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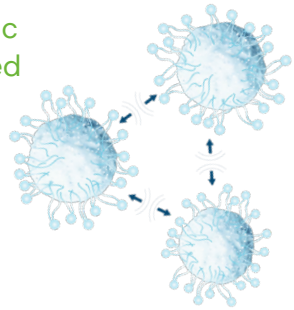
update

How would you react if things were suddenly almost 2x better?

PEA x 1.75

Published pharmacokinetic studies have demonstrated **superiority of PEA with LipiSperse coating® with an increased bio-availability of PEA by times 1.75 compared to standard PEA.**



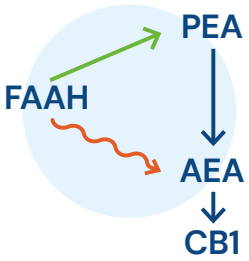
Palmitoylethanolamide (PEA) is an **endogenous saturated fatty acid derivate.** In the body, PEA is synthesized from palmitic acid (C16:0), the most common fatty acid. Synthesis of PEA takes place in membranes of various cell types, PEA is produced on demand and acts locally. When cells are subjected to potentially harmful stimuli, they express a selective enzyme that releases PEA from the membrane.

LipiSperse increases the efficacy of PEA

LipiSperse® coats the surface of the PEA molecule, reducing the hydrophobic nature of PEA and acting as a dispersing agentand likely responsible for the **increase in gastro-intestinal absorption.**

By increasing the absorption of PEA, there is the potential for increasing the efficacy of PEA in conditions where PEA LipiSperse® acts at a number of receptors and exerts its various effects.

5 indications of this enhanced PEA:

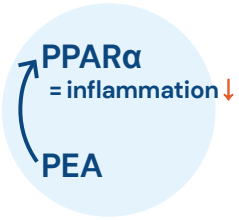


1_PEA enhances CB1

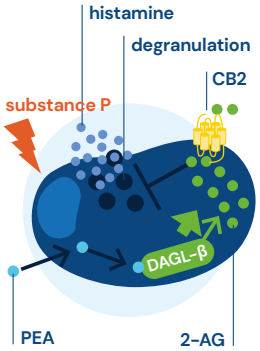
PEA is a cannabimimetic compound or indirect endocannabinoid. **PEA acts as an enhancer of the pain-reducing activities exerted by AEA. = PEA inhibits the metabolic degradation of AEA due to the ability to compete with AEA for the catalytic activity of FAAH.**

2_PEA exerts anti-inflammatory activity

PEA = PPAR alpha ligand = decrease in output of inflammatory mediators like TNF alpha and interleukins



3_PEA modulates microglia and reduces neuroinflammation



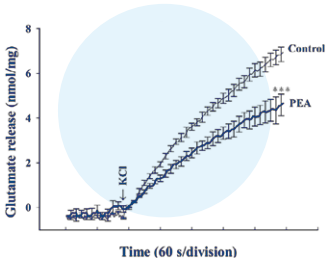
4_PEA is a mastcell stabilizer

Mechanisms of action:
Mast cells: PEA inhibits mast cell degranulation by enhancing 2-AG levels

PEA stimulates (dose dependant) DAGL activity,
which enhances 2-AG (endocannabinoid)
↓
2-AG interact with CB2 receptor
↓
CB2 activation inhibits mast cell degranulation

5_PEA reduces excitoxicity Glutamate/GABA

- **Depress glutamate release**
  Excessive glutamate release → excitotoxicity
- **Inhibition of glutamate release by PEA**
  reduction in Ca2+ influx mediated by Cav2.1 channels
- **PEA-inhibited glutamate release involves a PKA pathway**
  PKA is known to phosphorylate voltage-dependent Ca2+ channels and several synaptic proteins, subsequently increasing glutamate release
  → **Glutamate release measured in the presence of H89 (PKA inhibitor) and PEA was similar to that obtained in the presence of H89 alone**



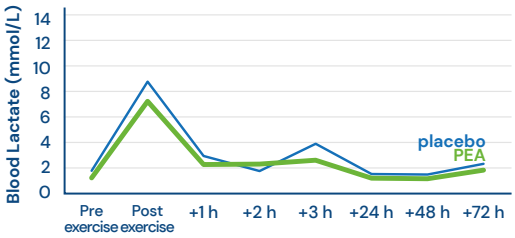
Recent studies show additional clinical possibilities

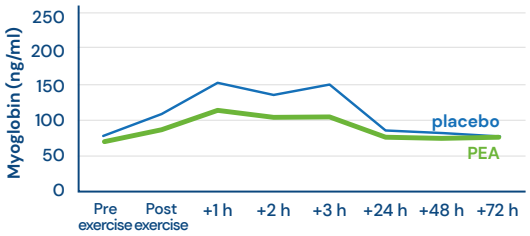
1_PEA LipiSperse improves sleep & relaxation

- **CB1 activation** exerts **calming effect, induces sleep**
- **TRPV1 activation/agonism** increases **restful REM sleep**
- **PEA reduces neuropathic pain & inflammatory pain.** Neuropathic pain & inflammation both disturb slow wave sleep.
- **PPAR alpha receptors** are located in sleep-regulatory areas including thalamus.

