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EPILEPSY: PATHOPHYSIOLOGY AND THERAPY

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ABSTRACT

Epilepsy is a brain disease that is characterized by seizures and associated comorbidities and afflicts 50 million individuals worldwide. The epileptic seizure, which can be of various degrees, involves neurons that emit abnormal signals, causing the pathological state characteristic of the disease consisting of convulsions and loss of consciousness. Epilepsy involves various brain pathologies such as neuroinflammation with the release of mediators such as cytokines, chemokines, and the products of arachidonic acid cascade. Epileptic seizures and neuronal loss can be triggered by various agents, including infectious ones (e. g. bacteria and viruses), which can induce or aggravate the situation by acting on toll-like receptor 4 (TLR4). Memory T cells, which are activated after an infection, may also participate in epileptic disease. Microglial cell activation leads to the generation of inflammatory cytokines IL-1, tumor necrosis factor (TNF), IL-6, interferon (IFN)-γ and transforming growth factor (TGF)-β. Endothelial cells are also implicated in epileptic seizures, through the overexpression of adhesion molecules such as P-selectin, E-selectin, and intercellular adhesion molecule 1 (ICAM). Therapy involves the use of anti-epileptic drugs which are not always effective. Therapy with steroids and non-steroidal anti-inflammatory drugs may help in some cases. The use of surgery can be an extreme remedy to be decided with great caution. Here we report an update of the status of epileptic syndrome with related seizures, and therapeutic approaches.

KEYWORDS: *epilepsy, seizure, neuroinflammation, therapy, immune*

INTRODUCTION

From Napoleon Bonaparte (1769-1821) to Margaux Hemingway (1954-1996), many famous subjects have been diagnosed with or are presumed to have had epilepsy. Epilepsy is a brain disease with emotional and cognitive dysfunction, characterized by an enduring predisposition to generate seizures and associated comorbidities, which affects approximately 50 million individuals worldwide. (Vezzani- The role of inflammation in epilepsy (1).

An epileptic seizure occurs as a result of an “electrical storm” in the brain, with neurons firing waves of abnormal signals (2). The consequences of this abnormal electrical activity lead to seizures, impaired loss of consciousness, and sensory changes (3). Seizures are a serious health problem, and the symptoms depend on which part of the brain is affected, how fast the abnormal electrical activity spreads through the brain, and the patient's overall health (4).

Individuals with epilepsy may have partial seizures and generalized seizures. Partial seizures involve only a small part of the brain, can be complex or simple, and can affect consciousness; while generalized seizures affect both hemispheres of the brain and usually cause more serious changes (5). The reason why an epileptic seizure occurs is still unclear and under study. Several mechanisms are implicated in the genesis of epilepsy including neuroinflammatory ones, neuronal

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death, and dysfunction of glycine concentrations (6). Some authors have reported that low concentrations of glycine may mediate seizures, while high concentrations inhibit seizure frequency Activation of glycine receptors modulates spontaneous epileptiform activity in the immature rat hippocampus (7).

The etiology of epilepsy can be structural, immune, infectious, metabolic, genetic, or unknown. In the etiology of epilepsy, there is cross-talk between astrocytes and neurons (8). Astrocytes are important in the modulation of synapse excitation and the homeostasis of neurons which may be implicated in the excitability and persistence of firings. Astrocytes, involved in the formation and regulation of synapses, are responsible for the control of cerebral potassium, but also for the concentrations of glutamate which increase in epilepsy and can be released following dysfunction of calcium flows, a phenomenon involving neuronal discharges (9). Thus, calcium may represent a pharmacological therapeutic target against epileptic seizures, even though the calcium blockade could cause adverse effects to the patient. Since glycine levels are altered during an epileptic crisis, it could also represent a therapeutic target, a hypothesis that future studies will clarify (10). Inherited systemic metabolic errors can also cause neurological changes, including epilepsy. The electro encephalogram (EEG) can be a valid diagnostic analysis, but it is a non-specific examination and therefore is considered only partially helpful. Thus, a thorough metabolic examination could detect a more targeted treatment for the etiology and would allow for early diagnosis and prompt intervention (11).

