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Gliotoxicity and Glioprotection: the Dual Role of Glial Cells

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Abstract
Glial cells (astrocytes, oligodendrocytes and microglia) are critical for the central nervous system (CNS) in both physiological and pathological conditions. With this in mind, several studies have indicated that glial cells play key roles in the development and progression of CNS diseases. In this sense, gliotoxicity can be referred as the cellular, molecular, and neurochemical changes that can mediate toxic effects or ultimately lead to impairment of the ability of glial cells to protect neurons and/or other glial cells. On the other hand, glioprotection is associated with specific responses of glial cells, by which they can protect themselves as well as neurons, resulting in an overall improvement of the CNS functioning. In addition, gliotoxic events, including metabolic stresses, inflammation, excitotoxicity, and oxidative stress, as well as their related mechanisms, are strongly associated with the pathogenesis of neurological, psychiatric and infectious diseases. However, glioprotective molecules can prevent or improve these glial dysfunctions, representing glial cells-targeting therapies. Therefore, this review will provide a brief summary of types and functions of glial cells and point out cellular and molecular mechanisms associated with gliotoxicity and glioprotection, potential glioprotective molecules and their mechanisms, as well as gliotherapy. In summary, we expect to address the relevance of gliotoxicity and glioprotection in the CNS homeostasis and diseases.

Keywords Glial cells · Gliotoxicity · Glioprotection · Glioprotective molecules

Introduction

Rudolf Virchow first described neuroglia as a connective tissue surrounding neurons in the nineteenth century [1]. Afterwards, different types of cells that constitute the neuroglia, also known as glial cells, were identified and referred as macroglia, composed by astrocytes and oligodendrocytes, and microglia. Each of these cells display several versatile functions necessary to maintain and support neuronal networks [2].

Glial cells are critical for the central nervous system (CNS) homeostasis, in both physiological and pathological conditions. In fact, it has been increasingly reported that these cells can be involved in the development and progression of neurological diseases [3]. Since each type of glial cell is able to directly affect the functionality of the others, dysfunctions in any of them can generate self-amplifying detrimental processes and synergistically impair the neuron-glia communication and/or neuronal function [4, 5]. In this sense, glial cells may represent important cellular therapeutic targets for CNS disorders. With this regard, cellular, molecular, and neurochemical changes in these cells, which enable them to mediate toxic effects or ultimately lead to an impairment of their ability to protect neurons and/or other glial cells, can be referred as gliotoxicity. On the other hand, glioprotection is associated with specific responses of glial cells, both in physiological and pathological conditions, by which they can protect themselves as well as neuronal cells,

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resulting in an overall improvement of the CNS functioning [6].

Considering that our research group has studied the role of glial cells on toxic and protective outcomes, this review will provide a brief summary of types and functions of glial cells and thus address molecular and cellular mechanisms associated with gliotoxicity and glioprotection, potential glioprotective molecules, and perspectives on gliotherapies (e.g., therapies for CNS pathologies focused on glial cells).

Types and Functions of Glial Cells

Astrocytes

Astrocytes are the most abundant glial cells and are recognized by a variety of homeostatic functions in the CNS. They have a refined cytoarchitecture with numerous stellate processes that allows their interaction with blood vessels, neurons, and other cell populations [7]. These morphological features of astrocytes make them important elements in the connection between peripheral and central systems, besides being associated with several of their functional roles, such as formation and maintenance of the blood–brain barrier (BBB); supply of oxygen and nutrients to the brain; regulation of synaptic transmission; and plasticity at the tripartite synapse [8–10]. The close contacts of astrocytes with synapses and blood vessels ensure their metabolic support to neurons through the coupling between synaptic activity and glucose utilization (neurometabolic coupling) [11].

Astrocytes participate in ionic homeostasis and metabolism of neurotransmitters, particularly of the glutamate [12]. They also regulate the diffusion and response to circulating factors, such as peripheral hormones, metabolites, and inflammatory mediators [13–16], in addition to participating in the defense against oxidative stress and in the detoxification of harmful molecules [17]. Moreover, astrocytes act as important secretory cells, releasing a wide range of signaling molecules (trophic and growth factors, gliotransmitters, peptides, and proteins) that will impact the functions of the surrounding glial, neuronal, and endothelial cells [18]. Inflammatory and immune responses are also important functional properties of astrocytes [19]. Moreover, astrocytes can respond to abnormal events in the CNS through a morphological, physiological, metabolic, biochemical, and transcriptional remodeling, which can impair their homeostatic functions and has been collectively called as reactive astrogliosis [20].

Oligodendrocytes

The major function of oligodendrocytes is synthesis of myelin sheath, a lipid-enriched specialized and compacted structure, which is extended in spirals around the axons of many neurons [21]. In an adult CNS, oligodendrocyte progenitor cells (OPCs) persist and can continuously proliferate and differentiate into mature and myelinating oligodendrocytes [22]. Both differentiation and myelination processes require a series of sequential steps and are orchestrated by several molecular and cellular signals, including those from neurons and other glial cells [23]. The rate of myelinating oligodendrocyte generation decreases throughout life, as the loss of myelin may result in cognitive disabilities and altered sensory and motor functions [21].

