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SYSTEMATIC REVIEW

Systematic review of neuroprotective actions of the ECP in the HT-22 neuronal line subjected to hypoxia and reoxygenation

Revisión sistemática de acciones neuroprotectoras del PEA en línea neuronal HT-22 sometida a Hipoxia y reoxigenación

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ABSTRACT

Introduction: palmitoylethanolamide (PEA) is an endogenous fatty acid amide that has recognized anti-inflammatory and analgesic actions. Given that inflammation, excitotoxicity, oxidation damage, and microvascular and blood-brain barrier dysfunction are neurodegenerative processes typical of cognitive impairment in diseases such as Alzheimer's and Parkinson's, it is considered possible that treatments with supplemental PEA can alleviate chronic pain and protect against neuronal damage. to the patient. The objective is to analyze neurodegenerative and anti-inflammatory protective actions of Palmitoylethanolamide (PEA) in murine hippocampal neuronal cell line HT-22 subjected to hypoxia and reoxygenation to apply in patients diagnosed with neurodegenerative diseases.
Method: the methodology applied was a systematic review of the literature, and the material used was 12 studies according to inclusion criteria.
Results: murine model and in patients focused on Alzheimer's and Parkinson's, being the effective treatment of PEA with antioxidant supplements, frequent protective action at the hippocampal level and modulation of cytokine and proteins in addition to a decrease in acetylcholine (ACh). Other neurodegenerative diseases may benefit from PEA with further specific investigations (in murine model or patients.
Conclusions: intracellular signaling under PEA and investigation into other neurodegenerative diseases should be further explored.

Keywords: Ethanolamides/Therapeutic Use; Neurodegenerative Diseases/Drug Therapy; Hippocampus/Drug Effects; Alzheimer's/Diagnosis; Parkinson's/Diagnosis.

RESUMEN

Introducción: la palmitoiletanolamida (PEA) es una amida de ácido graso endógena que posee acciones antiinflamatorias y analgésicas reconocidas. Dado que la inflamación, la excitotoxicidad, daño en la oxidación y disfunción microvascular y de barrera hematoencefálica son procesos neurodegenerativos propios del detrimento cognitivo en enfermedades como Alzheimer y Parkinson, se considera posible que tratamientos con PEA suplementario puede aliviar dolor crónico y proteger del daño neuronal al paciente. Se plantea como objetivo analizar acciones de protección neurodegenerativas y antiinflamatorias de la Palmitoiletanolamida (PEA) en línea celular neuronal hipocampal murina HT-22 sometida a hipoxia y reoxigenación para aplicar en pacientes con diagnóstico de enfermedades neurodegenerativas.
Método: la metodología aplicada fue una revisión sistemática de la literatura, y el material utilizado fueron 12 estudios acorde a criterios de inclusión.

Resultados: modelo murino y en pacientes enfocados en Alzheimer y Parkinson, siendo el tratamiento efectivo del PEA con complementos antioxidantes, acción frecuente de protección a nivel hipocampal y modulación de citocina y proteínas además de disminución de acetilcolina (ACh). Otras enfermedades neurodegenerativas pueden beneficiarse del PEA con mayores indagaciones específicas (en modelo murino o pacientes).
Conclusiones: debe profundizarse en señalización intracelular bajo PEA e indagación en otras enfermedades neurodegenerativas.

Palabras clave: Etanolamidas/Uso Terapéutico; Enfermedades Neurodegenerativas/Terapia de Drogas; Hipocampo/Efectos de Drogas; Alzheimer/Diagnóstico; Parkinson/Diagnóstico.

INTRODUCTION

Palmitoylethanolamide (PEA) is an endogenous fatty acid amide with recognized anti-inflammatory and analgesic properties. This naturally occurring substance is produced by enzymes involved in metabolic homeostasis.[1] As such, this lipid is believed to have potential benefits in the treatment of cognitive decline associated with certain diseases.

