Palmitoylethanolamide; An organic and cannabimimetic compound with pleiotrophic effects: A review.

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Abstract

Palmitoylethanolamide (PEA) is a compound that the body produces naturally to combat pain and inflammation. Dietary supplementation is a valid strategy to reduce the risk and severity of such disorders. 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 to enhance its effect. Palmitoylethanolamide (PEA) is an endocannabinoid-like lipid mediator with extensively documented anti-inflammatory, analgesic, antimicrobial, and immunomodulatory and neuroprotective effects. It is well tolerated and devoid of side effects. PEA's actions on multiple molecular targets while modulating multiple inflammatory mediators provide therapeutic benefits in many applications, including immunity, brain health, allergy, pain modulation, joint health, sleep, soul and recovery. PEA's poor oral bioavailability has been overcome by advanced delivery systems. PEA is a fatty acid amid like anandamide. 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 gene FAAH that breaks down natural cannabinoid anandamide. This increases the levels of anandamide in the body, helping to combat pain and increase relaxation. It may also activate cannabinoid receptors CB2 and CB1. A combination of PEA, high CBD, low THC, Terpenes, Luteolin and Polydatin along with some selected antioxidants and anti-inflammatory compounds might bring promising avenues in health and wellbeing.

Keywords: Palmitoylethanolamide, Cannabimimetic, Entourage effect, Pain, CNS, GI Diseases, Mood and sleep disorders, Immunity, General health, Longevity, Anti-aging.

Introduction

PEA is a lipid mediator utilized within the clinic for its neuroprotective, anti-neuroinflammatory and pain relieving properties [1] 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 demand and acts locally such as when cells are subjected to possibly hurtful stimuli, they express a specific protein that discharges PEA from the membrane. My personal understanding from my patients is that when the local effect is achieved the remaining molecules begin to locate themselves systematically yet this still has to be proven.

The protective and anti-inflammatory effects of PEA dates back to 1939 [2]. First identified in egg yolk, soybean, and peanut oil in 1957 [3] and thereafter in mammalian tissues in 1965 [4] the modifying effects of PEA on immunological reactions were established in 1971 [5]. PEA's anti-inflammatory and analgesic actions and activation of inflammatory cascades via the activation of nonneuronal cells, such as the mast cells has been discovered in 1993 [6]. PEA has been shown to reduce mast cell migration and degranulation and reduces the pathological over activation of these cells [7,8]. Mast cells shift from activated immune- to resting phenotypes under influence of PEA. PEA further reduces the activity of the proinflammatory enzymes, cyclooxygenase, and endothelial and inducible nitric oxide synthases. PEA has an additional number of other pharmacological and physiological

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properties, such as its affinity for the cannabinoid receptors GPR55, GPR119 and for the vanilloid receptor TRPV1, as well as for the PPAR-*α* [9,10]. PEA is one of the most common of the *N*-acylethanolamines (NAEs), which include the endogenous cannabinoid receptor ligand anandamide (AEA, arachidonoylethanolamide) and the satiety agent oleoylethanolamide (OEA).

It is worth to mention that as early as 1980, studies pointed out that PEA had a tendency to accumulate in the damaged heart muscle due to ischemia or deprivation of oxygen, and this might be of physiological importance because of its anti-inflammatory properties. It was suggested that these fatty molecules played a protective role, and that their presence, may signify a response of myocardial tissue to injury directed at minimizing damage and promoting survival. In other words, PEA and PEA like molecules were quick to be at the site of danger to offer protection [11].

Palmitoylethanolamide (PEA) is a cannabimimetic compound and lipid courier. PEA exerts most of its biological effects in the body secondary to the activation of peroxisome proliferator-activated receptor-α (PPAR-α), but PPAR-α-independent pathways involving other receptors (Transient Receptor Potential Vanilloid 1 (TRPV1), GPR55) have also been identified [12]. 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 [13]. PEA is an acylethanolamide and a cannabimimetic compound broadly dispersed completely different tissues, counting nervous tissues, and is synthesized on demand [14]. 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 [15].

It is a special food for therapeutic reason within the treatment of chronic pain and chronic depression and has been shown to have potentially beneficial effects in a wide variety of conditions such as systemic endothelial dysfunction in ocular hypertension [16]. PEA has no overt toxicity even at high doses (1000 mg/kg/day) [17], and clinical trials have reported that the compound is very well tolerated—indeed, a conspicuous lack of adverse effects is a common finding in most clinical studies with PEA.

