Glial Cells in Ischemia-Reperfusion Injury

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Ischemic stroke is the second cause of mortality and the first cause of long-term disability constituting a serious socioeconomic burden worldwide. Approved treatments include thrombectomy and rtPA intravenous administration, which, despite their efficacy in some cases, are not suitable for a great proportion of patients. Glial cell-related therapies are progressively overcoming inefficient neuron-centered approaches in the preclinical phase. Exploiting the ability of microglia to naturally switch between detrimental and protective phenotypes represents a promising therapeutic treatment, in a similar way to what happens with astrocytes. However, the duality present in many of the roles of these cells upon ischemia poses a notorious difficulty in disentangling the precise pathways to target. Still, promoting M2/A2 microglia/astrocyte protective phenotypes and inhibiting M1/A1 neurotoxic profiles is globally rendering promising results in different in vivo models of stroke.

ischemic stroke glia neuroprotection microglia astrocytes oligodendrocytes therapy

1. Introduction

Cerebrovascular accident or stroke is a major cause of long-term disability worldwide and the second leading cause of death [1][2][3]. The prevalence increases with advancing age in both males and females [1], but in some Asian countries, especially India and China, the prevalence of stroke in people under 40 years of age has recently increased, being a serious problem of public health [4]. The global tendency of an increment in the life expectancy predicts a parallel increase in the incidence of stroke in the next years. In Spain, according to data of Grupo de Estudio de Enfermedades Cerebrovasculares de la Sociedad Española de Neurología (GEECV-SEN), a stroke occurs every six minutes.

During 2020, a new risk factor for stroke occurrence has emerged related to COVID-19. Some reports indicated that COVID-19-related strokes are more severe and occur in younger patients than usual strokes, probably owing to coagulation abnormalities induced by SARS-CoV-2 infection [5][6]. The incidence of stroke in COVID-19 patients ranges from 1% to 6% [7].

Of all stroke types, the most common are ischemic (88%) and the rest are hemorrhagic (10% intracerebral and 2% subarachnoid) [1] (**Figure 1**B). Ischemic stroke (IS) occurs by a reduction or blockage of blood flow to the central nervous system (CNS) as a consequence of an embolus, thrombus, or atherosclerotic plate clogging a cerebral artery (**Figure 1**A). However, 30–40% of all ischemic strokes are cryptogenic, that is, of unknown cause [8]. The

size of the initial damage area depends of the caliber of the affected artery. The brain tissue affected by ischemia is not homogeneously damaged. The region more severely hypoperfused, named ischemic core, undergoes mainly necrotic cell death, whereas the surrounding region, known as penumbra, is less affected and is characterized by a high rate of apoptotic cell death [9] (**Figure 1**A). Duration of occlusion is also an important factor that determines the severity of the damage and the prognosis of the patients.