Recently, oligodendrocytes have been reported to provide metabolic support by transferring energy metabolites (particularly lactate and pyruvate) to neurons through monocarboxylate transporters (MCT) and cytoplasmic channels [24]. In addition, oligodendrocytes have been shown to perform immune functions by expressing both immune-related receptors and immunomodulatory molecules, which probably display pleiotropic roles in oligodendrocytes and other glial cells [25].

Microglia

Microglia are the resident immune cells of the CNS, distributed over the entire parenchyma and playing important roles to maintain brain homeostasis [26]. In response to brain damage or infections, they are usually the first cells to be activated to perform several well-established functions, among these, pathogen recognition, inflammatory responses, and phagocytosis [27, 28].

Under physiological conditions, microglia possess a specialized morphology with a small soma containing elongated, branched, and highly dynamic processes, which allows scanning the surrounding area and surveillance of the CNS [29, 30]. Upon CNS disorders, microglia quickly responds and can assume different activation patterns, which are usually associated with morphological changes. Microglial polarization may result in the neurotoxic M1-type or neuroprotective M2-type, based on the expression and release of cytokines, chemokines, and/or trophic factors [31, 32]. However, accumulating evidence has suggested that activation of microglia is heterogeneous and involves different but functionally overlapping phenotypes [33].

Besides their classical immune functions, microglia are implicated in several homeostatic processes, such as the release of trophic factors; promotion of neuronal survival, as well as the generation and maintenance of other neural cells; generation, maturation, regulation, and plasticity of synapses; synaptic pruning that redefines synapses and circuits; clearance of cells and debris; regulation of myelination; and memory formation and learning [26, 32].

Neurochemical Changes and Molecular Mechanisms Associated with Gliotoxicity

Considering the versatile and dynamic roles played by the different types of glial cells described in the previous section, it is not surprising that dysfunctions of these cells may be related to several pathological conditions. Interestingly, brain diseases may share many neurochemical, cellular, and molecular mechanisms related to gliotoxicity (Fig. 1), which is addressed in this section.