Epilepsy and inflammation

Temporal lobe epilepsy is the form that occurs most in adult patients and, therefore, is the most studied. The epileptic acute phase is followed by a latency period with activation of microglia, resulting in the generation of inflammatory mediators. Clinical studies have revealed that a seizure can often be triggered by stressful events, low blood sugar, bright lights, loud sounds, and poor sleep. In epilepsy, like many other inflammatory brain disorders, microglia, blood-brain barrier (BBB) endothelial cells, astrocytes, and peripheral immune system cells are activated (12). The activation of these cells leads to the generation of pro-inflammatory compounds including cytokines, arachidonic acid compounds, and inducible nitric oxide synthase (iNOS), amongst others. Thus, it can be inferred that brain inflammation in epilepsy can be both the cause and the consequence. it is known that in epilepsy, an inflammatory process takes place with aggravation of seizures and their frequency (13).

Infections with Gram negative bacteria and the induction of lipopolysaccharide (LPS) in mouse models, by binding to toll-like receptor 4 (TLR4), can exacerbate seizures. Peripheral circulating cytokines produced in the inflammatory process can activate afferent nerves to the brain by stimulating microglia and other brain cells to produce inflammatory proteins (14). In seizures, there can be loss of cells which often contributes to inflammation in the brain. Inflammatory pathologies of the central nervous system (CNS) may constitute a predisposition to epileptic convulsive phenomena. Inflammation is a defensive response to external insults and consists in the release of a cascade of chemical and biological mediators, but also of anti-inflammatory compounds (15). Inflammation is mediated by products released by both innate and adaptive immune cell responses implicated in several brain pathologies, including epilepsy. The activation of cerebral microglia leads to the secretion of inflammatory cytokines of innate immunity, such as IL-1, tumor necrosis factor (TNF), IL-6, interferon (IFN) and transforming growth factor (TGF)-β, which represent those that are the most studied in brain pathologies (16). After a brain injury, chemokines can be released as well. They are chemoattractant proteins that recruit immune cells that cross the BBB after an external insult (17).

Pro-inflammatory cytokines can trigger the release of chemokines that promote angiogenesis, microglia motility, and neural stem cell migration. Epileptic effects can occur more frequently in subjects suffering from autoimmune diseases, such as multiple sclerosis, systemic lupus erythematosus, vasculitis, encephalitis, etc. Severe epilepsy can lead to seizures with severe brain damage, hemiparesis, hemisphere atrophy, effects that may also be mediated by the presence of autoantibodies (18). In the brain regions where seizures are generated, there is a rapid release of inflammatory molecules and the involvement of different immune populations, with the upregulation of pro-inflammatory cytokine genes. During seizures, endothelial cells are also activated with overexpression of adhesion molecules such as P-selectin, E-selectin, and intercellular adhesion molecule 1 (ICAM) (19).

Therapy

The clinical spectrum in epilepsy and the mechanisms of immune system failure can be different in various individuals. The disease can arise acutely and for a limited time, while other times it can represent a first episode of a chronic disease. Epilepsy can be induced by the activation of memory T lymphocytes after an infection resulting in systemic inflammation, which can also reactivate an already existing pathology. In these cases, immunotherapy may be indicated (20).

Anti-epileptic drugs, while they are only 30-40% effective, inhibit the hyperexcitability of neurons to the benefit of epileptic seizures. However, it has been seen in clinical experiments that biochemical manipulations can prevent epileptic

seizures (21). Today, a wide range of anti-epileptic drugs are commercially available, although the most commonly used are carbamazepine and phenytoin, which reduce the abnormal firing of neurons in the cerebral cortex. Therapy with steroids and other anti-inflammatories (non-steroidal anti-inflammatory drugs) has shown anticonvulsant activity and, in some cases, may be helpful since pro-inflammatory compounds are released in epileptic seizures. These drugs are particularly effective in febrile seizures mediated by arachidonic acid products such as prostaglandins and leukotrienes that are inhibited by nonsteroidal anti-inflammatory drugs (NSAID) and steroidal anti-inflammatory drugs (corticosteroids), respectively. In the most serious cases, when these drugs are not effective, the surgical technique can be used by removing the part of the brain where the seizure starts (22). Corticosteroid or immunoglobulin therapy (or in combination) should be performed at intervals of time (about a month, and for a few years). Another surgical technique involves the removal of the corpus callosum to prevent the spread of the abnormal signals from one side of the brain to the other (23).

CONCLUSIONS

When drug treatment fails, surgical treatment to remove seizures could be considered, but this procedure should be decided by the surgeon in consultation with the family. In light of the above results, we can classify epilepsy, as not only a neurological dysfunction but also a neuro-inflammatory disease (24). These observations may help to find new and appropriate therapy.

