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NEUROINFLAMMATORY NEURODEGENERATIVE ALTERATIONS IN THE PATHOGENESIS OF MOOD DISORDERS

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Abstract: Objective: To explore the role of neuroinflammation, neurodegeneration, intestinal microbiota, blood-brain barrier dysfunction and alterations in neurotransmission in the pathogenesis of mood disorders, especially major depressive disorder and bipolar disorder. **Methodology:** An integrative bibliographic review using the PVO method, through the PubMed-MEDLINE database. Articles published between 2020 and 2024, in Portuguese or English, addressing the proposed themes were included. After inclusion and exclusion criteria, 31 studies were included in the final analysis. **Review:** Neurodegeneration and neuroinflammation are central processes in the pathogenesis of mood disorders, mediated by pro-inflammatory cytokines, microglial activation, and metabolic alterations. Strategies such as the use of vitamin D, and microbiota modulators show therapeutic potential, as well as transcranial magnetic stimulation, and electroconvulsive therapy are promising for neuromodulation. **Final considerations:** Understanding neuroinflammatory and neurodegenerative changes in mood disorders reinforces the importance of neuroprotective and anti-inflammatory therapies, although advances in specific studies and approaches are still needed.

Keywords: Neuroinflammation; Neurodegeneration; Mood disorders; Gut microbiota; Proinflammatory cytokines.

INTRODUCTION

Mood disorders, such as major depressive disorder (MDD) and bipolar disorder (BD), are pathologies that lead to significant changes in mood and behavior in affected patients, in addition to being among the main psychiatric disorders in the world population (Benedetti *et al*.,2020). These illnesses have been important targets for research and studies today, in order to understand the mechanisms responsible for their development and progression (Leonard; Wegener,2019). Among the main findings, inflammation stands out as one of the central factors in this process, acting through autoimmune, hormonal or chronic mechanisms, which are ultimately closely associated with neuroinflammatory and neurodegenerative factors (Sarnoa; Moeserb; Robison, 2023).

Several experimental studies show that neuroinflammation plays an important role in the development of depression and neurodegenerative diseases. In addition, research indicates alterations in the metabolism of tryptophan, which is the main pathway responsible for the production of serotonin, an essential neurotransmitter for mood regulation (Pearson *et al*., 2024). Imbalances in these mechanisms have been identified as responsible for oxidative stress and mitochondrial deregulation, which favors an increase in pro-inflammatory cytokines which, in turn, are associated with depressed mood (Pearson *et al*., 2024; Asslih; Damri; Cipriani, 2021). In this context, neuroinflammation is considered a neurotoxic and harmful factor, being associated with the activation of glial cells that precedes neuronal degeneration, and may even contribute to its cause. Inflammatory responses mediated by glial cells can be triggered by various stimuli, such as infections, head trauma, toxic metabolites or autoimmune conditions (Ting; Yang; Tsai, 2020). Clinical and experimental studies also suggest that increased oxidation may be related to endothelial dysfunction, which in turn contributes to alterations in the blood--brain barrier (BBB) observed in psychiatric disorders (Ting; Yang; Tsai, 2020).

The microbiota-intestine-brain axis, formed by a dynamic interaction between the brain, intestine, microbiota and immune system, plays a crucial role in homeostasis, influencing processes such as neuroinflammation, neurotransmission and behavior (Ting; Yang; Tsai, 2020). Evidence suggests that intestinal dysbiosis plays a role in the development of MDD and its metabolites are involved in regulating the production and availability of neurotransmitters, influencing neurogenesis and neuromodulation processes, which are often altered in cases of MDD (Reyes-Martínez *et al*., 2023).

This study aims to evaluate the role of neuroinflammation, neurodegenerative processes, intestinal microbiota and other mechanisms, such as blood-brain barrier dysfunction and alterations in neurotransmission, in the pathogenesis of mood disorders, with the aim of understanding their interactions and impact on the pathophysiology of these conditions.

