Glia function in the endocanabinoid system: narrative review

Função da glia no sistema endocanabinoide: revisão narrativa

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ABSTRACT

BACKGROUND AND OBJECTIVES: Evidence has highlighted a role of glial cell activation, and their interaction with different neural systems, especially the endocannabinoid system, in the mechanisms involved in the chronicity and maintenance of pain. The aim of this review is to bring an update on published data that demonstrate the interaction between glial cells and the endocannabinoid system in the pathophysiology of chronic pain and its treatment.

CONTENTS: A narrative review was performed based on a research in the Medline database, using the Keywords "endocannabinoid", "glial cells", "microglial", "astrocytes", "neuroinflammation".

CONCLUSION: Deepening the knowledge about the function of glial cells in the endocannabinoid system will open the possibility of acting on the pathophysiological origin of the pain chronification process, attenuating the mechanisms involved in central sensitization.

Keywords: Cannabinoids receptors, Neurogenic inflammation, Neuroglia, Pain.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A evidência científica tem ressaltado um papel da ativação das células da glia e de sua interação com diversos sistemas neurais, com destaque para o sistema endocanabinoide e mecanismos envolvidos na cronificação e manutenção da dor. O objetivo deste estudo foi atualizar os dados publicados que mostrem a interação entre as células da glia com o sistema endocanabinoide na fisiopatologia da dor crônica e seu tratamento.

CONTEÚDO: Foi realizada uma revisão narrativa baseada em pesquisa na base de dados Medline, com uso dos unitermos *"endocannabinoid", "glial cells", "microglial", "astrocytes", "neuroinflammation"*.

CONCLUSÃO: O aprofundamento do conhecimento acerca da função das células da glia no sistema endocanabinoide abrirá a possibilidade de atuação sobre a origem fisiopatológica do processo de cronificação de dor, atenuando os mecanismos envolvidos na sensibilização central.

Descritores: Dor, Inflamação neurogênica, Neuroglia, Receptores de canabinoides.

INTRODUCTION

The evidence accumulated in the last years has highlighted the preponderant role of glia cell activation and its interaction with several neural systems in the mechanisms involved in pain chronification and maintenance[1]. Among the systems that exert and suffer influence from glia, the endocannabinoid system should be highlighted. This system is seen as a powerful regulator of synaptic function throughout the central nervous system (CNS), acting by reducing the release of neurotransmitters in the synaptic cleft, in a transient and long-lasting manner, and acting on the function of ion channels in the spinal cord and dorsal root ganglion (DRG)[2,3].

The chronification of pain can be synthesized as a process of maladaptive neuronal plasticity, which results in sensitization of pain pathways. As a result of these alterations, there is an imbalance between facilitation and inhibition of painful stimuli in the dorsal horn of the spinal cord, favoring the former[4]. This state of increased excitation in the CNS results in a pathological amplification of the stimuli entering and leaving the spinal cord[1,3]. As a consequence, the activation of glial cells occurs, leading to increased expression of several membrane receptors, intracellular proteins, and transcription factors that are implicated in the development and maintenance of chronic pain (CP). However, among the receptors that have their expression increased are the

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HIGHLIGHTS

- Mycroglia activation is strongly involved in the development of neuropathic pain secondary to peripheral nerve injury.
- The endocannabinoid system provides a pathway for attenuation of neurogenic inflammation, which is involved in the process of pain chronification.
- Mycroglia plays a central role in the interaction of the endocannabinoid system with the pathophysiology of chronic pain.

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cannabinoids CB1 and CB2, which, through their inhibitory actions, may serve as therapeutic targets to counterbalance this state of neuronal excitation[3].

The present review's objective was to update the published data showing interaction between glia cells with the endocannabinoid system in the pathophysiology of CP and its treatment.

CONTENTS

Glia cells and pain

The glia cells in the central nervous system (CNS) are the astrocytes, the microglia, and the oligodendrocytes. In the peripheral nervous system (PNS), glial satellite cells are found in the DRG and trigeminal ganglion, and Schwann cells in the peripheral nerves.

Mycroglia cells are CNS resident macrophages, originating from the monocyte lineage produced in the bone marrow. In the CNS, these cells are heterogeneously distributed, interacting dynamically with synapses to maintain brain homeostasis. Mycroglia can be activated as a result of insults to neural tissue. When this occurs, a rapid proliferation of these cells begins in the spinal cord, associated with changes in their morphology, adopting an ameboid shape[1].

Mycroglia activation is strongly involved in the development of neuropathic pain secondary to peripheral nerve injury and depends on the presence of mediators such as ATP, colony-stimulating factor 1 (CSF1), chemokines (CCL2 and CX3CL1), and proteases, from injured or activated sensory neurons. In parallel, there is increased expression of receptors for ATP and CX3CL1 (P2X4, P2X7, P2Y12, CX3CR1) in the spinal cord microglia itself[5].

