Neuroscience Letters xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Mini-review

The dual role of astrocyte activation and reactive gliosis

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HIGHLIGHTS

- Astrocyte activation (AA) and reactive gliosis (RG) accompany many CNS pathologies.
- AA and RG alter the expression of many genes and astrocyte function.
- RG benefits include lesion sequestering, neuroprotection, and counteracting acute stress.
- If not resolved on time, AA and RG inhibit neuroplasticity and CNS regeneration.
- AA and RG is an important therapeutic target.

ARTICLE INFO

Article history:
Received 2 December 2013
Received in revised form
21 December 2013
Accepted 29 December 2013

Keywords:
Astrogliosis
Intermediate filaments (nanofilaments)
GFAP
CNS injury
Ischemic stroke
Alzheimer's disease
Neural plasticity and regeneration

ABSTRACT

Astrocyte activation and reactive gliosis accompany most of the pathologies in the brain, spinal cord, and retina. Reactive gliosis has been described as constitutive, graded, multi-stage, and evolutionary conserved defensive astroglial reaction [Verkhratsky and Butt (2013) In: Glial Physiology and Pathophysiology]. A well- known feature of astrocyte activation and reactive gliosis are the increased production of intermediate filament proteins (also known as nanofilament proteins) and remodeling of the intermediate filament system of astrocytes. Activation of astrocytes is associated with changes in the expression of many genes and characteristic morphological hallmarks, and has important functional consequences in situations such as stroke, trauma, epilepsy, Alzheimer's disease (AD), and other neurodegenerative diseases. The impact of astrocyte activation and reactive gliosis on the pathogenesis of different neurological disorders is not yet fully understood but the available experimental evidence points to many beneficial aspects of astrocyte activation and reactive gliosis that range from isolation and sequestration of the affected region of the central nervous system (CNS) from the neighboring tissue that limits the lesion size to active neuroprotection and regulation of the CNS homeostasis in times of acute ischemic, osmotic, or other kinds of stress. The available experimental data from selected CNS pathologies suggest that if not resolved in time, reactive gliosis can exert inhibitory effects on several aspects of neuroplasticity and CNS regeneration and thus might become a target for future therapeutic interventions.

Contents

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0304-3940/$ – see front matter © 2014 Published by Elsevier Ireland Ltd.
http://dx.doi.org/10.1016/j.neulet.2013.12.071

In mammalian brain, spinal cord, and retina, astrocytes have multitude of functions. Astrocytes induce the formation of neuronal synapses and are involved in their control [1–4] as well as in the control of the energy supply to neurons and the turnover of neurotransmitters [5–9]. Through their endfeet, which throughout the CNS cover and interact with endothelial cells of blood capillaries, astrocytes help to control the blood-brain barrier [10,11] and regulate the flow of blood within the CNS tissue [12–14].

An astrocentric view of the CNS is that of a system consisting of individual astrocytes and their interconnected domains that, to a large extent, control all the other cellular elements that are physically present within domains of individual astrocytes [15–19].

In the human cortex, a single astrocyte domain can contain as many as 2,000,000 neuronal synapses [20]. The complexity of interaction opportunities between astrocytes and the cellular elements within their action radius is truly enormous and is further increased by the existence of gap junctional coupling between astrocytes which turns each astrocyte unit into an element within the astrocyte network. It is highly probable that astrocytes are as heterogenous a cell population as neurons [21,22]. Attempts to define astrocytes in molecular terms are being made [22–26], and this will allow functional classification of astrocytes and a better understanding of their roles in disease pathogenesis.

In vivo, a number of molecules, such as transforming growth factor (TGF) -alpha, cilliary neurotrophic factor (CNTF), interleukin (IL) -6, leukeamia inhibitory factor (LIF), and oncostatin M induce astrocyte activation [27–31]. The levels of IL-6, LIF, and oncostatin M mRNA, all ligands of the gp-130/activator of transcription 3 (STAT3) signaling pathway, were elevated prior to phosphorylation and nuclear translocation of STAT3 in astrocytes and induction of astrogliosis [30]. However it is also conceivable that at least some of the cytokines exert their effects on astrocyte activation through other cell types such as microglia, neurons, or endothelial cells. Some molecular and morphological features of reactive astrocytes have long been considered by histopathologists and experimental researchers as hallmarks of astrocyte activation in conditions such as brain or spinal cord infections, injuries to the brain, spinal cord and retina, epilepsy, stroke, some brain tumors, and neurodegenerative diseases, e.g., AD, amyotrophic lateral sclerosis (ALS), or multiple sclerosis [32–38]. The most prominent of these hallmarks are hypertrophy of astrocyte cellular processes and upregulation of intermediate filament (nanofilament) proteins, in particular the upregulation of glial fibrillary acidic protein (GFAP), which is the main constituent of the intermediate filament system of adult astrocytes [39] (Fig. 1). Reactive gliosis can be graded as mild to very prominent, with the latter being often connected with a glial scar, to the formation of which pericytes also contribute [40]. Reactive astrocytes can be found within the lesion, and they can also constitute a physical barrier between the lesion and the surrounding tissue [41,42]. The latter can be exemplified by reactive astrocytes that surround focal traumatic or focal ischemic lesions.