METHODOLOGY

This is a literature review developed according to the criteria of the PVO strategy, which stands for: population or research problem, variables and outcome. This strategy was used to develop the research question: "How do neuroinflammatory and neurodegenerative alterations influence the development and progression of mood disorders?". The searches were carried out using the PubMed - MEDLINE (Medical Literature Analysis and Retrieval System Online) databases. The search terms were used in combination with the Boolean terms "**AND" and "OR"**, using the following search strategy: neuroinflammation **OR** neurodegenerative **AND** mood disorders. From

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this search, **3884** articles were found, which were then submitted to the selection criteria. The inclusion criteria were: articles in **English and Portuguese**; published between **2020** and **2024** and which addressed the themes proposed for this research, review-type studies, meta-analysis, observational studies, experimental studies. The exclusion criteria were: duplicate articles, articles available in abstract form, articles that did not directly address the proposal studied and articles that did not meet the other inclusion criteria. After applying the search strategy to the database, a total of **1281** articles were found. After applying the inclusion and exclusion criteria, **31** articles were selected from the PubMed database to make up this study's collection.

DISCUSSION

NEURODEGENERATION

According to the most recent studies, we can define neurodegeneration as the progressive loss of the structure or function of neurons, often accompanied by irreversible cell death (Tastan; Heneka, 2024). In neuropsychiatric disorders, such as major depressive disorder and bipolar disorder, neurodegeneration is a multifactorial phenomenon involving processes such as neuroinflammation, microglial activation and immune dysregulation. In practical terms, we can say that each system associated with the central networks of the nervous system can have an influence on the processes that cause neurodegenerative disorders. In relation to the Immune System, according to Saleki et al. (2023), the literature addresses neuroinflammation, mediated by pro-inflammatory cytokines and hyperactive microglia, which contributes directly to neuronal damage. As for the endocrine system, chronic stress and hormonal changes can exacerbate neurodegeneration by negatively regulating cell repair mechanisms. However, current research has also shown that the Genetic System through polymorphisms in genes associated with TLRs, such as TLR4, increases vulnerability to degenerative processes, through the modulation of Toll-like receptors (TLRs), especially TLR4 (Saleki et al., 2023). All of the above processes lead to structural and functional alterations in the Central Nervous System, such as the loss of synapses and axonal degeneration, which are common and have a high incidence (Battaglia et al., 2024).

Microglia, as the main immune cell in the CNS, act as a crucial regulator. However, its excessive activation can result in neuronal toxicity through the release of reactive oxygen species and pro-inflammatory cytokines (Tastan; Heneka, 2024). Astrocytes, another group of glial cells, also play an essential role in maintaining brain homeostasis and supporting neuronal circuits, releasing neurotransmitters such as glutamate, GABA and ATP, as well as neuromodulators such as BDNF, which are fundamental for synaptic plasticity and brain health. In the context of neurodegeneration, these cells show a reactive response to neuropathological conditions, such as traumatic brain injuries and neurodegenerative diseases, actively participating in the repair of damaged nerve tissue (Zhao et al., 2022).

An important aspect of this process is the activation of astrocyte P2X7 receptors, mediated by the release of ATP under stressful conditions. This activation is directly associated with neuroinflammation, a central factor in the progression of neurodegeneration. The ATP released stimulates the P2X7 receptors, generating ionic flows that trigger inflammatory responses and promote the secretion of pro-inflammatory cytokines, mechanisms that are implicated in the pathophysiology of conditions such as depression and in neurodegenerative changes (Zhao *et al.*, 2022).