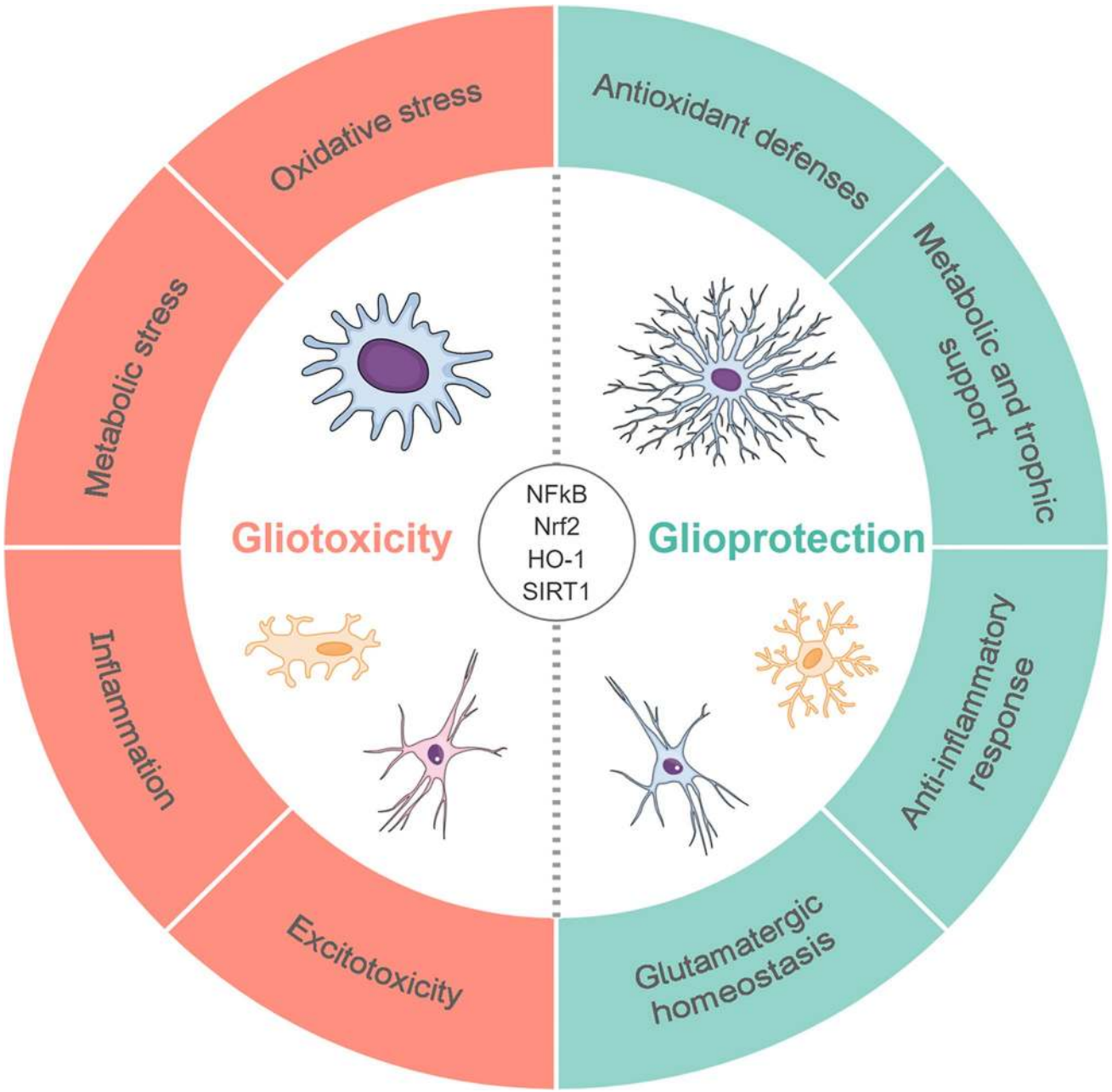

Fig. 1 Gliotoxicity and glioprotection-associated mechanisms. Gliotoxicity may be linked to several detrimental processes, including metabolic and oxidative stresses, inflammation, and excitotoxicity. On the other hand, antioxidant defenses, metabolic and trophic support, anti-inflammatory response, and glutamate homeostasis are mechanisms associated with glioprotection. Changes in several signaling pathways in glial cells may result in both gliotoxic and glioprotective effects. The cells on the left represent reactive (dysfunctional) glial cells (astrocyte is represented in blue, microglia is represented in yellow, and oligodendrocyte is represented in purple); while the cells on the right represent functional glial cells (ramified astrocyte is represented in blue, ramified microglia is represented in yellow, and oligodendrocyte is represented in blue)

Metabolic Stresses

Glucose is the essential energy substrate for the CNS; therefore, pathological conditions associated with altered availability of glucose and/or oxygen (hypoxia/ischemia, hypoglycemia and hyperglycemia), as well as impairments in the metabolic machinery of cells, can largely impact glial functioning, inducing gliotoxicity. Hypoglycemia/glucose deprivation, hyperglycemia, and/or fluctuations in glucose concentration (hyperglycemia followed glucose deprivation) have been associated with several glial dysfunctions. In astroglial cells, metabolic stress alters glutamate metabolism, mitochondrial activity/redox balance, inflammatory response, release of trophic factors, and different signaling pathways [34–36]. Glucose-related metabolic stress also affects microglia and oligodendrocytes/OPCs, promoting microglial activation and contributing to inflammatory and oxidative injuries to neurons [37, 38]. Hypoglycemia inhibits oligodendrocyte development and differentiation, in addition to trigger apoptosis in OPCs [39], while glucose-oxygen deprivation causes intracellular lactate accumulation and acidosis [40]. However, hyperglycemia increased the expression of the pre-oligodendrocyte marker O4 without affecting the expression of NG2, a marker of OPC that is downregulated during the process of cell differentiation. Although hyperglycemia can improve the differentiation rate of OPCs, the mechanisms underlying this effect and its impacts are largely unknown [41].

Another important gliotoxicity condition associated with metabolic stress is caused by ammonia. Brain detoxification of ammonia occurs mainly via glutamine synthetase (GS) [42], a specific astrocytic enzyme, but hyperammonemia can exceed the metabolic capacity of cells. Ammonia-induced gliotoxicity is associated with cellular edema, energy depletion, oxidative stress, impairment in glutamate clearance and inflammatory response [43–45]. Moreover, ammonia can upregulate the senescence marker p21, thus potentially causing a glial-inflammaging process [14]. Although astrocytes are the primary targets of ammonia toxicity, microglia may also be affected. In a co-culture model of astrocyte and microglia, ammonia decreased cellular viability and promoted microglial activation, with an increase in the percentage of phagocytic type of microglia [46]. Additionally, ammonia induced oxidative stress and up-regulated the microglial activation marker ionized calcium-binding adaptor molecule-1 (Iba-1) in cultured microglia and in post mortem brain tissue from patients with hepatic encephalopathy, a neuropsychiatric syndrome associated with hyperammonemia [47]. Our group also have demonstrated that azide, an inhibitor of cytochrome c oxidase, induces gliotoxicity, promoting alterations in redox homeostasis, inflammatory response, and glutamate metabolism [6, 48].

Oxidative Stress, Inflammatory Response, and Excitotoxicity

Reactive oxygen/nitrogen species (ROS/RNS) can play neuromodulatory roles at physiological concentrations, including the regulation of neuronal polarity and neurite outgrowth, differentiation, cytoskeletal changes, synaptic plasticity, and activation of a wide range of signaling pathways and gene expression [49–51]. ROS provide a rapid and reversible mechanism for alter protein function by modulating the redox state of amino acid residues, particularly of cysteine, thus modifying the function of signaling proteins, ion channels, transporters, and transcription factors [52, 53]. On the contrary, excessive production of ROS/RNS by activated astrocytes and microglia can induce gliotoxicity, contributing to the pathomechanisms of neuropathological conditions [54, 55]. Oxidative/nitrosative stress in the brain can also be associated with unsaturated lipid enrichment, the presence of redox active transition metals, the neurotransmitter auto-oxidation and metabolism, the excessive glutamatergic signaling, as well as the increased expression and/or activity of NADPH oxidase and inducible nitric oxide synthase (iNOS) [56].

Although brain cells are equipped with enzymatic antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR), the non-enzymatic antioxidant defense glutathione (GSH) plays a crucial role in maintaining brain redox homeostasis [54]. Furthermore, GSH depletion in glial cells is associated with oxidative stress, and the pathophysiology of brain disorders [57] and both this depletion and oxidative stress are closely related to inflammatory response in glial cells [58, 59]. Under pathological conditions, increased ROS production triggers inflammatory responses that, in turn, exacerbate the pro-oxidant status [53], thus establishing a self-amplifying cycle that contribute to gliotoxicity. This interplay between oxidative stress and inflammation is importantly mediated by the nuclear factor kappa B (NFκB) signaling [53].

