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PALMITOYLETHANOLAMIDE (PEA) IN NEUROLOGY: MECHANISMS, CLINICAL APPLICATIONS, AND THERAPEUTIC PERSPECTIVES

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ABSTRACT

Palmitoylethanolamide (PEA) is a fatty acid amide with anti-inflammatory and neuroprotective properties that acts on the endocannabinoid system and represents a potential therapeutic agent in neurological disorders as well as conditions accompanied by chronic and neuropathic pain. Numerous studies indicate that PEA plays a key role in modulating the neuroinflammatory response through the ALIA mechanism and activation of the PPAR-α receptor, thereby regulating mast cells, microglia, and astrocytes (1). These properties lead to reductions in neuropathic pain, inhibition of neurodegeneration, and improvements in neuronal function in various inflammation-related disorders. In recent years, the efficacy of ultramicronized PEA has been demonstrated in the treatment of chronic pain, neuralgia, migraine, and sciatica (2). However, large randomized clinical trials are still required to confirm its use in neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis.This article presents the current state of knowledge on PEA, its pharmacological properties, mechanisms of action, and potential therapeutic applications. Particular emphasis is placed on the innovative nature of PEA as an inexpensive, well-tolerated adjuvant therapy with significant potential in neurology.

KEYWORDS

Palmitoylethanolamide, PEA, Neuroinflammation, Neuropathic Pain, Microglia, PPAR-α, Neuroprotection, Neurology

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Methodology

This article is a literature review with elements of a semi-systematic review, aimed at presenting current knowledge on palmitoylethanolamide (PEA) in neurology and its clinical applications. The preparation process included: source identification, study selection, data extraction, and critical analysis of the collected material.

A literature search was conducted in PubMed/MEDLINE, Scopus, and Web of Science, covering publications from 2000 to 2025. Google Scholar and ClinicalTrials.gov were additionally reviewed. Searches were performed in English, with no restrictions regarding publication type. Studies involving PEA or its derivatives were included, encompassing in vitro and in vivo models as well as clinical research in neurology and neurobiology. From each article, data were extracted on: study model, population, form of PEA, mechanisms of action, safety, efficacy, and study limitations. The material was subjected to a qualitative critical analysis, including methodological assessment, comparison of findings, and identification of research gaps. Results are presented descriptively and organized according to the main themes of the article.

Introduction

Neurological diseases represent a significant challenge for modern medicine and healthcare systems. There is a growing prevalence of chronic neuropathic pain, neurodegenerative diseases, stroke, and inflammatory disorders of the nervous system. Increasing attention is being paid to the role of

neuroinflammation in their pathogenesis (3). Ongoing research seeks compounds capable of slowing disease progression by modulating inflammatory processes in the central nervous system.

Over recent decades, studies have focused on the potential to modulate the endocannabinoid system due to its role in maintaining homeostasis and influencing neuroinflammation. The key endocannabinoids are anandamide (AEA) and 2-arachidonoylglycerol (2-AG), yet structurally related compounds, including palmitoylethanolamide (PEA), also play an important role. PEA is an endogenous amide of palmitic acid synthesized in response to tissue damage and inflammation. As early as the 1990s, its anti-inflammatory properties and involvement in the endocannabinoid system were described. According to the ALIA concept (Autacoid Local Injury Antagonism), PEA limits excessive activation of inflammatory cells, including mast cells and glial cells (4). Additionally, it reduces the expression of pro-inflammatory genes, inhibits microglial activation, decreases oxidative stress, and supports neuroprotection (5). Due to these properties, PEA has been investigated in such conditions as fibromyalgia, migraine, dementia syndromes, neuropathic pain, and neurodegenerative diseases. The development of micronized and ultramicronized formulations has improved its bioavailability and clinical efficacy (6). The aim of this article is to present the mechanisms of action of PEA, its pharmacological properties, and its potential therapeutic applications in neurology, as well as to discuss research limitations and directions for future studies.