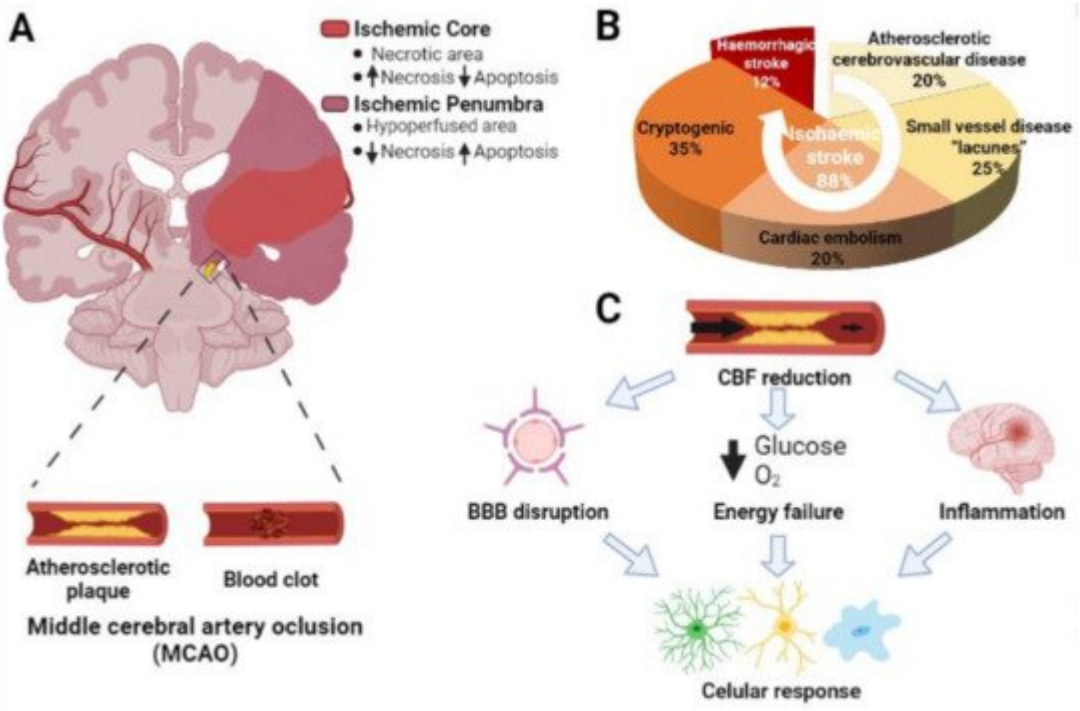


Figure 1. Main characteristics of the ischemic stroke. (**A**) Graphic representation of a coronal section of an adult human brain, which highlights the middle cerebral artery occlusion and its main causes: a blood clot and the formation of an arterosclerotic plaque. The ischemic core is highlighted in red and the penumbra region in fuchsia. (**B**) Epidemiological data of the incidence of the two main types of stroke (hemorrhagic and ischemic) and the main causes that lead to ischemic stroke. (**C**) Schematic representation of the main pathophysiological events triggered upon ischemia.

Symptoms usually vary depending on the affected brain area and include sensory and motor dysfunctions that may be permanent. In fact, between 30 and 50% of stroke patients do not recover functional independence, which has an important socioeconomic impact [10]. To date, the only approved direct stroke treatments are intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) and endovascular thrombectomy. Although both treatments have been shown to be beneficial, the proportion of eligible patients is relatively low and there is a short time window from the onset of the symptoms for an effective treatment. Moreover, both strategies increase the risk of hemorrhagic transformation [11]. This has been the driving force of an increasing interest in understanding the cellular and molecular basis of IS as a way to find new treatments. It is already known that brain ischemia triggers a sequence of pathological events named as the “ischemic cascade”, which may endure from minutes to days [12]. These events include energy failure, excitotoxicity, oxidative damage, disruption of the blood brain barrier (BBB), inflammation, and finally cell death [13] (**Figure 1**C).

2. Microglia

Microglia represent 10–15% of the total cells in the brain. These cells are considered as the resident macrophages and the first defense line in the central nervous system (CNS) against pathogens [14]. In physiological conditions, microglia have a high capacity to respond to changes in the CNS microenvironment owing to their processes [15]. These changes may be triggered by microorganisms such as bacteria or viruses, but also by neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, or cerebral ischemia. Particularly, microglia activation is one of the first events that occurs after an insult such as brain ischemia [16], taking place from minutes to a few hours after the start of the episode [17] (**Figure 2**).

