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The Neuroprotective Effects of Micronized PEA (PEA-m) Formulation on Diabetic Neuropathy in Mice

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Abstract

Diabetic peripheral neuropathy (DPN) is the most common complication of diabetes and is associated with significant morbidity and mortality. DPN is characterized by progressive, distal-to-proximal degeneration of peripheral nerves that leads to pain, weakness, and eventual loss of sensation. The pathophysiology of DPN includes a complex network of unified vascular, metabolic and neurotropic defects, in particular, involves oxidative and nitrosative stress, neuroinflammation, microvascular ischemia, inflammatory infiltrates, impaired angiogenesis within peripheral nerve tissue, neuroanatomical changes, including decreases in nerve conduction velocity and altered activity of the nervous fiber enzyme Na+, K+-ATPase, which determines endoneurial edema formation and reactive oxygen species (ROS) release. Accumulation of ROS increases lipid, DNA, and protein peroxidation, induces cellular apoptosis and reduces nerve blood flow. Increased oxidative stress leads to activation of the poly ADP ribose polymerase (PARP) pathway which regulates the gene expressions involved in inflammatory reactions and neural dysfunction. Activated mast cells contribute directly to neuropathic pain by releasing algogenic mediators after degranulation. Mast cells and nerve growth factor (NGF) appear involved in neuroimmune interactions and tissue inflammation. NGF exerts a modulatory role on sensory nociceptive nerve physiology, which appears to correlate with hyperalgesic phenomena occurring in tissue inflammation.

Mouse models of type 1 or 2 diabetes are critical to improving our understanding of DPN pathophysiology and developing novel treatment strategies. Some drugs may demonstrate their healing potential by regulating neuroinflammation. Palmitoylethanolamide (PEA) is a prototype ALIAmide well-known for its analgesic, anti-inflammatory, and neuroprotective properties in several experimental models of neuroinflammation.

Based on these findings, the aim of this work was to better examine the neuroprotective effects of a formulation of micronized PEA (PEA-m) in a mouse model of DPN induced by streptozotocin injection. Diabetic and control animals received PEA-m (10mg/kg) by oral gavage daily starting 2 weeks from streptozotocin injection. At 16 weeks, the animals were sacrificed and plasma, urine and sciatic nerve tissues were collected.

Our results demonstrated that after diabetes induction, PEA-m was able to reduce mechanical and thermal hyperalgesia and motor alterations as well as reduced mast cells activation and NGF expression. In addition, PEA-m decreased neural histological damage, oxidative and nitrosative stress, citokines release, angiogenesis and apoptosis maybe by modulating inflammatory pathways such as nuclear NF-κB or MAP kinases.

In conclusion, we demonstrated that PEA-m could represent a new therapeutic strategy to combat neuroinflammation and pain associated to diabetic neuropathy.

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