PEA is considered an endogenous PPAR agonist or activator and represses inflammatory pathways and oxidative stress. For example during neuropathic pain and any kind of stress and inflammation, PEA can modulate the PPAR pathway that is able to attenuate NFKB induced IL-1 or TNF, inhibit infiltration and activation of mast cells MC, reduce mesangial matrix proliferation induced by ROS [18].

There are a number of endogenous and synthetic PPAR-α activators, such as arachidonic acid and the fibrate family (examples include gemfibrozil, fenofibrate, and bezafibrate). The activation of PPAR-α results in an altered transcription of a large number of genes ranging from those coding for proteins involved in fatty acid transport and metabolism to those coding for pro-inflammatory molecules and oxidative stress [19]. Although fibrates possess anti-inflammatory effects they have many adverse effects, PEA has a safe profile. Thus, at the level of common (>1:100) unwanted effects, PEA is well tolerated [20].

Currently there are number of animal and human studies on the application of PEA in the following conditions: Endometriosis, Benign prostatic hyperplasia (BPH), Burning mouth syndrome, Inflammatory bowel disease and syndrome (IBD/IBS), Depression, Autism, Transient brain injury, Arthritis, Pain of various origins, Coronary heart disease, Chronic kidney disease, Atopic dermatitis and eczema, Vulvodynia, Cannabis dependence, Migraine, Infectious diseases. PEA blood levels are being considered as a biomarker for several of these diseases.

Pea's bondages for multiple stimuli and target

PEA is shown to reduce inflammation, pain and stress induced by various acute stimuli [21]. Its impact is dose-dependent. The anti-inflammatory and pain relieving impacts of PEA have been confirmed in models of chronic inflammation [22] and incessant or neuropathic pain [23]. Chronic treatment with PEA not only diminished pain but also 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 tissue modifications responsible for pain [24].

The 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 [25]. 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 [26]. The deficits in endocannabinoids system (ECS) signaling may result in neuropsychiatric disorders, mainly mood disturbances, while the augmentative therapeutic use of endocannabinoids is suggested to produce positive and affirmative results in affective disorders [27].

The N-methyl-D-aspartate (NMDA) receptors are also involved in the circuits affecting mood disturbances, and targeting of NMDA receptors are becoming of interest for example in the treatment of mood disorders [28]. As an N-acylethanolamine (NAE), an endogenous fatty acid amide PEA targets multiple pathways ranging from PPAR-α and cannabinoid-like G-coupled receptors to less discussed targets like NMDA receptors [29]. PEA affects endocannabinoids (eCB) signaling through PPAR-α activation and affects indirect regulation of microglial cannabinoid (CB) type2 receptor (CB2R) expression. For this reason 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. In this sense, the glutamate transmission and its dysregulation are

also included in depressive disorders. PEA reestablishes the glutamatergic neural connection proteins and changes amino acid discharge (homeostasis). PEA actuates and desensitizes TRPV1 channels possibly and mostly 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 is a target for treatment of neuropsychiatric conditions and pain management [30]. Considering that both the endocannabinoid system and inflammation play key roles in the pathogenesis of depression, PEA is a safe compound as an antidepressant agent possibly contributing to synaptic plasticity in a positive manner [31]. Evidence shows that PEA has the ability to induce brain-derived neurotrophic factor (BDNF) production in astrocytes that plays a central role in synaptic plasticity and enhance neurogenesis [32]. There is also evidence that cannabinoid receptor GPR55 (receptor with affinity to PEA) can modulate synaptic plasticity in the hippocampus [33].

Discovery of pea's medical properties

Since its discovery in the 1950s, PEA has been widely studied for its anti-inflammatory and analgesic properties. 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. PEA as a naturally occurring anti-allergic and anti-inflammatory compound [34] has multiple metabolic pathways [35].

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. Since 1970, the anti-inflammatory and other immune-modulating properties of PEA have been shown placebo-controlled double-blind clinical trials [36].

The mechanism by which tissue levels of PEA are regulated is largely unknown. All in all PEA is now emerging as an analgesic, anti-inflammatory and neuroprotective mediator, acting at several molecular targets in both central and sensory nervous systems as well as immune cells [37].

