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Mini-review

Dual role of astrocytes in perinatal asphyxia injury and neuroprotection

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HIGHLIGHTS

- Astrocytic response to perinatal asphyxia is extremely complex.
- Astrocytic response during perinatal asphyxia is not fully understood.
- We focus on the actions of the astrocytes in PA pathogenesis.
- This will allow us to get new insights about possible role either in damaging or neuroprotecting the injured CNS.

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ABSTRACT

Perinatal asphyxia represents an important cause of severe neurological deficits including delayed mental and motor development, epilepsy, major cognitive deficits and blindness. However, at the moment, most of the therapeutic strategies were not well targeted toward the processes that induced the brain injury during perinatal asphyxia. Traditionally, experimental research focused on neurons, whereas astrocytes have been more related with the damage mechanisms of perinatal asphyxia. In this work, we propose to review possible protective as well as deleterious roles of astrocytes in the asphyctic brain with the aim to stimulate further research in this area of perinatal asphyxia still not well studied.

Contents

1. Introduction

Birth hypoxia–ischemia or perinatal asphyxia (PA) is a serious complication with a high mortality and morbidity [1]. Following PA, approximately 45% of newborn die and 25% have permanent

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neurological déficits [2,3] including cerebral palsy, mental retardation and developmental delay [4], learning disabilities [5], visual and hearing problems [6], and different issues in the school readiness [7].

Astrocytes represent the more abundant neuroglial cell type found in central nervous system (CNS), generally outnumber neurons by over five fold. Therefore, nothing can enter or leave the CNS parenchyma without going through an astrocytic interphase. During the last five decades astrocytes have been subdivided into protoplasmic and fibrous [8] classification that still retains validity and usefulness. Subsequent to trauma, astrocytes proliferate, swell, and undergo fibrosis by the accumulation of filaments, expressed as an increase in glial fibrillary acidic protein (GFAP) and/or the novo expression of vimentin that represents the main feature of reactive astrogliosis in disease tissue [9]. Astrogliosis may be severe, in which case most of cell are lost, leaving a glial scar, or it may be a partial or generalized response occurring while CNS is normal or in a process of regeneration. Fibrous astrocytosis can occur in both the gray and white matter, thereby indicating common links between protoplasmic and fibrous astrocytes. With age, both fibrous and protoplasmic astrocytes accumulate filaments [10].

The general view of the possible functions of the astrocytes in pathological conditions is related with the fact that, reactive astrogliosis is only a clear marker of grade of the injured neural tissue. However, there is a body of evidence suggesting astrocytes can play a key role in CNS disease [11–16]. Since the astrocytic response to PA is extremely complex and is not still fully understood, this mini-review is focused on the actions of the astrocytes in PA pathogenesis and its possible role either in damaging or neuroprotecting the injured CNS.

2. Role of astrocyte during CNS asphyctic disorder

Two decades ago Choi and Rothman [17] described during hypoxia–ischemia insult, a fall of cellular energy reserves and Na^+ gradients. Theses metabolic modifications produce a failed uptake and over release of glutamate mediate a toxic increment of extracellular glutamate, leading to overstimulation of glutamate receptors and consequent neuronal cell death [17]. In addition, brains of the newborns babies differ from the adult in its sensitivity to all of these processes. *N*-Methyl-D-aspartate (NMDA) receptor activation is most devastating in the immature brain. Small alteration in receptor properties might contribute to the increased sensitivity of the neonatal brain to hypoxic-ischemic injury [18]. Although the astrocyte is probably the most disease-resistant component in the CNS because very few diseases, other than alcoholism, cause depletion of astrocytes [19–21] recently, have been described early astrocytes vulnerability in immature ischemic brain [22]. Astrocytic cells death with microglial activation was observed by combining electron microscopy, immunohistochemistry and cell death detection in P5 mice injected in the white matter with ibonetate to induced excitotocity insult [22]. In another study, 9 days old rat cortex injected with NMDA showed a neuronal degeneration and glial reaction [23]. Astrocytes showed nuclear cleaved active caspase-3 expression as 4 h post-hypoxic lesion and persisted until 14 days when the glial scar was already consolidated. Similar alterations were described in a vivo model of newborn piglets [24]. In a model of oxygen-glucose deprivation astrocyte demise was observed in P0–P2 [25]. In addition, hippocampus, neostriatum and neocortex in organotypic cell culture studies after 1 h of PA showed a clear astroglial reaction. However, treatment with allopregnanolone reduced astrogliosis only in hippocampus and neocortex but not in neostriatum suggesting that attenuation in glial reaction per se is not enough to repair PA deleterious effect. Moreover, in any area of the brain studied, allopregnanolone is able to increase the neuronal viability [26]. Taken together these data suggested that early death in reactive astrocytes after neonatal hypoxia–ischemia may promote deleterious alterations such as the formation of cystic lesion in newborn babies [27].

