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Current Neuropharmacology, **2014**, *12*, **303-307**

EDITORIAL

Neuroglia as a Central Element of Neurological Diseases: An Underappreciated Target for Therapeutic Intervention

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Abstract: Neuroglia of the central nervous system (CNS), represented by cells of neural (astrocytes, oligodendrocytes and NG2 glial cells) and myeloid (microglia) origins are fundamental for homeostasis of the nervous tissue. Astrocytes are critical for the development of the CNS, they are indispensable for synaptogenesis, and they define structural organisation of the nervous tissue, as well as the generation and maintenance of CNS-blood and cerebrospinal fluid-blood barriers. Astroglial cells control homeostasis of ions and neurotransmitters and provide neurones with metabolic support. Oligodendrocytes, through the process of myelination, as well as by homoeostatic support of axons provide for interneuronal connectivity. The NG2 cells receive direct synaptic inputs, and might be important elements of adult remyelination. Microglial cells, which originate from foetal macrophages invading the brain early in embryogenesis, shape the synaptic connections through removing of redundant synapses and phagocyting apoptotic neurones. Neuroglia also form the defensive system of the CNS through complex and context-specific programmes of activation, known as reactive gliosis. Many neurological diseases are associated with neurogliopathologies represented by asthenic and atrophic changes in glial cells that, through the loss or diminution of their homeostatic and defensive functions, assist evolution of pathology. Conceptually, neurological and psychiatric disorders can be regarded as failures of neuroglial homeostatic/ defensive responses, and, hence, glia represent a (much underappreciated) target for therapeutic intervention.

Keywords: Astrocyte, microglia, neurodegeneration, neuroglia, neurological diseases, NG-2 cells, oligodendrocyte, psychiatric diseases, therapy.

NEUROGLIA CONTROL HOMEOSTASIS OF THE CENTRAL NERVOUS SYSTEM

The nervous tissue is composed of numerous types of cells of neural (ectodermal: neurones and neuroglia) and non-neural (mesodermal: microglia, endothelial cells, pericytes, muscle cells, etc.) origins organised into tightly coordinated cellular networks. Evolution of the nervous system progressed through cellular specialisation, with neurones becoming chiefly occupied with fast information processing and transfer, and neuroglial cells assuming responsibility for housekeeping. Neuroglia of the central nervous system (CNS) is classified into macroglia (astrocytes, oligodendrocytes and NG2 cells) and microglia (which are the descendants of embryonic macrophages invading the brain early in development). The systemic function of neuroglia is the preservation of homeostasis at all levels of the CNS organisation, from molecular to organ [1, 2].

Homeostatic tasks performed by neuroglia are extremely broad. Astrocytes, which are arguably the most diversified type of glia, define the architecture of the grey matter being the central elements of the glio-vascular unit. Inside these glio-vascular units elaborated processes of astroglia cover synaptic contacts and neuronal membranes, and control molecular composition of the interstitium by regulated transport of water, ions and neuroactive agents such as neurotransmitters and neurohormones [3, 4]. Astrocytes are indispensable for synaptic connectivity; astroglial cradle governs synaptogenesis, synaptic maturation and synaptic maintenance [5, 6]. Astroglia are fundamental for neuro-transmission, being specialised in clearance of neuro-transmitters (such as glutamate, GABA and adenosine) and for supplying neurones with glutamine, which is a dual precursor for glutamate and GABA [7, 8]. Astroglial cells provide neurones with metabolic substrates [9] and protect nerve tissue against reactive oxygen species (ROS), being the chief source of ROS scavengers such as glutathione and

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ascorbic acid [10, 11]. Astroglia are responsible for: i) CNS development and adult neurogenesis [12]; formation and maintenance of the CNS-blood and cerebrospinal fluid-blood barriers [13]; and iii) the regulation of local blood flow [14]. In addition, specialised astrocytes appear as central chemoceptors involved in systemic regulation of Na^+, pH and CO_2 homoeostasis [15, 16], and regulation of sleep [17].

Oligodendrocytes contact, support and myelinate axons in grey and white matters, thus, being central elements of the CNS connectome. The NG2 glia (a lineage related to oligodendrocytes) possibly contribute to adult myelination and may also possess certain homeostatic functions. Finally, microglia are highly important for development of the CNS and shaping neuronal networks through synaptic stripping and removal of excessive neurones which undergo massive apoptosis at different stages of embryogenesis [18-20].

