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The Many Faces of Astrocytes in the Septic Brain

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Abstract

Sepsis is a life-threatening organ dysfunction that is caused by a dysregulated host response to infection. Surviving patients have cognitive and memory damage that started during sepsis. These neurologic damages have been associated with increased BBB permeability and microglial activation. However, a few discrete studies have seen over the years pointing to the potential role of astrocytes in the pathophysiology of neurological damage after sepsis. The purpose of this article is to review information on the potential role of astrocytes during sepsis, as well as to provoke further studies in this area. These published articles show astrocytic activation after sepsis; they also evidence the release of inflammatory mediators by these cells. In this sense, the role of astrocytes should be better elucidated during sepsis progression.

Keywords Sepsis-associated encephalopathy · Astrocytes · Neuroinflammation · Delirium · Brain

Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. This syndrome frequently affects individuals in intensive care units around the world and presents high rates of mortality and morbidity, with a prevalence of up to 60% in hospitalized patients [2]. In sepsis, the inflammatory response is amplified in such a way that it produces damage to organs other than those affected by the initial infection, and the brain is among those affected, which generates acute and long-term neurological changes [3]. For years, studies have associated the neurological damage in sepsis with an increased permeability of brain barriers caused by the exacerbated release of pro-inflammatory cytokines and peripheral oxidative stress [4], and this would activate immune cells in the brain, such as microglia [5].

Brain signaling can occur both as a response to invasion by microorganisms and in the absence of an infectious agent, as observed in sepsis [6]. Pro-inflammatory cytokines, reactive oxygen/nitrogen species, and patterns associated to tissue damage are among the molecules capable of upregulating brain cells by migrating from periphery through the meninges and brain barriers that protect the CNS; thus, the inflamed brain barriers lose their function of high selectivity, facilitating the influx of toxic molecules into the brain [3]. When passing through brain barriers, such molecules face the brain defense lines, which deposit in the microglia, an inflammatory and precursor cell of macrophages, a "saving" function for neurons. Consequently, microglia are activated and secrete inflammatory mediators, such as cytokines and reactive oxygen species, within the brain parenchyma to combat pathogens and restore homeostasis [7].

However, the mediators released by microglia may play a harmful role, especially in diseases where peripheral inflammation is chronic, sustained, or exacerbated [8]. In

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this sense, microglia-induced inflammation will activate the cells that compose the brain barriers, thus maintaining their high permeability to peripheral blood and restarting a cell activation cycle [3].

Nevertheless, this cycle does not only involve microglial cells [9]. Possibly, and especially during sepsis, astrocytes are being neglected in terms of their role in protecting from or enhancing neuroinflammation. In a simplistic form, microglia and astrocytes should restore homeostasis; however, here, they lose their role as good guys and become villains. However, these are only cells that are hyper stimulated by the flood of inflammatory mediators from the inflamed peripheral tissues and in situ production by themselves. In this review, we intend to create a new perspective regarding the role of astrocytes during sepsis, encouraging research on this topic.

Astrocytes in the Healthy CNS

Astrocytes represent the most abundant glial cells in the human brain (Verkhratsky & Parpura, 2015). Astrocytes were believed to be a homogeneous population; however, this hypothesis is increasingly being refuted [10]. Like microglia, astrocytes can exhibit different morphologies [11], and based on their morphology and spatial organization, astrocytes are classified into two basic subtypes: protoplasmic and fibrous astrocytes [12]. Protoplasmic astrocytes are found throughout gray matter and show several highly branched and bushy processes, which extend their end-feet to blood vessels and enwrap them to form the glial limiting membrane, which is the outermost wall of the BBB. Fibrous astrocytes, on the other hand, are mainly located within the white matter and have a stellate shape with smooth and long processes [13]. This type of astrocyte expresses high levels of glial fibrillary acidic protein (GFAP) as compared with protoplasmic astrocytes [14].

