



PEA

AND THE BRAIN



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What is PEA?

Palmitoylethanolamide (PEA) is a bioactive lipid mediator that belongs to the N-acetylanolamine class of phospholipids. It was initially discovered in egg yolk, soybean, and peanut oil. In animal cells, PEA is synthesised from palmitic acid, a fatty acid present in foods such as palm oil, meats, cheeses, butter, and other dairy products.¹⁻³

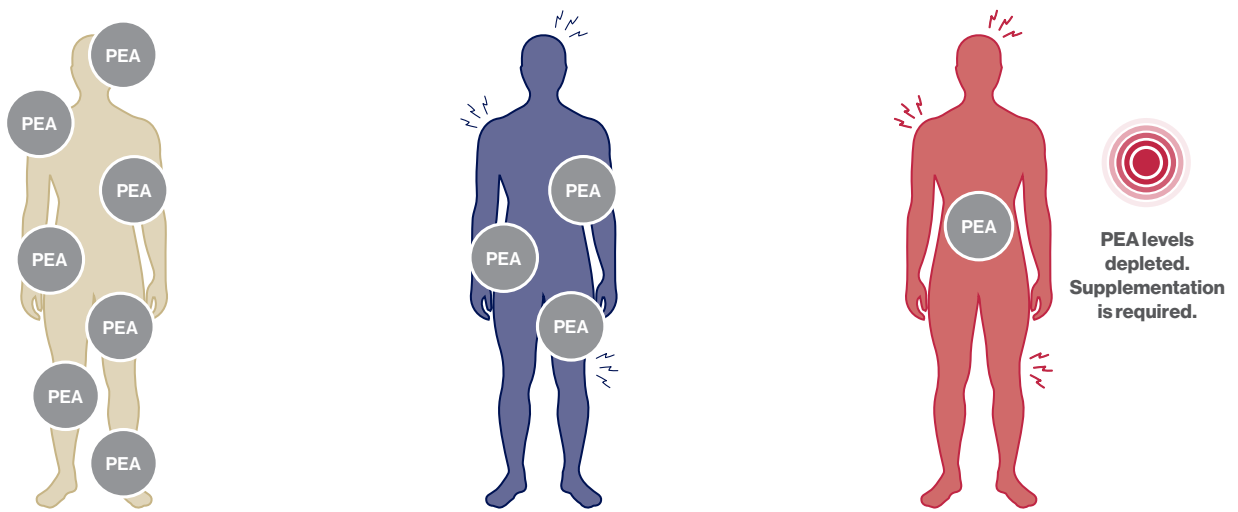
PEA is widely distributed around the body, appearing in the adrenal glands, diaphragm, spleen, kidney, testis, lung, liver, heart, plasma, erythrocytes, and retina. It penetrates the blood-brain barrier, primarily accumulating in the hypothalamus, pituitary, brain stem, cerebellum, and brain cortex.²

PEA and chronic inflammation

During pathological states, PEA levels are often altered. PEA is believed to be produced to help restore homeostasis after cellular injury and is usually upregulated under disease conditions.¹ In the brain, PEA is produced as required by neurons, microglia, and astrocytes, thus playing a pleiotropic and pro-homeostatic role. When faced with pro-inflammatory external stressors, PEA exerts a local anti-injury role by down-regulating mast cell activation and protecting neurons from excitotoxicity.^{2,3}

However, during chronic inflammation, tissue concentrations of endogenous PEA decrease due to reduced production and increased degradation. This makes endogenous PEA production inadequate to restore homeostasis. Therefore, supplementation with PEA presents a viable option to top up endogenous levels and restore bodily homeostasis.¹ (See Figure. 1)

Figure 1. When PEA demand outweighs supply, supplementation may be needed.



No pain

The body produces adequate PEA to meet its biological needs.

Acute pain/inflammation

The body uses its PEA supplies and increases PEA production to meet demand.

Unresolved pain/inflammation

The body cannot meet demand for PEA to reduce pain and inflammation.