Conflict of interest

The author declares that they have no conflict of interest.

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Letter to the Editor

EPINEPHRINE AND NOREPINEPHRINE INCREASE LYMPHOCYTE MIGRATION IN A DOSE-DEPENDENT MANNER

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KEYWORDS: *epinephrine, norepinephrine, lymphocyte, inflammation, immune response*

INTRODUCTION

Epinephrine and norepinephrine are endogenous anti-inflammatory catecholamines, highlighted in the 1960s by Spector and Willoughby (1). They are immediately released after an inflammatory process as a protective response to try to restore the normal physiological state of the tissue. Furthermore, norepinephrine inhibits vascular permeability, an effect that characterizes the inflammatory process (2).

Catecholamines are endogenous compounds that have long been known to modulate inflammatory responses (3-6). Receptors for catecholamines have been shown on the lymphocyte cell membrane; neurotransmitter agonists and antagonists have been used to study lymphocyte proliferation and modulate antibody synthesis (7,8). Catecholamines inhibit NF-kB in various cell types via the activation of cyclic AMP/protein kinase A (cAMP/PKA), which leads to the activation of 5' adenosine monophosphate-activated protein kinase (AMPK) (9). In addition, epinephrine and norepinephrine inhibit NF-kB, which leads to the suppression of pro-inflammatory cytokines (5).

Here, in this study, we report that epinephrine and norepinephrine increase the migration of lymphocytes in outbred young rats.

Chemotaxis assay:

Wistar rats were used as donors of lymphocytes from the thymus. The tissues were minced and passed through cotton wool and a nylon filter to eliminate the cell debris. After filtering the cells, they were washed in Eagle's minimal essential medium and spun at 150 x g.

Lymphocyte locomotion assay was performed using modified Boyden chambers. A cell suspension of 0.5 ml (1x106 cells/ml) was pipetted into the upper compartment of the chamber, which was separated from the epinephrine or norepinephrine-containing compartment below by an 8 μm pores filter. After incubation (at 37°C for 5 h), the filters were fixed, and cells were counted at every 10 μm level, starting from the proximal to distal surface. The locomotion index (LI+m) was calculated as described by Moderato et al. (10).

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RESULTS AND DISCUSSION

In this paper, we show that epinephrine or norepinephrine enhances the migration of lymphocytes in a dose-dependent manner. The dose-response bars are shown in Fig. 1(Fig.1). The locomotion index, LI+m of the controls, is 22.5 +/- 0.9.

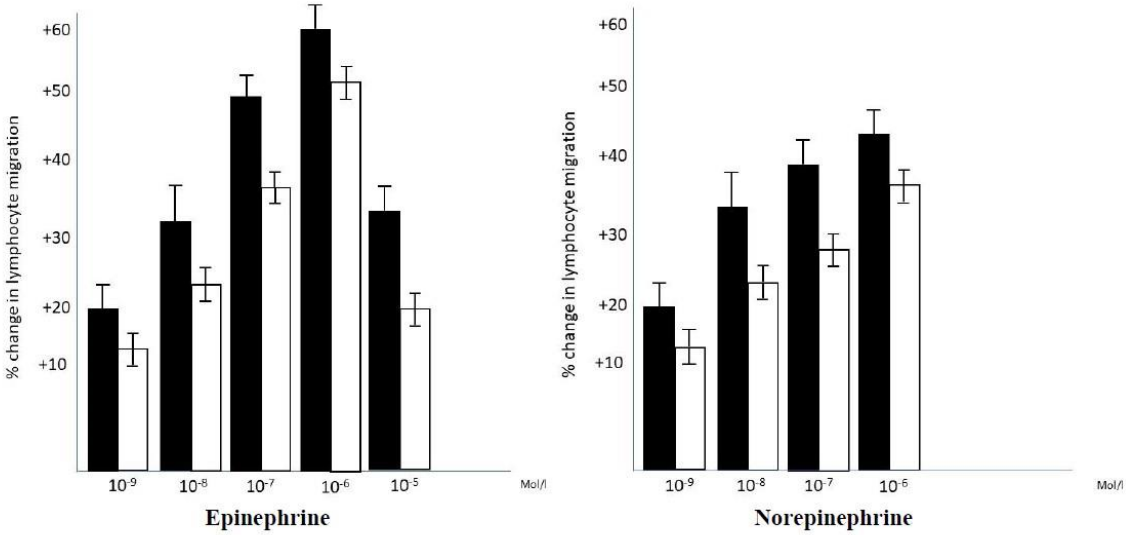

Fig. 1. *Effect of epinephrine and norepinephrine on the migration of rat thymus lymphocytes. Epinephrine treatment causes an increase in lymphocyte migration (black bars) compared to lymphocyte migration without treatment (white bars). Similar effects were obtained when the cells were treated with norepinephrine. These results show that these two catecholamines increase lymphocyte migration in a dose-dependent manner.*