Astrocytic cells, together with neurons, microglia, pericytes, endothelial cells and the basement membrane, form the neurovascular unit, a structure that involves multicellular relationships to establish a functional coupling between the brain and blood vessels [15]. Astrocytes exhibit different activities to maintain the normal functioning of the CNS, for example, provide almost complete coverage of the cerebral vasculature [16]. Also, with the release of prostaglandins (PGE), nitric oxide (NO), and arachidonic acid (AA), they can control the local blood flow of the CNS [17]. Its role in the metabolism is related to its ability to respond to neuronal activity, being able to increase the rate of glucose uptake, glycolysis, and lactate release in the extracellular space, contributing to neuronal function [18].

Despite the high metabolic activity, astrocytes use at most 15% of the total brain energy in the form of glucose. In fact, the rates of glucose uptake and glycolysis are high; however, as the oxidative phosphorylation rates are low compared to the astrocytic rates, astrocytes serve as a source of lactate production. The lactate is the main substrate for neuronal functioning during cerebral activation, and through the astrocyte-neuron lactate shuttle [19, 20].

In addition to lactate release, astrocytes are part of the tripartite synapses, which are synapses composed of two neurons and one astrocyte. These cells act synergistically with a functional unit for the functioning of plasticity and adequate for the release of neurotransmitters [12, 21].

Astrocytes in Pre-clinical Models of Sepsis

One of the most used animal models of human disease for the study of sepsis is the cecal ligation and perforation model (CLP) [22]. Briefly, a 3-cm midline laparotomy was performed to expose the cecum and adjoining intestine. The cecum was tightly ligated with a 3–0 silk suture in the middle of its length (below the ileocecal valve), perforated once with a 14-gauge needle, squeezed gently to extrude a small amount of feces through the perforation site, and returned to the peritoneal cavity, and the laparotomy was closed with 4–0 silk sutures [23]. This model is well accepted in the international literature for reproducing polymicrobial sepsis and allowing the induction of different degrees of severity, similarly to what is found in humans. Also, this model is effective to study neurological dysfunction during and after sepsis [24].

Astrocytes from CLP animals display an increased gene expression of pro-inflammatory cytokines, such as tumor necrosis factor- α (TNF-α), interleukin (IL)-1β, IL-6, IL-18, monocyte chemoattractant protein-1 (MCP-1), and cyclooxygenase-2 (COX-2), with a reduction in IL-10, accompanied by augmented levels of Toll-like receptor (TLR)-2 mRNA expression but no changes either in TLR4 or in vascular endothelial growth factor (VEGF) gene expression [25]. These results are like those found in rat brain tissue homogenate after CLP [26]. This cytokine profile has been closely related to the action of microglial cells [27], but interestingly, a study provided evidence that mediators released by peripheral blood mononuclear cells (PBMC) directly promote astrocyte reactivity during sepsis, independently of microglia [28], corroborating our previous finding that sepsis causes astrocytic activation [26].

The Table 1 summarizes the main findings concerning CLP-induced sepsis effects on astrocytes. The studies point the occurrence of astrocytic activation as early as 4 h after polymicrobial sepsis [29], which may persist for up to 15 days after sepsis [30]. The hippocampus was the most prevalent brain structure evaluated in the studies.

Table 1 The effects of polymicrobial sepsis induced by CLP on astrocytic activation in animal models

Reference	Time (hours) after sepsis	Brain region
Rotaru-Zavaleanu et al., 2021 [29]	4, 8, 48	Elevation of the number of astrocytes in the hippocampus at 4 h after CLP, lasting up to 48 h after CLP, with no change in the cortex. Elevation in the corpus callosum at 4 and 8 h after CLP
Moraes et al., 2015 [31]	24	Astrocytic activation after 24 h in the hippocampus and cortex
Danielski et al., 2020 [26]	24	GFAP elevation after CLP independently of NLRP3 activation
Catalão et al., 2017 [32]	48	Astrocytic activation after 48 h prefrontal cortex, dentate gyrus and hippocampal CA1
Huang et al., 2020 [33]	120	GFAP elevation after CLP in whole brain
Xiong et al., 2019 [34]	168	Astrocytic activation after 7 days in the hippocampus
Catalão et al., 2020 [35]	240	Elevation of GFAP after CLP in prefrontal, dentate gyrus and CA1 region
Tian et al., 2020 [30]	360	GFAP elevation after CLP in hippocampal CA3

