FOR HEALTHCARE PROFESSIONALS

PEA Technical Education Brochure

What is PEA?

Overview

Palmitoylethanolamide (PEA) is a naturally occurring endocannabinoid-like lipid mediator found in many tissues throughout the body, including the brain, spinal cord, muscle, skin, blood, liver, and gastrointestinal system.[1] PEA is synthesized from the most common saturated fatty acid in the body, palmitic acid,[2] which accounts for 20-30% of total body fatty acids.[3] Small amounts of PEA are also naturally present in a variety of plant and animal food sources.[4]

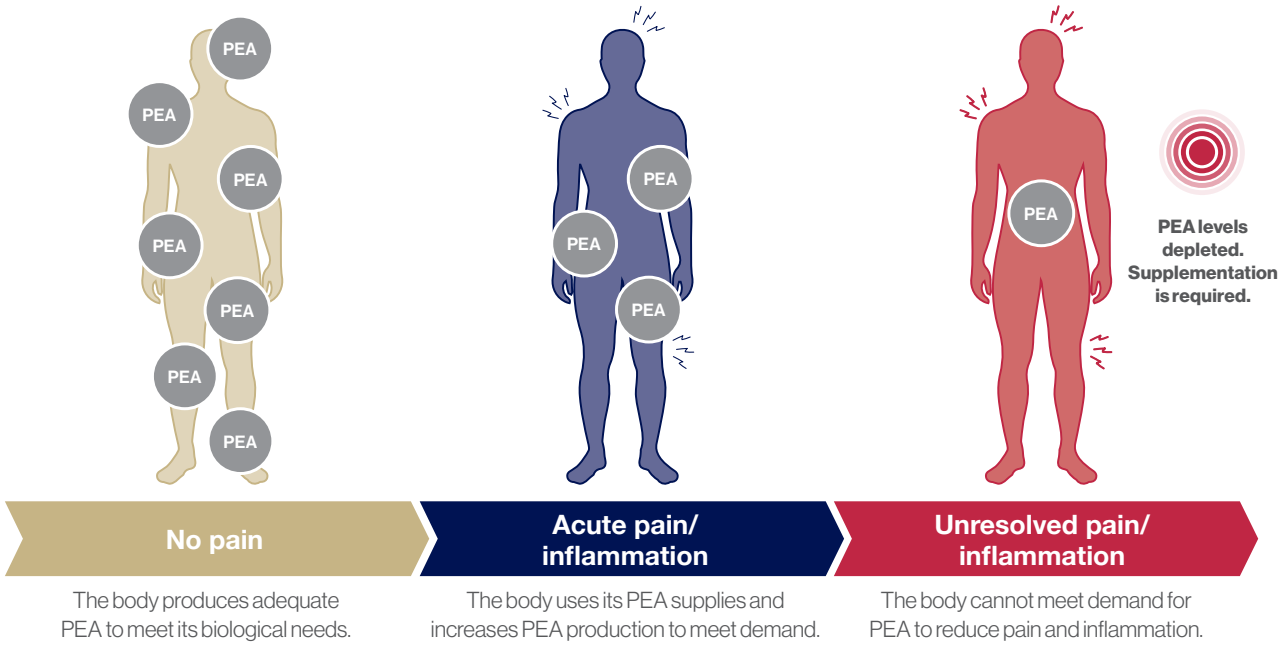
Through its anti-inflammatory, analgesic, antimicrobial, immunomodulatory, and neuroprotective properties, PEA is the body's internal protective mechanism.[5] In response to potential or actual cellular stress, whether from injury, inflammation, or pain, production of PEA within local tissues increases to stop the progress of inflammation, counteract potential damage, and support the body in restoring balance.[5]

In the absence of inflammation, appropriate levels of PEA can be obtained through a balanced diet and the body's own 'on demand' production.[1] However, this combination is often not enough to tackle long-lasting stress on the body, as seen in inflammatory disorders, and supplementation may be required to meet the body's needs.[5] *(See Figure. 1)*

Why do chronic pain sufferers need to 'top up' their PEA?

