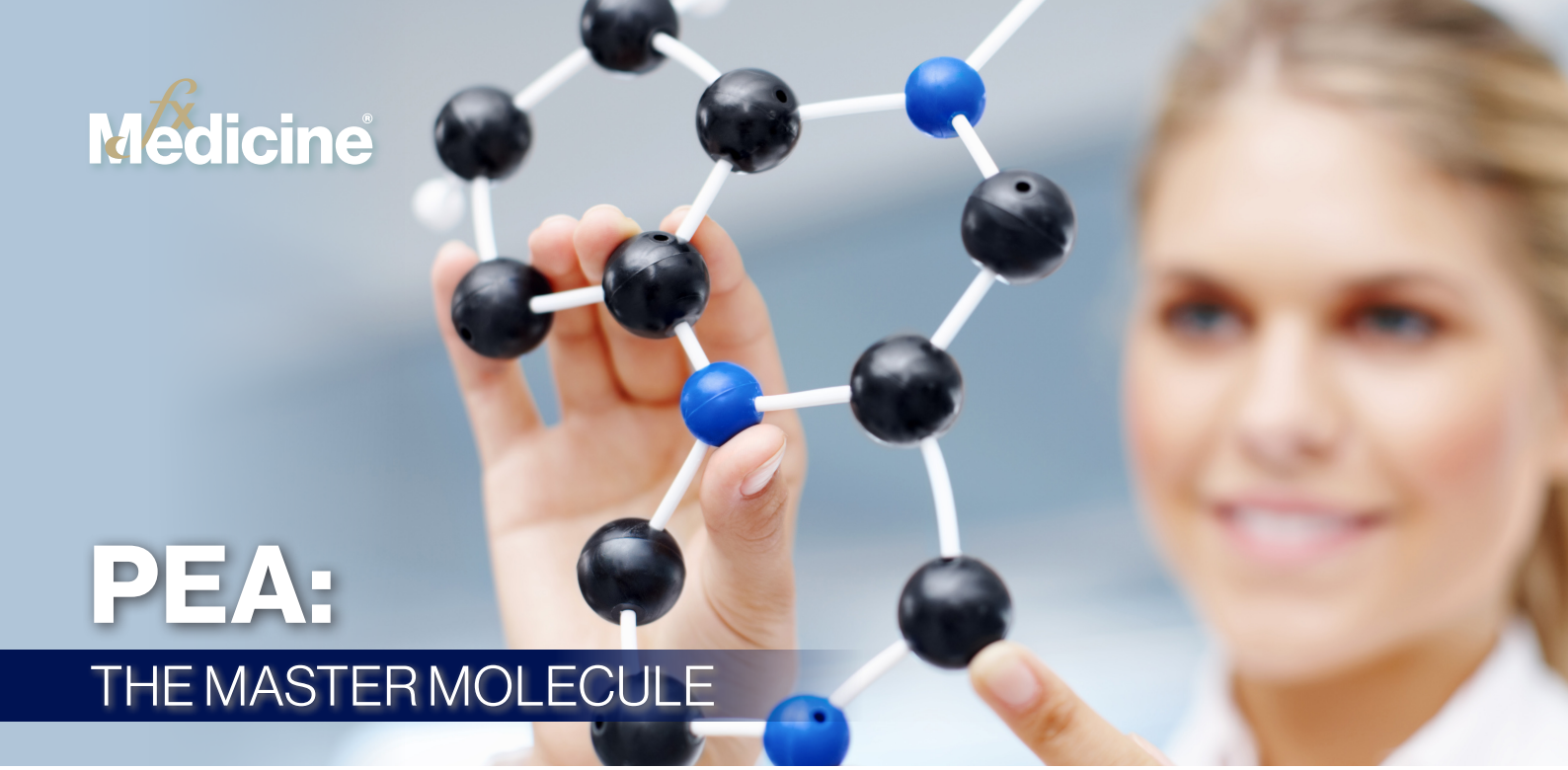

PEA:

