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Astrocyte physiopathology: At the crossroads of intercellular networking, inflammation and cell death

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ABSTRACT

Recent breakthroughs in neuroscience have led to the awareness that we should revise our traditional mode of thinking and studying the CNS, *i.e.* by isolating the privileged network of "intelligent" synaptic contacts. We may instead need to contemplate all the variegate communications occurring between the different neural cell types, and centrally involving the astrocytes. Basically, it appears that a single astrocyte should be considered as a core that receives and integrates information from thousands of synapses, other glial cells and the blood vessels. In turn, it generates complex outputs that control the neural circuitry and coordinate it with the local microcirculation. Astrocytes thus emerge as the possible fulcrum of the functional homeostasis of the healthy CNS. Yet, evidence indicates that the bridging properties of the astrocytes can change in parallel with, or as a result of, the morphological, biochemical and functional alterations these cells undergo upon injury or disease. As a consequence, they have the potential to transform from supportive friends and interactive partners for neurons into noxious foes.

In this review, we summarize the currently available knowledge on the contribution of astrocytes to the functioning of the CNS and what goes wrong in various pathological conditions, with a particular focus on Amyotrophic Lateral Sclerosis, Alzheimer's Disease and ischemia. The observations described convincingly demonstrate that the development and progression of several neurological disorders involve the de-regulation of a finely tuned interplay between multiple cell populations. Thus, it seems that a better understanding of the mechanisms governing the integrated communication and detrimental responses of the astrocytes as well as their impact towards the homeostasis and performance of the CNS is fundamental to open novel therapeutic perspectives.

Contents

Abbreviations: Ca^{2+}, calcium; $[Ca^{2+}]_i$, intracellular concentration of calcium ions; BBB, blood–brain barrier; GFAP, glial fibrillary acidic protein; GS, glutamine synthetase; Cx, connexin; K^+, potassium; Kir, inward rectifying potassium channel; NMDA, N-methyl-D-aspartate; IP_3, 1,4,5-triphosphate; GPCR, G-protein-coupled receptor; ER, endoplasmic reticulum; GABA, γ-amino butyric acid; SON, supraoptic nucleus; OT, oxytocin; mGluR, metabotropic glutamate receptor; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; LTP, long-term potentiation; mGluR5, metabotropic glutamate subtype 5 receptors; GJC, gap junction channel; SMC, vascular smooth muscle cell; BK, large-conductance Ca^{2+}-operated K^+ channel; PLA_2, phospholipase A_2; AA, arachidonic acid; COX-2, cyclooxygenase 2; PG, prostaglandin; 20-HETE, 20-hydroxyeicosatetraenoic acid; AD, Alzheimer's Disease; APP, amyloid precursor protein; PS1, presenilin 1; ROS, reactive oxygen species; TNFα, tumor necrosis factor α; TLR, toll-like receptor; IL, interleukin; IFNγ, interferon γ; TGFβ, transforming growth factor β; NGF, nerve growth factor; AxD, Alexander's disease; EGFR, epidermal growth factor receptor; ALS, Amyotrophic Lateral Sclerosis; FTLD, Frontotemporal Lobe Dementia; sALS, sporadic ALS; fALS, familial ALS; SOD1, copper, zinc superoxide dismutase; hSOD1, human copper, zinc superoxide dismutase; TARDBP, TAR DNA binding protein 43 gene; TDP-43, TAR DNA binding protein 43; miR-124a, microRNA 124a; DAO, D-amino acid oxidase; TGFβ-RII, TGFβ type II receptor; Aβ, amyloid-β; NFAT, nuclear factor of activated T-cells; DENN/MADD, differentially expressed in normal versus neoplastic/MAPK activating death domain; α7nAChR, α7 nicotinic acetylcholine receptor; EP receptor, prostaglandin receptor.

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1. Introduction

The structural and functional complexity of the mammalian CNS can be explained by the presence in brain and spinal cord of a multitude of different cell types that interact at the cellular and network level. These categories of cells include various subsets of neurons as well as a broad variety of non-neuronal cell populations.