In addition, prolonged exposure to stress increases the secretion of inflammatory cytokines and causes deregulation of neurotransmission, phenomena mediated by glial P2X7 receptors. These alterations compromise neuroplasticity, favoring the development of depressive behaviors and contributing to neurodegenerative processes. Another critical point is the atrophy of astrocytes in brain regions such as the medial prefrontal cortex, observed in cases of depression. These morphological changes are associated with metabolic dysfunction, including glucose hypometabolism and reduced ATP production by mitochondria, factors that aggravate depressive symptoms and potentiate the progression of neurodegeneration (Zhao *et al.*, 2022; Visentin *et al.*, 2020).

Another critical point in the neurodegenerative processes associated with mood disorders is the combination of dysfunction of the dopaminergic and cholinergic systems with dysregulation of intracellular calcium channels and hyperactivity of glycogen synthase kinase-3 (GSK-3). According to Rippin and Eldar-Finkelman (2021), dysregulation of the dopaminergic system, frequently observed in Parkinson's disease and severe depression, results in neuronal loss and impaired neurotransmission, contributing to symptoms such as apathy, anhedonia and cognitive alterations. Simultaneously, calcium channel dysfunction affects the regulation of neurotransmitter release, activating pathways that lead to neurodegeneration, including mitochondria-mediated apoptosis and altered synaptic plasticity (Davis *et al.*, 2023; Visentin *et al.*, 2020).

In addition, GSK-3 hyperactivity plays a central role in neurodegeneration and mood disorders, influencing mood, behavior and neuronal viability. When deregulated, GSK-3 compromises axonal transport and mitochondrial dynamics, impairing the ability of mitochondria to meet the metabolic demands of neurons. In Alzheimer's disease, for example, GSK-3 hyperactivity is an important marker and is associated with the accumulation of hyperphosphorylated tau proteins and synaptic dysfunction (Rippin; Eldar-Finkelman, 2021). These interrelated mechanisms - dysfunction of neurotransmitter systems, intracellular calcium imbalance and aberrant GSK-3 activity - create a favorable environment for progressive neurodegeneration, contributing significantly to the clinical manifestation of mood disorders.

Studies suggest the relevance of vitamin D as a promising ally in neuroprotection, demonstrating its ability to reduce neuroinflammation, modulate the activity of microglial cells and promote neuronal survival. By inhibiting the TLR4/MYD88/NF-κB pathway, vitamin D acts directly to mitigate exacerbated inflammatory processes, one of the main triggers of neurodegeneration. Furthermore, by facilitating the switch of microglial cells to the anti-inflammatory M2 phenotype, vitamin D stands out as a potential regulator of the neuroinflammatory balance. These findings are complemented by in vivo and in vitro evidence suggesting significant therapeutic benefits, such as preservation of neurocognitive function and reduction of brain damage (Alghamdi, 2024). Although more clinical research is needed, the study sheds light on the role of vitamin D and other neuroprotective components, such as antioxidants and anti-inflammatory agents, in the prevention and management of neurodegenerative diseases, consolidating their importance as promising strategies for slowing the progression of neuronal damage.

Although discoveries about neurodegeneration and neuroinflammation are advancing significantly, there are still important gaps in the literature. For example, the role of the P2X7 receptor, widely studied in animal models, has not yet been fully validated

in humans. This receptor is involved in the activation of inflammatory cascades and the release of cytokines, such as IL-1β, exacerbating psychiatric symptoms in stressful conditions (Silberstein et al., 2021). In addition, the interaction between IL-1β and corticotropin--releasing hormone (CRH) in the hypothalamic-pituitary-adrenal (HPA) axis intensifies stress responses, aggravating emotional dysregulation and contributing to the development of mood disorders. Despite advances in pre-clinical models, these mechanisms still lack robust studies.

NEUROINFLAMMATION

Neuroinflammation has emerged as a central factor in understanding mood disorders, especially MDD and BD (Ruiz *et al.*,2022). Studies indicate that these disorders are associated with low-grade systemic inflammation, characterized by high levels of pro-inflammatory cytokines such as TNF-α, IL-6 and IL-1β. These molecules play a critical role in mediating inflammatory responses that affect the central nervous system (CNS), resulting in emotional, cognitive and behavioral alterations (Bauer; Teixeira, 2021). It is noteworthy that the abnormal activation of microglia and alterations in the functioning of specific proteins, such as Cx43 and TSPO, play central roles in the pathogenesis of these disorders (Cai *et al.*, 2024; Jiang *et al.*, 2023).