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. PEA acts by down-regulating mast-cell degranulation by means of an "Autacoid Local Inflammation Antagonism" (ALIA) impact. PEA acts by means of ALIA to down-regulate pole cell enactment. Afterward, the presence of a 'direct receptor-mediated mechanism' was proposed, later studies indicated that PEA can act through PPAR-α and the GPCR 55 [38].

PEA has been shown to increase levels of neurotrophic growth factors, such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF). These families of growth factors have well characterized 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 endocannabinoids system. An increasing body of research now shows that the optimal function of the endocannabinoids system is important for immune system health, mood, and memory and brain development. PEA's activation of this system may be one of the contributing factors to improved mood.

The entourage effect

The entourage effect [39], 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 TRPV1 channels [40]. PEA can bind to endocannabinoids receptors and PPAR-α. PEA is not considered a classical cannabinoid since it cannot bind to the endocannabinoids receptors CB1 and CB2 but can modulate the binding of other cannabinoids to these receptors through the entourage effect.

PEA acts as a protective endogenous mediator during inflammatory and neurodegenerative conditions to counteract inflammation, neuronal damage and pain. In fact, several studies demonstrate that, as with the endocannabinoids, AEA and 2-arachidonoylglycerol, also the tissue concentrations of PEA are altered during different pathological conditions [41].

In fact, numerous studies indicate an entourage mechanism of PEA. A few specific receptor antagonists seem to be utilized in arrange to clarify the relative commitment of cannabinoid, vanilloid and PPAR to PEA-induced impacts. CB1, PPARg and TRPV1 receptors mediate the anti-nociceptive impact of PEA, indicating an entourage activity due to the upgrade of AEA impacts at these receptors [42]. The literature proposes that PEA mirrors an endogenous ligand for the CB2 receptors [43], which intercedes pain-relieving impacts in neuropathic pain states [44].

PEA has only very weak affinity for CB2 receptor [45], explaining why CB2 receptor antagonists do not block some of its anti-inflammatory effects. As a result, the theory of the 'entourage' effect was put forward to raise the possibility that PEA could produce indirect receptor-mediated effects [46]. For example, PEA, through the inhibition of the expression of FAAH, the enzyme responsible for the degradation of the endogenous cannabinoid receptor ligand (or endocannabinoids), anandamide (AEA) may indirectly activate CB2 and CB1 receptors [47]. Likewise, PEA can indirectly activate the transient receptor potential vanilloid receptor type 1 (TRPV1) channels, which are also targets for the endocannabinoids [48]. In addition, PEA is also able to increase AEA- or 2-AG-induced TRPV1 activation and desensitization [49].

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, 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 been revealed [50].

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, neuroinflammation and pain.

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 [51]. Among these is a class of lipid signaling molecules, the N-acylethanolamines (NAEs) [52]. One NAE, in particular N-palmitoylethanolamine (PEA), maintains cellular homeostasis by acting as a mediator of resolution of inflammatory processes. PEA plays an important role in suppression of inflammation by reducing the activity of the pro-inflammatory enzymes such as COX, eNOS, and iNOS and by reducing mast cell activation. PEA reduces mast cell migration, degranulation, and over-activation of astrocytes and glial cell [53].

New directions: There are many proven health benefits of PEA, which should be summarized here briefly. 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 did not cause side effects or drug interactions in any of the above studies [54].

Obesity-driven neuroinflammation is also associated with the disruption of blood-brain barrier (BBB) in the hippocampus. PEA limits the albumin extravasation and restores tight junction transcription modified by High-Fat Diet. PEA directly counteracts inflammation and mitochondrial dysfunction in a PPAR-α-dependent manner since the pharmacological blockade of the receptor reverted its effects. Clinical results strengthen the therapeutic potential of PEA in obesity-related neuropsychiatric comorbidities, controlling neuroinflammation, BBB disruption, and neurotransmitter imbalance involved in behavioral dysfunctions. In fact, a clinical and lab study found out that PEA treatment promotes an improvement in anxiety-like behavior of obese mice and the systemic inflammation, reducing serum pro-inflammatory mediators (i.e., TNF-α, IL-1β, MCP-1, and LPS). In the amygdala, PEA increases dopamine turnover, as well as GABA levels. PEA also counteracts the overactivation of HPA axis, reducing the expression of hypothalamic corticotropin-releasing hormone and its type 1 receptor and attenuates the immunoreactivity of Iba-1 and GFAP and reduced pro-inflammatory pathways and cytokine production in both the hypothalamus and hippocampus. This finding, together with the reduced transcription of mast cell markers (chymase 1 and tryptase β2) in the hippocampus, indicated the weakening of immune cell activation underlying the neuroprotective effect of PEA [55].