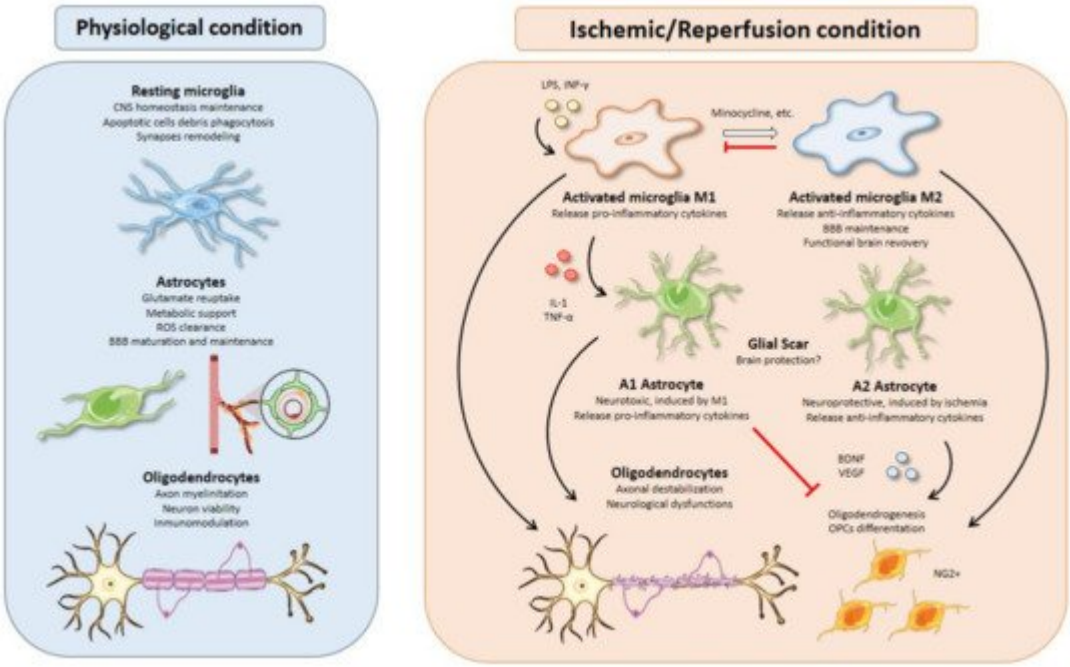


Figure 2. Glial cell functions, responses, and interactions in physiological and I/R conditions. **Microglial activation** is one of the earliest events after brain ischemia. The inflammatory landscape generated in the ischemic brain by inflammatory cytokines, debris, or molecules released from dead cells triggers microglia activation. Activated microglia are typically divided into M1 and M2 phenotypes. M1 microglia present a pro-inflammatory profile releasing cytokines such as IL-1 or TNF-α that can polarize astrocytes toward a neurotoxic phenotype, aggravating the inflammatory response. On the other hand, M2-microglia release anti-inflammatory cytokines, sustain blood brain barrier (BBB) integrity, and stimulate oligodendrogenesis through oligodendrocyte progenitor cells' (OPCs) differentiation into $NG2^+$ cells, thus promoting functional recovery after brain ischemia. All therapeutic strategies based on microglia are focused on minimizing the effects of M1-microglia using drugs like minocycline to switch phenotype from M1 to M2. Besides, M2 microglia could promote an inhibition of M1 microglia. **Activated astrocytes** are usually classified into A1 and A2 phenotypes. In line with M1 microglia, A1 astrocytes present a neurotoxic profile releasing pro-inflammatory cytokines with inhibitory effects over oligodendrogenesis and OPCs' differentiation. In contrast, A2 astrocytes have neuroprotective functions releasing anti-inflammatory cytokines and trophic factors, such as BDNF or VEGF with similar effects over oligodendrocytes as those of M2 microglia. **Oligodendrocytes** are especially sensitive to oxidative stress and excitotoxicity generated during brain

ischemia. Demyelination affects neurons owing to axonal destabilization, generating neurological dysfunctions. Moreover, these events are aggravated in the presence of M1 microglia and A1 astrocytes. At the same time, trophic factors released by M2 microglia and A2 astrocytes increase oligodendrogenesis and OPCs' differentiation in order to repair damaged white matter in the injury area.

2.1. Microglial Activation Timing upon Brain Ischemia

Morioka et al. [18], using Nissl staining, described an activation of microglia after 24 h of permanent middle cerebral artery occlusion (pMCAO) in cortical and thalamic regions. Years later, Schoroeter et al. [19] showed that, after 24–72 h of pMCAO, microglia presented star shape with thick and short processes located near the damaged area, while 6 days after pMCAO, microglia acquired an amoeboid shape in the same area. Thanks to the development of imaging techniques such as MRI, there has been deep progress in the study of microglia activation after cerebral ischemia. Rupalla et al. [20] described the activation of microglia as early as 30 min after pMCAO, showing hypertrophic cell body and processes in the penumbra. This revealed a high capacity of microglia to activate after a disruption in tissue homeostasis. Recently, a series of studies revealed the presence of activated microglia in the acute phase [21], sub-acute phase [22], and chronic phase [23] of IS. The aforementioned morphology changes are associated with different activated microglia functions. Some of these functions include an increase in phagocytosis rate, release of anti- or pro-inflammatory cytokines, proliferation, and migration [24].