THE MASTER MOLECULE

ARTICLE BY
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N-Palmitoylethanolamide (PEA), is an endogenously produced lipid[1] found in the plasma membrane[2] with concentrations increasing in response to tissue damage, inflammation, and nociceptive fibre stimulation.[1] Dietary sources include egg yolks, soy lecithin, bovine and human milk, roasted coffee, apples, potatoes, lentils, black-eyed peas, tomatoes, corn, peanuts, common beans, garden peas, and soybeans.[3]

Initially positioned as a supplement for the prevention of influenza and the common cold,[2] and treatment of rheumatic fever,[2,4] today PEA is regarded for its anti-inflammatory, analgesic, immunomodulatory, antimicrobial, and neuroprotective effects with the ability to effect numerous pathways and sites within the body.[5]

> **Supplemental PEA is used to counteract deficiency associated with chronic inflammation, stress, diet, lifestyle, ageing, and other factors.[5]**

The musculoskeletal system

From a lifestyle perspective, PEA supports exercise recovery and may reduce exercise withdrawal due to pain and loss of strength from inflammation. It also supports individuals looking to increase their strength, fitness, and overall health.[5] In clinical trials, PEA reduced muscle damage, supported aerobic energy metabolism, and reduced lactate levels to encourage protein synthesis.[6]

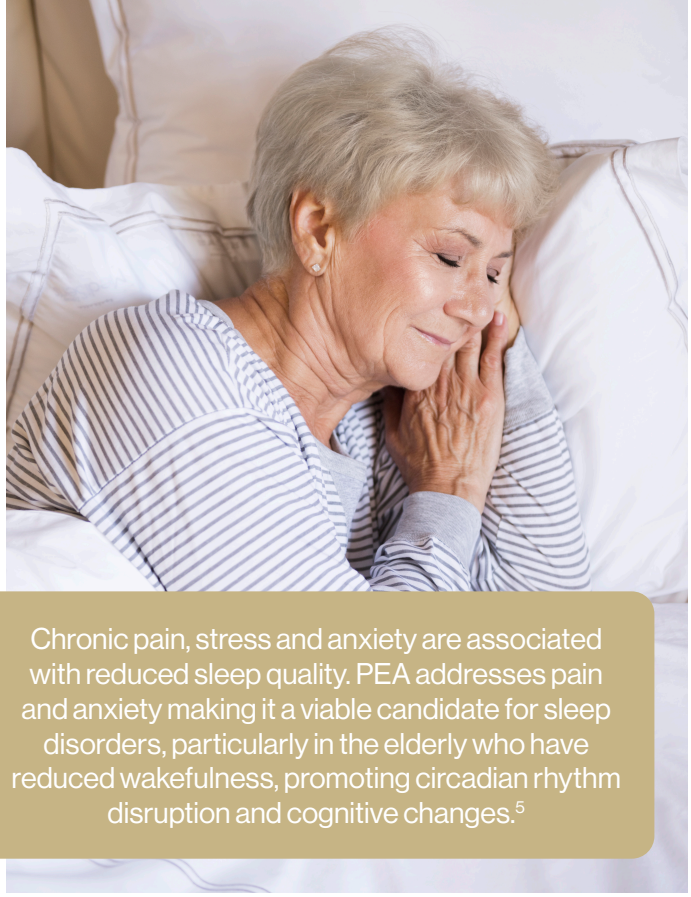
PEA may reduce pain and inflammation in joints, with studies showing arthritis and rheumatoid arthritis joints had lower PEA levels in the synovial fluid.[1] Meanwhile, PEA levels increased in chronic neck and shoulder pain subjects to reduce pain and inflammation, however, PEA levels did not increase in chronic widespread pain subjects suggesting a potential for PEA supplementation.[7] Carpal tunnel syndrome patients demonstrated an objective improvement in sleep quality and associated pain intensity,[1] while animal studies on fracture pain demonstrate PEA improved fracture repair.[2]

The nervous system

PEA reduces pain, stress, depression, and anxiety, as well as supporting post-traumatic stress disorder. It has shown to support γ-aminobutyric acid function and reduce animal seizure activity via allopregnanolone production.[2] Concomitant use with analgesics and PEA has demonstrated pain reduction and decreased medication reliance.[1] It is observed endogenous PEA levels rise in acute situations, with chronic demand potentially exhausting PEA levels, warranting exogenous supplementation.[5]