1. Experimental models to understand injury- or ischemia-triggered astrocyte activation and reactive gliosis

Over the past two decades, several animal models have been used in a series of experimental studies to understand the role of astrocyte activation and reactive gliosis in neurological diseases as well as neuroplasticity and regeneration processes.

What are the consequences of the elimination of astrocytes, elimination of reactive astrocytes or inhibition/attenuation of astrocyte activation? Elimination of astrocytes in a mammal is lethal [43]. The demarcation of CNS lesion by reactive astrocytes was manipulated in animal experimental models by astrocyte specific ablation of STAT3 and suppressor of cytokine signaling 3 (Socs3) [44,45]. STAT3 was shown to affect reactive gliosis following CNS injury, by being downstream of the action of IL-6, LIF, and CNTF [30,46,47]. Socs3 functions as a negative feedback molecule of STAT3 and an inverse relationship between STAT3 and Socs3 has been reported [48,49]. When STAT3 was specifically ablated in reactive astrocytes, astrocyte migration and the demarcation of the spinal cord traumatic lesion by astrocytes was inhibited, and the infiltration by CD11b positive inflammatory cells was increased. This resulted in the expansion of the lesion area and led to a more pronounced functional impairment [44,45,50]. In the injured spinal cord of mice with conditional ablation of Socs3 in reactive astrocytes, phosphorylation of STAT3 in reactive astrocytes and astrocyte migration increased; contraction of the lesion area was more prominent and the functional recovery improved [45]. These results showed that reactive astrocytes have a key role in the repair of the injured CNS tissue and positively affect the recovery process after spinal cord injury, and that this function of reactive astrocytes depends on STAT3 signaling. Thus, the demarcation of a lesion by reactive astrocytes allows the isolation and protection of the relatively unaffected CNS tissue and might have evolved as the means of sequestering the toxic environment of the lesion [44,45,51,52], albeit at the price of restricted regenerative response at a later stage [53].

The ablation of the dividing fraction of reactive astrocytes in mice aggravates the negative consequences of brain or spinal cord injury [54–57]. This was achieved in a transgenic mouse model with GFAP promoter-driven herpes simplex virus thymidine kinase that allows elimination of proliferating astrocytes after CNS injury [54] with the results suggesting that reactive astrocytes play a positive role in attenuating acute neurodegeneration and repairing the blood-brain barrier [54–56].

Elimination of the astrocyte intermediate filament (nanofilament) system by genetic ablation of intermediate filament proteins GFAP and vimentin in mice results in attenuated reactive gliosis [58,59] and decreased resistance of the CNS tissue to severe mechanical stress [60,61]. The astrocyte intermediate filaments system is both a structural component of the cytoskeleton and an important signaling platform in situations connected with cellular stress [62–64]. Intermediate filaments of reactive astrocytes contain GFAP, vimentin, and nestin, with a subpopulation of reactive astrocytes containing also an intermediate filament protein synemin [25,65,66]. The introduction in mice of null mutations in the gene coding for GFAP ($GFAP^{-/-}$) or vimentin ($Vim^{-/-}$) still allows formation of intermediate filaments (in $GFAP^{-/-}$ reactive astrocytes composed of vimentin and nestin, and in some of these astrocytes also of synemin, in $Vim^{-/-}$ reactive astrocytes composed of GFAP only) [58,65]. However, simultaneously present null mutations in GFAP and vimentin genes ($GFAP^{-/-}Vim^{-/-}$) lead to a complete deficiency of intermediate filaments in reactive astrocytes [59] because in the absence of both GFAP and vimentin, neither nestin [58] nor synemin [65] can form intermediate filaments. After brain injury, astrocytes of $GFAP^{-/-}Vim^{-/-}$ mice show similar abundance and access volumes of brain tissue comparable to those assessed by astrocytes of wild-type mice [67]. However, $GFAP^{-/-}Vim^{-/-}$ astrocytes do not exhibit the reactive phenotype with characteristic processes as do astrocytes in wild-type mice [67–69]. The $GFAP^{-/-}Vim^{-/-}$ astrocytes also display altered levels of some molecules such as plasminogen activator inhibitor I [70,71] under conditions leading to astrocyte activation, exemplified by exposure to fetal calf serum in primary astrocyte cultures *in vitro* [68], which suggests a less prominent response of $GFAP^{-/-}Vim^{-/-}$ astrocytes to activation. The formation of glial scar is reduced in $GFAP^{-/-}Vim^{-/-}$ mice; posttraumatic healing takes longer time and there is a more prominent loss of neuronal synapses in the acute period following hippocampal de-afferentation induced by entorhinal cortex lesion [59,67]. Experimental ischemic stroke in

Please cite this article in press as: M. Pekny, et al., The dual role of astrocyte activation and reactive gliosis, Neurosci. Lett. (2014), http://dx.doi.org/10.1016/j.neulet.2013.12.071