With acute pain and inflammation, the body increases its production of PEA to meet the demand. However, if pain and inflammation persist and is unresolved, PEA levels can become depleted.[6] There is an inverse relationship at play, with chronic inflammation hindering PEA levels by reducing synthesis and promoting degradation, and the subsequently low PEA levels impeding the resolution of inflammation.[7] Therefore, supplementation of PEA may be required to replenish PEA levels, working to reinstate its protective, anti-inflammatory, and analgesic effects.[6]

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



How PEA Works

PEA is both anti-inflammatory and analgesic

Anti-inflammatory

PEA acts on receptors and signalling pathways to reduce inflammation by:

- Regulating the response to inflammatory mediators
- Reversing the effect of the inflammation
- Influencing the production of anti-inflammatory mediators[5]

Analgesic

The pain modulating effects of PEA are primarily a result of its ability to interact with and act on several molecular targets throughout the body, either directly or indirectly influencing various biological pathways involved in inflammation.[8]

Combination anti-inflammatory and analgesic

Regulates immune cells

PEA modulates the activation and breakdown of mast cells and regulates microglial activity, significantly influencing inflammation levels and pain sensitivity.[9] When activated mast cells degranulate or breakdown, various pain-inducing mediators are released which increases pain hypersensitivity.[9] Mast cell degranulation also triggers the recruitment of other immune cells which release pro-inflammatory mediators such as histamine, tumour necrosis factor alpha (TNF-a), interleukins, and prostaglandins.[9]

Activates anti-inflammatory receptors

Peroxisome proliferator-activated receptors (PPARs) are found in many tissues around the body and can 'switch on or off' different genes which can either promote or stop inflammation.[10] PEA directly activates PPAR-a, which switches off pro-inflammatory genes, reducing the production of inflammatory enzymes such as TNF-a and cyclooxygenase 2 (COX-2).[11]

Omega-3 fatty acids and curcumin also work to reduce inflammation through their impact on receptors such as PPARs.[13,14]

G-protein coupled receptors (GPCRs) are involved in a wide variety of physiological functions, including playing a key role in regulating inflammation.[15] Opioids primarily exert their anti-inflammatory and pain-relieving actions by acting on GPCRs.[16] PEA also activates G-protein coupled receptor 55 (GPR55).[5]

NSAIDs primarily work by inhibiting COX-1 and COX-2 enzymes to prevent prostaglandin synthesis. COX-1 is important for the maintenance of the gastric mucosa and supports kidney function and blood clotting. COX-2 is mainly involved in inflammation and pain. Whilst some NSAIDs selectively inhibit COX-2 only, most NSAIDs are non-selective and inhibit both enzymes and therefore are not appropriate for everyone.[12]