Biochemical and Pharmacological Characteristics and Bioavailability of PEA

Palmitoylethanolamide (PEA) is an endogenous fatty acid amide belonging to the N-acylethanolamide (NAE) family; chemically, it is a combination of palmitic acid and ethanolamide (7). As a natural lipid mediator, PEA is synthesized by various cells to restore disturbed homeostasis in response to cellular stress, tissue injury, ischemia, and inflammation (8). Its levels increase in tissues affected by neuroinflammation; however, in many cases, endogenous production is insufficient to fully exert protective effects. PEA exhibits pleiotropic activity through a complex and multidirectional mechanism of action. The primary mechanism is the ALIA (Autacoid Local Injury Antagonism) concept (4), according to which PEA counteracts excessive activation of cells responsible for inflammatory responses, particularly mast cells and glial cells.

Another key mechanism is activation of the peroxisome proliferator-activated receptor alpha (PPAR-α) (5). Upon binding to PEA, this receptor regulates the expression of numerous genes relevant to inflammatory processes, oxidative stress, and lipid metabolism, leading to a reduction of the inflammatory response and supporting neuroprotective mechanisms (1).PEA also allosterically modulates TRPV1 (Transient Receptor Potential Vanilloid 1) receptor channels, which interact with CB1 and CB2 receptors through the so-called “entourage effect,” enhancing the activity of anandamide (AEA) and other endocannabinoids (9). At the cellular level, PEA inhibits microglial and astroglial activation, reduces oxidative stress, improves mitochondrial function, and supports neuronal repair processes (10).

However, PEA is characterized by low solubility and poor intestinal absorption, which limit its bioavailability (6). To overcome this problem, an ultramicronized form of PEA was developed, improving its pharmacokinetic profile. Micronization reduces particle size to the submicron range, increasing the surface area, enhancing bioavailability, and improving intestinal absorption (11). Studies have shown that ultramicronized PEA has several-fold higher pharmacological efficacy in inflammation and pain models compared to non-micronized PEA (12). PEA is also available as a complex with luteolin (PEA-LUT), which-due to strong neuroprotective properties-enhances its anti-inflammatory effects and modulation of microglial activity (13).New delivery systems for PEA are currently being developed, including lipid nanocapsules, PLGA systems, and liposomes, which may increase absorption, stability, and targeted delivery to nervous tissue (14). PEA is characterized by an excellent safety profile-unlike classical analgesics and anti-inflammatory drugs, it does not exhibit hepatotoxicity, nephrotoxicity, or psychoactive effects (15).

PEA in Experimental Models of Neurological Diseases

PEA has been widely studied in animal models. In neuropathic pain models, it has been shown to reduce hyperalgesia, inhibit microglial activation, and decrease the release of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 (16). In neurodegenerative disease models, including Alzheimer’s disease, PEA has been shown to reduce β-amyloid deposition and improve synaptic function (17). In Parkinson’s disease models, PEA limits the loss of dopaminergic neurons in the substantia nigra and inhibits toxin-induced neuroinflammation (1). PEA has also been studied in the context of stroke. In cerebral ischemia models, it reduces infarct size and stabilizes the blood–brain barrier (18). It has also demonstrated anticonvulsant effects by reducing excessive neuronal excitability and inhibiting microglial activation (19). In spinal cord injury

models, PEA reduces edema, inflammatory cell infiltration, and improves axonal regeneration (20).Preclinical evidence clearly indicates that PEA acts multidirectionally, with inhibition of pathological neuroinflammation-an underlying mechanism of many neurological diseases-being a key effect.

Clinical Evidence for the Use of PEA in Neurology

The strongest clinical evidence for PEA concerns chronic pain. Studies have demonstrated significant pain reduction in patients with postherpetic neuralgia, carpal tunnel syndrome, diabetic neuropathy, trigeminal neuralgia, and radicular pain (21). In the case of ultramicronized PEA, pain reductions of up to approximately 40% have been reported (2). Migraine is another promising field of application. Several studies have shown that PEA reduces pain intensity, migraine attack frequency, and the need for analgesics, which is associated with modulation of neuroinflammation within the trigeminal system (22). PEA has also been investigated in median nerve neuropathy in carpal tunnel syndrome. In patients awaiting surgery, pre- and postoperative administration of ultramicronized PEA reduced pain symptoms and improved sleep quality and sleep latency. Studies have additionally explored the use of PEA in neurodegenerative disorders. In patients with Alzheimer's disease, supplementation with PEA-LUT improved cognitive function and reduced neuropsychiatric symptoms. In Parkinson's disease, it decreased pain symptoms and improved sleep quality (23).