Cognitive decline is associated with neurodegenerative processes involving excitotoxicity, inflammation, oxidative damage, microvascular dysfunction, and blood-brain barrier dysfunction.[2] Therefore, the anti-inflammatory actions of PEA are of interest, considering that its possible supplementation is an alternative treatment, not only to deal with chronic pain but also to protect or prevent increased neuronal damage, restore the body's balance, and counteract the pathophysiological mechanisms of neurodegeneration.[3]

According to the above, the symptoms of diseases such as Alzheimer's, Parkinson's disease, and similar neurodegenerative disorders can be treated with the amide and prevent the accelerated increase in their prevalence since studies of these disorders indicate that the number of cases doubled between 1990 and 2016, projecting a caseload of 100 million patients with these diseases by 2050.[4]

However, the effects of PEA as a neuroprotective agent on the murine hippocampal cell line HT-22 subjected to hypoxia and reoxygenation have not been studied in depth. This is because most studies focus on anti-inflammatory and analgesic actions, and the cases studied involve samples from patients with chronic conditions such as sciatic pain.[5,6]

For its part, PEA's neuroprotective action can be seen precisely in the hippocampus, generating regenerative effects from the initial anti-inflammatory effects since inflammatory processes that continue for a certain period of time lead to neurodegeneration.[7,8]

Currently, no known treatments counteract neurodegenerative damage or delay the progression of these disorders, so investigating the anti-inflammatory actions of PEA may provide insights into the type of hippocampal neuronal protection derived from it. It may also prevent severe cognitive impairment, as similar effects have been found in other endocannabinoids such as PEA, for example, anandamide (AEA) and oleoyl ethanolamide (OEA).[9,10]

Justification

Neurodegenerative diseases such as dementia, Alzheimer's, and Parkinson's affect more than 46,8 million people worldwide, according to 2015 data, with a projected prevalence of 131,5 million by 2050. Given this prognosis, it is essential to investigate the neuroprotective effects of PEA, given the current lack of treatment, to determine whether supplementation in patients diagnosed with these diseases can reverse neurological damage or prevent its chronicity through action on the murine hippocampal neuronal cell line HT-22.

The results of this review may be relevant for the patient population because they would provide theoretical and practical support for future direct treatments, whether medicinal or not, immediately improving their quality of life. In turn, this would impact the number of cases seen in health services, preventing saturation. In this way, the review reinforces the academic presentation of the results of studies in patients, informing the community and generating scientific contributions on the need for further research, given the limited data available on this specific topic.

Research question

Can implementing PEA as a neuroprotective agent concerning hypoxia and reoxygenation applied to the murine hippocampal neuronal cell line HT-22 reduce and/or prevent neurodegenerative and inflammatory processes in patients diagnosed with neurodegenerative diseases?

P- Study population: patients diagnosed with neurodegenerative diseases such as Alzheimer's and Parkinson's.

I- Intervention: implementation of palmitoleic acid (PEA) as a neuroprotective agent.

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C- Comparison group: hypoxia and reoxygenation methodology of murine hippocampal neuronal cell line HT-22
O- Results: neurodegenerative and inflammatory processes.

Hypothesis

Palmitoylethanolamide (PEA) in the murine hippocampal neuronal cell line HT-22 subjected to hypoxia and reoxygenation has neurodegenerative and anti-inflammatory protective actions, which can be used in patients diagnosed with neurodegenerative diseases such as Alzheimer's and Parkinson's.

General objective

To analyze the neurodegenerative and anti-inflammatory protective actions of palmitoylethanolamide (PEA) in murine hippocampal neuronal cell line HT-22 subjected to hypoxia and reoxygenation for use in patients diagnosed with neurodegenerative diseases.

METHOD

The method used to conduct this research was a systematic literature review. A systematic review allows for research focused on a well-defined problem to identify, select, evaluate, and synthesize the relevant results found. In addition, systematic literature reviews follow a rigorous construction process, allowing them to be reproduced by other researchers.

This study aimed to systematically review the literature from the last ten years (2014–2024). To achieve this purpose, scientific articles were searched using the following descriptors: palmitoylethanolamide, PEA, neuroprotective effect, hippocampal mouse model, and hypoxia and reoxygenation. These are available in the following databases: Scielo (Scientific Electronic Library Online), PubMed, Google Scholar, Redalyc, and LILACS. Initially, articles were selected based on their titles and abstracts. Studies containing palmitoleic acid, neuroprotective effect, hypoxia, and reoxygenation were collected.

The database was selected because it contains reliable sources that are most widely used for scientific research in the country. Twelve articles that met all the inclusion criteria were selected. The systematic review will consider both prospective and retrospective cohort studies.

Study Design

This is a systematic, retrospective, prospective, and qualitative literature review. The systematic literature review report recommends the following steps: 1) Preparation of a research question that concludes; 2) How to select the sources of studies in the research; 3) Analysis of the content of the selected articles by abstracts and keywords; 4) Conference of information, by the proposed objectives; 5) Relative interpretation of thematic axes related to objectives; 6) Updating of the topic, to provide new criticisms/suggestions, thus contributing to further studies.[11]

To select the works used, a keyword search will be carried out. If repetitive articles appear in the electronic search, they will be catalogued only once. The articles will be selected, and the Thematic Content Analysis Method will be applied to categorize the works and give meaning to the sample collected. They will be grouped according to the similarity of the main topics covered within the proposed main topic.