2.2. M1 versus M2 Microglial Profiles

Under physiological conditions, microglia are in a "resting" status, from which they are able to lead a wide range of responses upon detection of changes in the environment like modulation of their dynamic processes, removing of debris and apoptotic cells by phagocytosis and remodeling of synapses [25]. Resting microglia present a low expression profile of surface molecular markers that include CD45, MHC-II, CD80, CD86, and CD11cc [26]. After an ischemic insult, activated microglia change this profile, presenting high expression of CD45, MHC-II, or CD86, among others. Moreover, Iba1, IB4, F4/80, and CD68 can also be used to identify activated microglia in this context [27]. Interestingly, there are differences in activated microglia molecular profile between the penumbra and ischemic core that could be used to delimit both regions. For example, the activated microglia in the penumbra are MHC-II+, associated with anterograde degeneration, while the core's activated microglia are MHC-I+ phagocytic cells [28]. Activated microglia have been classically categorized into two general groups according to the paradigm of macrophage activation (**Figure 2**). In general, the scientific community named a pro-inflammatory profile as M1 activated microglia, while an anti-inflammatory profile was termed M2 activated microglia [29][30]. Despite the persistence of this binary classification, there are many works supporting a heterogeneity in the population of activated microglia and a coexistence of intermediate phenotypes as M2-a, M2-b, or M2-c [31][32][33]. Precisely identifying the different subpopulations of activated microglia that appear after an ischemic insult could be of great relevance for the development of effective treatments. Kanazawa et al. [34] defined a temporal polarization after ischemic stroke by activated microglia markers. They described a majority of M2 activated microglia population during the first 24 h after brain ischemia followed by an increase in M1 microglia population. Other studies support the idea that the balance between both activated phenotypes could determine the neurodegenerative disease

progression, so that a majority of the M1 population is associated with a worse clinical prognosis [35]. Interestingly, activated microglia are known to switch from one profile to another and a great number of therapies are focused on this property [36][37][38]. M1 activated microglia contribute to an increase in the inflammation and cytotoxicity levels through the release of the cytokines TNF-α and IFN-γ; interleukins such as IL-1β, IL-6, IL-15, IL-18, and IL-23; chemokines like CCL2 and CXCL10; the metalloproteinases (MMPs) MMP-3 and MMP-9; and reactive oxygen/nitrogen species (ROS/RNS) [39][40]. On the other hand, M2 activated microglia promote the recovery of injured tissue and decrease inflammatory levels by secreting molecules such as IL-4, IL-10, IL-13, TGF-β, IGF-1, the neurotrophic factor BDNF, and vasoactive proteins [41].

2.3. Inductors of Microglial Activation in Stroke

There are several pathways that lead to microglial activation after brain ischemia. Classic activation is associated with M1 activated profile, while alternative activation is associated with the M2 activated profile [42]. There is a great range of molecular mechanisms underlying microglia activation after cerebral ischemia. Damage-associated molecular patterns (DAMPs) are molecules released in a passive way from cell debris or apoptotic cells after brain ischemia, driving microglial activation towards pro- or anti-inflammatory phenotypes [43]. Among these molecules, high mobility group box 1 (HMGB1) protein appears in the early stages of stroke and is recognized by several toll-like receptors (TLRs) like TLR2 or TLR4, which trigger an inflammatory response through the release of pro-inflammatory cytokines in an NF-κB-dependent process. In fact, TLR4 blockade has shown to be protective against brain ischemia with a reduction of the infarcted area, which could be due to a decrease in pro-inflammatory cytokines secreted by microglia [44]. Peroxiredoxins (Prdxs) constitute another important group of DAMPs with redox-activity. Prdx-1, Prdx-2, Prdx-5, and Prdx-6 are secreted by necrotic cells in the brain early after stroke inducing the release of pro-inflammatory cytokines, which are then recognized by TLR2 and TLR4 [45].