PEA as a potential sleeping aid seems also capable of reducing sleep onset time and improving cognition on waking. PEA works synergistically with the endocannabinoid, anandamide (AEA) and AEA concentrations are low at sleep onset, increase during sleep and high at wakening. It is proposed that increased AEA signaling could facilitate deep non-rapid eye movement (NREM) sleep through inducing adenosine release. However, disturbed sleep is possibly related to impaired AEA signaling. Therefore, an exogenous dose of PEA restores dysregulated AEA signaling and facilitate better sleep and a change in inflammatory signaling or reduction in pain sensitivity due PEA contributes additionally to promote faster sleep. PEA is also proposed to have an effect on sleep due to its ability to act through transient receptor potential cation channel subfamily V member 1 (TRPV1). Activation of TRPV1 via increased AEA initiates vasorelaxation through a release of vasodilators facilitates sleep [56].

Clinical trials with PEA in the very past times suggested that the compound reduced the incidence of acute respiratory infections [57]. With respect to PEA and pain, the largest study so far published in recent years is a multi-center, double-blind randomised study with patients with low back pain/sciatica [58], where PEA was found to be efficacious and extremely well tolerated.

Neuroinflammation is the most debilitating factor in many disorders whenever the non-neuronal cell supervision is inadequate. It has been shown that the regulation of non-neuronal cells—and therefore the control of neuroinflammation—depends on the local "*on demand*" synthesis of the PEA and related endocannabinoids. When the balance between synthesis and degradation of this bioactive lipid mediator is disrupted in favor of reduced synthesis and/or increased degradation, the behavior of non-neuronal cells may not be appropriately regulated and neuroinflammation exceeds the physiological boundaries. In these conditions, it has been demonstrated that the increase of endogenous PEA either by decreasing its degradation or exogenous administration is able to keep neuroinflammation within its physiological limits [59].

Neuropathic pain is a condition caused by a lesion or disease of the somatosensory nervous system. It may present as debilitating pain with a sensation of burning and electric-

like symptoms and is often difficult to manage effectively. Although pharmacological medications are the first line of treatment, multidisciplinary teams are sometimes required to provide appropriate treatment to improve quality of life and overall wellbeing. In a case study PEA demonstrated effective pain relief within 48 hours at an administered daily dose of 900 mg (10 mg/kg) [60].

In a study of 250 stroke sufferers, PEA with luteolin improved recovery. It had a beneficial effect on cognitive skills, overall brain health, pain, and daily functioning. The effects were noticeable even after one month and further improved over another month of supplementation [61].

Both with luteolin and alone, PEA prevented Parkinson's disease in mice, reducing damage in the brain and protecting dopamine neurons. Since the destruction of dopamine neurons is what causes Parkinson's disease, PEA may be able to prevent this disease or its worsening. In another study, PEA with luteolin enhanced the healing of nerves in mice with spinal cord injuries. It increased neurotrophic factors (BDNF, NGF); small but powerful proteins that help create new brain cells needed to regenerate tissues after traumatic damage of the spinal cord or brain. However, aside from its direct effects on brain cells, PEA is important for brain health due to its action on our endocannabinoid system. In the brain, our natural cannabinoids play diverse roles in behavior, cognition, mood, and seizure risk, among others. Impaired natural cannabinoids may also play a role in epilepsy. PEA could relieve seizures and shorten their duration in rats by increasing cannabinoid activity in the brain [62].

Retinopathy is an eye disease that can result in vision loss. It is triggered by inflammatory damage to the nerves in the eye, caused by glaucoma and diabetes. PEA reduced eye nerve damage in over 9 clinical trials used in doses up to 1.8 g/day and reduced high eye pressure and improved vision over 6 months without any side effect [63].