In multiple sclerosis, PEA has been used as an adjunct therapy, showing improvements in pain, spasticity, and fatigue (24). A key clinical advantage of PEA is its safety-it is non-addictive, and adverse effects are rare and mild. Long-term use is characterized by excellent tolerability (15).

PEA as a Component of Interdisciplinary Therapy

Current evidence indicates that PEA may become an important component of comprehensive treatment programs for various neurological disorders, particularly those in which neuroinflammatory mechanisms play a significant role. PEA can be used as an adjunct to other medications, such as pregabalin, gabapentin, or duloxetine, enabling dose reduction and limiting adverse effects (25). It has been demonstrated that in migraine, PEA used alongside non-pharmacological interventions enhances their effects, and ultramicronized PEA reduces symptom severity in neuralgias and radicular pain when combined with physiotherapy (26,27).

Preclinical studies also suggest a synergistic effect of PEA with anti-inflammatory interventions such as the Mediterranean diet or omega-3 fatty acid supplementation in neurodegenerative diseases (28). PEA can be successfully incorporated into interdisciplinary therapy due to its lack of significant pharmacological interactions and absence of psychoactive effects. This is particularly important in older adults, multimorbid patients, and in the context of long-term care, neurological rehabilitation, and chronic pain management. Modern medicine aims for an integrated approach that includes pharmacotherapy, physiotherapy, neuropsychology, pain management, and patient education (29). In this context, PEA-through activation of PPAR-α and modulation of microglia and mast cells-may enhance the effects of other therapies without increasing the risk of adverse events (10).

Limitations of Current Research and Future Directions

Despite promising findings regarding the use of PEA, large, randomized, double-blind clinical trials are still lacking. Most available studies involve relatively small patient groups (40–120 individuals) and often do not include long-term follow-up (30). Another limitation is the heterogeneity of existing studies-including differences in PEA dosage, formulation, treatment protocols, and patient populations-which prevents the development of clear recommendations (6). Although preclinical evidence strongly supports the neuroprotective effects of PEA, there is a lack of studies evaluating its impact on neuroinflammatory biomarkers in humans, such as cytokine levels in cerebrospinal fluid or neuroimaging parameters of microglial activity (3).

Although the safety of PEA has been demonstrated, most safety assessments cover periods of less than 90 days, leaving insufficient data on long-term use. Small study populations remain a major weakness of current research, and therefore large, randomized clinical trials are needed to assess the effectiveness of PEA in treating Alzheimer's disease, Parkinson's disease, multiple sclerosis, and neuropathies (31). Studies using neuroimaging are particularly important, as they can help determine how PEA modulates neuroinflammation in humans. It is also essential to investigate the synergistic effects of PEA with other therapies, including biological drugs, omega-3 fatty acids, and luteolin. Previous studies indicate beneficial outcomes of such combinations (10).

In parallel, new delivery systems-such as nanoparticles, liposomes, blood–brain barrier transport systems, and polymer-based carriers-are being developed to increase PEA bioavailability (32). Long-term safety studies are also necessary, including assessments of potential interactions between PEA and medications commonly used chronically in neurological patients, such as antiepileptic drugs, SSRIs, and dopaminergic agents.

Conclusions

Palmitoylethanolamide is one of the most promising endogenous molecules involved in the modulation of neuroinflammation. Its pleiotropic effects-anti-inflammatory, neuroprotective, and analgesic-have been confirmed in multiple scientific studies (1). The efficacy of PEA has been demonstrated in chronic pain, neuralgias, migraine, and radicular syndromes, particularly in its ultramicronized form (2). There remains a significant need to clarify the role of PEA in the treatment of neurological disorders, which requires large, well-designed clinical trials. This is especially relevant for neurodegenerative diseases, where current data come mainly from pilot studies. PEA is a natural compound with an excellent safety profile, and its use in treatment-resistant pain syndromes yields noticeable benefits and improves patients' quality of life. By enabling dose reduction of other medications, PEA serves as a valuable adjunct therapy.

Neuropathic pain, neurodegenerative diseases, and chronic pain syndromes pose major economic and healthcare challenges, generating multi-billion-dollar treatment costs (29). Therefore, the societal and economic value of PEA is substantial, particularly in the context of aging populations and the increasing prevalence of neurological diseases. Broad implementation of PEA as an inexpensive, safe, and orally available compound may help reduce healthcare burden by decreasing hospitalizations and limiting the need for more invasive or higher-risk pharmacological therapies.

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