Long term studies using a murine model of PA does not show any evident astrocytic alterations at 30 days after hypoxia [28]. However a diffuse astrogliosis was observed after 120 days of PA [15]. This astroglial reaction is consistent with some observations that showed impairments in the lost-lasting behavioral tests in PA animals. On other hand, estradiol treatment in PA rats significantly reduced the number of GFAP immunoreactive astrocytes in comparison to PA rats treated with vehicle. Moreover they did not show significant differences with CTL rats injected with vehicle suggesting a reversion of astrogliosis associated with hypoxia at birth by 17β estradiol treatment in the adulthood. Reduction of the astrogliosis was observed together with a decreased in axonal neurofilaments and microtubules dendritic shaft alterations and neuron death [29]. After 6 months of PA, severe astrogliosis with compact glial scar formation was described [19]. These finding were well correlated with clear signs of degeneration in the synpases and high level of local ubiquination [21]. Together, this data suggest that under this period of PA, glial astrocytes might induce detrimental effects on the CNS.

Microglia cells are involved, as nervous system macrophages cells, in several insults including infection, inflammation, neurodegeneration and ischemia. The immunoinflammatory system is activated in the secondary neurotoxic cascade after hypoxic and ischemic event [30,31]. Microglial cells may contribute to perinatal brain injury being beneficial or detrimental according to the grade of its activation. While microglia contribute to the angiogenesis [32,33], it has been also suggested that microglia can induce brain damage through the release of cytokines [34] excitotoxins [35] and reactive oxygen species [36]. Recently a clinical research study [36] described an increased of microglia potentially neurotoxic inflammatory factors (Galectin-3 and MMP-9) in asphyxiated infants with severe clinical course and adverse outcome [37]. Therefore further studies should be also conducted to elucidate the role of microglia during PA and its possible connection with the astroglial reaction.

3. Potential astrocytes function in neuroprotection in perinatal asphyxia

During several decades, researchers have emphasized on glial scar formation as an inhibitor of axon regeneration and the scar formation was the main impediment for the functional recovery after CNS injury. This negative viewpoint of reactive astrogliosis is no longer accepted and several lines of experiment showed reactive astrogliosis exert beneficial actions. Recent studies point toward roles for reactive astrocytes in restricting inflammation and protecting neurons and oligodendrocytes, thereby helping to limit tissue degeneration and preserve function after adult ischemia [38]. Reactive astrocytes provide essential metabolic support to neurons during transient ischemia and that failure of astrocyte functions may contribute to neuronal degeneration [16,39]. In addition, experimental disruption of astroglial scar formation in transgenic mice after stroke is associated with loss of barrier functions along the margins of infarcts, resulting in increased spread of inflammation and increased lesion volume [40]. Stroke may also induce neurogenesis from periventricular neural progenitor cells that express GFAP [41]. Recently an interesting work conducted in mouse model of focal stroke showed that intact part of the brain contributes to the functional recovery of the stroke region of the brain through the synaptic remodeling. This study also shows that astrocytes have a critical role reducing the accumulation of glutamate [42]. Beside all of this evidences about the astrocytes protective role of astrocytes during ischemia, a little is known about

