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Commentary: Neuroinflammation: An Overview of Neurodegenerative, Metabolic Diseases and Biotechnological Studies

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1. Abstract

Neuroinflammation is a factor contributing to cognitive impairment and neurodegenerative and metabolic diseases. These diseases are characterized by progressive injury of neuron cells, and loss of motor or cognitive functions. Microglia, which are the resident macrophages in the brain, play an important role in both physiological and pathological conditions. In this commentary, we provide a brief discussion of the main points covered in the review "Neuroinflammation: an overview of neurodegenerative, metabolic diseases and biotechnological studies". We approach to how the oxidative stress and metabolic disease induce pathological mechanisms of activation of the microglial cells and consequently release cytotoxins, increasing to the neurodegenerative process. New insights into therapeutics bioinspired by neuropeptides from venomous animals, supporting high throughput drug screening in the near future was also shown by the authors.

Keywords: microglia, inflammation, animal toxin, animal models of neurodegenerative disease.

In this review, Boleti and collaborators demonstrate the importance of studies aimed at understanding inflammatory processes, especially those caused in the central nervous system, where neuroinflammation is related to the development of neurodegenerative diseases, such as amyotrophic lateral sclerosis, Alzheimer's, multiple sclerosis and Parkinson's [1]. Neuroinflammation is also associated with metabolic diseases such as hypertension, diabetes and obesity. And to better understand neurodegenerative processes, *in vitro* and *in vivo* models are used to elucidate possible biomarkers, inflammatory mechanisms and environmental factors involved. However, the understanding of these mechanisms allows the development of new treatments, such as the use of peptides found in animal toxins against neuroinflammation and neurodegeneration.

Boleti and collaborators, emphasize the importance of the participation of microglia, which are macrophages of the innate immune system in the central nervous system (CNS), and play an important role in the mechanism of neuroinflammation. These cells have great functions in the CNS, from helping in neural development processes, actively participating in the synapse's construction , and are also responsible for protecting the CNS, as antigen-presenting cells and looking for immunogens. Microglia are classified into two subtypes, M1 responsible for pro-inflammatory activity and potentiating neural damage, and M2, characterized by having an anti-inflammatory, pro-regenerative and phagocytic function, against bacterial and viral infections, or other inflammatory processes [2].

The review cites studies that show that lipopolysaccharides (LPS) and viral infections are responsible for causing inflammation. Such factors are responsible for initiating the inflammation cascade, which activate microglia that release pro-inflammatory mediators, responsible for the recruitment of immune system cells, which express toll-like receptors (TRL4s), activated by protein aggregates or associated molecular patterns. to the pathogen (PAMPs) [3]. Inflammation time is also responsible for the degree of degenerative severity, acute inflammations have a more protective character, however chronic inflammations are more damaging to neural tissue. This exposure time will depend on the factors that promote inflammation, which may be extrinsic (bacteria or viruses) or intrinsic (genetic or metabolic factors).

Intrinsic factors such as oxidative stress, result in the release of free radicals, resulting from natural metabolism, mainly reactive oxygen species (ROS), which are important in the study of neurodegenerative diseases [4,5]. However, mitochondria are responsible for the regulation of cellular oxidative stress, demonstrating an effective anti-oxidative system, mediated mainly by superoxide dismutase and decreasing the pool of reduced glutathione. However, genetic factors that modify these organelles may be responsible for its dysfunction, resulting in brain tissue inflammation [6]. These oxidative processes may also be related to metabolic diseases.

Diseases of metabolic origin, such as obesity, caused by excess calories consumed, consequently lead to an increase in adipose cells, an increase linked to the release of adipokines, cytokines secreted by excess adipose tissue, causing changes in the immune response. Excess adipose tissue also increases circulating fat in the blood, causing an increase in pro-inflammatory mediators, which amplify the expression of cytokines, chemokines and prostaglandins, promoting inflammation of the system and also insulin resistance [7]. The increase in these circulating cytokines also affect the brain and hypothalamus, causing local inflammation, associated with loss of cognitive function, which is directly linked to several neurodegenerative diseases, given the pathophysiological characteristics.

