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Review

Palmitoylethanolamide for Neurological Disorders

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Abstract

Neurological tissue along with the cartilage remains one of the tissues that escapes human efforts of regeneration after injury. The human body, after an injury, can repair its tissues only to a certain extent that can help in recovering the function of organs. However, this is not the case in some organs, such as the brain and spinal cord. For a long time, basic medical science has been investigating the regeneration process that helps the human body, which is mainly through the pharmacological agents, proteins/other molecules acting as cellular transmitters or by the scaffolding of tissues that allows the cells to grow in them and also by other techniques such as electrical currents or electromagnetic waves.

Keywords

Palmitoylethanolamide; neurological disorders

Neuroinflammation is characterized by the infiltration of the immune system cells and the activation of inflammatory mediators. It is one of the components of neural damage, which, if eliminated, could be a key to neurological recovery. The inflammatory cascade, with the activation

of mast cells and glial cells, along with the release of inflammatory agents, creates an unfavorable environment for tissue recovery. Thus, if the tissues could be "cleaned from inflammation", a favorable environment could be created for tissue regeneration. In this regard, several pharmacological agents and chemical mediators have been investigated. The family of ALIAmides (Autacoid Local Injury Antagonist Amides), particularly palmitoylethanolamide (PEA), emerged as mediators of inflammation in the pursuit of agents that heal the neurological tissues and play a role in the improvement of neurological conditions. This family of endogenous molecules plays a role in modifying physiological processes within the physiological pathways, hence, this approach is less prone to side effects in a clinical setting [1, 2].

PEA is an endogenous fatty acid amide proved to reduce inflammation in several experimental models [3-5], hence it is used clinically in reducing pain [6-8]. An experimental study in rats showed a positive effect of PEA on the neuroinflammation of the sciatic nerve that occurred due to compression [9]. Its effect is mediated by peroxisome proliferator-activated receptor-(PPAR-)α, which is a nuclear receptor that plays a role in controlling the inflammatory responses [10]. In this study, the rats showed both clinical and histological improvement, along with a reduction in macrophage infiltration.

Some years ago, we conducted a randomized double-blinded clinical study to evaluate the effects of PEA in carpal tunnel syndrome (CTS) [11]. At that time, the pharmaceutical company that commercialized PEA recommended its dosage as 600 mg per day for treating CTS. Although the electrodiagnostic testing showed no improvement with this treatment, improvements were seen in some items only in the questionnaire. The functional status scale (FFS) and symptom severity scale (SSS) of Levine's questionnaire showed a statistically significant improvement with the values of 11.3% in the former and 13.1% in the latter. Our results showed no clear benefits of this approach in treating the condition. However, the dosage was also lower than the ones reported in the other studies. A study with a 1200 mg dosage per day of PEA indicated a clinical improvement in CTS [12] even though the case was associated with diabetes. Therefore, one of our conclusions recommends a higher dose of PEA in further clinical studies to determine its usefulness in the treatment of carpal tunnel syndrome.

Most of the studies that used PEA were performed to treat peripheral nerve conditions, but this molecule was also found in brain disturbances [13]. Since we know PEA's role as a modulator in neuroinflammation, we may also consider its effects in several brain pathologies where inflammation was detected. However, the first subject to be addressed was to know if the exogenous administration of PEA could reach the brain as it could reach the peripheral nerves. Once this was ascertained, the clinical effect of PEA in brain disturbances could also be studied. PEA is thought to penetrate the blood-brain barrier in small amounts [14], which is attributed to PEA being poorly water-soluble. This reduced its digestive absorption and bioavailability, or also its degradation by hydrolases. Therefore, delivering this molecule to its target site in the brain cells becomes the first challenge.

The different formulations available in theory have different degrees of digestive absorption that add to the difficulty of assessing its bioavailability. Reducing the particle size of the formulation with this compound can increase the digestive absorption of PEA, where micronized and ultra-micronized PEA can improve its diffusion in the body tissues [15].

The nuclear receptor PPAR-α, targeted by the PEA, can also interact with other molecules such as fenofibrate and Wy-14643 to protect against cerebral injury during stroke in mice models [16,

17]. PEA also targets other receptors such as GPR55, which is found in the brain cells, and may play a role in reducing inflammation [18] by reducing the pro-inflammatory enzyme expression while increasing the neurosteroid synthesis [19]. Also, the combination of other molecules, such as antioxidant flavonoids, can act synergistically with PEA to achieve therapeutic effects [15]. A reduction of inflammation in the neurological tissue could decrease the effects of an injury (for example, ischaemic or traumatic injury in the brain) and facilitate a favorable clinical outcome.

The promising results of PEA in the treatment of peripheral nerve neuroinflammation makes us believe that it could also be useful in brain neuroinflammation. Experimental studies in rats have shown the effects of PEA in behavioral dysfunction [20]. Some clinical studies have also suggested that PEA can be used in amyotrophic lateral sclerosis (ALS) [21] and ischaemic stroke [22], but our knowledge remains limited in this field. Hence, extensive studies are further required to define the role of PEA in the treatment of neurological disorders.

Author Contributions

Dr. Jordi Faig-Martí did all work.

Competing Interests

The author has declared that no competing interests exist.

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