Subsequent activation of these receptors leads to intracellular signaling mediated by phosphorylation of p38 protein kinase for increased production and release of inflammatory cytokines such as TNF-α, interleukins IL-1β, IL-18, brain-derived growth factor (BDNF) and cyclooxygenase (COX). These mediators are able to amplify synaptic transmission, and therefore potentiate pain transmission to the brain[5]. Some alterations in the microglia have the potential to produce prolonged effects. In a study evaluating enhancers in spinal microglia, persistent modifications near transcription-regulated genes were shown to exist. Enhancers are areas of open chromatin that define the binding point of cellular transcription factors. Changes in these regions may be implicated in the persistence of the facilitation state, which allows for the maintenance of CP[6].

Astrocytes are the greatest number of cells present in in the CNS, and although histologically they have a structural function as support cells, they are known to be involved in the development of acute and chronic neurological, neurodegenerative, neuropsychiatric diseases, and gliomas[1]. Differently from the other glial cells, astrocytes have a physical intercellular connection, determined by the communicating junctions, forming the blood-brain barrier, and performing other physiological functions, such as regulation of ionic concentration, modulation of synaptic transmission, among others[5]. Similarly to what happens to the microglia, astrocyte activation leads to a state of neuroinflammation, with participation in the pathophysiology and maintenance of CP[7].

Although both cells are involved in the development of CP, some differences mark the involvement of each of them. Astrocytes are involved in virtually all diseases that course with persistent pain, whereas microglia activation seems to occur in only a few specific situations. Peripheral nerve lesions exhibit participation of both cells, but in chemotherapy-induced neuropathy, only astrocyte participation has been identified. Similarly, only astrogliosis (not microgliosis) was observed in the dorsal root horn of patients with human immunodeficiency human related neuropathy. Models of neuropathic pain from bone cancer also show astrocyte involvement, but the participation of microglia in these cases is not yet definitive[7].

Finally, oligodentrocytes, cells in charge of myelin sheath production, have also been associated with the pain chronification process. It was shown that the expression of IL-33 derived from oligodendrocytes preponderantly contributed to the development of neuropathic pain after peripheral nerve injury. An interesting finding is that toxin-mediated ablation of these cells leads to the development of neuropathic pain symptoms, suggesting a protective role of oligodendrocytes in CP[5].

ENDOCANNABINOID SYSTEM

The knowledge about the endocannabinoid system as a modulator of synapses in the CNS has been developed over the last 25 years, and robust evidence points to its action as a retrograde messenger, capable of suppressing the release of neurotransmitters in a transient and prolonged manner, both in excitatory and inhibitory synapses[2].

The endocannabinoid system is a complex biological network, consisting of the cannabinoid receptors (CB1 and CB2), their respective endogenous ligands, 2-araquidonoil glycerol (2-AG) and ethanolamine O-araquidonoil (AEA), as well as their synthesizing and degrading enzymes. Physiologically, it is related to the maintenance of homeostasis and, therefore, its components are found dispersed throughout the body, such as in the CNS, immune system cells, liver, as well as in the reproductive, respiratory, gastrointestinal, cardiovascular, and musculoskeletal systems[8,9].

The CB1 receptor is expressed primarily in the nervous system, with greater evidence for GABAergic axon endings. CB2, on the other hand, is present primarily on cells of the immune system, including microglia. However, this receptor is also present in the CNS, especially in the brainstem and mesencephalic dopaminergic pathways. Unlike CB1, which is among the G protein-coupled receptors with the highest expression in the CNS, CB2 has a reduced basal quantity and has a high inductivity when facing inflammatory stimulus[9].

In the glia, astrocytes express CB1 receptors, whose function is to regulate glutamine synthesis and, therefore, to control the amount of glutamate available in the synaptic cleft and the influx of calcium, modulating synapse strength. Mycroglia, on the other hand, expresses mainly CB2 and participates in the modulation between pro-inflammatory and anti-inflammatory states[8,9]. Both CB1 and CB2 are G protein-coupled receptors with inhibitory function, with their activation leading to blockade of sodium channels, activation of potassium channels, and inhibition of adenylyl cyclase[3].

The activation of cannabinoid receptors acts modulating the transmission of nociception, having already been shown the attenuation of pain behavior in animal models[10].