To date, endocannabinoids constitute the most recent of the neuromodulators found in neural and non-neural tissues throughout the body. Regarding the retina, there is general agreement that cannabinoids suppress dopamine release and presynaptically reduce transmitter release from cones and bipolar cells. Glaucoma, a leading cause of irreversible blindness worldwide, is an optic neuropathy characterized by the progressive death of retinal ganglion cells (RGCs). Elevated intraocular pressure (IOP) is recognized as the main risk factor. Despite effective IOP-lowering therapies, the disease progresses in a significant number of patients. Oral intake of PEA (600 mg/day) for fifteen days prevented the significant increase of postoperative IOP in patients who had undergone bilateral laser iridotomy as compared to those pretreated with placebo. After three months of PEA oral intake, a reduction of IOP and a significantly improvement endothelial function were observed in ocular hypertension (OHT) patients as compared to placebo-treated. Interestingly, this effect lasted longer than the period of PEA administration. A significant reduction of IOP values was observed in POAG and OH patients after oral administration of PEA for two months [64].

Endocannabinoids can provide a direct as well as indirect effect on IOP regulation. In human eyes, CB1 receptors were found in the Schlemm canal and in the trabecular meshwork, while CB2 receptors were found in the same structure of a porcine model, both receptors have the property of modulating trabecular meshwork cells behaviour by promoting severals modifications. PEA has no effect on CB1 or CB2 receptors, the effect of PEA could be mediated by an entourage effect, which leads to an increase of the cannabinoid tone. Furthermore, in glaucomatous eyes, due to the lower levels of PEA in choroid and ciliary body, it has been hypothesized that PEA has an active role in the IOP regulation and that PEA levels raise in blood flow and tissues as a response to different insults. PEA has an improving effect on endothelial dysfunction, protecting cells and improving their homeostasis perhaps also through the involvement of epoxyeicosatrienoic acids and renin angiotensin system. In addition, PEA treatment reduces blood vessel damage, proinflammatory cytokines production and Interleukin 1 beta, the inducible nitric oxide synthase and polymerase formation, nuclear factor kappa-B expression and apoptosis activation attenuating the inflammatory process. PEA improved both PERG exam and quality of life; the IOP reduction itself acts as indirect neuroprotection, and PEA is able to significantly reduce the IOP [65].

In a recent study people with depression, PEA (1.2 g/day) given over 6 weeks greatly and rapidly improved mood and overall symptoms. PEA was added to antidepressant treatment (citalopram) and lowered symptoms by 50%. As an add-on to standard therapy, PEA reduced adverse effects and pain, improving the quality of life and cognition in a trial of 29 people with MS. The supplement increases serum and plasma levels of PEA and anandamide [66].

Among anti-inflammatory and pro-resolving lipid arbiters, PEA has been detailed to down-modulate mast cell activation [67] and to control glial cell behaviors [68]. At the earliest stage of Alzheimer's disease (AD), although patients are still asymptomatic, cerebral alterations have already been triggered. In addition to beta amyloid (Aβ) accumulation, both glial alterations and neuroinflammation have been documented at this stage. Starting treatment at this prodromal AD stage could be a valuable therapeutic strategy. AD requires long-term care; therefore, only compounds with a high safety profile can be used and PEA and luteolin normalizes such Aβ-induced alterations [69]. In fact chronic treatment with PEA (100 mg/kg/day for three months) in animals models rescued cognitive deficit, restrained neuroinflammation and oxidative stress, and reduced the increase in hippocampal glutamate levels [70]. Another study showed that PEA prevents the enteric glial hyperactivation, reduces AD protein accumulation and counteracts the onset and progression of colonic inflammatory condition, as well as relieves intestinal motor dysfunctions and improves the intestinal epithelial barrier integrity. Therefore, PEA represents a viable approach for the management of the enteric inflammation and motor contractile abnormalities associated with AD [71]. In fact PEA and CBD are anti-inflammatory in the human colon [72]. There are findings that with respect to the brain morphology such as Parkinson's

Disease PEA seems also to alter the course of negativity like demonstrated in patients by improved dyskinesia and reduced camptocormia [73]. In the same area like migraine PEA reduces pain intensity and the number of attacks per month in pediatric patients with migraine [74].

Same positive results have been also observed very recently in patients with refractory Tourette's syndrome [75]. In one other debilitating disease as Autism spectrum disorder (ASD) PEA has been proven to be effective in controlling inflammation, depression, epilepsy, and pain, possibly through a neuroprotective role against glutamate toxicity and by modulation of immune response, neuroinflammation, neurotrophy, apoptosis, neurogenesis, neuroplasticity, neurodegeneration, mitochondrial function, and microbiota activity, possibly PPAR-α activation [76]. Studies indicate that PEA offers potential to restore brain function and slow down brain aging in humans [77]. Uncontrolled neuroinflammation, orchestrated in the central nervous system mainly by astrocytes, microglia, and resident mast cells, is currently acknowledged as a hallmark of neurodegeneration. Within the endocannabinoidome, attention has been paid to PEA due to its safe and pro-homeostatic effects. PEA helps to accomplish successful brain aging.