Table 2 The effects of LPS injection on astrocytic activation in animal models

Reference	LPS dosage	Time (hours)	Effect on astrocytes
Montoya et al., 2019 [36]	5 mg/kg i.p	3	Dopamine receptor D3 was expressed in astrocytes
Alexander et al., 2008 [37]	0.15 mg/kg i.p	8	Elevation of TNF-α receptor in astrocytes
Beck-Schimmer et al., 2017 [38]	1 mg/kg i.v	12	LPS induced prominent astrogliosis
Semmler et al., 2005 [39]	10 mg/kg i.p	24	Activation of astrocytes cortex, striatum, hippocampus
Hasegawa-Ishii et al., 2016 [40]	3 mg/kg i.p	24	CCL11, CXCL10 and G-CSF expressed by astrocytes
Lu et al., 2020 [41]	5 mg/kg i.p	24	IFN-y deficiency restores microglia-induced A1 astrocytes
Fu et al., 2014 [42]	2 mg/kg i.p	24, 72, 168, 720	Astrocytic activation and TNF-α release in the dentate gyrus Release of IL-1β by astrocytes Activation of NF-kB

The animal model of sepsis by CLP generates endotoxemia in animals, especially due to the presence of gram-negative bacteria. Therefore, the administration of lipopolysaccharide (LPS) alone can mimic the inflammatory response that occurs in sepsis in animal models of human diseases. The effects of LPS on astrocytic activation in animal models are shown in Table 2. The systemic effects of LPS induce important changes in the brain of animals submitted to sepsis, and these

Table 3 The effects of LPS on astrocyte cell culture

Reference	Treatment	Time (hours)	Effect on astrocytes
Chen et al., 2018 [46]	LPS 150 ng/mL IFN-γ 200 U/mL, IL-6: 10 ng/mL	-	IL-6 enhances mitochondrial biogenesis in astrocytes
Hua X et al. [47],	LPS 50, 100 or 200 ng/mL + IFN-γ 20 ng/mL	-	Cell viability decreased at all doses of LPS
Wang et al., [48]	LPS 50 ng/ml + IFN-γ 200 U/ml	6	Mitochondrial biogenesis of astrocytes increased
Fernandes A et al.,[49]	LPS 1000 ng/mL	4, 6, 24	LDH elevation
Rama Rao KV et al.,[50]	IFN-y 10 ng/ml	6, 12, 24	Elevation of cell volume
Korcok J et al.,[51]	LPS 25 ng/mL + IFN-y 100 U/mL	12, 24	Elevated expression and activity of iNOS
Bellaver B et al., [52]	Astrocyte culture after CLP	24	Astrocytic activation with elevation of mRNA for TNF-α, IL-1β and COX-2 and levels of TNF-α, IL-1β, IL-6, IL-18, MCP-1
Peng W et al., [53]	150 ng/ml LPS + 200U/ml de IFN-y	24	Increases UCP2 expression
Sun et al., 2019 [54]	LPS 100 ng/ml	24	Increase content of NLRP3, ASC, Casp-1 and gasdermin
Falcão AS et al., [55]	LPS 1 ng/mL	120, 240, 480	Normal LDH levels
Bian Y et al., [56]	LPS 5 or 10 mg/kg	168, 720	Astrocytic activation

studies demonstrate a more mechanistic evaluation involving the astrocytes, although they also show astrocytic activation and release of pro-inflammatory cytokines provoked by LPS injection.