Initial disturbance of BBB integrity after an ischemic insult is also known to recruit and activate microglia, which start to secrete pro-inflammatory cytokines including IL-1β, TNF-α, and IL-6. IL-1β strongly induces activation of the astrocytes implicated in the neurovascular unit (NVU), promoting disruption of this functional structure, and thus leading to a metabolic uncoupling between neurons and the proximal blood flow [46]. The same population of activated microglia increases paracellular permeability of the surrounding blood vessels and further disrupts the NVU mainly through altered cytoskeletal organization, defective tight junction proteins' (TJPs) expression, and MMPs' release [36]. On the other hand, the M2 microglia population has been shown to exert angiogenic functions and promote BBB integrity, mainly through expression of TJPs [47].

Glutamate receptors (mGluRs) are also considered as microglial-related targets in brain ischemia. It is known that blockage or ablation of mGluR5 reduces acute microglial activation and promotes neuroprotection and neurofunctional recovery [48][49]. On the other hand, purinergic receptors, like P2X4R, P2X7R, and P2Y6R, have been related to neuroprotection mediated by microglia after brain ischemia owing to their anti-inflammatory effects [50][51]. This is a very complex process in view of the wide variety of receptors and channels on the microglial cell surface that get activated at the same time, triggering their own signaling cascade, and that must be tightly regulated to guarantee a harmonized response [52].

2.4. Therapies Based on Activated Microglia

From a therapy point of view, the available data suggest different alternatives to use activated microglia as a therapeutic target for brain ischemia. In vitro experiments using oxygen and glucose deprivation (OGD) offer an excellent model to study activated microglia response. These experiments usually focus on the molecular mechanisms underlying microglial polarization through the use of different agents such as LPS and IFN-γ, as a way to study the possibility to revert detrimental M1 profile and induce a neuroprotective M2 profile (**Figure 2**). On the other hand, in vivo experiments offer a better approach to study the role of activated microglia after an ischemic insult and their relation to other cell types, which remains poorly understood. By collecting data through these two approaches, we could know more specifically the response of activated microglia in this pathological context and develop effective strategies to reduce the detrimental effects of brain ischemia.

Minocycline is an antibiotic of the tetracycline family and it is the main compound used to abrogate inflammation induced by microglia activation [53]. Minocycline promotes a switch between microglial phenotypes, reducing the expression of M1 profile mRNA levels (IL-1β, IL-6, iNOS, and TNFα) and increasing typical M2 mRNAs (Arg-1, IL-10, TGF-β, and Ym1) [54]. Such an effect results in a reduction of the amoeboid morphology near the ischemic cortex and the infarct area [55]. Minocycline is also known to reduce cell death through the STAT1/STAT6 pathway [54]. Moreover, LPS-activated BV-2 microglial cell line presented a reduction in pro-inflammatory markers (CCL2, IL-6, and iNOS), with a concomitant decrease in caspase 3/7 activity and cell death [56]. Additionally, there are many studies supporting the idea that minocycline also increases the integrity of blood vessels, contributing to maintenance of the BBB integrity by an M2 microglia polarization [57][58].

Minocycline is one of the few glial-related components that have been tested in several clinical trials with promising results. An open-label, evaluator-blinded study of 152 patients showed minocycline, administered within 6 to 24 h of onset of stroke, to be associated with significantly lower National Institutes of Health Stroke Scale score and modified Rankin Score (mRS) compared with placebo [59]. By contrast, a multicenter randomized, double-blind, placebo controlled trial, “Neuroprotection With Minocycline Therapy for Acute Stroke Recovery Trial” (NeuMAST), in which patients were orally administered with either minocycline or placebo within 3 to 48 h of symptom onset, failed to prove any long-term beneficial effects over neurological outcome [60].

Apart from minocycline, there are a number of other compounds with promising efficiency in reverting microglia-derived detrimental effects in IS. Melatonin administration post-stroke is able to switch from M1 to M2 activated microglia through the STAT3 pathway, increasing secretion of anti-inflammatory cytokines and, therefore, reducing the damaged brain area [61]. Using GAPIs (a molecular cocktail from *Ginkgo biloba*), Zhou et al. [62] showed a reduction in the secretion of pro-inflammatory cytokines in BV-2 microglial cells, which acquired an M2 phenotype. Protocatechuic acid used after a cerebrovascular accident reverts M1-commited microglial cells and promotes expression of M2 markers [63]. Mechanistic target of rapamycin (mTOR) inhibitors like rapamycin are known to reduce the inflammatory microenvironment and infarct volume, decreasing the number of $Iba1^+$ cells and the expression of M1 markers after pMCAO [64]. ABIN1, a NF-κB inhibitor, has also been shown to attenuate both microglia activation and the levels of pro-inflammatory cytokines after brain ischemia [65]. Interestingly, L-3-n-

butylphthalide, an extract from seeds of *Apium graveolens Linn*, administered during 7 consecutive days after 45 min of pMCAO, improved the sensorimotor functions and reduced brain infarct volume, leading to an M2 microglia polarization [66].

