management.

Considering that both the endocannabinoid system and inflammation play key roles in the pathogenesis of depression, utilization of the natural substance PEA as an antidepressant agent seems reasonable. PEA mechanism of action in depression is not clearly understood. Synaptic plasticity might be considered as a more general hypothetical mechanism of action of PEA. Evidence shows that PEA has the ability to induce brain-derived neurotrophic factor (BDNF) production in astrocytes and enhance neurogenesis.

BDNF is known to play a central role in synaptic plasticity. This hypothesis requires further assessment because based on available evidence, weeks of typical antidepressant administration is needed to only achieve subtle alterations of BDNF release required to alleviate depressive symptoms . There is also evidence that cannabinoid receptor GPR55 (receptor with affinity to PEA) can modulate synaptic plasticity in the hippocampus.

Since its discovery in the 1950s, PEA has been widely studied for its anti-inflammatory and analgesic properties. PEA is reported to act by down regulating mast cell degranulation at local sites and therefore exerts an antagonistic action against inflammation and pain receptor stimulation. 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 [3]. It was isolated for the first time from purified lipid fractions of soybeans, egg yolk and peanut meal and was then found in a wide variety of food sources, tissues and body fluids of several animal species and human subjects.

Following the discovery of PEA as a naturally occurring anti-allergic and anti-inflammatory compound and of endogenous metabolic pathways for PEA, investigations have been carried out to identify the molecular mechanism of action through which PEA exerts its pharmacological effects. This research has revealed that PEA can act via multiple mechanisms. The mechanism by which tissue levels of PEA are regulated is largely unknown. 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.

PEA belongs to the family of the N-acylethanolamines (NAEs) which: 1) include the first endocannabinoid to be discovered, N-arachidonoyl-ethanolamine (anandamide, AEA) and the anorectic mediatorN-oleoyl-ethanolamine (OEA); and 2) share with PEA similar anabolic and catabolic pathways. Three mechanisms have been proposed so far to clarify the anti-inflammatory and pain relieving impacts of PEA. The primary instrument, which does not avoid the other two, recommends that PEA acts by down-regulating mast-cell degranulation by means of an “Autacoid Local Inflammation Antagonism” (ALIA) impact. The first mechanism of activity for PEA was proposed by Rita Levi- Montalcini’s research group, who

proposed that PEA acts by means of 'Autacoid Local Injury Antagonism (ALIA)' to down-regulate pole cell enactment (45). Afterward, the presence of a 'direct receptor-mediated mechanism' was proposed, and a few ponders illustrated that PEA can act through coordinate actuation of at slightest two diverse receptors: the PPAR-α (46) and the orphan GPCR 55 (GPR55).

PEA has been shown to increase levels of neurotrophic growth factors, such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF). This family of growth factors have well characterised roles in neuronal survival, regeneration, plasticity and protection. Hence, the increase in these molecules induce by PEA may be one of the underlying mechanisms of the supplement's neuroprotective effects. PEA can also interact with and indirectly activate the endocannabinoid system. An increasing body of research now shows that the optimal function of the endocannabinoid system is important for immune system health, mood, memory and brain development. PEA's activation of this system may be one of the contributing factors to improved mood.

The "entourage effect", postulates that PEA acts by enhancing the anti-inflammatory and anti-nociceptive effects exerted by AEA, which is often produced together with PEA, and activates cannabinoid CB1 and CB2 receptors or transient receptor potential vanilloid receptor type 1 (TRPV1) channels. In particular, PEA can bind to endocannabinoid receptors and the peroxisome proliferator-activated receptor alpha (PPAR-α). PEA is not considered a classical cannabinoid since it cannot bind to the endocannabinoid receptors CB1 and CB2. However, it's thought that the molecule can modulate the binding of other cannabinoids to these receptors through the 'entourage' effect.

The "receptor mechanism" is based on the capability of PEA to directly stimulate either an as-yet uncharacterized cannabinoid CB2 receptor-like target, or the nuclear peroxisome proliferator-activated receptor-a (PPAR-a), which clearly mediates many of the anti-inflammatory effects of this compound, or the orphan receptor G-protein coupling, GPR55, 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 [4].

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.

