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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 neurological deficits including cerebral palsy, mental retardation

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and developmental delay, learning disabilities, visual and hearing problems, and different issues in the school readiness [2–7].

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 [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

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