The Endocannabinoid System and Palmitoylethanolamide (PEA)

Research highlights

- ✓ The endocannabinoid system (ECS) is an important biological system that regulates and balances a wide range of physiological functions in the body.[1]
- ✓ Imbalance in the endocannabinoid tone may contribute to the development of several pathological conditions such as psychological and neurodegenerative disorders.[2-4]
- ✓ Palmitoylethanolamide (PEA) is an endocannabinoid-like lipid mediator with analgesic and anti-inflammatory properties.[5]
- ✓ PEA supports the ECS via modulating endocannabinoid signaling and indirectly activating cannabinoid receptors. This is known as the entourage effect.[5-7]
- ✓ The effects of PEA on reducing inflammation and pain are supported by a significant number of clinical studies, and no serious side effects or drug-drug interactions are reported so far. [8,9]

Introduction

The endocannabinoid system (ECS) is an important biological system that regulates and balances a wide range of physiological functions in the body.[1] Research on the ECS has led to the identification of not only endocannabinoids such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG), but also endocannabinoid-like lipid mediators such as palmitoylethanolamide (PEA). These endocannabinoid-like compounds often share the same metabolic pathways of endocannabinoids but lack binding affinity for the classical cannabinoid receptor type 1 and type 2 (CB1 and CB2).[5]

PEA naturally occurs in lipid extracts of foods such as egg yolk, peanut oil, and soybean lecithin.[10] Endogenously, PEA (fatty acid amide of palmitic acid) is synthesized in various body fluids and cell types, such as immune cells, neurons, and microglia. These cells are relevant to chronic pain and inflammation signaling.[5] When facing external stressors such as tissue damage and inflammation, endogenous levels of PEA change in order to maintain cellular homeostasis.[11]

However, in chronic pathological situations, endogenous PEA levels may be inadequate to address the imbalance and to maintain homeostasis.[11] In these cases, supplementation of exogenous PEA has been demonstrated to provide antinociceptive activities, antidepressant actions, and inhibition of peripheral inflammation as well as neuroprotective actions in several preclinical studies.[2-]

Mechanisms of action

- PEA is produced "on demand" from membrane phospholipids and exerts its pharmacological effects via multiple mechanisms.
- The anti-inflammatory effects of PEA were first identified by modulation of mast cell activation and degranulation.[6,12]
- Later, the direct receptor activation, including the nuclear receptor peroxisome proliferator-activated receptor-α (PPAR-α) and G-protein coupled receptor 55 (GPR55), was identified (Figure 1). The binding of PEA to selective receptors present on the surface of neurons and immune cells activates signaling pathways leading to inhibition of expression of proinflammatory genes and pain-related signaling, both in the central and peripheral nervous systems.[13]
- In addition, PEA supports the ECS via the entourage effect (Figure 1):
  - PEA increases levels of AEA by inhibiting the expression of fatty acid amide hydrolase (FAAH), the enzyme responsible for the breakdown of AEA, thereby indirectly activating classical cannabinoid receptors and increasing AEA actions.[6]
  - PEA enhances 2-AG- and AEA-induced activation and desensitization of the transient receptor potential vanilloid receptor type 1 (TRPV1) channels, thus potentiating TRPV-1-mediated anti-inflammatory or analgesic actions.[7]
  - PEA indirectly increases CB2 receptors expression or activates TRPV1 channel via PPAR-α.[5]

Increasing numbers of studies indicate that PEA's therapeutic actions are mediated by synergistic interactions among these mechanisms. For example, in a mouse model of Parkinson's disease, sustained administration of PEA over 1 week has been shown to protect dopaminergic neurons and ameliorate motor performance.[4] These actions may be mediated by PEA acting through both direct and indirect interactions with different receptors, such as cannabinoid receptor CB2 and PPAR-α.[14]