In animal models, PEA has shown to reduce mast cell-induced neuroinflammation, demyelination and neuropathic pain. Additionally, it functions to lower mast cell-mediated toxicity, brain oedema and ischaemia, delayed post glutamate excitotoxic neuronal death, depression, anhedonia, and amyloid γ-peptide-induced learning and memory impairment[2] in neurodegenerative disorders.[5] Parkinson's disease patients prescribed ultra-micronised PEA (um-PEA) with levodopa demonstrated motor and nonmotor symptom improvement[2] while multiple sclerosis clinical studies support a reduction in pain with increased plasma PEA levels.[2,8]

A clinical study using PEA in conjunction with risperidone demonstrated an improvement in irritability and hyperactivity in autistic patients[2] while reduced dopamine rewarding effects of nicotine and cocaine were determined in animal studies,[9] suggesting a potential therapeutic role for autism and addiction support. Observational studies on stroke patients identified improved cognitive function, spasticity, and ability following PEA administration,[10] with circulation levels at the time of the stroke correlating with the degree of neurological impact.[11]



Chronic pain, stress and anxiety are associated with reduced sleep quality. PEA addresses pain and anxiety making it a viable candidate for sleep disorders, particularly in the elderly who have reduced wakefulness, promoting circadian rhythm disruption and cognitive changes.[5]

The immune system

Preclinical studies demonstrate PEA's bacterial and viral resistance to infections through innate immune support by binding to macrophages and mast cells, supporting inflammatory cytokine modulation.[5]

Mast cell modulation by PEA inhibits histamine, prostaglandin D2, and tumour necrosis factor-a release, leading to the prevention of allergic rhinitis, dermatitis, asthma, and wheals that involve mast cell degranulation and inflammation.[5] Topical application of PEA demonstrates a reduction of eczema.[12]

The gastrointestinal system

PEA is a ligand for cannabinoid-like-G-coupled receptors GPR55 and GPR119. The GPR55 receptor is expressed throughout the body although mainly in the gastrointestinal tract, frontal cortex, hippocampus, hypothalamus, cerebellum, and brainstem,[2] whereas the GPR119 receptor is predominantly expressed in the gut and pancreas. Connections have been made between increased GPR119 expression and type 2 diabetes, obesity, and metabolic disorders.[1] Mice with diabetic neuropathy demonstrated increased cutaneous PEA levels following irritation and inflammation.[13]

Gastrointestinal GPR55 expression modulates inflammation, gastric motility, secretion, cellular proliferation, and intestinal permeability.[2] Gastrointestinal dysbiosis correction is enhanced with PEA increasing commensal bacteria including *Akkermansia muciniphila*, *Eubacterium*, and *Enterobacteriaceae*.[5] Intestinal lipopolysaccharides promote inflammation and intestinal hyperpermeability, crossing the blood-brain-barrier where they promote neuroinflammation. PEA reduces the impact of lipopolysaccharides by preserving the gastrointestinal barrier integrity[5] and stimulates the ligand-activated nuclear receptor Peroxisome proliferator-activated receptor-α (PPAR-α) subtype involved in the regulation of macronutrient metabolism.[3]

Clinical studies of ulcerative colitis demonstrated intestinal PEA levels 1.8 times greater than healthy controls,[13] and two times greater for untreated coeliac disease patients, while pancreatitis, pancreatic cancer, cirrhosis, and colonic inertia also increase localised PEA.[2] Studies on irritable bowel syndrome showed reduced symptoms[14] while an increase in intestinal PEA reduced local and systemic inflammation in colitis-induced mice indicating therapeutic potential.[2]

The reproductive system

PEA reduced pelvic pain associated with painful bladder syndrome, dysmenorrhea, and endometriosis following PEA administration.[15] PEA prevents mast cell recruitment, degranulation, and inflammation by downregulating COX-2, reducing pain associated with menstruation, hormonal fluctuation, and endometrial lesions.[5] PEA combined with transpolydactin reduced dysmenorrhea, dyspareunia, and endometriosis symptoms, providing patients with a reduction in pain in a murine model.[2]