Content analysis is a systematic process that uses the description of content and message to infer existing knowledge data in the literature. For this reason, any author intends to obtain indicators that aid in interpreting the knowledge contained in the messages. Therefore, content analysis is a communication analysis technique.

In this work, we will initially consider analyzing the content of the articles' titles and/or phrases. The analysis will also consider Abstracts and citations in the text. As guides to the literature, an initial reading of the articles will be carried out, followed by a more careful reading, in which a more accurate understanding of the information is possible.

Study population

The study population consists of male and female patients diagnosed with neurodegenerative diseases such as Alzheimer's, Parkinson's, and similar disorders with symptoms of hypoxia and subsequent reoxygenation in the HT22 line of the mouse model.

Inclusion criteria

- Clinical studies of patients diagnosed with Alzheimer's.
- Clinical studies of patients diagnosed with Parkinson's.
- Clinical studies of patients diagnosed with various neurodegenerative disorders.
- Clinical studies of patients diagnosed with neurodegenerative diseases being treated with endocannabinoids.
- Experimental studies in a mouse model (mice) of the HT22 cell line.

Exclusion Criteria

- Clinical studies of patients diagnosed with neurodegenerative and psychiatric disorders.
- Clinical studies in patients with psychoactive substance addiction.
- Clinical studies of patients diagnosed with neurodegenerative disease and chronic sciatic pain
- Clinical studies of patients diagnosed with unrelated or unspecified neurological diseases

Sample Selection and Size

As this is a systematic review of previously published articles, no sample selection or sizing is performed.

Scope of the study

The scope of the study will be university-based, as this is a systematic review of the literatura.

Table 1. Operational description of variables

Variables	Definitions	Type	Scale	Indicators
Age	Life span measured in years.	Quantitative	All ages	Effects associated with regression of cognitive impairment, preservation of memory, speech, and preserved behavioral manifestations in diagnosed patients.
Gender	Phenotypic characteristics possessed by the study subject	Nominal qualitative	Female	Clinical alterations
Neuro-protective action of pea	Consequences that protect neural systems from damage due to the activation of palmitoylethanolamide (PEA)	Nominal qualitative	Male	Diagnostic evaluation tests
Neuro-degenerative disease		Nominal qualitative	Has action in the hippocampal neural cell line HT-22 subjected to hypoxia and reoxygenation	The following diagnostic tests are recommended to assess the presence of cognitive impairment in patients with Alzheimer's disease:

Proposed intervention and data collection tools

Electronic tools such as Microsoft Excel will collect data and create tables and graphs to represent the results of the articles selected for this research.

Data analysis plan

The data collected through the evaluation of the observed variables will be analyzed and disseminated through tables and graphs using Microsoft Excel statistical software and calculations.

Necessary resources

Table 2. Schedule of activities

Activities	Home	End	January	February	March	April	May	June
1: Initial planning	05/02/2024	28/02/2024		X				
2: Bibliographic search strategy	05/02/2024	28/03/2024		X	X			
3: Data extraction and analysis	15/02/2024	03/04/2024		X	X			
4: Thesis writing	08/04/2024	01/06/2024				X	X	X
5: Updates and necessary adjustments	05/02/2024	01/06/2024		X	X	X	X	X
6: Final conclusions	14/02/2024	18/06/2024		X	X	X	X	X
7: Pre-delivery (protocol)	03/04/2024	08/04/2024			X	X		
8: Thesis delivery	01/06/2024	19/06/2024						X

The following will be necessary for the development of this project:

- Computer and internet connection to access databases.
- In addition, it is important to have stationery so that notes can be taken on the articles' most important topics and themes.
- Microsoft Excel software or similar statistical package for preparing graphs of results.

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- A printer and binding materials will be needed to print the final work.
- Therefore, financial resources are essential.

RESULTS

The results obtained from the systematic review were first organized according to sociodemographic aspects.

A total of 22 articles related to the topic were collected, of which 12 were selected because they referred to most or all of the criteria and were appropriate for the information needed to meet the objectives. They also responded accurately to the specificity of the search terms.

Of the 12 articles, they were divided into two research groups: the first group on human patients and the second group on a mouse model or experimentation with rats.

For each aspect analyzed, the results of the first group are presented followed by the results of the second group, so that each group consisted of six studies.