Lends a helping hand – *The entourage effect*

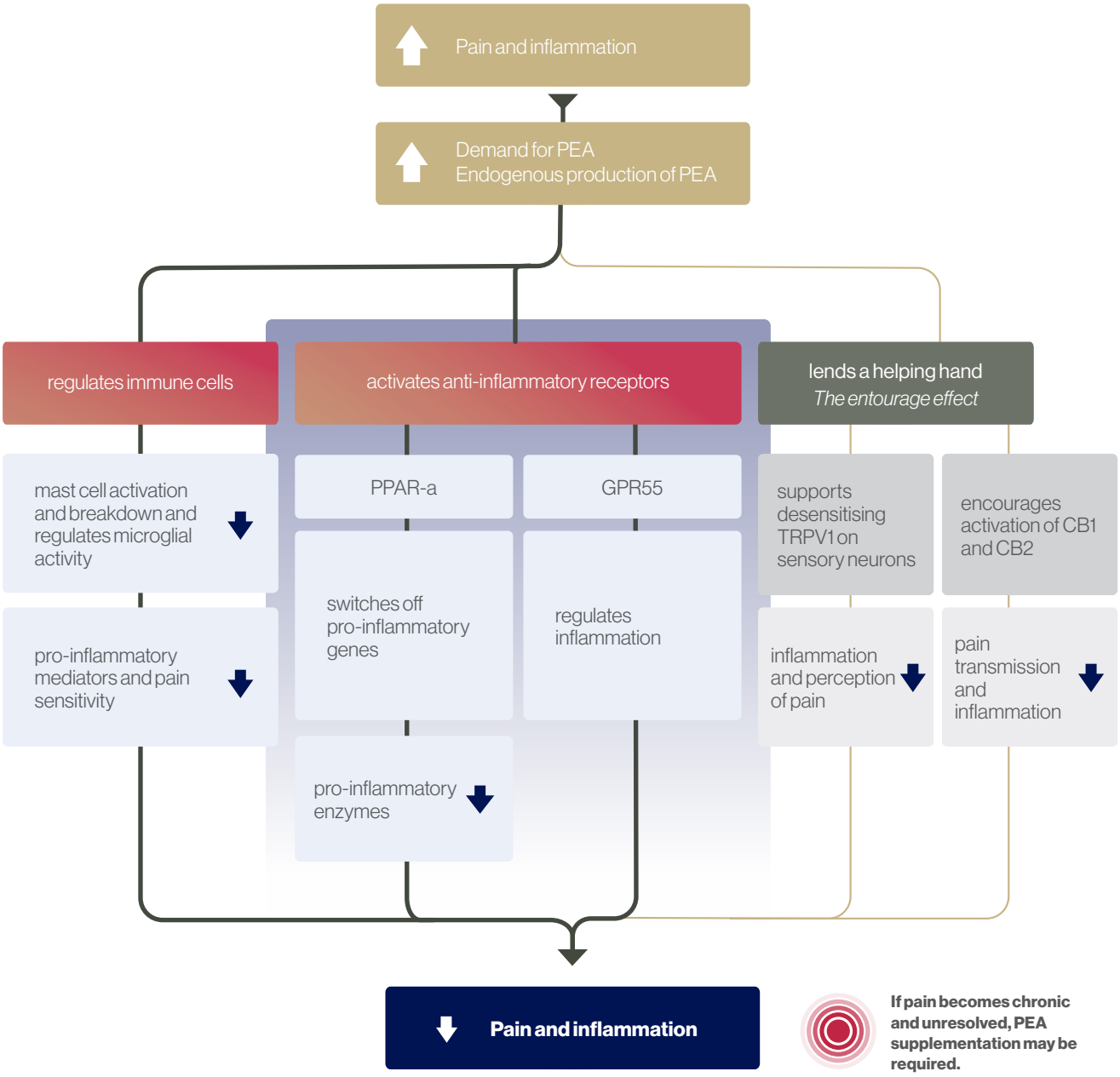
PEA has an indirect action on pain and inflammation via the endocannabinoid system (ECS). The ECS is a vast network of chemical signals and cellular receptors that are found throughout the body, including the brain and immune tissues. The ECS plays a fundamental role in many physiological processes, including immune function, pain modulation, and inflammation.[17] PEA encourages the activation of cannabinoid receptors 1 and 2 (CB1 and CB2), in a process known as the entourage effect, which reduces inflammation and the perception of pain.[5]

Paracetamol (Acetaminophen) primarily exerts its analgesic effects by also acting on TRPV1 and CB1 receptors in the central nervous system.[18]

Another important receptor that initiates inflammation and transmission of pain signals is the transient receptor potential vanilloid receptor 1 (TRPV1).[19] PEA helps to desensitise this receptor on sensory neurons, reducing pain transmission and inflammation.[20] *(See Figure. 2)*

PEA Mechanism of Action

Figure 2.



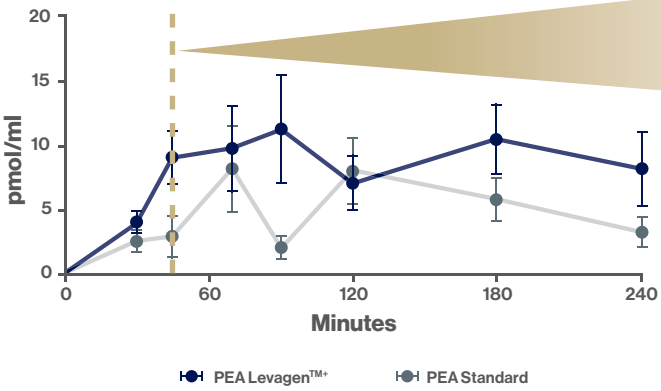
If pain becomes chronic and unresolved, PEA supplementation may be required.

Absorption and bioavailability

Typically, standard supplemental PEA is poorly absorbed with low bioavailability due to its poor water solubility.[21] Supplemental forms of PEA with advanced absorption technology can significantly counteract these absorption challenges.