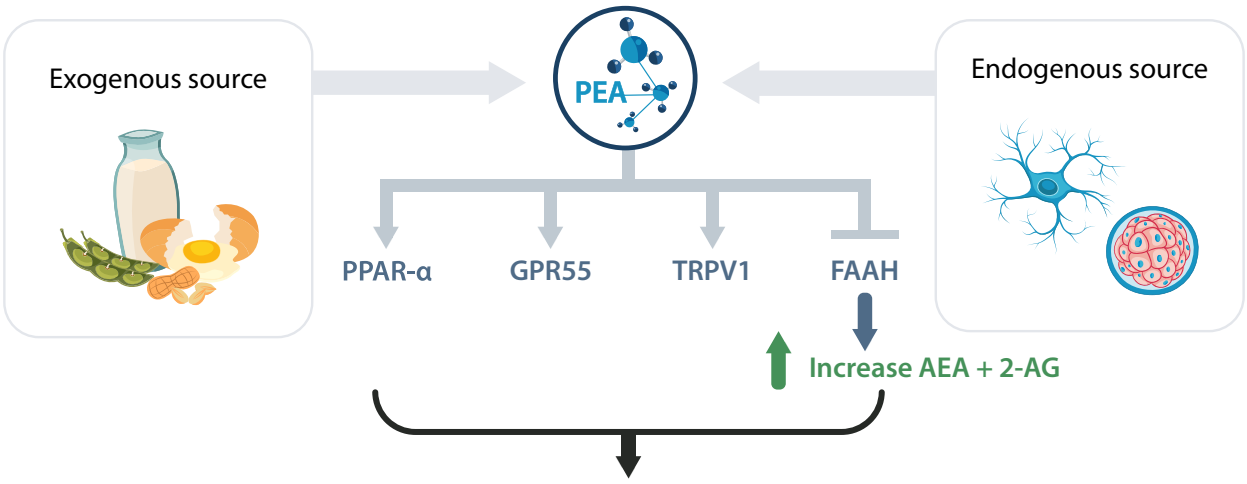

Figure 1. PEA exerts an entourage effect by interacting with the endocannabinoid system.[3,7]

Clinical benefits

The health benefits of PEA have been studied in many different areas. Key human clinical studies involving PEA are summarized below.

Analgesic and immune response effects

Subject Condition (Sample Size)	Study Design; PEA Dosage	Main Findings
Chronic sciatic pain (n=636)[15]	DB RCT; 300 or 600 mg/d for 3 weeks	• Pain was significantly reduced in a dose-dependent manner
Fibromyalgia (n=407)[16]	OS; 600 mg t.i.d. for 10 d followed by 600 mg b.i.d. for 20 d, and 600 mg/d for 15 mo as add-on therapy	• Pain intensity as measured by VAS significantly reduced over time • Quality of life as measured by FIQ significantly improved over time
Fibromyalgia (n=35)[17]	OS; 600 mg b.i.d. the 1st mo and 300 mg b.i.d. the next 2 mo as add-on therapy	• PEA administration for 3 months significantly reduced pain symptoms as assessed by tender points and VAS compared with prior to PEA administration
Chronic low back pain (n=55)[18]	OS; 600 mg b.i.d. for 6 mo as add-on therapy	• Pain intensity as measured by VAS significantly reduced over time • Permanent functional disability as evaluated by ODQ significantly improved over time • Addition of PEA allowed a dose reduction over time in existing therapy (analgesic treatment)
Chemotherapy-induced neuropathy (n=20)[19]	OS; 300 mg b.i.d. for 2 mo	• Pain and neurophysiological measures (function of nerve fiber A-α, A-β, A-δ subtypes) significantly improved over time
Endometriosis-related chronic pelvic pain (n=81)[20]	Review of 4 diverse studies (2 RCTs and 2 OS); PEA+PO* (400 mg+40 mg) b.i.d. for 3 mo	• A clinically relevant improvement of chronic pelvic pain and dysmenorrhea was observed
Carpal tunnel syndrome (n=56)[21]	DB RCT; 600 mg/d for 30 d	• Sensory conduction was improved with PEA, increased cross-section of median nerve with PEA, pilot and underpowered for significance
Carpal tunnel syndrome (n=61)[22]	DB RCT; 300 mg b.i.d. for 60 d	• An improvement in functional status as assessed by BCTQ was observed
Geriatric noncancer chronic pain (n=10)[23]	N-of-1 trial; two 3-wk PEA 600 mg b.i.d. versus placebo comparison, separated by 2-wk washout periods (other medications p.r.n.)	• 3 subjects did not complete the trial: 1 had diarrhea (under placebo), 1 excluded for low adherence, and 1 for intercurrent pneumonia • A significant improvement in pain intensity of function in 3 of 7 subjects who completed the trial
TMJ inflammatory pain related to OA or arthralgia (n=24)[24]	DB RCT; 300 mg AM and 600 mg PM for 7 d and then 300 mg b.i.d. for 7 more d. Comparison group received ibuprofen 600 mg t.i.d. for 14 d	• After 14 d, PEA significantly decreased pain intensity compared with ibuprofen • Maximum mouth opening (indication of pain relief) at 14 d was significantly greater in PEA group compared with ibuprofen group
Knee OA (n=111)[25]	DB RCT; 300 mg/d, 600 mg/d or placebo for 8 wk	• A significant reduction in the WOMAC total score, pain score, and stiffness score in both PEA groups compared with placebo • A significant reduction in the WOMAC function score in the 600 mg PEA group compared with placebo • Evaluations for "worst pain" were significantly reduced in both PEA groups compared with placebo • A significant reduction in anxiety as assessed by DASS in both PEA groups compared with placebo
Common cold and influenza (n=3,627)[26]	Review of 6 DB RCTs; 600-1,800 mg/d for 12 d to 9 wk	• 2 studies found that adult individuals receiving PEA had significantly fewer episodes of fever, headache, and sore throat, compared with placebo; PEA also reduced total number of sickness days and the incidence rate • 3 studies found that adult individuals in the PEA group had significantly fewer symptoms and were less often diagnosed as flu patients • 1 study involving children (age 11-15) found that PEA reduced incidence of common cold compared with placebo
Glaucoma (n=129)[27]	Review of 4 DB RCTs; 600 mg/d for 2 wk to 6 mo	• 1 study in individuals with glaucoma and ocular hypertension found that PEA reduced intraocular IOP compared with placebo • 1 study in ocular hypertensive patients found that PEA reduced IOP and significantly improved FMD values compared with placebo • 1 study in individuals affected by normal-tension glaucoma found that PEA reduced IOP and improved visual field indices compared with placebo • 1 study in individuals undergoing procedure for the prevention of primary closed-angle glaucoma found that PEA attenuated postsurgery increase in IOP compared with placebo