Sociodemographic aspects of patients diagnosed with neurodegenerative diseases from the systematic review

The sociodemographic aspects collected from the studies were the age and sex of the sample studied, both for human research and for the mouse model (rats).

Age

The age of the samples investigated in the studies is shown in the following graph:

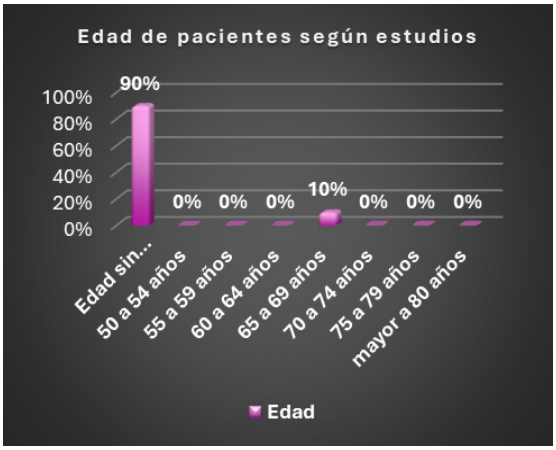

Figure 1. Age of patients with neurodegenerative diseases according to studies

Studies on this topic conducted in patients showed a lack of specificity regarding the age of the sample in most articles (5 studies out of 6 total).

Meanwhile, the second group of experimental studies, conducted in a murine model (rats), yielded the following data on age:

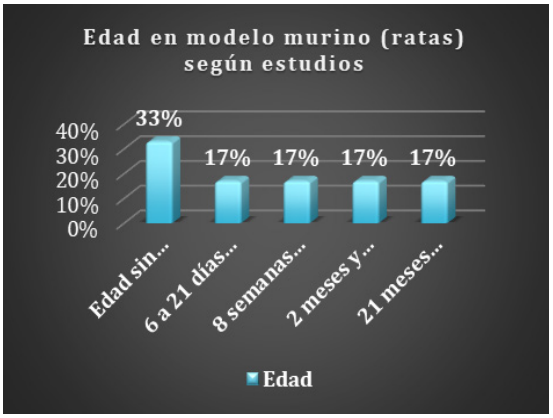

Figure 2. Age of samples in experiments with rats (murine model)

Two studies did not specify the age of the rats used in the simulation model. In comparison, the remaining four studies were based on varying ages, with the youngest model being within the first week of birth (six days) and the oldest being 21 months old (almost two years).

Sex

The sex of the patients or samples in the first group of studies (in humans) is as follows:

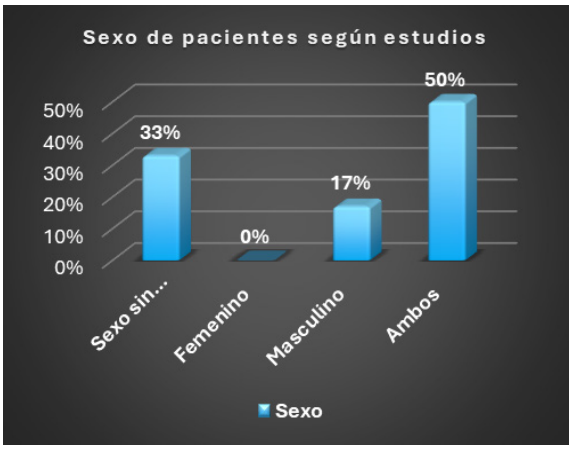

Figure 3. Sex of patients with neurodegenerative diseases according to studies

In patient samples, three of the six studies reported using samples from both sexes (female and male). At the same time, two did not specify the sex of the sample, and only one investigated male patients.

Regarding the sex of the rats used in the mouse model, the following results were obtained according to the systematic studies:

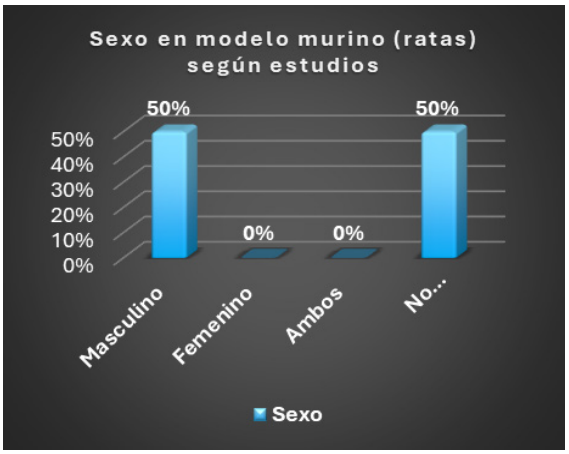

Figure 4. Sex in a mouse model (rats) according to studies

Three studies conducted their experiments on male rats, while the remaining three did not specify the rats' sex.