LipiSperse® technology ensures effective absorption of Levagen®+ PEA, **enhancing absorption by 1.75 times that of standard forms of PEA - taking just 45 minutes to be absorbed.[2] This results in consistently higher plasma concentrations of PEA, supporting longer and more sustained pain relief.[2]** *(See Figure. 3)*

Figure 3. PEA Plasma Concentration



Levagen®+ PEA enhances absorption by 1.75 times that of standard PEA

Plasma concentration time curves for PEA after a single 300 mg dose of the two different PEA preparations. Concentrations are expressed in pmol/mL ± SE. n=14 per group.

Briskey D, Mallard AR, Rao A. Increased absorption of palmitoylethanolamide using a novel dispersion technology system (LipiSperse®). J. Nutraceuticals Food Sci. 2020;5(2).

PEA has an excellent safety record AND can be used as an adjunct to pharmaceutical analgesics

Supplementation with PEA is generally well tolerated[5] with no known drug interactions or contraindications associated with PEA supplementation.[22] Individuals with renal and hepatic impairment can safely use PEA as its metabolism is independent from kidney and liver functions.[23]

PEA can be used as a stand-alone therapy, or as a complement to pharmaceutical analgesics for the management of pain.[24]

Opioids & PEA

- Good pain control with excellent tolerability was found when generally ineffective doses of oxycodone were administered alongside PEA supplementation, suggesting the potential to combine these therapies to reduce opioid dose, dependence, and undesirable side effects.[9]
- Supplementation of PEA has been shown to delay the development of tolerance to the analgesic effects of morphine.[9]
- Combination treatment of PEA and tapentadol for chronic lower back pain reported significantly higher reduction in pain intensity when compared to treatment with tapentadol alone.[25]

NSAIDS & PEA

- In patients using NSAIDs to treat migraines, add-on supplementation of 1200 mg/day of PEA in conjunction with NSAIDs resulted in a statistically significant reduction in pain, and it reduced the number of migraine attacks per month.[5]

PEA Prescribing Guide

Condition-specific dosages for PEA

Clinical trials and case reports have used PEA in dosages ranging from 300-1200 mg daily for periods ranging from 14-120 days.[21]

CONDITION	DOSAGE
Chronic pain	600 mg PEA twice daily for 3 weeks, then once daily for 4 weeks, either as a single therapy or in addition to other analgesic therapies.[26]
Fibromyalgia	600 mg ultra-micronised PEA (PEA-um) twice daily for 1 month, then 300 mg micronised PEA (PEA-m) twice daily for 2 months, with duloxetine and pregabalin.[27]
Joint pain	175 mg (Levagen®+ PEA) twice daily for 14 days.[28]
Lower back pain	600 mg PEA twice daily, as an adjuvant to tapentadol, for 6 months.[25]
Sciatica	300-600 mg PEA daily for 21 days.[29]
Osteoarthritis of the knee	300-600 mg PEA daily for 8 weeks.[30]
Headache	525 mg (Levagen®+ PEA).[31]
Migraine	1200 mg PEA once daily, with NSAIDs for 90 days.[32]
Carpal tunnel syndrome	600-1200 mg PEA daily for 30 days.[33]
Diabetic peripheral neuropathy	300 mg (Levagen®+ PEA) twice daily for 8 weeks.[34]
Multiple sclerosis	600 mg PEA once daily for 12 months.[35]
Burning mouth syndrome	600 mg PEA twice daily for 60 days.[35]
Dysmenorrhea	400 mg PEA, with 40 mg of transpolydatin, once daily for 10 days from the 24th day of menstrual cycle.[36]
Endometriosis	400 mg PEA twice daily, with polydatin, for 3 months.[37]

PEA and supportive nutrients

SYNERGISTIC NUTRIENTS	EFFECT / BENEFIT
Alpha lipoic acid	Powerful antioxidant to further support the reduction of inflammation and counteract any damage that may have occurred due to the oxidative stress process.[38]
Magnesium	Supports nervous system function further assisting with pain relief[39], facilitates muscle relaxation[40], and assists with reducing inflammation.[41]
Curcumin	Antioxidant with significant anti-inflammatory properties to further support the reduction of pain and inflammation.[14]

TGA 21-day prescribing guidelines

PEA supplementation may be appropriate for long-term use.[5] However, to ensure chronic pain is managed appropriately, TGA regulations advise that PEA is not to be used for more than 21 consecutive days to encourage patients to regularly check in with their healthcare provider.

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