Here we show that epinephrine or norepinephrine stimulates the migration of rat thymus lymphocytes in physiological and pathophysiological concentrations, an effect that makes these two catecholamines important players in the dynamics of the inflammatory and immunological responses.

Conflict of interest

The author declares that they have no conflict of interest.

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INFLAMMATORY RESPONSE TO MICROORGANISMS AND NEUROLOGICAL DYSFUNCTION

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ABSTRACT

Infectious agents such as pathogenic microorganisms enter our body, activate the immune system and generate an inflammatory response with tissue damage, causing diseases. The commensal microorganisms that house our intestines live symbiosis with the host and regulate homeostasis. The alteration of the balance between microorganisms and the immune system leads to the activation of the latter, with critical consequences. Numerous studies indicate that the gut-brain axis is implicated in neurological diseases, an important crosstalk involving the gut microbiota and the whole body. Dysbiosis, an imbalance of the microbiota, can generate inflammation with increased intestinal permeability, resulting in the entry of microorganisms and bacterial products, aggravating the inflammatory state. In these cases, pro-inflammatory cytokines are produced, which can reach the central nervous system (CNS), generating brain diseases, including encephalitis. The microbiota regulates the function of immune cells, including T lymphocytes, which act to control the pathogenesis of the neurological disease. In cerebral inflammation, it releases neurotransmitters such as substance P, which act on specific receptors located on immune cells, which are activated to produce pro-inflammatory cytokines. Therefore, the alteration of the gut-brain axis contributes to inflammation and aggravates the pathogenesis of neurological disease. In this article, we describe the immune and inflammatory effects of pathogenic bacteria in relation to neurological disease.

KEYWORDS: *inflammation, microorganism, neurological dysfunction, immune, CNS*

INTRODUCTION

The number of neurological infectious diseases is constantly evolving due to the significant trafficking of travelers across the globe (1,2). The increase of these and other pathologies of the central nervous system (CNS) is also due to antibiotic resistance, the lack of vaccines, immunodeficiency, and unavailable or ineffective therapies (3). Microorganisms from the external environment infect the host and alter the immune system by activating microglia, influencing neuronal pathologies (4). The dysregulation of the microbiome, composed of over 700 microbial species and protects the intestine, can communicate with the brain through the vagal nerve that innervates the villi of the intestinal mucosa, causing inflammation (5). In humans, bacterial infections of the CNS are an important cause of morbidity and mortality. Therefore, understanding the pathophysiological damage induced by bacteria can represent an important weapon for diagnosis and therapy.

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DISCUSSION

A large number of microorganisms, including bacteria and viruses, can cause damage to the CNS, such as vasculitis, encephalopathies, strokes, convulsions, migraines, ischemia, aneurysms, subdural empyema, etc. (6). Different types of microorganisms can cause different pathologies which can affect the brain and the whole body. When infecting the CNS, bacteria primarily attack the meninges and brain parenchyma, causing various brain damage, including meningitis, seizures, and epilepsy (7,8). Bacterial infection in the CNS can occur via the bloodstream crossing the blood-brain barrier (BBB), and if the cerebral cortex is damaged, seizures can occur (9). Some bacteria, such as tuberculosis, reach the brain via the bloodstream from the lungs (10). These infections can cause ischemia and inflammation by producing inflammatory mediators such as cytokines and arachidonic acid compounds.

The pathogenic signs of inflammation can occur a few hours after the infection, reaching the acute phase response, an effect that must be counteracted by taking antibiotics or, occasionally, neurosurgical interventions. Damage-associated molecular patterns (DAMPs) from damaged neurons and microglia, and the activation of pattern recognition receptors (PRRs), such as toll-like receptors (TLRs) expressed by these cells, participate in the inflammatory process with cellular dysfunction (11). DAMPs can activate the NLR family pyrin domain containing 3 (NLRP3), contributing to the cerebral pathogenic process (12). In this dynamic event, transcriptional upregulation of pro-inflammatory cytokines occurs. In the brain, NOD-like receptors respond to a variety of pathogen associated molecular patterns (PAMPs) which are linked to various microorganisms, as well as DAMPs that are generated during a tissue insult (13).