Type of neurodegenerative disease

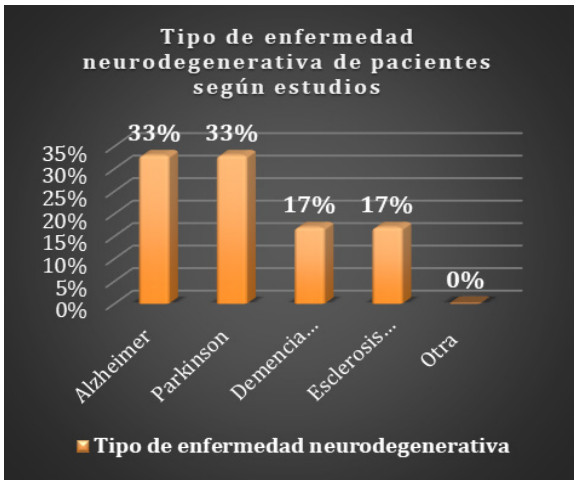

Figure 5. Type of neurodegenerative disease in patients according to studies

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Regarding the type of neurodegenerative diseases studied, the systematic review yielded the following results in the first group (in humans).

Studies in patients showed that Alzheimer's and Parkinson's were each studied in two investigations, while frontotemporal dementia and amyotrophic lateral sclerosis were each investigated in one study.

In mouse model studies, the systematization of neurodegenerative diseases studied indicated the following:

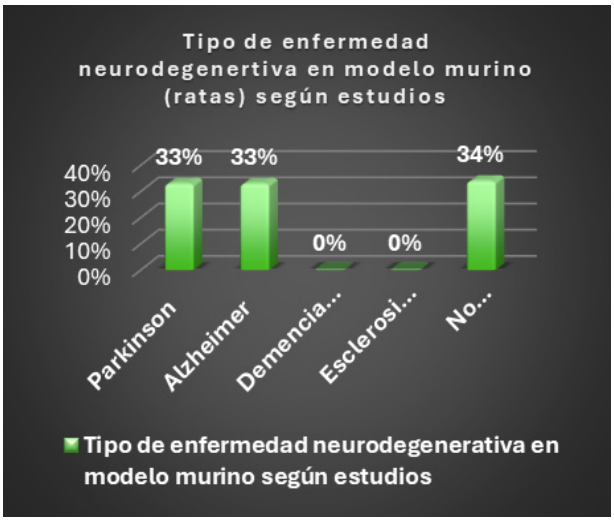

Figure 6. Type of neurodegenerative disease in mouse models (rats) according to study

In most of the studies reviewed, the neurodegenerative diseases experienced in the mouse model were not specified (3 studies), while 2 studied Parkinson's disease and 2 studied Alzheimer's disease.

Types of intracellular signaling variants that generate neuroprotective effects in patients and selected mouse models from a systematic review.

The results on intracellular signaling with neuroprotective effects in patient studies indicated the following:

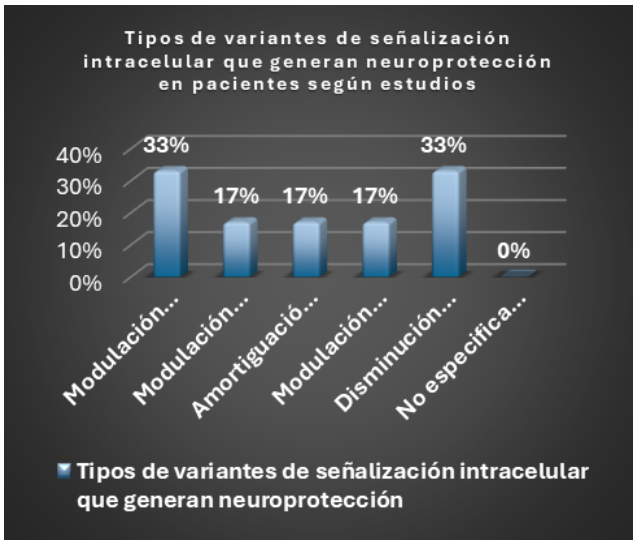

Figure 7. Types of intracellular signaling variants that generate neuroprotective effects in patients

The investigations indicated that the most frequently mentioned intracellular signals were TNF-α and IL-1ß modulation (in two studies) and decreased desensitization to ACh (acetylcholine)-evoked currents in two other studies. The other variants were only mentioned in one article each.