The main mechanism by which modulation of synaptic function occurs is retrograde signaling. This occurs when a postsynaptic activity leads to the production of endocannabinoids, which bind to CB1 expressed on the presynaptic membrane, leading to inhibition of neurotransmitter (glutamate) release. However, the endocannabinoid ligand can still act through the vanilloid receptor (TRPV1) and postsynaptic CB1 activation, as well as through activation of glia cells[2].

Microglia and endocannabinoid signaling

As already described, in situations where nociception is present, engagement of the microglia is expected from the activation of its cells, leading to the induction and perpetuation of neuroinflammation and a state of facilitation, which makes it conducive to the development of pain chronification. However, activation of CB2 receptors can profoundly modify the immune function of the microglia, converting it to an anti-inflammatory state, in which there is limited phagocytosis migration, increased production of anti-inflammatory mediators, and reduced production of pro-inflammatory ones[3].

With the activation of CB2, some changes are expected in the microglial response to injury. Reduced nitric oxide production, reduced synthesis of IL-1β, TNF-α, and BDNF can be observed as a result of attenuation of the p38 protein kinase pathway, and reduced ERK-mediated proliferation of mycroglia[3,11]. CB2 activation is also associated with increased release of IL-10, an anti-inflammatory cytokine[11]. A reduction in P2X4 purinergic receptor expression has also been shown following CB2 activation[12]. The switch to an anti-inflammatory state was also associated with reduced pain behavior[3].

Studies also suggest the presence of non-CB1 and non-CB2 receptors in the microglia, which are activated by cannabinoid ligands, and lead to a reduction in the release of IL-1α and TNF-α, pro-inflammatory cytokines[13,14].

Another pathway that has been gaining prominence is the palmitoylethanolamide (PEA) fatty acid, which, despite not binding to CB2, has anti-inflammatory and antinociceptive action indirectly mediated by this receptor. This could be observed from the reversal of its effect by a CB2 antagonist[15].

Microglia not only express cannabinoid receptors, but also produce endocannabinoids. With a production at least 20 times higher than that of other glia cells or neurons, the microglia is the major responsible for the production of endocannabinoids in the CNS3. The production of these ligands depends on signaling through the activation of purinergic receptors (P2X4 and P2X7), with a consequent increase in intracellular calcium[3]. In situations such as the presence of neuropathic pain, the microglia increases the production of endocannabinoids, as well as reduces the expression of its degrading enzyme, fatty acid amide hydrolase (FAAH)[3].

Besides the action of endocannabinoids on their receptors, other antinociceptive actions are observed from the action of these ligands in other systems. At the spinal level, there is inhibition of adenylate cyclase activity and reduction of cyclic AMP, which reduces nociceptive signaling to higher order neurons[3]. Endocannabinoids also inhibit the serotoninergic 5-HT3 pathway, reduce sodium influx, and block voltage-dependent (Cav3.2) presynaptic calcium channels[3].

Astrocytes and endocannabinoid signaling

Astrocytes mainly express CB1 receptors, which are involved in neuronal homeostasis and control of metabolic functions[7]. However, experimental studies have brought to light evidence that the activation of this receptor plays a role in modulating neurogenic inflammation and nociception. This effect could be observed in a study that showed that the activation of CB1 led to attenuation of allodynia, persistent activation of astrocytes in the spinal cord, and the phosphorylation of p38 protein kinase in spinal astrocytes in a model of plantar incision[16].

Interaction of glia and endocannabinoid system: perspectives

The evidence for a central role of neurogenic inflammation in the pathophysiology of CP chronification and perpetuation has become increasingly robust[4]. And it is natural to search for mechanisms that are capable of alleviating or reversing these processes.

The data obtained, mostly from experimental studies about the influence that the endocannabinoid system exerts on neurogenic inflammation and on nociception pathways, brings an important direction towards this objective. These findings show us that, when stimulated, cannabinoid receptors, in particular CB2 receptors present in the microglia, prevent the development of an inflammatory state, both acute and long-lasting. In this way, central sensitization would also be prevented, a determining step in the development of CP.

Cannabinoids present great potential in the treatment of pain, including in preventing the processes involved in pain chronification. However, the efficacy and consequences of long-term use of these agents are still being checked in the literature. To date, entities such as the International Association for the Study of Pain (IASP) still do not place cannabinoids as the first line of treatment for CP[17]. Further studies are needed to ensure the efficacy and safety of these agents.

CONCLUSION

The deepening of knowledge about the function of glia cells in the endocannabinoid system will open the possibility of acting on the physiopathological origin of the CP process, attenuating the mechanisms involved in central sensitization.

AUTHORS' CONTRIBUTIONS

José Osvaldo Barbosa-Neto
Methodology, Writing - Preparation of the Original, Writing - Review and Editing, Supervision
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Writing - Preparation of the Original, Writing - Review and Editing

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