Among glial cells, inflammatory and immune responses are primarily associated with microglia and astrocytes [60], although oligodendrocytes can be also involved to a lesser extent [25]. A wide range of extracellular stimuli can elicit inflammatory responses in glial cells, including pathogen-associated molecular pattern (PAMPs) and damage-associated molecular pattern (DAMPs), cytokines, and other molecular insults [19, 27]. PAMPs are small-molecule motifs present in pathogenic bacteria, protozoa, and viruses; DAMPs are molecular motifs associated with cellular injury and tissue damage (e.g., misfolded and aggregated proteins, miss-localized nucleic acids and other alarmins originated from damaged cells). Both molecular motif types can be recognized by specific pattern recognition receptors, in

particular Toll-like receptors (TLRs), which are expressed by glial cells and can trigger innate immune responses [19, 26]. Mainly under the control of NFκB, the master regulator of inflammation, microglia, and astrocytes becomes an important source of several inflammatory mediators, including tumor necrosis factor alpha (TNF-α), interleukins (IL-1β, IL-6, IL-18), chemokines, and prostaglandins, in addition to nitric oxide (NO) and ROS [32, 61]. This plethora of inflammatory mediators will impact the surrounding environment, importantly participating in the inflammatory activation of the other glial cells and in the recruitment of peripheral immune cells [32, 62]. Excessive and chronic inflammatory responses lead to neuronal death and are involved in several CNS disorders [63].

Glutamate is the predominant excitatory neurotransmitter in the CNS and can be neurotoxic when inappropriately remaining at high levels in the synaptic cleft, a phenomenon referred as excitotoxicity [64]. Glial cells, particularly astrocytes, are responsible for the rapid removal of glutamate from synaptic cleft through excitatory amino acid transporters, EAAT1 (or glutamate-aspartate transporter, GLAST), and EAAT2 (or glutamate transporter 1, GLT-1) [65]. With this regard, downregulation and/or hypofunction of glutamate transporters may be associated with pathological conditions [64, 66], and their activity can be impaired as consequence of oxidative stress and/or inflammatory responses. It is well documented that glutamate transporters are highly susceptible to oxidation, which impairs their ability to take up extracellular glutamate [67]. Moreover, TNF-α has inhibitory effect on glutamate transport [68], probably associated with TNF-α-induced oxidative stress. Therefore, excitotoxicity, oxidative stress, and inflammation are processes closely related and represent important gliotoxicity mechanisms.

Gliotoxicity and CNS Diseases

Neurochemical changes and processes related to glial cells previously discussed represent, individually or collectively, crucial points in the pathogenesis of several brain diseases, including Alzheimer's and Parkinson's diseases, amyotrophic lateral sclerosis (ALS), multiple sclerosis, psychiatric disorders, stroke, diabetes mellitus, hepatic encephalopathy, the aging process, and infectious diseases.

Neuropsychiatric Disorders and Aging Process

Alzheimer's disease, Parkinson's disease, and ALS are neurodegenerative diseases that present the accumulation and aggregation of proteins, such as β-amyloid and tau, α-synuclein, and TAR DNA-binding protein 43 (TDP-43), respectively, as a common hallmark [69]. The pathophysiology of psychiatric disorders including major depressive disorder, bipolar disorder, and schizophrenia pointed toward monoamine disturbances and glutamatergic hypothesis [70]. However, the mechanisms of cognitive dysfunctions, neuronal degeneration, onset, and progression of these neuropsychiatric disorders have not yet been clearly elucidated. Interestingly, although they affect different CNS areas, producing different outcomes and symptoms, neuropsychiatric disorders share deleterious processes that may involve glial cells, including neuroinflammation, glutamate excitotoxicity, oxidative stress, and metabolic/trophic support [71–74]. Moreover, astrocyte reactivity can contribute to the pathomechanisms of the above-referred diseases. By definition, astrocyte reactivity involves morphological, molecular, and functional changes in response to pathological situations in surrounding tissue, such as CNS disease or injury, which may be reversible or chronic. When astrocytes undergo a reactive state, loss of homeostatic functions and gain of detrimental functions may occur, including some involved in glutamate and ionic homeostasis, glucose metabolism, production of inflammatory mediators and ROS/RNS, proliferation, BBB integrity, and Ca^{2+} signaling [20]. These astrocyte dysfunctions potentially lead to a transition from physiologic to pathologic roles that, without being the sole or primary initiators of pathology, may affect disease outcomes/progression [20]. With this regard, glial cells are the basis of many biomarkers of CNS diseases and, consequently, have emerged as important therapeutic targets for these pathological conditions. In addition, changes in several signaling pathways in glial cells corroborate their role in the pathomechanisms of neuropsychiatric disorders and neurodegenerative diseases [75–77].