NEUROGLIA MOUNTS BRAIN DEFENCE

Homeostatic function of neuroglia is linked to its wide defensive capabilities. Indeed, brain lesions trigger homeostatic response such as the containment of excitotoxicity through buffering an excess of K^+ and glutamate, and by the release of ROS scavengers. In conditions of ischaemia and glucose deprivation astrocytes and oligodendrocytes protect neurones by supplying them with lactate. Neuroglial cells are in possession of an evolutionary conserved defensive programme known as reactive gliosis, triggered in response to polyaetiological insults [21, 22]. The gliotic response is further sub-classified into reactive astrogliosis, reactive response of NG2 cells and activation of microglia. Oligodendrocytes (as well as Schwann cells in the peripheral nervous system) are also activated in response to axonal damage, this activation being a part of Wallerian degeneration. Reactive gliosis is a complex and multistage response of glial cells, which is disease- and context- specific, and involves activation of thousands of genes. This glial reactivity is a defensive response aimed at protecting stressed neurones (and the brain in general) isolating injured area, removing pathogens, dying cells and cellular debris, and remodelling the nerve tissue after the resolution of pathology.

The hallmarks of reactive astrogliosis are hypertrophy and proliferation of astrocytes associated with up-regulation of cytoskeletal components such as glial fibrillary acidic protein (GFAP), vimentin or nestin [23, 24]. An increased expression of these intermediate filaments are, however, only considered as broad markers of this process, because astrogliotic metamorphosis may produce many different, yet to be fully characterised, reactive phenotypes specific for different diseases. In the process of a productive gliotic response astrocytes undergo a complex remodelling of their biochemistry and function, which generally leads to neuroprotection. In severe lesions astrocytes produce glial scar aimed at isolating the area of damage; astrogliosis is also critical for regeneration of nerve tissue after resolution of pathology. All in all, the suppression of astrogliotic response is detrimental for nerve tissue viability and exacerbates pathological progression (for details and exhaustive reference lists see [22-26]). Morphologically, astrogliosis is broadly divided into isomorphic gliosis in which domain organisation of astrocytes is preserved and anisomorphic gliosis in which astrocytes proliferate and lose their domain organisation with their processes becoming densely overlapped. Isomorphic gliosis is fully reversible, whereas anisomorphic gliosis is frequently resolved in the formation of a glial scar. Reactivity of NG2 glia has been studied to a much lesser extent; their response to a pathological insult is represented by shortening and thickening cellular processes and a strong increase in the expression of NG2. Together with astrocytes NG2 glia may contribute to the formation of a glial scar through secreting chondroitin sulphate proteoglycan 4 [27]. In certain conditions NG2 cells may possibly act as stem cells; in particular, they can generate new oligodendrocytes which in turn can assist in post-lesion remyelination of axons [28, 29].

Microglial activation is the second major component of reactive gliosis. Activation of microglia progresses through many stages and cell phenotypes characterised by distinct morphological, biochemical, functional and immunological changes. Similarly to astroglia, activation of microglia is a multistage, complex and context-specific process, which produces multiple phenotypes of activated cells, many of which demonstrate prominent neuroprotective features [30-32]. In conditions of severe or specific brain lesions, such as, infectious encephalitis, microglial cells start to proliferate, become motile, accumulate around sites of damage and become phagocytotic, thus, actively removing foreign agents and cell debris [30].

PATHOLOGICAL POTENTIAL OF NEUROGLIA: NEUROLOGICAL DISEASES AS NEUROGLIOPATHIES

The philosophy of contemporary clinical and experimental neurology is created around neuronal doctrine that regards neurones as a central element for pathological progression. This is reflected by drug development, with most of the agents being specifically aimed at affecting neuronal excitability or neuronal receptors. This neuronocentricity is somewhat surprising in the light of common definition of the disease as a homeostatic failure. In this respect, the homeostatic arm of the nervous system, the neuroglia, shall naturally be considered as a fundamental element for initiation, development and outcome of neurological disorders. Indeed, neurones when left to their own devices have limited capacity for self-protection and for meeting environmental challenges; it is the neuroglia that protect and maintain the nervous system operation. The gliocenric angle in neurology is still *in statu nascendi* (as reviewed recently [33-45]), although it is rapidly gaining popularity.