PEA mechanisms of action

PEA has anti-inflammatory, analgesic, anticonvulsant, antimicrobial, antipyretic, antiepileptic, immunomodulatory and neuroprotective activities. It exerts its analgesic and anti-inflammatory effects primarily by activating the peroxisome proliferator-activated receptor alpha (PPAR)- α . Activation of the PPAR- α receptor initiates a range of actions that suppress pain and inflammatory signals, including inhibiting the release of pro-inflammatory cytokines such as interleukin (IL)-1 β , IL-6 and tumour necrosis factor- α . PEA also down-regulates mast-cell degranulation and regulates microglial activity. Moreover, even though PEA has a low affinity for the cannabinoid receptors CB1 and CB2 and, therefore, cannot be considered a classic endocannabinoid, it is an endogenous endocannabinoid-like compound that targets similar pathways to cannabinoids.^{1,2,4}

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PEA and its receptors are present in different cell types in the central nervous system. Moreover, as PEA crosses the blood-brain barrier, supplementing with PEA may help prevent and manage various neuroinflammatory conditions. Recently, there has been increasing interest in its potential to slow the progression of diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, Frontotemporal dementia, Amyotrophic Lateral Sclerosis, and Multiple Sclerosis.^{3,10}

In animal and ex vivo models of Alzheimer's disease, Parkinson's disease, autism spectrum disorder, stroke and traumatic brain injury, PEA administration has attenuated gliosis and neuroinflammation; modified mast cell, microglia and astrocyte activation; protected against neuronal degeneration, apoptosis, and glutamate toxicity; inhibited oxidative stress processes in the brain; and improved deficits in behavioural, motor, and cognitive function.^{3,10}

In stress conditions, PEA levels are increased, and in people with post-traumatic stress disorder (PTSD) and bipolar disorder, PEA levels are higher.^{11,12} These increased PEA concentrations are presumably a protective response to aversive and/or hazardous situations and a modifier of the induced Cell Danger Response.

Although research is limited, there is evidence that PEA has antidepressant and anxiolytic effects.¹³

In patients with major depressive disorder, 600 mg of PEA administration twice daily for 6 weeks reduced depressive symptoms more than the placebo.¹³ In an 8-week randomised, double-blind, placebo-controlled study on people with schizophrenia, PEA administration in conjunction with risperidone led to greater improvements in negative symptoms.¹⁴ Similarly, when PEA was administered as an adjunct to psychiatric medications, it was associated with greater improvement in manic symptoms in people with bipolar disorder.¹⁵ As a stand-alone treatment, PEA administration for 8 weeks also reduced sleep onset time and improved cognition upon awakening in people experiencing sleep disturbances.¹⁶

Potential therapeutic effects of PEA

Because of PEA's multiple mechanisms of action, it potentially has many therapeutic benefits, such as a treatment for allergic reactions, influenza, common cold, chronic pain, and joint pain.¹ Currently, it is commonly used for the treatment of different types of neuropathic pain, such as fibromyalgia, osteoarthritis, and carpal tunnel syndrome.⁵⁻⁷ It may also reduce post-operative pain, enhance muscle recovery following exercise, and reduce the prevalence of migraines.⁷⁻⁹

Bioavailability of PEA

With its lipid structure and large particle sizes, PEA has poor solubility and bioavailability.⁴ To overcome these problems, PEA has been micronised and ultra-micronised, which has enhanced its absorption and bioavailability.

Using a novel crystalline dispersion technology (LipiSpense®), where a combination of surfactants, polar lipids and solvents are used to increase the wettability of lipophilic substances in aqueous environments, the increased absorption of PEA has also been achieved. Compared to non-micronised PEA, the administration of this unique PEA product known as Levagen®+ was associated with faster absorption and 1.75 times greater PEA plasma concentrations.¹⁷ This enhanced absorption is essential as lower dosages may be used to achieve therapeutic benefits.

Administration and dosing

The doses of PEA used in clinical trials vary but generally range from 300 mg to 600 mg daily. Typically, PEA is administered for 4 to 8 weeks, although if used as a neuroprotective agent, it may require administration for more extended periods.^{1,3,10}

In sum, PEA is an exciting ingredient that can potentially have therapeutic benefits for a range of conditions. The bulk of evidence supports its pain-relieving properties, although it has promise as a natural agent to support mood, reduce neuroinflammation, and provide neuroprotection.

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