Preclinical studies indicated a systematically reduced PEA tone accompanied by alterations of endocannabinoid levels. PEA supplementation reduced seizure frequency and severity in animal models of epilepsy and acute seizures, in some cases, similarly to available anti-seizure medications but with a better safety profile. The peripheral-brain immune system seemed to be more effectively modulated by subchronic pretreatment with PEA, with positive consequences in terms of better responding to subsequent epileptogenic insults. PEA treatment restored the endocannabinoid level changes that occur in a seizure episode, with potential preventive implications in terms of neural damage. Neurobiological mechanisms for PEA antiseizure effect seemed to include the activation of the endocannabinoid system and the modulation of neuroinflammation and excitotoxicity. Although no human study was identified, there is ground for testing the antiseizure potential of PEA and its safety profile in human studies of epilepsy.

Chronic low back pain caused by intervertebral disc herniation was reported in the 2010 Global Burden of Disease study to be the main reason for years lived with disability. A very recent trial with PEA 600 mg twice a day therapy on chronic pain in patients suffering from multiple herniated discs in the lumbar spine brought positive results.

The potential role of brown and beige adipose tissue against obesity has been recognized. Browning or beiging of white adipose tissue (WAT) is associated with the remodeling of adipocytes and the improvement of their metabolic and secretory functions. PEA has been shown to restore the plasticity of brown and white adipocytes possibly by PEA and PPAR-α activation as the main mechanism by which PEA can rewire energy-storing white into energy-consuming brown-like adipocytes via multiple and converging effects that restore WAT homeostasis and metabolic flexibility.

PEA was used to relieve symptoms of inflammatory bowel disease IBD in animals. Mice with chronic gut inflammation have low PEA levels, while PEA supplements normalized bowel movement and prevented damage to the gut lining. In tissues taken by biopsy from people with ulcerative colitis, PEA lowered inflammatory cytokines and the buildup of neutrophils, immune cells that worsen symptoms and contribute to gut damage**.** In fact recent studies provide novel proofs on the effects of PEA in colon carcinogenesis [78].

The human body creates endogenous compounds and transforms the exogenous ones to the desired levels in the system under normal conditions so making the survival and healthy aging possible. Virtually every cellular process is affected by diet and so the dietary management regarding the health disorders is vital. In today's world the nutrition transition has created multiple pandemics of chronic degenerative diseases. Negative lifestyle changes, exposure to environmental and industrial pollutants, the erosion of circadian rhythm, decreased physical activity, high intakes of processed foods results in increased dependence on pharmaceuticals which harbour long term adverse effects. These create dysnutrition, chronic inflammation, dysbiosis and a process of immune dysfunction that occurs with age and includes remodeling of lymphoid organs, leading to changes in the immune function of the elderly, which is closely related to the development of infections, autoimmune diseases, and malignant tumors. Also the susceptibility to metabolic disease, cardiovascular disease, cancers, chronic pain, joint disease, asthma, gastrointestinal disorders, affective disorders and neurodegenerative disease gets heightened making human beings vulnerable never seen so much in the history and make them dependent of the synthetic chemicals unknown to the body and soul. To restore the deficiencies supplements containing molecules familiar with human system seem a way to protect against inflammatory and oxidative stress and to target pathways involved in pain sensation, immune regulation, brain health, muscle recovery, improved cognition, mood and sleep. Endogenous PEA due dietary changes and unhealthy food resources is no longer sufficient to counter chronic allostatic load id est cumulative burden of chronic stress and life events as seen in chronic inflammatory disorders, so its exogenous administration seems a viable therapeutic strategy to enhance endogenous levels and restore homeostasis both in soul and body.