Electroacupuncture (EA) is another neuroprotective strategy known to inhibit inflammation after brain ischemia, with many physical points available to apply this therapy including Baihui (GV20), Shuigou (GV26), Neiguan (PC6), Hegu (LI4), and Taichong (LR3), among others. There are some studies reporting the use of EA preconditioning to decrease pro-inflammatory effects triggered by brain ischemia. Using EA pre-treatment before pMCAO in rats, Liu et al. [67] showed a significant reduction of the infarct volume paralleled by functional motor recovery. From a molecular point of view, there is a reduction in the levels of different pro-inflammatory effectors such as TNF-α, IL-1β, and IL-6 in the damaged area and blood serum after I/R. Moreover, EA blocks the nuclear translocation of NF-κB (p65), preventing the expression of p38 MAPK and MyD88. In addition, another work explained that EA was able to induce a α7nAChR-dependent significant decrease of infarcted area and improve the neurological outcome [68].

3. Astrocytes

Astrocytes account for 50% of the human brain volume [69] and are normally classified into two mayor types according to morphological and spatial criteria: fibrous astrocytes in the white matter and protoplasmic astrocytes predominant in the grey matter [70]. The functional implications of each cell type in ischemic stroke are beyond the scope of this review, so the global term “astrocyte” will be used herein to encompass this complexity. Astrocytes have long been considered as a mere buffering system to sustain the correct functioning of the neuronal circuitry. However, in light of the evidence accumulated along the last decades, it becomes clear that astrocytes are active players in every physiological functions of the CNS as well as in pathological events following ischemic injury.

3.1. Excitotoxicity Modulation

Astrocytes play a major role in glutamate uptake from the surrounding neuronal synapsis and its posterior recycling into glutamine, which can then be reused by neurons as a substrate for glutamate synthesis. To this end, astrocytes present several glutamate transporters on their cell surface in direct contact with tripartite synapsis space, including the Na^+-dependent transporters EAAT1 and EAAT2 (human gene names), also known as GLAST and GLT-1 (mouse gene names). It has been reported that the astrocyte-dependent glutamate buffering system becomes altered shortly after ischemia in several ways. These include epigenetic modulation of GLT-1 and GLAST promoters, resulting in lower gene expression; aberrant histone methylation giving rise to dysfunctional, but not increased, expression [71]; and S-Nitrosylation of GLT-1 with a concomitant reduction in its activity [72]. At a later stage, a decrease in ATP levels in astrocytes, mainly in the ischemic core, induces glutamate transporters reversal, further contributing to glutamate excitotoxicity and neuronal damage [73]. In vivo upregulation of GLT-1 using ceftriaxone [74] or by targeted overexpression with adeno-associated viral vectors [75] was neuroprotective and reduced brain damage. Similar results were obtained in cultured astrocytes subjected to OGD [76]. Carnosine was also proved to preserve GLT-1 activity in astrocytes after pMCAO, improving neurological function and decreasing