Conceptually, the glial involvement in a neuropathological process could be primary or secondary, i.e., primary neurogliopathy (manifested by the loss or change of the glial functions) and secondary reactivity, respectively. The boundary between these two faces of glial pathology is blurred and often they are present in combination. A striking example of astrogliopathy (which can be considered as an astroglial asthenia) is associated with the down-regulation of astrocyte-specific glutamate transporters (excitatory amino acid transporters 1 and 2), which is a common cause

of many neurotoxic (e.g., mercury, lead or aluminium encephalopathies) and neurodegenerative (e.g., amyotrophic lateral sclerosis-also called motor neurone disease, Wernike-Korsakoff encephalopathy or Huntington's disease) disorders; a compromised astroglial glutamate clearance acts as a primary mechanism of neurotoxicity, neuronal death and brain atrophy [44, 46-51]. Similarly, toxic damage to astrocytes produced by ammonia that leads to the occlusion of glutamate-glutamine shuttle, exocytotic release of glutamate, failure in glutamate clearance and K^+ buffering is a central element for hepatic encephalopathy [52-55].

Atrophy and asthenia of neuroglia have been identified in major neuropsychiatric diseases such as schizophrenia and major depression; in both pathologies degradation of astrocytes and oligodendrocytes are prominent histopathological features [40, 45]. Similarly, atrophic astrocytes have been observed in the pre-symptomatic stages of Alzheimer's disease (AD) in animal models [56-58]; the earliest occurrence of this atrophy was found in entorhinal and prefrontal cortices, the most vulnerable regions in AD pathology [59, 60]. The asthenic astroglial cells in these two brain regions failed to mount gliotic response to extracellular depositions of amyloid which might be a relevant explanation for this high vulnerability. Astroglial asthenia in AD was paralleled with a loss of microglial functions. Namely, in the animal models, microglial cells almost doubled their density at pre-plaque stages of the disease, this being very similar to changes found in normal ageing [61-63]. Formation of plagues trigger activation and accumulation of activated microglia around plaques [38, 64]; these activated cells, however, are deficient in their phagocytotic function [65].

Another facet of glial contribution to neuropathology is represented by reactivity. Reactive astrogliosis and activation of microglia usually appear in response to disease-specific lesions. For example, reactive glia in AD is recruited in response to an appearance of senile plaques or perivascular amyloid depositions. Similarly, gliotic response accompanies late stage of amyotrophic lateral sclerosis [66, 67]; is detected in fronto-temporal dementia [68] and is prominent in thalamic dementia (in which astroglial activation has been claimed to be associated with a loss of function, which causes neuronal death [69]). In neuronal ceroid lipofuscinosis, also known as Batten disease, astroglial reactivity (manifested by significant increase in GFAP expression and hypertrophy) occurs at the very early stages [70]; inhibition of astrogliosis (by genetic removal of intermediate filaments GFAP and vimentin) accelerates disease progression and exacerbates neurodegeneration [71]. Unresolved gliotic response, however, may have various detrimental consequences to the outcome of neurological diseases. Chronic astrogliosis, for example, suppresses neurogenesis, whereas an astroglial scar prevents axonal regrowth. Suppression of astroglial reactivity improved regeneration in lesioned nerves and enhanced regenerative processes in animal models of ischemia, stroke and injury and facilitated integration of retinal grafts, as well as differentiation of transplanted neural stem cells [24].

TARGETING NEUROGLIA FOR NEUROTHERAPY

Neuroglial cells are one of the central elements of neuropathology; loss of neuroglial function as well as neuroglial reactive responses contribute to most (if not all) neurological, neuropsychiatric and neurodevelopmental diseases. A multitude of molecules, specifically expressed by neuroglial cells and responsible for their homoeostatic and defensive functions, are potential and legitimate targets for therapeutic management. In this special issue we collected papers specifically dedicated to neurogliopathology with an aim to expand glio-centric views into translational medicine.

ACKNOWLEDGEMENTS

VP research is supported by the National Institutes of Health (Eunice Kennedy Shriver National Institute of Child Health and Human Development award HD078678). AV was supported by the Alzheimer's Research Trust (UK), by European Commission, by IKERBASQUE and by a research grant of Lobachevsky State University of Nizhny Novgorod. LP research is supported by the National Natural Science Foundation of China.

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