Aging is a complex process characterized by an intrinsic physiological and functional decline of an organism. Although brain aging increases the risk of neurodegenerative diseases, it is not pathological and may be related to adaptive mechanisms of cell physiology over time [78]. Aged human brains display only mild and heterogeneous changes in astrocyte morphology or GFAP levels [79]. However, other cellular and molecular hallmarks of aging have been studied in glial cells. Aging has been associated with decreased glucose and glycogen metabolism, as well as with decreased ATP production, decreasing astrocytic fuel provision of neurons [80–82]. Glutamate transporter downregulation and/or hypofunction has been also observed with aging [81, 83], which impair glutamate uptake and favor excitotoxicity. In addition, aged astrocytes and microglia have been shown to accumulate ROS and produce increased amounts of pro-inflammatory mediators, which may be exacerbated in response to harmful stimuli [84, 85]. Considering both senescence and inflammation in particular, the phenomenon of inflammaging has emerged as a mechanism shared by age-related diseases [86], notably involving astrocytes and microglia.

Neurological Dysfunctions Associated with Infectious Diseases

Despite the protective barriers, such as BBB, CNS can be directly and/or indirectly affected by bacterial and viral infections. In the context of bacterial infections, lipopolysaccharide (LPS), a toxin present in the outer membrane of gram-negative bacteria, has been widely used as a model of peripheral and central inflammatory responses and their related cognitive decline [87]. A large body of evidence has demonstrated that LPS peripherally administrated is able to induce inflammatory responses within CNS [88, 89]. Due to the position of astrocytes, they can serve as a bridge between systemic inflammation and neuroinflammation [15]. Although LPS classically activates microglia and astrocytes, oligodendroglial cells can also respond to this bacterial inflammogen [90]. Of note, glial cells can be major responsible for LPS-induced neuronal damage [91, 92]. Therefore, LPS has exhaustively used as an in vivo and in vitro experimental model of brain diseases, such as Alzheimer's disease and schizophrenia, among others.

With regard to viral infections, glial cells can be primary targets of neurotropic viruses, such as the human immunodeficiency virus type 1 (HIV-1) and zika virus (ZIKV). Microglia and astrocytes constitute CNS reservoirs of HIV-1 [93, 94], promoting neuroinflammation, which can explain neuronal damage and neurocognitive disorders in a number of patients, considering the relative incapacity of HIV-1 to directly infect neurons [95]. Due to the presence of AXL receptor, astrocytes and microglia are potentially the primary cells targeted by ZIKV in the CNS [96]. In both astrocytes and microglia, ZIKV elicited classical inflammatory responses [96], while, for astrocytes, it induced oxidative stress, mitochondrial failure, and DNA damage in astrocytes [97]. Our group have demonstrated that an acute hippocampus exposure to ZIKV is also able to induce neuroinflammation and oxidative stress, affecting neuron-glia communication [98].

COVID-19 has been also recently associated with neurological dysfunctions, yet it is unclear whether they are consequence of direct CNS infection by SARS-CoV-2 or whether they result from peripheral cytokine storm and metabolic dysfunctions, although investigators have found that neurons and astrocytes are susceptible to SARS-CoV-2 infection [99, 100]. Anosmia and ageusia are common neurologic symptoms in COVID-19 patients, which can be associated with dysfunction in the olfactory bulb [101]. In addition, this brain structure can mediate direct viral invasion [102]. Interestingly, olfactory impairment is a common and early (preclinical) sign of neurodegenerative diseases, including Alzheimer's and Parkinson's diseases, in addition to be associated with depression and other neuropsychiatric disorders [103, 104]. The precise mechanisms that connect these diseases with olfactory loss are also still unclear but potentially involve neuroinflammation [103, 104]. Therefore, infectious diseases mainly target glial cells and might generate long-term consequences including cognitive deficits, neurodegenerative diseases, psychiatric disorders, and others that are currently unknown.

Mechanisms Underlying Glioprotection

Glioprotection can be achieved by endogenous homeostatic and protective functions of glial cells, which in turn may be positively modulated by a wide range of exogenous molecules, named as glioprotective molecules. They can promote protection to the CNS by improving glial functions and avoiding gliotoxicity. This section will discuss the main points associated with glioprotection (Fig. 1).

Metabolic Support

Astrocytes are recognized as energy substrate suppliers, since they are responsible for glucose uptake and its distribution to other neural cells, besides being able to store it as glycogen [9]. Moreover, astrocytes largely metabolize glucose glycolytically to produce ATP, generating lactate, which can be later transferred to neurons to be fully oxidized under conditions of high energy demands or when glucose supply is low [9, 105]. More recently, it has been demonstrated a metabolic coupling between oligodendrocytes and neurons, in which lactate derived from the glucose metabolism of these glial cells can also be transferred to the axon, contributing to ATP synthesis in neurons [106]. Of note, besides its metabolic function, signaling roles of extracellular lactate have been also recently investigated particularly in neurons, associated with neuronal excitability, synaptic plasticity, memory consolidation, and expression of trophic factors. Such signaling effects can be mediated either by the G protein-coupled receptor GPR81, extracellular acidification, changes in redox state, or depolarization of target cells [107, 108]. In addition to lactate, astrocytes can also transfer healthy mitochondria to neurons, replacing damaged organelles of these cells and thus providing a protection against neuronal mitochondrial dysfunction [109].

Another important metabolic cooperation between astrocytes and neurons comprises the glutamate-glutamine cycle [11]. Once taken up by astrocytes, glutamate can be converted into glutamine by the enzyme GS, which participates both in glutamate metabolism and in ammonia detoxification [42]. Glutamine is then exported to neurons, allowing recycling of glutamate. Since glutamate is also the precursor of gamma aminobutyric acid (GABA), the glutamate-glutamine cycle is crucial for maintaining glutamate and GABA-based neurotransmission [110]. Moreover, de novo

synthesis of glutamate in the brain occurs in astrocytes via the pyruvate carboxylase pathway and thus also depends on glucose [111].