The first acknowledgment of the existence of a non-neuronal component of the CNS is dated back to 1856 when the German pathologist Rudolph Virchow coined the term "neuroglia" to describe a sort of connective substance that holds together the actual nervous elements (Virchow, 1856). Later, with the advent of cellular histology and, hence, the elaboration of the concept of "cell", the notion of glia (Greek; meaning "glue") was completely revised and used to define a group of cell types that form, at least in some areas, the predominant cell population (Kettenmann and Ransom, 2012). Although not all studies agree (Herculano-Houzel, 2012, 2014; Hilgetag and Barbas, 2009), several reports in rodents and humans indicated that the ratio of glia to neurons changes across species and increases with brain complexity and size (Nedergaard et al., 2003; Oberheim et al., 2006; Sherwood et al., 2006). Furthermore, early histological studies suggested that the glia-neuron ratio raises in brain regions from rodents exposed to enriched environments, thus strengthening the relevance of glial cells in the context of the CNS functioning (Diamond et al., 1966; Szeligo and Leblond, 1977).

Several classes of glial cells were described, which differ in ontology, morphology and function. These include microglia, the resident macrophages of the brain and spinal cord; Schwann cells and oligodendrocytes, which myelinate neuronal axons in the peripheral and central nervous system, respectively; NG2-glia, an atypical form of glial cells that receive direct synaptic contacts; and astrocytes, which have recently emerged as the main effectors of the CNS homeostasis. Each of these glial cell types appears to include heterogeneous cell subpopulations, which display a variable degree of biochemical and functional diversity, depending on the CNS areas and evolutionary stages taken into consideration.

In this review, we specifically focus on astrocytes in view of the importance these cells have acquired, over the last twenty years, for the comprehension of the functioning of the CNS (Di Castro et al., 2011; Henneberger et al., 2010; Jourdain et al., 2007; Navarrete and Araque, 2008; Santello et al., 2011; Suzuki et al., 2011) and, more recently, for the shaping of animal behaviors (Gourine et al., 2010; Halassa et al., 2009; Huxtable et al., 2010).

In this respect, it should be mentioned that the earliest studies on the central nervous tissue, performed during much of the past century, have addressed the classification of neural cells only from a morphological standpoint, using classical histological stainings. At that time, the characterization of glial cells paralleled the one of neurons. Yet, the advent of the functional approaches in the early 1950s, particularly the voltage clamp technique, revealed the current–voltage properties of the neuronal membrane, and led to the definition of the ionic mechanisms underlying the initiation and propagation of action potentials (Hodgkin and Huxley, 1952). These advances in the comprehension of the physiological features of nerve cells moved the focus of the investigations on the functioning of the CNS towards neurons, and studies on astrocytes were neglected for some time. In fact, neuroscientists reasonably started to believe that the brain information processing was linked to the occurrence of action potentials and, thus, to the transmission of electrical signals. Because astrocytes do not generate action potentials and have "passive" membrane properties, they were just classified as non-excitable cells, and therefore unable to communicate. Hence, they were relegated to submissive roles and, thus, ignored for a few decades.

Astrocytes gained again attention in the 1980s, when electrophysiological recordings with the patch-clamp technique (Hamill et al., 1981; Neher et al., 1978) revealed the presence of voltage- and ligand-gated ion channels in cultured cells (Barres et al., 1988, 1990; Bevan et al., 1985; MacVicar, 1984; MacVicar and Tse, 1988; Sontheimer et al., 1988). Additional molecular studies further confirmed the expression of ionotropic and metabotropic receptors for a large number of neurotransmitters in both cultured and tissue astrocytes (reviewed in Kettenmann and Zorec, 2012). The latter discovery represented a turning point in the general conception of the functioning of the CNS, as it introduced the idea that astrocytes can sense neuronal activity and be activated by neurotransmitters spilled over from synaptic sites. In the last two decades, this view has been extraordinarily expanded owing to the development of fluorescence imaging approaches. Thus, application of calcium (Ca^{2+}) imaging techniques allowed to demonstrate that astrocytes actually display a peculiar form of excitability, which is based on variations in the intracellular concentration of Ca^{2+} ions ($[Ca^{2+}]_i$). Subsequent investigations revealed that astrocytes can even respond to neuronal inputs by releasing various messengers, *i.e.* chemical transmitters (also called gliotransmitters), proteins and lipid factors (reviewed in Araque et al., 2014; Santello et al., 2012). This suggests that astrocytes have many levels of active interaction with their cellular neighbors and exert multimodal influences on their functions. Consequently, they emerge as skillful elements, whose activities cannot be further neglected if one wants to have a comprehensive vision of the CNS performance in health and disease.

In this review, we will delineate the current knowledge of astrocyte activity in normal conditions, and we discuss how the divergence from physiology can contribute to injury and disease in the mature CNS. We will not consider the role of the astrocytes during development, as we refer the reader to other excellent and