IL-1 is a cytokine produced essentially by macrophagic cells after activation with microorganisms, and it causes neuroinflammation by activating microglia and astrocytes, but these cells also can generate IL-1, producing an autocrine effect. IL-1 activates cells to produce chemokines and other pro-inflammatory proteins by recruiting microglia to the CNS, resulting in tissue neurodegeneration (14). NOD-like receptors, also called NLRs, ranging from 1 to 12, form the inflammasome and mediate the release of pro-inflammatory cytokines such as IL-1 and IL-18 that play a crucial role in cerebral inflammation (12) (Fig.1).

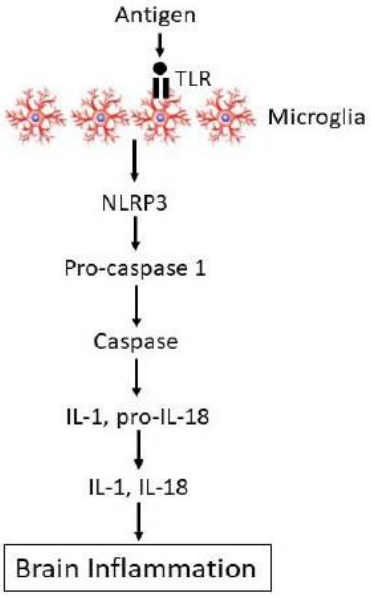

Fig. 1. *The microorganism, or active part of it, binds to the toll-like receptor (TLR) and causes the activation of the NLRP3, which initiates the cleavage of pro-caspase and subsequently, the mature form caspase-1, which cleaves pro-IL-1 and pro-IL-18 with consequent generation of the mature forms IL-1 and IL-18 that are implicated in brain inflammation induced by microorganisms.*

In infections caused by microorganisms, high levels of NLRP1 that are expressed by brain tissue can occur, and this inflammasome is important for the study of inflammatory diseases, and it can also represent a therapeutic target (15). In addition to causing brain inflammation, IL-1 activation through the inflammasome can cause dizziness, cognitive impairment (16), headache, memory impairments, behavioral changes, and fever, symptoms that can be resolved with accurate anti-microbial therapy. These reactions lead to the extracellular loss of potassium, water, and glutamate,

promoting the formation of reactive oxygen species (ROS). The inflammatory process is activated by the cytokines IL-1, TNF, and IL-6 that are produced by microglia and neurons and also cause changes in cell receptors. Bacterial meningitis and convulsions can cause purulent edema with strong inflammation that can provoke very serious neuropathological states. Brain abscesses that form as a result of the infection can cause damage to the ear (otitis), to the nasal cavities (sinusitis), and to the heart (heart disease). It should be emphasized that ear infections and sinusitis are generally caused by anaerobic bacteria.

Microbial products can be detected in the brain tissue with the reverse transcription polymerase chain reaction (RT-PCR) technique. Microorganisms can lead to inflammation of the CNS resulting in encephalopathy, convulsions, neuromuscular pain, neuropathy, myopathy, Guillain-Barré syndrome (with weakness of the limbs and sensory changes), and others. (17). The infections can be serious, slightly symptomatic, or asymptomatic, and can aggravate neurological diseases due to other causes including drugs, metabolic dysfunctions, hypoxia, toxic products, etc. Often these pathologies lead to a complete recovery of the patient, although sometimes they are irreversible. In addition, encephalopathy and other symptoms caused by microorganisms and their compounds lead to inflammation of the brain caused by an infection or the generation of self-antibodies (18). Microorganisms can also cause vascular disease in the brain, vasculitis that can be detected with different diagnostic tests, including brain angiography and blood tests. If the infection becomes chronic, neuronal loss and death can occur, followed by neuroinflammation involving microglia and astrocytes with oxidative stress, mitochondrial dysfunction, cytokine production, and BBB disruption.