In the murine model, the following was observed:

Two studies observed similar types of intracellular neuroprotective signaling by PEA: reduced cytokine proinflammation and reduced nitric oxide synthesis. Two studies also showed activation of microglial cells or reduction of glial protein. The other types of signaling were mentioned in one study each.

Neuroprotective process and actions of PEA in murine hippocampal HT-22 neuronal cell lines subjected to hypoxia/reoxygenation and in selected patients from a systematic review.

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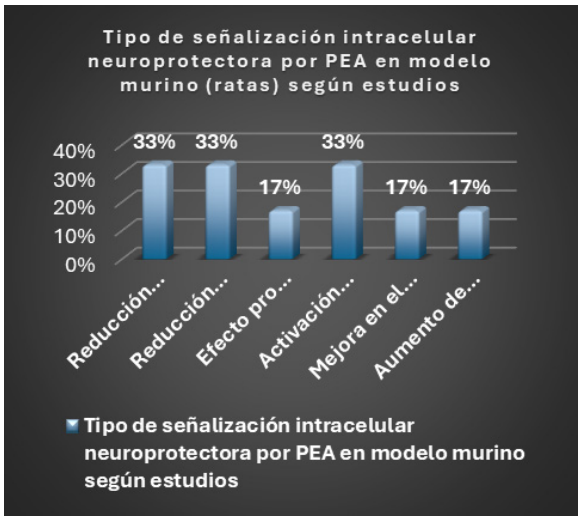

Figure 8. Types of neuroprotective intracellular signaling variants by PEA in a murine model (rats)

Studies in patients yielded the following data on the processes and actions of PEA in neurodegenerative diseases:

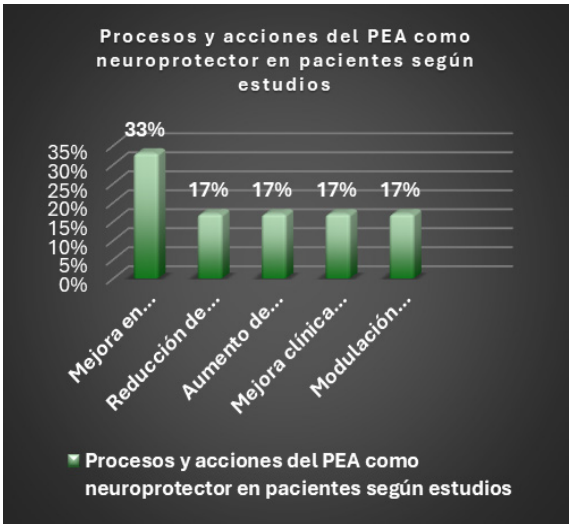

Figure 9. Processes and actions of PEA as a neuroprotective agent in patients according to studies

Two studies indicated that neuroprotective effects were observed in improved bradykinesia, while in one study each, the other effects were observed.

The following information was obtained regarding the processes and actions of PEA in the mouse model:

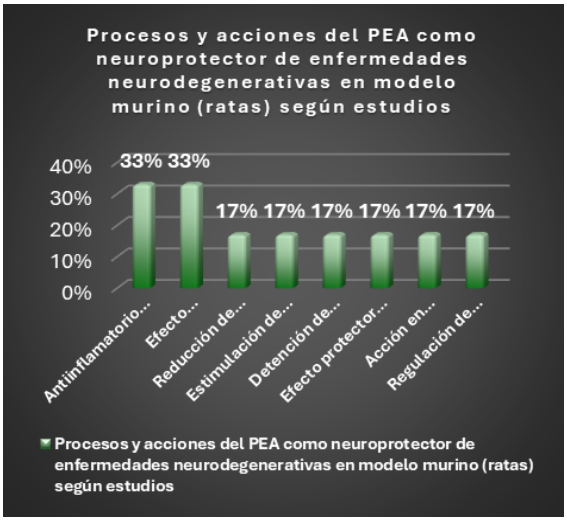

Figure 10. Processes and actions of PEA as a neuroprotective agent in a mouse model (rats) according to studies

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Two studies each identified the anti-inflammatory action of cytokine and the pro-neurogenic effect in the unspecified hippocampus. In contrast, the other specified actions were mentioned in one study each.

Possible alternative neuroprotective treatment with PEA supplementation in patients with neurodegenerative diseases, according to a systematic review.