SUPPLEMENTATION

Dietary modification does not increase circulating PEA levels, supplementation is required to increase its therapeutic effect.[2] PEA-containing nutraceutical products generally contain 1,200 mg/day of PEA.[16]

PEA is rapidly metabolised and excreted, with a short half-life as plasma levels return to baseline two hours following supplementation.[5] It reaches its highest concentration 15 minutes following oral administration. Manufacturing of PEA into micronised-PEA or um-PEA form increases bioavailability by up to six times.[3]

Levagen®+ PEA utilises LipiSperse® technology, a cold water dispersion technology that improves the absorption of PEA, supporting lower therapeutic doses.[24]

PEA has a strong safety profile, making it safe for prophylactic use with its catabolism producing palmitic acid and ethanolamine, causing no adverse effects and making it ideal to support healthy ageing.[5] PEA has no known safety concerns and can be administered either alone or in combination with other medications.[5]

Toxicity and adverse events

An animal toxicity study found a no-observed-adverse-effect level of PEA for maternal toxicity, embryotoxicity, fetotoxicity, and teratotoxicity greater than 1,000 mg/kg body weight/day suggesting a human equivalent of 9.7 g/day.[17]

Patients with renal and hepatic impairment can safely use PEA as its metabolism is localised and cellular.[18]

Clinical and animal trials using PEA have not identified any adverse drug-drug interaction and adverse effects have been limited to occasional stomach upset or diarrhoea[2] with PEA being well-tolerated.[5]

Dosage chart

CONDITION	EVIDENCE	DOSE/REGIMEN	OUTCOME
Irritable bowel syndrome	Pilot, 12-week, randomised, double-blind, placebo-controlled, multicentre study	200 mg PEA with 20 mg polydatin twice daily	PEA/polydatin combination notably improved severity of abdominal pain, compared to placebo.[14]
Migraine without aura	Clinical trial	600 mg twice daily of um-PEA administered sublingually for 3 months	A reduction in frequency, duration, intensity, and analgesic use related to migraines without aura.[20]
Migraine with aura	Clinical trial	1,200 mg/day um-PEA	A reduction in time-dependent pain, the number of migraines and days in pain.[21]
Paediatric migraine	Clinical trial	600 mg/day um-PEA for 3 months	A reduction in frequency and intensity of migraines.[22]
Osteoarthritis	Placebo-controlled clinical trial	300 or 600 mg/day for 8 weeks	A greater reduction in knee joint pain in osteoarthritis than ibuprofen and knee joint pain in sufferers of osteoarthritis by 40 per cent (300 mg/day) and 49.5 per cent (600 mg/day) after 8 weeks of treatment.[23]
General joint pain	Double-blind, randomised, placebo-controlled study	350 mg/day of highly bioavailable PEA	A reduction in pain based on a self-assessed visual analogue scale.[24]
Depression	Double-blind, randomised, placebo-controlled study	600 mg twice daily PEA in combination with citalopram for 6 weeks	Reduced major depressive disorder depression scores and symptoms.[25]
Autism	Case study	600-700 mg/day over several months	Improvement in behaviour, cognition, and social interaction in autistic children.[26]
Diabetic neuropathy	Open-label study	300 mg um-PEA twice daily for 60 days	Subjects reported significant reductions in pain, burning, paraesthesia, and numbness from 30 days.[27]
Exercise recovery	Clinical trial	176.5 mg/day of liquid PEA	Reduced myoglobin and lactate dehydrogenase levels and muscle damage and supported aerobic energy metabolism.[6]
Carpal tunnel	Randomised controlled trial	600 mg/day or 1,200 mg/day PEA for 30 days	Subjects in PEA groups reported significantly reduced median nerve latency time. Tinel's sign presence and symptoms of discomfort were reduced compared to placebo.[28]
Primary dysmenorrhea in young women	Randomised, placebo-controlled study	400 mg/day PEA with 40 mg/day transpolydatin for 10 days	Reduced pelvic pain.[29]
Post dental extraction	Randomised, split-mouth, singleblind study	300 mg/day um-PEA tablets for 6 days pre-surgery and 9 days post-surgery	Subjects experienced significantly less postoperative pain compared to the control group.[30]

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