The endocannabinoid system (ECS) is a widespread cell signaling network that maintains homeostasis in response to endogenous and exogenous stressors. This has made the ECS an attractive therapeutic target for various disease states. The ECS is a well-known target of exogenous phytocannabinoids derived from cannabis plants, the most well characterized being Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD). However, the therapeutic efficacy of cannabis products comes with a risk of toxicity and high abuse potential due to the psychoactivity of THC. CBD, on the other hand, is reported to have beneficial medicinal properties including analgesic, neuroprotective, anxiolytic, anticonvulsant, and antipsychotic activities, while lacking the toxicity of THC. PEA as an endocannabinoid-like lipid mediator seems to have

a multi-modal mechanism of action, by activating the PPAR-α while also working through the ECS, thus targeting similar pathways as CBD. With proven efficacy in several therapeutic areas, its safety and tolerability profile PEA is an alternative and a treatment combination to and with CBD.

Entourage effect is the enhancement of a biological effect by another molecule through various mechanisms. For example, it is commonly known that pure THC or CBD (isolates) is not as effective as the whole plant extract that contains CBD, THC and the many other components mentioned earlier. These other components like terpenes, flavonoids, etc. assist in an enhanced action of THC or CBD. The entourage effect may occur through different mechanisms, e.g., preventing the breakdown of the eCB's by enzymes that are responsible for their destruction in which case the eCB's last longer in the body giving a prolonged and enhanced action, or improving the binding of eCB's on various receptors, or by activating other receptors, e.g., opening up ion channels that causes a synergistic effect of the major molecule e.g., THC or CBD. I personally aplly CBD not in purest isolate form but in the form with terpenes. Terpenes are fat soluble compounds that easily cross cell membranes and are easily absorbed including into the blood brain barrier. For example D-limolene from the citrus essential oils has anxiolytic, anti-cancer and immune-stimulating properties; Beta-myrcene from hops has analgesic and anti-inflammatory properties; Alpha-pinene prevents acetylcholine uptake so may help in memory and cognition; Linalool found in lavender may have anticonvulsant, anti-inflammatory, analgesic and anti-anxiety properties; Beta-caryophyllene (BCP) which is a sesquiterpene, is widely present in black pepper, cloves, and many other plants has anti-inflammatory and gastro-protective properties. Interestingly, BCP binds selectively to CB2 receptor like CBD and could be considered a phytocannabinoid without having any psychoactive side effects. Research has shown that BCP inhibits triggering of toll like receptors complex CD14/TLR4/MD2, which leads to production of inflammatory cytokines as well as enhanced Th1 response. BCP has been found to down regulate (inhibit) leucocyte proliferation, promote both T cells and restore the Th1/Th2 balance; Beta-amyrin is an anti-bacterial, anti-fungal and anti-inflammatory and so on; flavonoids added to that mixture brings enhanced efficacy. Intake of a combination of PEA and various other ingredients like polydatin, a resveratrol precursor, reduces the severity of chronic pelvic pain and the size of endometriotic nodules in patients with endometriosis. Other natural anti-inflammatories like quercetin, curcumin, boswellia etc. would make excellent combinations with PEA.

PEA supplements have become widely used for the treatment of a variety of conditions. This includes neuropathic pain, chronic pain, multiple sclerosis and fibromyalgia and depression mood disorders. More research is required to fully understanding the mechanisms underpinning these beneficial effects. PEA has a calming effect on overactive genes, which code for inflammation and pain signalling, to adapt cellular metabolism. This action of PEA requires ample time and as such, PEA should be used long term, as it is not a quick fix but a long-term solution to balancing out the ECS for better health, improved response to pain signaling and reduction in the causes of chronic pain.

It has also a positive effect as I observed on hypertension, insulin-resistance and obesity; in fact as reflected in blood tests PEA in long term application restored the alterations of serum biochemical and inflammatory parameters, inducing a marked reduction of ALT, AST, cholesterol, and pro-inflammatory cytokines, such as TNF-α, IL-1 and monocyte chemoattractant protein (MCP)-1. PEA also normalized metabolic hormone levels and restored insulin sensitivity most probably by modulating glucose homeostasis at hypothalamic level.

Conclusion

It is observed in patients that a daily supplementation with 1200 mg of PEA over a 2 months period improves mood and symptoms of patients with depression and mood disorders including sleep patterns. In stubborn cases, this dosage does not suffice and titrating with a dose of 2400 mg and tapering within time by observation brings better results. PEA first does its job by restoring the deficiencies and damages then starts with healing process. It is also observed that adding luteolin and high CBD-CBG-Terpenes %99 and low THC %1 to PEA brings healthy results in all aspects. PEA's anti-inflammatory abilities and its capacity to enhance and shape the desired homeostasis contribute to overall feelings of well-being in soul and a healthy body.

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