According to the reported effects, the following results were found for possible alternative treatments in patients:

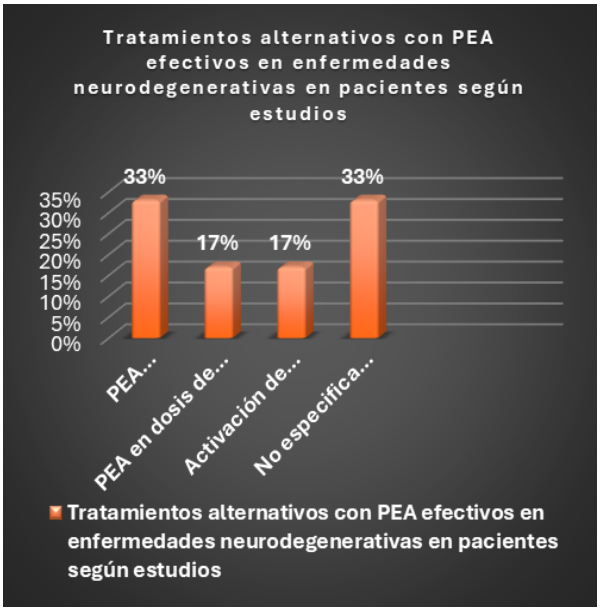

Figure 11. Alternative treatments with PEA effective in neurodegenerative diseases in patients according to studies

In articles on patients, the most frequently mentioned treatment (in two studies) was ultramicronized PEA at a dose of 600 mg with levodopa, although no treatments were specified in two other studies. One study mentioned treatment with micronized PEA at a dose of 700 mg + 70 mg in a second dose for 4 months, and another study indicated the effectiveness of treatment by PEA activation via microtransplantation in Xenopus oocytes.

Regarding alternative treatments with PEA that are effective in neurodegenerative diseases in mouse models (rats), the results indicated that:

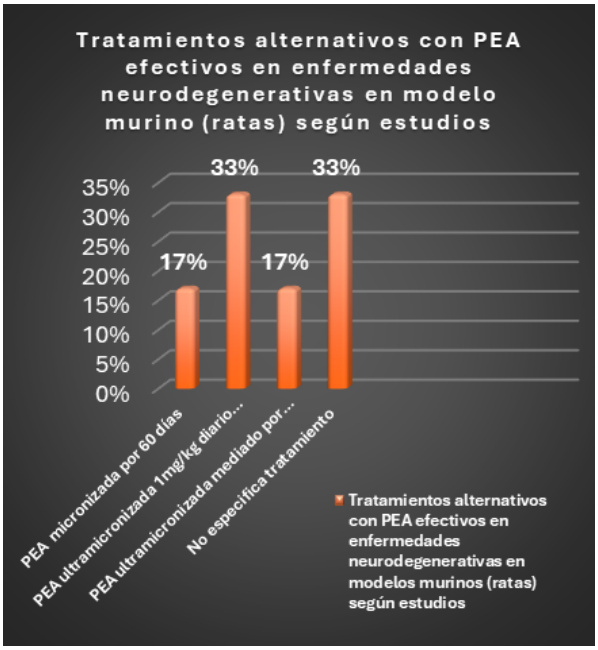

Figure 12. Alternative treatments with PEA effective in neurodegenerative diseases in a mouse model (rats) according to studies

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Two studies in mouse models indicated that micronized PEA at 1 mg/kg daily with the flavonoid antioxidant luteolin was effective, while two other studies did not specify treatments. Another study reported micronized PEA for 60 days as an effective alternative treatment in the model, and one study also indicated that ultra-micronized PEA mediated by PPAR-alpha activation was effective in the model.

DISCUSSION

The systematic review clearly shows that PEA is effective in protecting patients with neurodegenerative diseases from neurological damage. This is indicated mainly in relation to diseases such as Alzheimer's and Parkinson's, which are the most studied.[7,8,9,12,13,14]

This distinction clearly limits further investigation of the effects of PEA in other diseases, such as amyotrophic lateral sclerosis[17] or frontotemporal dementia.[4,15]

The review highlights that PEA can be administered alone or as a supplement as it does not interfere with other medications, making it easy to dose. Both in the review and other findings,[1,2,12,18,19] the doses administered vary between weight per kilogram or a fixed dose in two doses per day, short treatments of 60 days or longer treatments of four months, and PEA can act together with antioxidants or be activated by the sensitivity of specific proteins. These results are mainly based on studies in mouse models; therefore, the lack of precision and detail in patient studies is debatable.