The neurodegenerative effects caused by the inflammation of neural tissue are associated with the emergence of diseases such as Alzheimer's, Parkinson's and multiple sclerosis. Alzheimer's is a disease characterized by the deposition of β-amyloid peptide in the extracellular portion of neural tissue, causing amyloid plaques, which change the M2 to M1 microglial cells, which produce pro-inflammatory cytokines [1,8]. Microglial cells are not able to degrade the plaques, which ends up increasing the damage caused by inflammation, resulting from the secretion of cytokines in the medium, which cause a neurotoxic effect. In the same context, Parkinson's is also characterized by the accumulation of α-synuclein and ubiquitin in the extracellular environment, better known as Lewis bodies, which also affect animal and human nervous tissue [9]. Multiple sclerosis is caused by demyelination of the axon, causing loss of cognition, weakening of the brain barrier and increased presence of inflammatory cells in the CNS [10].

The review emphasizes the use of *in vitro* and *in vivo* models to better understand the pathophysiology of these diseases, identifying biomarkers, environmental factors of psychopathologies and genetic mechanisms. In the most used *in vitro* models, the induction of inflammation in microglia by LPS, which stimulates the production of pro-inflammatory cytokines. The BV-2 and N9 microglial cell lines, when stimulated by LPS, have 90% similarity with primary microglia, proving to be excellent models of neuroinflammation [11]. *In vivo* models, which include rodents, insects, fish and nematodes, rodents are widely used in clinical trials to screen drugs that treat neurodegeneration, especially for diseases such as Alzheimer's and Parkinson's. Some transgenic insects such as *Drosophila melanogaster*, with genes related to Parkinson's, are used as study models [12]. The models developed with *Caenorhabditis elegans* are easy to maintain and obtain results, given their characteristics, modified models for studies of specific diseases such as Alzheimer's and Parkinson's are used, where they are subjected to different stimuli and respond differently, according to the disease model [13]. These models are used to test possible future drugs, as well as alternative treatments, such as the use of toxin components to combat neuroinflammation and neurodegeneration.

For the treatment of these neurodegenerative diseases, some drugs are used, but in most cases to slow or stop the progress of the disease, or just treat the symptoms, some diseases have only one drug on the market to be treated, while others have a wider range of drugs, however they are still not capable of reversing the damage caused by the disease. However, some companies invest in research in the field of peptides found in animal toxins, which demonstrate interactions with ion channels, neurotransmitter receptors and transporters. These neuropeptides show promise in the treatment of these diseases, found in scorpions, snakes and bees, have shown promise in anti-inflammatory activity and against neurodegenerative diseases. At different concentrations, activities are reported, melittin found in bee toxins causes itching, inflammation and pain, at low concentrations they demonstrate anti-inflammatory activity. Snakes, in their toxins, have neuropeptides with neuroprotective activity, demonstrating activity that regulates apoptosis. And neuropeptide found in scorpion demonstrated neuroprotective activity, having preventive activity against neurodegeneration [14,15,16].

In view of the information listed on the neurodegenerative mechanisms correlated with neuroinflammation, it can be noted that the inflammation signaling pathways are varied, and all lead to the inflammatory process that can affect from the site to the CNS, through the mechanisms mentioned in the review. However, the possibility of numerous other factors related to neuroinflammation makes the review open the door for researchers to investigate deeper into the subject. And the small survey on alternative treatments, with the use of neuropeptides from animal toxin, demonstrates a promising area in the development of new drugs against these diseases. I congratulate the authors for elucidating the subject, and may it be the direction for other researchers to follow in the area, in order to find new methods of experimentation and also new possible drugs for the treatment of patients affected by neurodegenerative diseases.

2. Author contributions

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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