2_PEA LipiSperse shows better recovery from sports performance

In this study 28 healthy male volunteers (18-35 years old) received the treatment regimen: **PEA lipiSperse versus placebo.**



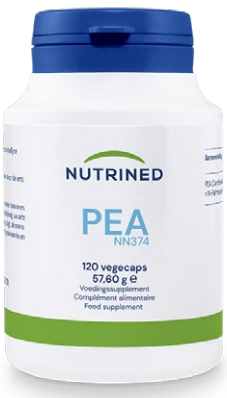


Outcome measures

- Change in blood indicators of muscle damage/recovery, Creatine Kinase
- Muscle pain (VAS Pain score) and soreness (DOMS)
- Change in blood indicators of muscle damage, Myoglobin, Lactate Dehydrogenase
- Exercise recovery: the number of leg presses a participant can complete
- Lab markers CRP, IL-6, IL-10, TNF-alpha
- Pain Questionnaire
- Muscle swelling
- MSFI Multidimensional Symptoms Fatigue Inventory
- Safety markers like GI tolerance

Conclusions

- Athletes who consumed PEA LipiSperse® may be subject to **higher exercise intensities for longer time**, allowing for an improved training response or performance
- A lower blood lactate concentration is correlated with **increased aerobic energy metabolism**
- Injured players **recover better and faster**
- **Improved sleep quality** among players with sleep disturbances



PEA LipiSperse coating®

= N-Palmitoylethanolamide

indication	Neuroinflammation / Indirect CB1 activation / Excitotoxicity / Insomnia / Sports recovery
dosage	2 x 1 - 2 caps per day
packaging	120 vegecaps per container
composition (amount per 2 vegecaps)	PEA LipiSperse coating® (Certified grade) 600 mg

References
PEA

References on the indications

2_PEA exerts anti-inflammatory activity

Mattace Raso G, Esposito E, Vitiello S, Iacono A, Santoro A, D'Agostino G, et al. Palmitoylethanolamide stimulation induces allopregnanolone synthesis in C6 Cells and primary astrocytes: involvement of peroxisome-proliferator activated receptor-. J Neuroendocrinol 2011;23:591–600.

D'Agostino G, La Rana G, Russo R, Sasso O, Iacono A, Esposito E, et al. Centraladministration of palmitoylethanolamide reduces hyperalgesia in mice via inhibition of NF-kB nuclear signalling in dorsal root ganglia. Eur J Pharmacol 2009;613, 54-9.

Straus DS, Glass CK.Anti-inflammatory actions of PPAR ligands: new insights on cellular and molecular mechanisms. Vol. 28, Trends in Immunology. 2007. p. 551–8.

3_PEA modulates microglia and reduces neuroinflammation

Holubiec MI, Romero JI, Suárez J, Portavella M, Fernández-Espejo E, Blanco E, et al. Palmitoylethanolamide prevents neuroinflammation, reduces astrogliosis and preserves recognition and spatial memory following induction of neonatal anoxia-ischemia. Psychopharmacology (Berl). 2018;235(10):2929–45.

4_PEA is a mastcell stabilizer

Petrosino S, Schiano Moriello A, Verde R, Allarà M, Imperatore R, Ligresti A, et al. Palmitoylethanolamide counteracts substance P-induced mast cell activation in vitro by stimulating diacylglycerol lipase activity. J Neuroinflammation. 2019;16(1).

5_PEA reduces excitoxicity Glutamate/GABA

Lin TY, Lu CW, Wu CC, Huang SK, Wang SJ. Palmitoylethanolamide inhibits glutamate release in rat cerebrocortical nerve terminals. Int J Mol Sci. 2015 Mar 11;16(3):5555–71.

Briskey, D., A. R. Mallard, and A. Rao. "Increased absorption of palmitoylethanolamide using a novel dispersion technology system (LipiSperse®)." J. Nutraceuticals Food Sci 5.3 (2020).

References on recent studies

1_PEA Lipisperse improves sleep & relaxation

Rothhaas, Rebecca, and Shinjae Chung. "Role of the preoptic area in sleep and thermoregulation." Frontiers in Neuroscience 15 (2021).

Leys, Laura J., et al. "Disturbances in slow-wave sleep are induced by models of bilateral inflammation, neuropathic, and postoperative pain, but not osteoarthritic pain in rats." PAIN® 154.7 (2013): 1092-1102.

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References
PEA

Briskey, D., A. R. Mallard, and A. Rao. "Increased absorption of palmitoylethanolamide using a novel dispersion technology system (LipiSperse®)." J. Nutraceuticals Food Sci 5.3 (2020).

Rao, Amanda, et al. "Palmitoylethanolamide for Sleep Disturbance. A Double-blind, Randomised, Placebo-controlled Interventional Study." (2021).

2_PEA LipiSperse shows better recovery from sports performance

Mallard, Alistair, et al. "The Effect of Orally Dosed Levagen+™(palmitoylethanolamide) on Exercise Recovery in Healthy Males—A Double-Blind, Randomized, Placebo-Controlled Study." Nutrients 12.3 (2020): 596.

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