This may be because, in humans, the study of PEA focuses on demonstrating its anti-inflammatory properties, leaving aside its neuroprotective capacity. For this reason, experiments in rats, through the observation of actions in the HT-22 neuronal line, favor the simulation of diseases under more effective control. However, it is acknowledged that the experimentation time used in the mouse model is usually limited (months or weeks depending on the hypoxia/reoxygenation process applied).[18,21]

Although the hypoxia/reoxygenation process was not applied in all of the studies reviewed, lesions in the neuronal chain associated with the hippocampus were observed in the mouse model as a precursor to endocannabinoid administration. Indeed, other findings confirm the protective action of PEA at the hippocampal level.[8,10,12,18,20,22,23]

The differences between mouse models and patient studies should be considered regarding neuroprotection. Still, most results indicate similar actions associated with PEA's modulatory or intracellular regulatory capacity.[12,13,15,23] Many studies specify that glial cells are protected by PEA treatment.[18,21]

Several findings[8,19,20,21] indicate astrocyte activation. However, this activation does not represent the most prominent intracellular signaling. Cytokine modulation and cellular homeostasis are the most frequent signaling events in patients with cognitive impairment, but acetylcholine depletion is more common in PEA-mediated neuromotor protection in humans.[12,13]

Thus, the neuroprotective effects of PEA studied in the HT-22 neuronal cell line mouse model are multiple and generally resemble the results or actions of endocannabinoids in humans. This allows PEA to be considered an effective endocannabinoid for treating neurodegenerative diseases. However, the literature is scarce on the multiplicity of these pathologies, restricting their application almost exclusively to Alzheimer's and Parkinson's.

In developing this systematic review, methodological limitations were noted in collecting sufficient research articles on this complex and specific topic. This was further hampered by the fact that not all of the articles found provided the relevant information to fully meet the objectives, which limited the overall scope of the review.

Nevertheless, there is growing interest in this subject, which is undeniably relevant and topical. It is concluded that the specific contributions on the topic refer to the application of PEA treatment, which transcends its anti-inflammatory and pain-preventing effects and, alone or in combination with other supplements such as antioxidants, influences the prevention of cognitive and neurological damage, in some cases associated with memory and its preservation. The usefulness of studying the HT-22 neuronal line of the murine model to study the effects of neurodegenerative diseases, particularly Alzheimer's and Parkinson's, and the variety of possible treatments with PEA for this purpose has also been reaffirmed, suggesting the existence of multiple effective alternative treatments using endocannabinoids.

Even so, it is considered necessary further to investigate the characteristics of the samples in these studies, whether in patients or mouse models, as well as the specificity of the treatment and its duration with its derived effects.

At the same time, there is a current need to investigate the effects of PEA in other neurodegenerative diseases, given the focus of interest in Alzheimer's and Parkinson's and the lack of studies on other pathologies with similar symptoms.

Based on the above, the following conclusions are theorized:

- Neurodegenerative diseases such as Alzheimer's and Parkinson's can be treated with PEA, with or without a supplement, to reduce neurological damage.
- Other neurodegenerative diseases with symptoms similar to Alzheimer's or Parkinson's may benefit

from alternative treatment with PEA to counteract the effects of neurological damage.

- The effects of PEA are associated with its protection of neurons in the hippocampus and its anti-inflammatory and protein-regulating properties.
- The sex and age of the patient are not variables that influence the effects or actions of alternative treatment with PEA.
- The experimental mouse model is suitable for supporting the actions of PEA in neurodegenerative diseases and promoting its use in patients under supervision.

CONCLUSIONS

This systematic review allows us to conclude that palmitoylethanolamide (PEA) has significant therapeutic potential as a neuroprotective agent in the context of neurodegenerative diseases, especially Alzheimer's and Parkinson's. Its anti-inflammatory action and ability to modulate cellular processes and protect neurons, particularly in the hippocampus, position it as a viable alternative for preventing or attenuating cognitive decline. In mouse models, especially in the HT-22 cell line subjected to hypoxia and reoxygenation, results are consistent with those obtained in patients, strengthening the possibility of transferring these effects to the human clinical context.

Despite the limitations encountered, such as the scarcity of studies focusing on other neurodegenerative diseases or the lack of uniformity in samples and treatments, the growing interest in this line of research highlights the need to continue exploring the topic. Future research should expand the exploration of PEA in other diseases in the same group, standardize clinical and experimental variables, and evaluate the duration and combinations of treatment more accurately.

In summary, PEA represents a promising therapeutic alternative, not only because of its safety profile and anti-inflammatory effects but also because of its positive impact on neuroprotection. This could significantly contribute to improving the quality of life of patients with neurodegenerative diseases and reducing the burden on healthcare systems.

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None.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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