Activation of microglia - the main immune cell in the CNS - is one of the most significant mechanisms in this process. This activation exacerbates the release of pro-inflammatory cytokines, which in turn impair neuronal plasticity, negatively impacting the functioning of regions such as the prefrontal cortex and hippocampus, responsible for regulating mood and memory (Kuzior *et al.*, 2020).

One of the main mediators of neuroinflammation in mood disorders is interleukin-6 (IL-6), a pro-inflammatory cytokine often found at high levels in MDD patients (Ting; Yang; Tsai, 2020). These increased levels of IL-6 are particularly evident in specific subtypes of depression, such as melancholic and postpartum depression, reinforcing its relevance as a biomarker. IL-6 negatively influences neuroplasticity by reducing the production of neurotrophic factors, such as BDNF, and by activating the hypothalamic--pituitary-adrenal (HPA) axis, perpetuating a chronic inflammatory state. Experimental studies show that an increase in IL-6 levels is associated with depression-like behaviors in animal models, while a reduction in this cytokine can improve depressive symptoms (Ting; Yang; Tsai, 2020; Ruiz *et al.*,2022).

In addition to IL-6, other molecular elements have been implicated in neuroinflammation related to mood disorders. The translocator protein TSPO, for example, is a multifunctional mitochondrial protein that has its expression increased in conditions such as MDD and obsessive-compulsive disorder (Rupprecht *et al.*, 2022). TSPO is involved in cholesterol transport and the synthesis of neurosteroids, which positively modulate GABA-A receptors, promoting anxiolytic and antidepressant effects. Positron Emission Tomography (PET) has been used to assess TSPO expression in specific brain regions, such as the prefrontal cortex and anterior cingulate, which are often compromised in mood disorders (Meyer *et al.*, 2020). However, the heterogeneity of the studies and the lack of methodological standardization make it difficult to generalize the findings, pointing to the need for more research into the clinical viability of these biomarkers (Sæther *et al.*,2024).

Another relevant mechanism in neuroinflammation is the role played by the protein connexin 43 (Cx43), which regulates cell communication channels and homeostasis in the central nervous system. Alterations in Cx43 function have been observed in areas

such as the prefrontal cortex and hippocampus of MDD patients, compromising neural plasticity and exacerbating inflammatory processes (Jiang *et al.*, 2023). These abnormalities in Cx43 are also linked to treatment resistance, a challenging condition that affects between 33% and 50% of patients with depression (Candee; Wilkerson; Schreiber; Decenzo, 2023). Drugs that modulate Cx43, such as ketamine and COX-2 inhibitors, have shown potential in reducing inflammation and improving therapeutic response (Jiang *et al.*, 2023).

Altaruma et al. explore the relationship between inflammatory biomarkers, cognitive functioning and brain imaging abnormalities in bipolar disorder (BD), highlighting their importance for understanding the pathophysiology of the disease and its implications for cognitive and functional outcomes. Inflammatory markers, such as C-reactive protein, have been associated with mood states in BD, although their connection with cognitive impairment remains uncertain. Peripheral inflammation, in turn, correlates with neuroanatomical alterations, such as a reduction in the volume of the prefrontal cortex and hippocampus. Neuroimaging studies reveal hypoactivation in frontal areas and progressive changes, including ventricular enlargement and gray matter reduction, as indicative of neuroprogression. Cognitive impairment in BD, which is often persistent, impacts psychosocial outcomes, with evidence suggesting the role of neurotrophic factors, such as BDNF, whose reduction is associated with the severity of depression. Despite significant advances, the complexity of the interactions between inflammatory biomarkers, neuroimaging and cognitive impairment reinforces the need for standardized methodologies and larger samples to improve clinical management and therapeutic strategies.