Concerning the lipid metabolism, astrocytes are an important cholesterol source to mature neurons, since these glial cells express the enzymes for cholesterol synthesis and the apolipoproteins necessary to export it [112]. Moreover, although oligodendrocytes are able to synthesize cholesterol, a critical component of the myelin structure, they also depend on the supply from astrocytes [112]. In addition, there is a metabolic coupling between astrocytes and neurons regarding detoxification of neuronal-derived toxic fatty acids, which are transferred to astrocytes and metabolized via mitochondrial β-oxidation [113].

Trophic Support

Synthesis and release of a wide range of trophic factors by glial cells, especially by astrocytes, constitute another important mechanism of glioprotection. These trophic factors include brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), S100B, transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), nerve growth factor (NGF), and neurotrophins 3 and 4. These multifunctional molecules can mostly act on nearby neurons, regulating neuronal survival, differentiation, function, plasticity and regeneration, as well as neurogenesis [32, 114, 115]. In addition, trophic factors can also target other glial and even endothelial cells, regulating several processes, such as oligodendrocyte differentiation, survival and remyelination; microglial activation; astrocyte proliferation, function and metabolism; angiogenesis; and BBB integrity [116–118].

Modulation of Triad Oxidative Stress, Excitotoxicity, and Inflammatory Response

Glial cells display efficient antioxidant defense mechanisms that allow their functions in the defense and repair of the brain. In particular, astrocytes are able to maintain their protective roles even after surviving intense oxidative stress, thus playing a crucial role for providing antioxidant support to neurons [119]. In light of this, neuron-astrocyte interactions mediate an essential mechanism for recycling of ascorbic acid, an important neuronal antioxidant defense [120]. In addition, GSH, a tripeptide consisting of glutamate, cysteine, and glycine that is synthesized by the enzymes γ-glutamyl cysteine ligase (GCL) and GSH synthase [121], is an important antioxidant molecule able to react with free radicals or participate in enzymatic reactions, such as those catalyzed by GPx and glutathione-S-transferase (GST). While microglia and oligodendrocytes synthetize GSH for their self-protection, astrocytes are also able to readily release it [121, 122]. This is particularly important because neurons are dependent on astrocytic GSH for providing extracellular cysteine for their synthesis of GSH, since they are less capable of importing cystine [122, 123]. Extracellular GSH, in turn, can be protected from oxidation by other "guardian" molecules, including the SOD, secreted by astrocytes [124].

GSH metabolism and glutamatergic neurotransmission/homeostasis are processes closely interconnected in several ways. Besides astrocytes, microglia and oligodendrocytes also express glutamate transporters and uptake glutamate, but they are probably associated with the GSH demands of these cells [125, 126]. Thus, glial glutamate transporters can provide intracellular glutamate for GSH synthesis, as well as for Cys-Glu exchanger (system xc^-) operation. This transporter, present in glial cells, plays a crucial role for GSH synthesis, since it mediates the uptake of cystine, the bioavailable form of cysteine, in exchange for glutamate [127]. Maintenance of adequate GSH levels, therefore, is important to protect glutamate transporters from oxidation and avoid excitotoxicity. Moreover, and interestingly, it has been recently hypothesized that GSH is a relevant glutamate reservoir and could supply it for synaptic transmission when the glutamate-glutamine cycle is impaired [128].

Additionally, both microglia and astrocytes can be involved in suppression of inflammation and immune responses [129, 130]. Alternative activation patterns adopted by these glial cells are related to production and release of several anti-inflammatory molecules, such as IL-4, IL-10, IL-11, and IL-27, as well as TGF-β, that function mainly by suppressing the pro-inflammatory milieu [131, 132]. Thus, they establish a bidirectional crosstalk for a reciprocal anti-inflammatory modulation of microglia and astrocytes. To illustrate this relationship, activated M2-like microglia produce anti-inflammatory cytokine IL-10 that stimulate astrocytes to secrete TGF-β, which in turn reduces microglial pro-inflammatory activation, ultimately preserving neuronal and oligodendroglial functioning [132].

Signaling Pathways associated with Glioprotection

The nuclear factor erythroid-derived 2-like 2 (Nrf2) is a stress-responsive transcription factor that acts as a key regulator of redox, metabolic, and inflammatory homeostasis [133–135]. Upon activation, Nrf2 is translocated into the nucleus and controls the expression of genes that encode antioxidant enzymes, including SOD, GPx, and GST [133, 135]. It also stimulates the expression of proteins that contribute to GSH biosynthesis and homeostasis, such as system xc^-, GCL, GSH synthase, and the NADPH-generating enzyme glucose-6-phosphate dehydrogenase [133]. Moreover, Nrf2 may directly or indirectly influence intermediary metabolism and mitochondrial function. It directly

regulates the expression of important enzymatic steps of metabolic pathways related to synthesis of carbohydrates, nucleic acids, lipids, and amino acids. Indirectly, Nrf2 can affect its own expression [136] and the other transcription factors [e.g., peroxisome proliferator-activated receptor γ (PPARγ) and retinoid X receptor α (RXRα)] [137] that in turn regulate metabolic genes, in addition to influence the activity of metabolic enzymes that are susceptible to thiol modifications [e.g., pyruvate dehydrogenase kinase 2, pyruvate kinase, AMP-activated protein kinase (AMPK)], since Nrf2-mediated expression of antioxidant genes can prevent or reverse oxidation of cysteine residues [133].