infarct size [77]. A compound similar to ceftriaxone, sulbactam, was efficiently used to prevent hippocampal neuronal damage in a rat global brain ischemia model, while this effect was suppressed by either antisense knockdown or pharmacological inhibition of GLT-1 using dihydrokainate [78]. Furthermore, antisense knockdown of astrocytic GLT-1, but not EAAC1 neuronal glutamate transporter, increased neuronal damage induced in a transient focal cerebral ischemia (tMCAO) rat model [79], highlighting the special relevance of astrocytes in buffering ischemia-induced excitotoxicity. Nonetheless, astrocytes are also known to exacerbate excitotoxicity upon ischemia by releasing glutamate into the synapsis through volume-sensitive outwardly rectifying anion channels (VRACs) and connexin hemichannels. In fact, knocking out Swell1 (*Lrrc8a*), the only obligatory subunit of astrocytic VRACs, results in reduced brain damage and better neurological outcome upon I/R [80]. In accordance with this, pharmacological inhibition of VRAC using tamoxifen in MCAO-subjected rats reduced infarct area and improved neurological outcome [81]. Additionally, astrocytic P2X7 receptors (P2X7Rs) are also able to release glutamate upon ATP binding [82]. Given the increase in ATP extracellular concentration that takes place in the early phases of ischemic injury, P2X7Rs could be significantly contributing to excitotoxicity.

Connexin 43 (Cx43) is the predominant connexin in astrocytes and localizes to the cell surface where it conforms gap junctions and hemichannels. It has been described that, early after an ischemic insult (1–30 min), Cx43 gap junctions are phosphorylated by several kinases, like MAPK, PKC, pp60Src, and casein kinase 1δ, which triggers internalization of Cx43 hexamers. The remaining Cx43 hemichannels are dephosphorylated in a subsequent stage (after 60 min), increasing their opening probability and allowing harmful molecules into the extracellular space (ECS), like ATP and glutamate [83]. Leptin was found to suppress Cx43 rise after I/R reducing brain damage in a mouse model of MCAO, and it also blocked Cx43 hemichannels in cultured U87 cells [84]. Mimetic peptides are another way to block hemichannels. More precisely, Gap19 is a highly selective blocker that spares gap junctions at the initial moments of treatment (first 30 min), while effectively blocking hemichannels. At higher exposure times Gap19 slightly inhibits gap junctions. Suppression of Cx43 by Gap19 showed beneficial effects in MCAO mouse models [83].

3.2. Astrocyte-Neuron Metabolic Relationships in Stroke

Neurons heavily depend on glucose oxidative metabolism for their normal functioning, which makes them selectively vulnerable to hypoxia/hypoglycaemia [85]. For this reason, the role of astrocytes as metabolic supporters is key for neuronal survival during an ischemic insult. Neuronal energy demands can be mirrored by vascular regulation through astrocytic signaling pathways in what is known as neurovascular coupling. Released glutamate upon synaptic activity is bound by mGluR5, which then leads to a rise in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) through PLCβ1 activation. This event triggers the release of arachidonic acid (AA) from the membrane. In the presence of low surrounding oxygen pressure, as happens upon ischemia, AA is preferentially transformed into PGE2 by COX-1, and is then exported inducing vasodilation and diffusion of oxygen and glucose from the nearby blood vessels into brain parenchyma [86].

Astrocytes provide neurons with lactate as a precursor for the tricarboxylic acid (TCA) cycle, in a proposed mechanism known as “astrocyte-neuron lactate shuttle hypothesis” [87], which remains controversial [88]. As

previously stated, synaptic glutamate uptake by astrocytes triggers Na^+-K^+ ATPase, which in turn stimulates glycolysis and glycogenolysis to produce lactate [89]. Metabolism of lactate inside neurons implies that the pyruvate dehydrogenase complex (PDHC) is susceptible to inactivation through oxidative stress generated upon ischemic insults [90]. Energy depletion in an ischemic scenario leads to an increase in AMP levels and activation of AMPK, which in turn phosphorylates and thus inactivates acetyl-coA carboxylase, with the subsequent decrease in malonyl-CoA, a natural inhibitor of mitochondrial carnitine palmitoyltransferase I (CPT-I) [91]. Consequently, hypoxia/hypoglycaemia lead to increased activity of CPT-I and higher production of ketone bodies (KBs) through mitochondrial β-oxidation of free fatty acids (FAs) obtained from the bloodstream [90]. Astrocytes release KBs into the ECS, captured by neurons through MCTs and used as precursors for TCA cycle. Given that PDHC becomes partially inhibited in the presence of I/R-derived ROS, KBs become the most important source of energy over lactate after brain ischemia [92].