BCTQ: Boston Carpal Tunnel Syndrome Questionnaire; d: day (or days); DB: double-blind; FIQ: Fibromyalgia Impact Questionnaire; mo: month (or months); ODQ: Oswestry Disability Questionnaire; OS: observational study; OA: osteoarthritis; RCT: randomized controlled trial; TMJ: temporomandibular joint; VAS: Visual Analogue Scale; wk: week (or weeks); DASS; Depression Anxiety Stress Scale; FMD: flow-mediated dilation; IOP: intraocular pressure; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index. *PO: trans-polydatin, a precursor of resveratrol

Neuroprotective effects

Subject Condition (Sample Size)	Study Design; PEA Dosage	Main Findings
Parkinson's disease (n=30)[28]	OS; 600 mg b.i.d. for 3 mo followed by 600 mg q.d. for up to 12 mo as add-on therapy	• Compared with baseline; addition of PEA led to a significant and progressive reduction in both motor and nonmotor symptoms as assessed by MDS-UPDRSr
Stabilized stroke subjects in neurorehabilitation (n=250)[29]	OS; PEA+Lut† (1,400 mg+140 mg) for 60 d as add-on therapy	• An improvement in neurological status (assessed by CNS), cognitive abilities (by MMSE), degree of spasticity (by AS), and pain (by NRS) was observed after 30 d • An improvement in independence in daily living activities (assessed by BI) was observed at 30 d, which continued to improve at 60 d
Relapsing-remitting multiple sclerosis (n=29)[30]	DB RCT; 600 mg/d for 1 year as add-on therapy	• PEA administration for 3 months significantly reduced pain symptoms as assessed by tender points and VAS compared with prior to PEA administration
MCI (n=1)[31]	Case report; PEA+Lut† (700 mg+70 mg) for 9 mo	• Neuropsychological evaluation was almost normal with a significant improvement in RAVLT, AM, and TMT compared with pretreatment period • Improvement in cognitive performance was almost within normal range as measured by brain SPECT
Sporadic ALS (n=1)[32]	Case report; 600 mg sublingual, b.i.d. for 13 d and increase to 600 mg t.i.d. for the next 27 d	• An improved clinical picture, as evidenced by electromyographic analysis and pulmonary function

ALS; amyotrophic lateral sclerosis; AM: attentive matrices; AS: Ashworth Scale; BI: Barthel Index; CNS: Canadian Neurological Scale; d: day (or days); MCI; mild cognitive impairment; MDS-UPDRS: Movement Disorder Society/Unified Parkinson's Disease Rating Scale questionnaire; MMSE: Mini Mental State Examination; mo: month (or months); MSQoL-54: Multiple Sclerosis Quality of Life-54 questionnaire; NRS: Numeric Rating Scale; OS: observational study; RAVLT: Rey Auditory Verbal Learning Test; SPECT: single-photon emission computed tomography; TMT: Trail Making Test. †Lut: luteolin, an antioxidant flavonoid

Safety

In a meta-analysis of 12 human clinical studies, PEA was generally well-tolerated, and no serious, nonserious, or suspected adverse events associated with PEA (dose as high as 1,200 mg/day for 365 days) were seen.[8,9]

Conclusion

PEA has been the subject of numerous preclinical and clinical studies, mainly with a focus on several pathological conditions such as pain, neurodegenerative, and psychological disorders.[8,9] With respect to the safety of PEA, no serious side effects or drug-drug interactions have been reported so far.[8,9] Further research is needed to better understand pharmacokinetics and potential of PEA in non-pain-related conditions.

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