Heme oxygenase 1 (HO-1) is one of the classical genes regulated by Nrf2, which is associated with responses against oxidative challenges. This enzyme catalyzes the degradation of heme into biliverdin, bilirubin, carbon monoxide, and free iron. Products of HO-1, in particular bilirubin and CO, mediate protective effects since they have antioxidant and anti-inflammatory properties [138]. Of note, they can inhibit iNOS activity and NFκB activation [135]; thus HO-1 is an important element in the connection between Nrf2 and NFκB signaling pathways. In fact, Nrf2 signaling negatively regulates NFκB-driven inflammatory and oxidative stress responses [135]. In the context of glioprotection, although microglia and oligodendrocytes exhibit functional Nrf2/HO-1 signaling, astrocytes may be the predominant neural cell type for activation of Nrf2 [139].

Other signaling pathways that act as key regulators of cell survival, responses to stressful conditions, and metabolic effectors can mediate glioprotective effects, including sirtuin 1 (SIRT1), AMPK, phosphoinositide3-kinase (PI3K)/Akt, and protein kinase C (PKC) [35, 140, 141].

Glioprotective Molecules

A wide range of molecules has been investigated as candidates to mediate protective effects on the CNS by targeting glial cells (Table 1). Resveratrol, a polyphenol stilbene found in grapes and wine, is one of these promising molecules. Several studies have shown that resveratrol regulates diverse astroglial functions, including antioxidant defenses, inflammatory response, trophic factor release, and glutamate homeostasis, both at basal conditions and against harmful stimuli [43, 48, 140, 142–147]. Additionally, resveratrol is able to prevent age-related functional alterations of astrocytes [148]. These effects are associated with different signaling pathways, including Nrf2/HO-1, SIRT1, PI3K/Akt, AMPK, adenosine receptors, and NFκB [48, 140, 144, 149]. Moreover, resveratrol also exhibits glioprotective effects on microglial and oligodendroglial cells [90, 145, 150] and in different in vivo experimental models [151–153].

Besides resveratrol, other naturally occurring molecules of plant origin can promote glioprotection, such as curcumin (polyphenolic compound found in the rhizome of *Curcuma longa Linn*) [154–163], isoflavones (flavonoid polyphenols present in leguminous plants) [164–174], and sulforaphane (isothiocyanate found in cruciferous vegetables) [175–179]. Endogenous mammalian compounds including lipoic acid (an essential cofactor for different mitochondrial enzymes) [141, 180–185] and guanosine (a guanine-based purine) have been also investigated as potential glioprotective agents [6, 35, 83, 186–190]. The mechanisms underlying the protective effects of these molecules in glial cells involve antioxidant and anti-inflammatory activities, improvement of mitochondrial function, Nrf2/HO-1 activation and NFκB inhibition, glutamate clearance and metabolism, regulation of microglial activation, survival of oligodendrocytes, and delay of demyelination (Table 1).

Perspectives on Gliotherapies

A wide variety of medications currently used to treat psychiatric disorders and neurodegenerative diseases are shown to have beneficial effects on glial cells, which may participate in their therapeutic effects. Antipsychotics, such as risperidone, haloperidol, clozapine and quetiapine are able to regulate inflammatory responses in astrocytes and/or microglia [191–193]. Risperidone, in particular, modulate glutamate uptake, GS activity, GSH content, and S100B release in astroglial cells [191, 194, 195]. Major antidepressants (serotonin-specific reuptake inhibitors, tricyclic antidepressants) also demonstrate anti-inflammatory properties [196], as well as improving the release of trophic factors by glial cells [196, 197]. In addition, riluzole, the only drug approved for ALS, mainly target glutamate excitotoxicity, at least in part, by improving astroglial glutamate uptake [198], and it may also increase synthesis of trophic factors and induce Nrf2/HO-1 signaling [199].

In line with this, many studies strive to develop specific gliotherapies for treatment of neurological diseases [200, 201], demonstrating that glial cells can represent a novel basis for understanding, preventing, and treating these conditions, such as Alzheimer's disease and schizophrenia. Moreover, characterizing the role of glial cells in the pathophysiology of CNS diseases as well as identifying gliotherapeutic targets can improve future gliotherapies [202].

Concluding Remarks

The last 25 years have brought significant progress in the understanding of glial functionality, since these cells play a critical role in CNS homeostasis, as well as in

