South Health and Policy. 2024; 3:140
doi: 10.56294/shp2024140

REVIEW

Therapeutic potential of palmitoylethanolamide in neurodegenerative diseases

Potencial terapéutico de la palmitoiletanolamida en enfermedades neurodegenerativas

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Cite as: Petrone Arifa I, Udovin LD. Therapeutic potential of palmitoylethanolamide in neurodegenerative diseases. South Health and Policy. 2024; 3:140. https://doi.org/10.56294/shp2024140

Submitted: 04-08-2023 **Revised:** 14-11-2023 **Accepted:** 31-03-2024 **Published:** 01-04-2024

Editor: Dr. Telmo Raúl Aveiro-Róbalo

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ABSTRACT

The therapeutic potential of palmitoylethanolamide (PEA) in the treatment of neurodegenerative diseases such as Alzheimer's and Parkinson's. He described how PEA, an endogenous compound with anti-inflammatory and neuroprotective properties, acted on neuroinflammation and oxidative stress by activating the PPAR-α receptor. Preclinical and clinical studies were reviewed that showed cognitive and motor improvements after administration, as well as its combination with luteolin to enhance its effect. The need for further research into other diseases such as amyotrophic lateral sclerosis and frontotemporal dementia was also highlighted, emphasising the importance of rigorous methodologies to validate its efficacy.

Keywords: Palmitoleic Acid; Neuroinflammation; Alzheimer's Disease; Parkinson's Disease; Neuroprotection.

RESUMEN

El potencial terapéutico de la palmitoiletanolamida (PEA) en el tratamiento de enfermedades neurodegenerativas como el Alzheimer y el Parkinson. Describió cómo la PEA, un compuesto endógeno con propiedades antiinflamatorias y neuroprotectoras, actuó sobre la neuroinflamación y el estrés oxidativo mediante la activación del receptor PPAR-α. Se revisaron estudios preclínicos y clínicos que evidenciaron mejoras cognitivas y motoras tras su administración, así como su combinación con luteolina para potenciar su efecto. También se señaló la necesidad de ampliar la investigación hacia otras patologías como la Esclerosis Lateral Amiotrófica y la Demencia Frontotemporal, destacando la importancia de metodologías rigurosas para validar su eficacia.

Palabras clave: Palmitoiletanolamida; Neuroinflamación; Alzheimer; Parkinson; Neuroprotección.

INTRODUCTION

Neurodegenerative diseases represent a growing challenge for contemporary medicine due to their progressive impact on the central nervous system and the lack of effective curative treatments. Among the most prevalent are Alzheimer's and Parkinson's, diseases that involve significant deterioration in cognitive and motor functions. Given this scenario, scientific research has begun to explore new therapeutic avenues focused on endogenous compounds with neuroprotective potential. One such compound is palmitoylethanolamide (PEA), a fatty acid amide with anti-inflammatory and analgesic properties that has shown promising results in preclinical and clinical studies. This paper analyzes the role of PEA in modulating neuroinflammatory processes and its potential application in treating neurodegenerative diseases.

DEVELOPMENT

Neurodegenerative diseases, such as Alzheimer's and Parkinson's, are characterized by progressive deterioration of the central nervous system, affecting cognitive and motor functions. The pathophysiological mechanisms involved include neuroinflammation, oxidative stress, excitotoxicity, blood-brain barrier dysfunction, and loss of intracellular homeostasis.[1,2] In the absence of curative treatments and the limited efficacy of available therapies, the therapeutic potential of endogenous compounds such as palmitoylethanolamide (PEA), a fatty acid amide with anti-inflammatory, analgesic, and neuroprotective properties, has been explored.[3,4]

PEA is synthesized in response to cellular stress and acts by regulating inflammatory processes through the activation of the PPAR-α receptor, with effects on glial cells such as astrocytes and microglia, which are key in neuroinflammation.[5,6] Thus, PEA has been shown to modulate the release of proinflammatory cytokines such as TNF-α and IL-1β, as well as reduce nitric oxide synthesis, contributing to neuroprotection in various experimental models.[7,8,9]

In murine models, particularly in the HT-22 neuronal cell line of the hippocampus, it has been observed that PEA administration can prevent or reverse neuronal damage induced by hypoxia and reoxygenation, conditions that simulate cerebral ischemia and oxidative stress.[5,10] This model helps explore new treatments' molecular and functional effects before their application in humans.

Preclinical and clinical studies reviewed by Colizzi et al.[4] suggest that PEA may positively improve cognitive symptoms, even in advanced stages of neurodegeneration. In the case of Parkinson's disease, Brotini et al.[11,12] documented motor and functional improvements with the administration of ultra-micronized PEA, either as monotherapy or as an adjuvant. In Alzheimer's disease, research such as that by Altamura et al.[13] and Beggiato et al.[14] has linked the action of PEA with the preservation of cognitive functions, decreased neuroinflammation, and reduced excitotoxic glutamate.

The association of PEA with other compounds, such as luteolin, a flavonoid with antioxidant properties, has shown synergy in reducing neuronal damage and stimulating neurogenesis in experimental models.[6,8] This combination appears to enhance the treatment's neuroprotective action, which is particularly promising for the development of combination therapies.

However, the majority of clinical studies in humans have focused on the anti-inflammatory and analgesic effects of PEA, especially in chronic pain conditions such as sciatica or carpal tunnel syndrome,[15,16] Its direct application as a neuroprotective agent in degenerative diseases has yet to be explored.

Furthermore, although the beneficial effects of other endocannabinoids such as anandamide (AEA) and oleoyl ethanolamide (OEA) have also been recognized in the literature, the therapeutic profile of PEA stands out for its safety and low pharmacological interference, which allows its combined use with other treatments without significant risks.[9,17]

The current challenge lies in expanding research on PEA in less studied pathologies such as Amyotrophic Lateral Sclerosis[18,19] and Frontotemporal Dementia,[20,21] given that most trials have focused on Alzheimer's and Parkinson's disease. In addition, greater methodological uniformity is required regarding dosage, treatment duration, and sample characterization in both clinical and preclinical studies.

Finally, the review by Pardal-Refoyo and Pardal-Peláez[22] highlights the importance of applying rigorous and systematic criteria in the collection and analysis of data in scientific reviews, emphasizing that only through well-structured methodologies can valid and generalizable conclusions be reached on emerging interventions such as PEA.[23]

CONCLUSIONS

Palmitoylethanolamide (PEA) is emerging as an interesting therapeutic alternative in treating neurodegenerative diseases, thanks to its ability to modulate inflammatory processes and protect neurons from oxidative stress and excitotoxicity. Although existing studies offer encouraging evidence, especially in Alzheimer's and Parkinson's models, further clinical evaluation with more homogeneous methodologies should be applied to a broader spectrum of pathologies. The combination of PEA with other compounds, such as luteolin, as well as its safety profile and low pharmacological interference, position it as a promising candidate for developing more effective and safer combination therapies. Progress in this field will depend on rigorous research to validate its efficacy and expand its field of application.

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FUNDING

None.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTION

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