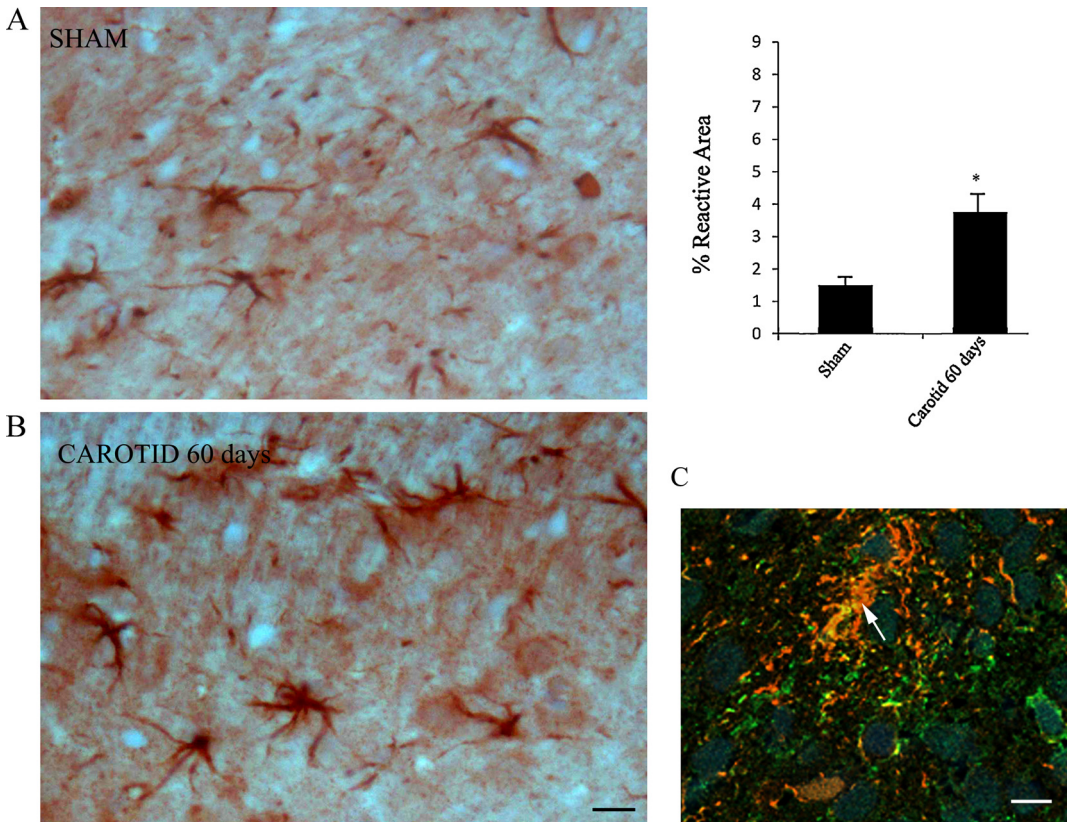

Fig. 1. Thioredoxin-2 immunostaining from 60 days old rats in hippocampus CA1 area. (A) Representative pictures show astrocities immunostained for Trx-2. (B) Assessment of the astrocytes immunostained with the Trx-2 antibodies in the CA1 hippocampus area. Reactive area of immunostaining was increased in carotid CA1 hippocampus area stained with Trx-2. Bars and error bars represent mean + SEM. $^{*}p > 0.005$. (C) Confocal microscope images of double staining between GFAP and Trx-2 in astrocytes. Colocalization between these two markers was observed (arrow). $n = 6$ sham and 6 carotid animals Scale bar: 20 μm.

putative neuroprotective function of astrocytes in the evolution of the asphytic brain lesions.