A critical aspect related to neuroinflammation is the dysfunction of the blood-brain barrier, which allows inflammatory mediators and toxic metabolites to enter the CNS. This dysfunction facilitates the spread of inflammatory processes and affects the homeostasis of the nervous system. Patients with MDD, for example, often have high levels of IL-8 in the cerebrospinal fluid, indicating a direct link between systemic inflammation and neuroinflammatory changes in the CNS (Kuzior *et al.*, 2020). This increase in IL-8 has also been associated with the severity of depressive symptoms and resistance to treatment in some subgroups of patients.

In addition, intestinal dysbiosis plays an important role as a mediator of neuroinflammation. Alterations in the gut-brain axis, including the translocation of bacterial products and inflammatory cytokines to the CNS, amplify inflammatory processes and aggravate psychiatric symptoms (Carloni; Rescigno, 2023). The intestinal microbiota directly influences tryptophan metabolism, diverting its conversion to the kynurenine pathway, which generates neurotoxic metabolites such as kynurenic acid. These compounds are implicated in neurotransmitter dysfunction and neuroplasticity, exacerbating symptoms of depression and anxiety (Kouba *et al.*, 2024; Bruno *et al.*, 2021). This finding highlights the need to explore interventions aimed at restoring the gut microbiota as a way of modulating neuroinflammation.

The relationship between neuroinflammation and mood disorders has also been explored in innovative therapeutic approaches. Neuromodulation techniques, such as transcranial magnetic stimulation (TMS) and electroconvulsive therapy (ECT), have been shown to reduce levels of inflammatory cytokines, such as IL-1β and TNF-α, and improve neural circuits associated with emotional processing and reward (Guo *et al.*, 2023). These interventions, in addition to improving symptoms, have the potential to act directly

in reducing neuroinflammation, making them viable alternatives for patients who do not respond to traditional pharmacological therapies. Finally, the circular RNA circ-UBE2K has emerged as a prominent molecular element, regulating microglia activation and promoting neuroinflammation in experimental models (Cai *et al*., 2024). Overexpression of circ-UBE2K exacerbates depressive behaviors and inflammatory levels, while its suppression reverses these effects, positioning it as a possible biomarker and therapeutic target.

Cytokines such as IL-6 and TNF-α, as well as the P2X7 receptor, are emerging as relevant targets for new therapeutic approaches. Interventions that combine the use of anti-inflammatory drugs, such as celecoxib, and non-pharmacological approaches, such as physical exercise and microbiota modulators, show potential for reducing neuroinflammation and improving symptoms associated with mood disorders (Gorlova *et al*., 2023; Kouba *et al*., 2024). In addition, personalizing treatments based on patients' inflammatory profiles can optimize results and minimize side effects, highlighting the importance of precision medicine in this context.

FINAL CONSIDERATIONS

It has been shown that neuroinflammatory and neurodegenerative alterations play a fundamental role in the development and progression of mood disorders, highlighting mechanisms such as the activation of microglia, the imbalance of pro-inflammatory cytokines and the impairment of neuroplasticity. These findings reinforce the importance of therapeutic approaches aimed both at controlling neuroinflammation and preserving neuronal functions. However, the methodological limitations of some studies and the heterogeneity of the populations analyzed represent challenges for translating these findings into clinical practice. Thus, new studies are needed to explore more specific interventions, as well as to integrate biomarkers to aid in the early diagnosis and follow-up of these patients. Finally, future research should delve deeper into the interactions between neuroinflammatory and neurodegenerative mechanisms, considering variables such as genetic and environmental factors and individual responses to therapies. This could contribute to the development of more personalized and effective therapeutic strategies for the management of mood disorders.

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