Exogenous KBs could constitute an interesting therapy for I/R injury. KBs increase mitochondria health and activity, reduce ROS and astrogliosis [93], and increase neurotrophin secretion (BDNF, bFGF) [94]. It has been recently reported that the axis SIRT3–FoxO3a–SOD2 becomes upregulated upon treatment with KBs, increasing mitochondria complex I activity and reducing protein oxidation, with a concomitant improvement in neurological outcome after an ischemic insult [95]. Adiponectin could also constitute a good therapy as it promotes oxidation of FAs and production of KBs through AMPK activation [96].

3.3. Oxidative Stress Management

Endogenous ROS in the CNS is generated by the mitochondrial electron transport chain and NADPH-oxidized pathway, while reactive nitrogen species (RNS) mainly proceed from L-arginine metabolism by nitric oxide synthase (NOS) [97]. Clearance methods can be classified into enzymatic and non-enzymatic. The former group includes Nrf2-controlled ones, catalases, SODs, and glutathione peroxidase. Non-enzymatic methods consist of molecules able to scavenge ROS/RNS including glutathione (GSH), bilirubin, uric acid, melatonin, and vitamins C and E. Another non-enzymatic method is the thioredoxin (Trx) system, where NADPH is used to reduce cysteine residues on Trx, making it a potent antioxidant [98].

Neurons are less efficient than astrocytes in dealing with oxidative stress owing to a continuous repression of Nrf2, which is a master regulator of redox genes including *GCLC*, glutathione reductase, *NQO-1*, and *HO-1* [99]. Increased levels of Nrf2 have been observed in I/R injury mainly in the penumbra, both in mouse and human [100]. It has recently been described that Nrf2 activation in astrocytes relies on glutamate binding to NMDA receptors (NMDARs), which suffer subunit composition changes in different models of ischemia [101]. GluN3A is known to increase in MCAO mice [102], rendering lower $[Ca^{2+}]_i$ elevations, which is expected given the inhibitory effect of GluN3A on NMDARs [103]. This could negatively impact GSH production and global antioxidant capacity of astrocytes.

One detrimental effect of ROS accumulation in astrocytes during ischemia is the activation of NLRP3 inflammasome. This process may depend on a two-step event (priming and activation) or on a single event (activation). Detection of ischemia-related DAMPs by TLRs can prime NLRP3 transcriptionally through NF-kB

activation, which induces expression of NLRP3 and pro-inflammatory cytokines in a process partially dependent on mtROS [104]. Another way of NLRP3 non-transcriptional priming is through its deubiquitination by BRCC3, which can be triggered by mtROS and is a crucial step for NLRP3 activation [105]. ROS accumulation can directly activate NLRP3, promoting the release of TXNIP from Trx, to facilitate inflammasome polymerization [106].

Adiponectin (APN) is an adipose tissue-derived hormone released into the bloodstream that increases upon ischemia [107] and presents neuroprotective properties [108]. A very recent study proves that APNp, an APN-derived peptide able to cross the BBB, reduces ROS and NLRP3-mediated inflammation. APNp was shown to increase AMPK activation, Nrf2 nuclear translocation, and Trx1 levels [109]. Ascorbic acid is another molecule able to scavenge ROS directly. It is produced in astrocytes by GSH-mediated reduction and then transported into neurons [110]. Oral administration of nanocapsuled ascorbic acid has been shown to reduce ROS-mediated mitochondrial damage [111]. Peng et al. [112] recently described that DJ-1, which is an important antioxidant molecule mainly produced by reactive astrocytes, exerts a neuroprotective function upon ischemia through upregulation of Nrf2 and a concomitant increase in GSH levels. The AMPK-PGC-1α axis, which is induced upon ischemia owing to an increase in AMP levels, drives expression of *GCLM* specifically in astrocytes, and thus facilitates GSH synthesis. Accordingly, those AMP analogous molecules, like metformin and AICAR, improve neuroprotection and are good candidates for therapies [113]. Astroglia-specific ROS scavengers metallothionein(MT)-I and MT-II presented increased mRNA levels early after brain ischemia and deficient mice for these two proteins presented larger infarct sizes after ischemic injury compared with control mice [114].

Given the conspicuous relevance of ROS-mediated neurotoxicity in I/R, promoting the aforementioned astrocyte-related mechanisms to scavenge these toxic species represents a promising therapeutic approach in stroke, especially those Nrf2-centered strategies.

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