Oxidative stress – following an ischemia/reperfusion produces devastating effects on the brain organization. In the last few years, Thioredoxin protein family (Trxs) has been proposed as a key regulator of the redox state cell [43,44]. Trxs are a class of enzymes that utilize the thiol groups of cysteinyl residues for the catalysis of thiol–disulfide exchange and peroxidatic reactions [43]. This family of proteins includes: thioredoxins (Trxs), glutaredoxins (Grxs), and peroxiredoxins (Prxs) which are all characterized by a common structural motif known as the thioredoxin fold [44,45]. Although the Trx family includes more than ten proteins, the major Trx isoforms are the cytosolic Trx1 and the mitochondrial Trx2 [46,47]. Moreover Trxs are characterized by their active site motifs, containing either one or two cysteinyl residues. These thiol groups are essential for (a) the reduction of protein disulfides, (b) protein de-/glutathionylation and de-/trans-/nitrosylation or (c) the reduction of hydrogen peroxide. Recently we describe the cellular localization of Trxs in the CNS. We have observed several remarkable differences in both abundance and regional distribution of Trx-s immunopositive cells that point to a complex interplay and crosstalk between the proteins of this family. One of the most striking localization was in hippocampal astrocytes stained with Trx-2 [44]. Using a model of perinatal hypoxia–ischemia reoxygenation induced by common carotid artery ligation combined with nitrogen exposure in 7 days old rats, we have observed increased in the percentage of reactive area of astrocytes immunostained with Trx-2 in hippocampus CA1 area, one of the areas most sensitive to PA (Fig. 1B). These observations are well correlated with an increment in the astrogliosis from 21 days to 90 days (Fig. 2A). Previous studies have shown that Trxs contribute to mechanisms of brain tolerance in early periods after exposure to stress [46–48] suggesting that Trx-2 expression might be a protective answers against the hipoxic impairment. Trx1 itself is regulated by hypoxia [49] and by oxidative conditions, binding of nuclear factor E2-related factor 2 (Nrf2) to an antioxidant responsive element (ARE) in the Trx promotor [50,51]. In addition, knockout of p53 and DJ-1 in mice resulted in either up-, or down-regulation of Trx1 via increased or decreased levels of Nrf2, respectively [52,53]. Other studies showed that astrocytes exert protection form oxidative stress via glutathione production. Then astrocytes might contribute to reduce the damage produce by PA modifying the redox signaling [54]. Since several members of the Trxs have been implicated in cell survival, proliferation and regeneration processes [55] further studies should be conducted to determine the role of Trxs in PA neuropathology probably exerting neuroprotective and or reparative actions.

Some studies in the past have shown that excess of glutamate produced by inactivation of excitatory amino-acid transporter (EAAT) is the mechanism used by TNF-α to induce damage during hypoxia [56]. While TNF-α signaling through TNFR1, can be neurotoxic to cells and induce apoptosis while TNF-α signaling through TNFR2 and gene transcription pathways has neuroprotective effects in neurons and glia [57]. Most recently, it has been shown that TNF-α is neuroprotective against hypoxia-hyperexcitability in hippocampal neurons [58]. In addition the levels of glutamate are not controlling only by astrocytes levels of Ca^{2+} if not also for TNFα [59]. Therefore, this data suggests that inflammatory answer could drive also a neuroprotective effect depending of the receptor that is activated.