In fact, numerous papers illustrate an "entourage mechanism" of PEA. In specific, the intraperitoneal organization of PEA in mice with persistent constriction injury of sciatic nerve evoked a relief of both thermal hyperalgesia and mechanical allodynia in neuropathic mice . A few specific receptor antagonists were utilized in arrange to clarify the relative commitment of cannabinoid, vanilloid and PPAR to PEA-induced impacts. The results demonstrated that CB1, PPARg and TRPV1 receptorsmediate the anti-nociceptive impact of PEA, recommending an "entourage" activity due to the upgrade of AEA impacts at these receptors. The literature moreover proposes that PEA mirrors an endogenous ligand for the CB2 receptors, which intercedes pain relieving impacts in neuropathic pain states.

PEA has only very weak affinity for CB2 receptor, explaining why some of its anti-inflammatory effects are not blocked by CB2 receptor antagonists. As a result, the theory of the 'entourage' effect was put forward to raise the possibility that PEA could produce indirect receptor-mediated effects. For example, PEA, through the inhibition of the expression of FAAH, the enzyme responsible for the degradation of the endogenous cannabinoid receptor ligand (or endocannabinoid), anandamide (AEA) may indirectly activate CB2 and CB1 receptors. Likewise, PEA can indirectly activate the transient receptor potential vanilloid receptor type 1 (TRPV1) channels, which are also targets for the endocannabinoids.

In spite of the fact that PPAR-α is the molecular target that straightforwardly intervenes a few of the neuroprotective, anti-(neuro)inflammatory and pain relieving impacts of PEA , the presence of roundabout components of activity for this compound has too frequently been illustrated. In specific, endocannabinoid-mediated components of activity taking after the activation of CB1, CB2 receptors or TRPV1 channels, known as the entourage effect, and a CB2 receptor- TRPV1-mediated instrument of activity through PPAR-α (67), have been recognized. These discoveries recommend that the presence of the 'direct or through PPAR-α mechanisms' does not prohibit the entourage effect, and in reality, a synergistic Palmitoylethanolamide and its new formulations interaction can occur between the different components and clarify why PEA has numerous effects and the capacity to act on distinctive cell sorts.

Indeed, while the ALIA mechanism that is, the ability of PEA to inhibit mast cell degranulation, has been widely confirmed and the participation of astrocytes, microglia and keratinocytes in PEA anti-inflammatory actions has also been revealed.

These features distinguish PEA from classical steroidal and non-steroidal anti-inflammatory drugs that act by inhibiting the cascade of arachidonic acid. Preclinical and human studies indicate that PEA, especially with antioxidants, such as luteolin and polydatin, is a therapeutic tool with high potential for the effective treatment of different pathologies characterized by neurodegeneration, (neuro)inflammation and pain. Likewise, PEA also shows high safety.

In response to tissue injury and stress, the body is known to respond by producing molecules on demand which function to restore homeostatic balance and prevent further damage (Buckley CD,].

One NAE, in particular Npalmitoylethanolamine (PEA or palmitoylethanolamide), is surrounded by a large number of observations supporting its role in maintaining cellular homeostasis by acting as a mediator of resolution of inflammatory processes. These past years have witnessed a continually growing number of studies confirming the anti-neuroinflammatory and neuroprotective actions of PEA. Many clinical trials and studies using animal models have been conducted to assess the clinical relevance of PEA as a stand-alone analgesic agent or as a part of combinational therapy.

PEA's analgesic actions may be due to its agonism of peroxisome proliferator activated receptor-α (PPAR-α) which has been shown to have a pivotal role in the PEA pharmacodynamics mechanisms for pain relief. PEA plays an important role in suppression of inflammation by reducing the activity of the pro-inflammatory enzymes such as COX, eNOS, and iNOS (78) and by reducing mast cell activation. PEA reduces mast cell migration, degranulation, and over-activation of astrocytes and glial cell. Several controlled clinical trials have been conducted over recent years to examine the efficacy of PEA in treating chronic pain associated with a variety of conditions [5].

PEA seemed to relieve pain caused by diverse health conditions. Women with pelvic pain caused by endometriosis PEA (300 mg/day) relieved pain and improved sexual function over 6 months; pain caused by fibromyalgia; people with sciatica who don't respond to painkillers like Oxycodone; diabetics with pain from carpal tunnel syndrome caused by nerve compression; pain after failed back surgery; cancer pain; arthritis pain. Importantly, PEA didn't cause side effects or drug interactions in any of the above studies.

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