Table 1 Potential glioprotective molecules and their effects

Molecule	Glioprotective functions	References
Curcumin	Improvement of mitochondrial functioning in astrocytes	[157, 158]
	Antioxidant and anti-inflammatory effects through Nrf2 and HO-1 expressions in microglial cells	[156, 159]
	Anti-inflammatory effects in microglia through downregulation of TLR4, NFκB, p38 MAPK, and PI3K/Akt signaling pathways	[160, 161]
	Reduction of NO and PGE2 production by inhibiting iNOS and COX-2 expression in microglial cells	[162]
	Inhibition of cytoskeletal disruption in astroglial cells	[158]
	Reduction of apoptosis, glial activation, and glial scar formation	[154, 163]
	Promotion of OPC differentiation	[155]
Guanosine	Regulation of astroglial oxidative and inflammatory responses through HO-1	[6, 188]
	Modulation of glutamatergic parameters and oxidative/nitrosative damages in astroglial cells with involvement of adenosine receptors, PI3K, MEK, and PKC pathways	[35, 189]
	Antiapoptotic effect in astrocytes through PI3K/Akt pathway	[190]
	Anti-aging effects in astrocytes in an HO-1 dependent manner	[83]
	Prevention of oxidative stress and excitotoxicity in focal ischemia	[186]
	Promotion of myelinogenesis and remyelination	[187]
Isoflavones	Anti-inflammatory effects in astrocytes through suppression of NFκB and increase of PPARγ expression	[164, 165]
	Induction of synthesis and secretion of neurotrophic factors in astrocytes	[168]
	Anti-inflammatory and immunomodulatory properties in microglia by inhibiting TLR4/NFκB signaling and expression of COX-2, iNOS, TNF-α, IL-1β and IL-6	[166, 169–171]
	Regulation of glutamate uptake in rat brain	[172]
	Increased glial cell migration	[173]
	Prevention of oxidative stress and decreased monoamine oxidase enzyme activity in brain tissue	[174]
	Alleviation of demyelination in mouse hippocampus	[167]
Lipoic acid	Antioxidant and anti-inflammatory effects in astroglial cells through HO-1	[141, 180, 182]
	Regulation of glutamate uptake, glutamate transporter expression, GS activity, and GSH content in astroglial cells	[141, 180, 183]
	Reduction of hyperammonemia-induced damage by regulating ERK and HO-1 pathways	[141, 182]
	Prevention of inflammation and dysfunction caused by TLR3 and PKR in viral pathologies in glial cells	[183]
	Inhibition of GSK-3β with anti-inflammatory effects in microglial cells	[184]
	Induction of M2 phenotype in microglia, reduction of ROS and NFκB signaling, improved cell survival, autophagy, and inhibition of apoptosis	[185]
	Prevention of demyelination via oligodendrocyte survival and promotion of regenerative mechanisms	[181]
Resveratrol	Improved glutamate uptake, GS activity, S100B secretion, and GSH system in astroglial cells	[59, 142]
	Antioxidant, anti-inflammatory, and genoprotective effects in astroglial cells	[48, 144, 147]
	Prevention of ammonia toxicity in astroglial cells by modulating glutamate metabolism, redox status, and inflammatory response	[43–45]
	Anti-inflammatory effects in astrocytes and microglia through NFκB, HO-1, adenosine receptors, ERK, and p38 MAPK	[140, 143, 145]
	Enhancement of astroglia-derived trophic factor release	[140, 146]
	Increased antioxidant defenses and decreased pro-inflammatory cytokines in astrocytes during aging	[148]
	Regulation of microglia M1/M2 polarization via PGC-1α	[150]
	Modulation of inflammation, oxidative stress, and release of trophic factors in OPC through Nrf2/HO-1 pathway	[90]
Sulforaphane	Modulation of inflammatory response, antioxidant defenses, glutamatergic system, and trophic factor release in astroglial cells challenged with LPS	[175]
	Prevention of oxidative stress associated with oxygen and glucose deprivation by Nrf2 induction	[176]
	Anti-inflammatory effect through inhibition of JNK/AP-1/NFκB and activation of Nrf2/HO-1 in activated microglia	[178, 179]
	Activation of microglial processes via Akt signaling	[177]

AP-1, activator protein-1; COX-2, cyclooxygenase-2; ERK, extracellular signal-regulated kinases; GS, glutamine synthetase; GSH, glutathione; GSK-3β, glycogen synthase kinase-3 beta; HO-1, heme-oxigenase 1; IL-1β, interleukin-1β; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; JNK, c-Jun N-terminal kinases; LPS, lipopolysaccharide; MEK, mitogen-activated protein kinase kinase; NFκB, nuclear factor kappa B; NO, nitric oxide; Nrf2, nuclear factor erythroid-derived 2-like 2; OPC, oligodendrocyte precursor cells; p38 MAPK, p38 mitogen-activated protein kinases; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PGE2, Prostaglandin E2; PI3K, phosphoinositide3-kinase; PKC, protein kinase C; PKR, protein kinase R; PPARγ, peroxisome proliferator-activated receptor gamma; ROS, reactive oxygen species; TLR3, toll-like receptor 3; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor alpha

pathogenesis and progression of CNS diseases. With these concept changes, it is believed that we will be able to make rapid progress in the findings, as well as in a broader and more efficient way to demonstrate that glial cells can be targets to drug development. Currently, it is well established that under oxidative and inflammatory challenges, glial cells can switch from having a protective role to a harmful phenotype. In addition, triad oxidative stress, neuroinflammation, and excitotoxicity are strongly associated with several neurological and psychiatric disorders. Considering the relevance of glial cells for physio/pathological processes, our Lab has studied these cells in different models of gliotoxicity to propose glioprotective strategies in the future, as well as to characterize the mechanisms of glioprotection. By understanding gliotoxicity, glial-based preventive/therapeutic strategies might emerge to delay and to prevent the development of CNS diseases and their consequences.

Finally, this review represents an overview of gliotoxicity and glioprotection and was wrote by researchers from the Neurotoxicity and Glioprotection Lab of Federal University of Rio Grande do Sul, as a remote activity during COVID-19 pandemic.

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