However, most information about the role of astrocytes comes from studies in cell culture. However, in sepsis, these profiles are still little explored; Table 3 presents the studies carried out with astrocyte culture stimulated essentially with LPS. In addition to the astrocytic activation being evident, there is evidence of alteration in inflammatory mediators, which supports the hypothesis of a greater influence of these cells on the pathophysiology of sepsis. Recent, study has shown that neuroinflammation or ischemia induced two different types of reactive astrocytes, referred to as "A1" and "A2" [43]. It was shown that the A1 phenotype positively regulates different classical complement cascade genes and complement 3 (C3), which is harmful to neurons and oligodendrocytes. On the other hand, the A2 phenotype induced by ischemia positively regulates many neurotrophic factors that promote the survival and growth of neurons [44]. In fact, melatonin was able to reduce the number of A1 astrocytes and increase

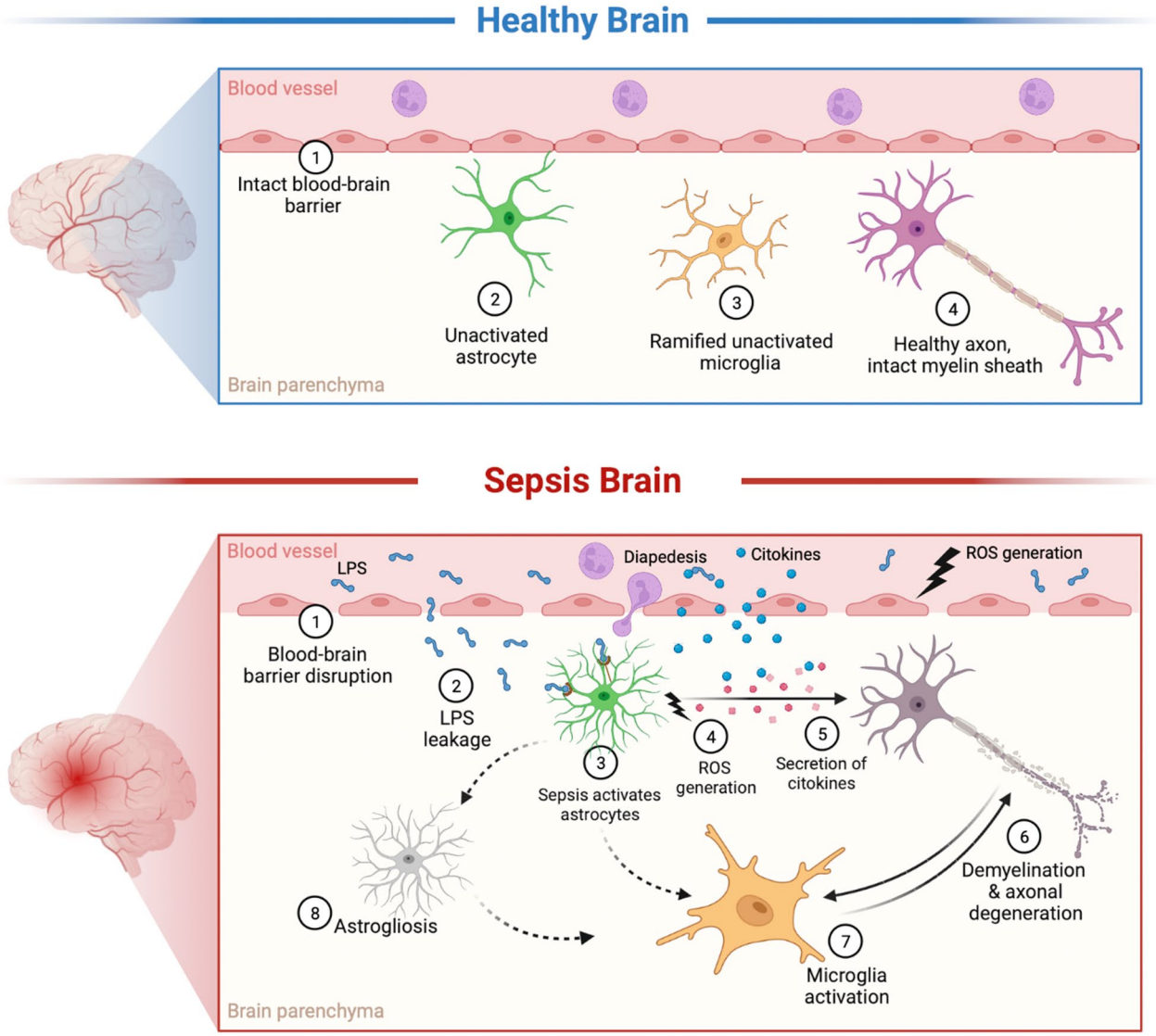

Fig. 1 Role of astrocytes in sepsis development. During sepsis, pathogens, inflammatory and oxidative mediators are released in the blood. These mediators interact with the cells of blood brain barrier, increasing your selective permeability (1). Lipopolysaccharide (LPS) and other molecules entry in the brain parenchyma (2), lead to activation of glial cells, such as astrocytes and microglia. Activated astrocytes can activate microglia cells (3), besides release reactive oxygen species (4) and cytokines (5). These events culminate in neuronal damage (6). On the other hand, stressed neurons can also activate microglia (7) and increase de neuroinflammatory response in septic brain. There is also evidence of astrogliosis during sepsis (8). Thus, astrocytes may play a much more important role in sepsis than has been attributed to them

the number of A2 astrocytes in the periventricular white matter of neonatal septic rats [45].

Although there is a lot of evidence about the activation of astrocytic cells after sepsis or LPS stimulus, however, there is no direct evidence of the interaction between these cells' with the BBB. The role of BBB dysfunction after sepsis has been extensively studied, and its impairment is known to play an important role in acute neuroinflammation and long-term damage after sepsis [3]. However, in some other publications, the authors strongly suggest that astrocytes release several substances that regulate the function of the BBB since it is formed [56, 57]. In this sense, probably, the changes in astrocytic profiles could influence mostly the BBB function after sepsis, leading to increase the neuroinflammation and the neuronal damage e after this the cognitive decline.

Astrocytes in the Human Septic Brain

Data about the astrocytes activation in humans are scarce; however, evidence suggests that, as occurs with microglia, astrocytes also change from a resting to an activated state when stimulated [58]. Human brain astrocytes are more diverse, more complex, and in greater numbers when compared to the rodent brain [59, 60].

In the post-mortem analysis of tissue from the right frontal lobe of 3 sepsis cases, an elevation of the GFAP marker was identified, thus indicating high astrocytic activity in the region when compared to controls [61]. Other studies with pediatric, adult, and elderly septic patients show in common an elevation of the s-100β marker at the expense not only of microglial activation, but also of astrocytic activation. This activation was associated with longer delirium duration, higher delirium severity, and in-hospital mortality [12, 62, 63].

Conclusion

In summary, there is robust preclinical evidence of astrocytic activation after sepsis and few clinical studies. The inflammatory stimulus generated by polymicrobial sepsis (CLP model) or by the LPS stimulus can generate systemic responses that influence the functioning of astrocytes in the brain (Fig. 1). However, little is known about the effects of this activation on the pathophysiology of sepsis. In view of the data presented here, the emerging need to establish the role of astrocytes in the pathophysiology of neurological dysfunction during sepsis becomes evident. Some questions still need scientific evidence, for example, how homeostatic functions of astrocytes are affected in sepsis, how occurs the astrocyte activation after BBB activation, and how astrocytes interact with the BBB after this. These and other questions may explain how astroglial activation can contribute to the long-term consequences of sepsis.

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Declarations

Ethics Approval Not applicable.

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