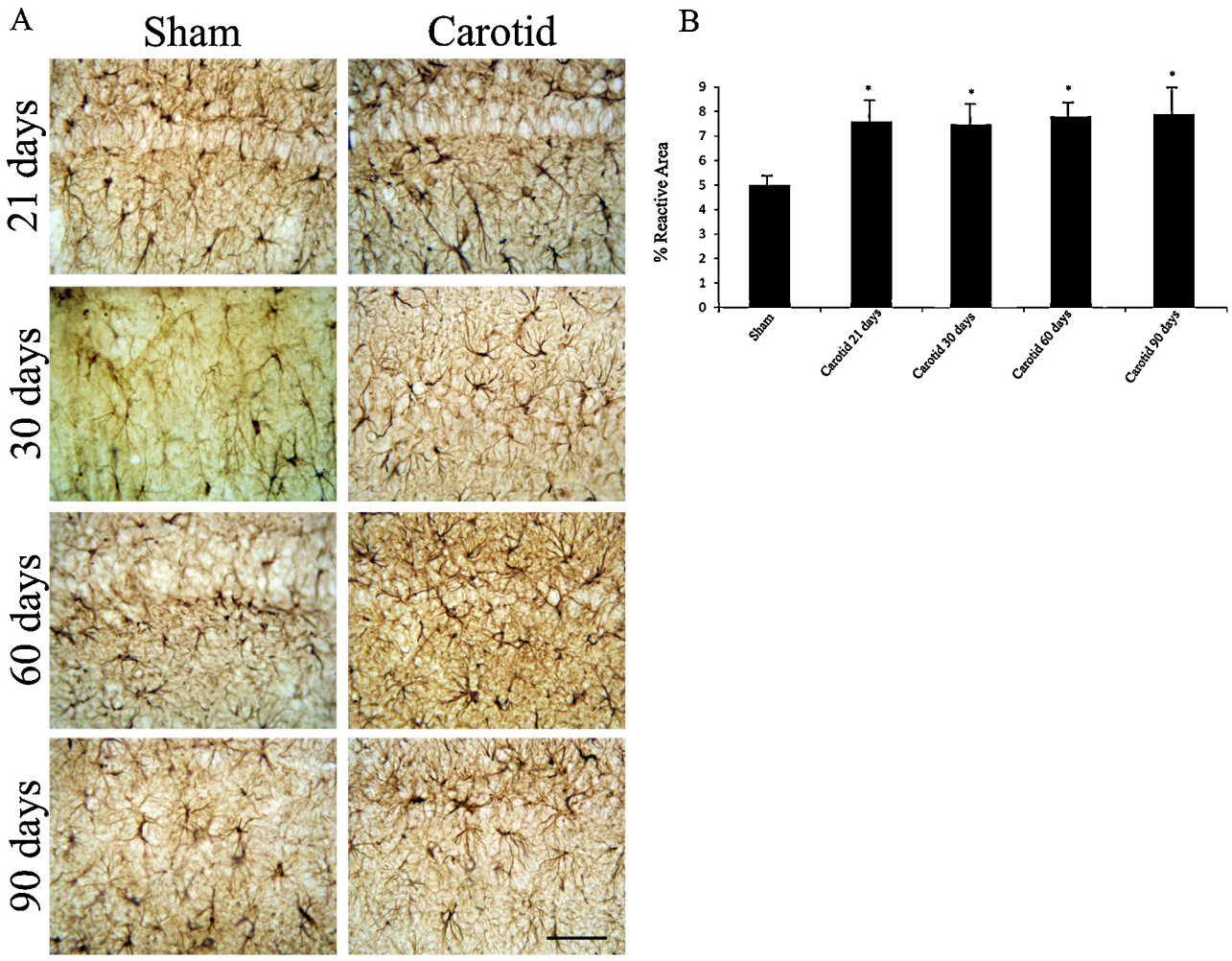

Fig. 2. GFAP expression pattern in sham and carotid animals from 21 days to 90 days after the ischemic insult. (A) Representative pictures from CA1 area of the hippocampus of carotid and control animals immunostained for GFAP. (B) Assessment of the GFAP immunoreactive astrocytes in the CA1 hippocampus. Slight increment in the percentage of reactive area could be observed. Bars and error bars represent mean + SEM. $^{*}p > 0.005$ $n = 6$ sham and 6 carotid animals. Scale bars: 50 μm.

4. Conclusion

Further experiments will be necessary to conduct for dissecting the role of the astrocytes in the pathophysiology of perinatal asphyxia. These new studies are undoubtedly critical to design new therapeutic tools that can mitigate the brain damage and its neurological consequences induced by perinatal asphyxia.

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