CONCLUSIONS

In light of these results, we can state that since brain antibacterial therapies are not very effective, they still remain a challenge in medical therapy (19). This article offers a basic review of neurological diseases due to microorganism infections, with an approach to diagnostic, therapeutic, and prognostic strategies.

Conflict of interest

The author declares that they have no conflict of interest.

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Letter to the Editor

PARKINSON'S IMMUNITY AND INFLAMMATION: NEW ASPECTS

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INTRODUCTION

Parkinson disease (PD) is a multisystem disorder which affects dopaminergic neurotransmission that is characterized by movement disorder with motor impairment, tremors, stiffness of the neck, trunk, and limbs, bradykinesia, postural instability, depression, anxiety, apathy, and soft voice. In PD, which typically develops around the age of 60 with an incidence of approximately 1.5% (1), there is neuroinflammation and a malfunction of the immune system that can lead to gastrointestinal dysfunction and sleep alterations (2,3). Individuals with PD present with a neurodegenerative syndrome involving both thalamocortical and non-motor motor circuits.

DISCUSSION

PD is one of the most frequent neurodegenerative diseases (4) and presents a degeneration of neurons in the substantia nigra causing motor dysfunction (5). The disease presents neuronal loss with the presence of proteins such as Lewy bodies (absent in mouse), but this mechanism still needs to be elucidated. The cause of these phenomena has often been attributed to oxidative stress, cytotoxicity, mitochondrial dysfunction, apoptosis, and low-grade inflammation (6-9). Inflammation is due to microglial activation, astrogliosis, and lymphocyte infiltration, contributing to neurodegeneration. Neurodegeneration could stimulate inflammatory proteins, causing brain dysfunction (10). Laboratory blood tests show that some cytokines such as IL-2, tumor necrosis factor (TNF), and IL-6 (11), as well as the chemokine RANTES (12), are increased in the serum of patients with PD. These highly inflammatory immune molecules could contribute to neurodegeneration. Autoantibodies against dopaminergic neurons may also be responsible or participate in this inflammatory process. Activated CD4+ and CD45RO+ T lymphocytes are involved in this immunopathological reaction, while naive CD45RA+ non-activated T lymphocytes are decreased. CD25 Treg lymphocytes are also increased in PD patients, demonstrating an immune reaction of the organism against the pathological phenomena. However, these results are still unclear and need to be confirmed.

The brain is an organ that has its own immune system in which cytokines can mediate both physiological and pathological phenomena. Pro-inflammatory cytokines such as IL-1, TNF, and IL-6, which can be generated by microglia and are important inflammatory markers, are also found in the cerebrospinal fluid of these patients (13). Microglia, which

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are sentinels of the central nervous system (CNS), exert a protective effect on the brain by maintaining homeostasis. These blood monocyte-like cells generate neurotrophic factors such as nerve growth factor (NGF) and fibroblast growth factor (FGF) (14). The activation of microglia by external insults leads to the production of pro-inflammatory cytokines, an effect that has also been confirmed in rodents (15). Inflammatory cytokines play a key role in the pathogenesis of neurodegenerative diseases (16,17). The cerebrospinal fluid of PD patients shows high levels of cytokines IL-1, IL-6, TNF, TGF-β1, VEGF, and the inflammatory chemokines MCP-1 and MIP-1α, highlighting that this disease also has inflammatory origins and that these cytokines/chemokines could be used as a target of this neurodegenerative pathology (18,11) (Table I).

Table I. *Some factors that mediate neuroinflammation.*

• Tumor necrosis factor (TNF)	• Interferon γ
• CD68, CD23	• β2-microglobulin
• Interleukin-1 (IL-1)	• Epidermal growth factor,
• Cyclooxygenase	• Transforming growth factors α and β
• Inducible nitric oxide synthase	• Interleukin-2 (IL-2)

CONCLUSIONS

PD can be relieved by treating the affected patient with the dopamine precursor levodopa or with dopaminergic inhibitors (19). Therapeutic treatment with levodopa proves to be effective in the long term with neurological improvement and quality of life. Patients with PD can also be treated with the surgical technique of brain stimulation which consists of a pulse generator that sends electrical stimuli to the brain.

However, studies underway in our laboratory as well as others aim to clarify the etiological and pathogenetic mechanisms, and the specific action of cytokines in PD, allowing for better therapeutic treatment for this neurodegenerative disease which ranks, by incidence, in second place in the world after Alzheimer's among brain disorders.

Conflict of interest

The author declares that they have no conflict of interest.

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