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Review

Neuroglia and their roles in central respiratory control; an overview☆

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ABSTRACT

While once viewed as mere housekeepers, providing structural and metabolic support for neurons, it is now clear that neuroglia do much more. Phylogenetically, they have undergone enormous proliferation and diversification as central nervous systems grew in their complexity. In addition, they: i) are morphologically and functionally diverse; ii) play numerous, vital roles in maintaining CNS homeostasis; iii) are key players in brain development and responses to injury; and, iv) via gliotransmission, are likely participants in information processing. In this review, we discuss the diverse roles of neuroglia in maintaining homeostasis in the CNS, their evolutionary origins, the different types of neuroglia and their functional significance for respiratory control, and finally consider evidence that they contribute to the processing of chemosensory information in the respiratory network and the homeostatic control of blood gases.

Contents

1. Introduction

Neuroglia has become a generalized term that refers to a range of cells in the central and peripheral nervous systems that are neither electrically excitable nor vascular and includes macroglia (oligodendrocytes and astrocytes, NG2 glia), cells of the choroid plexus, ependymal cells, radial glia of the retina and microglia (Fig. 1) (Verkhratsky and Butt, 2013). Surprisingly, there is no consensus on a formal definition for neuroglia. These cells have diverse embryonic origins, and a vast array of morphologies, physiological properties and specialized functions. Despite these differences, they share one unifying function, which is the basis of the suggestion by Parpura and others that neuroglia be

Abbreviations: CSF, cerebrospinal fluid; CNS, central nervous system; Cx26, , connexin 26; GFAP, glial fibrillary acidic protein; LPS, lipopolysaccharide; NOS, nitric oxide synthase; nNOS, neuronal nitric oxide synthase; P2R, purinergic receptor; P2YR, metabotropic purinergic receptor; preBötC, preBötzinger Complex; RTN, retrotrapezoid nucleus; TLR4, toll-like-receptor-4.

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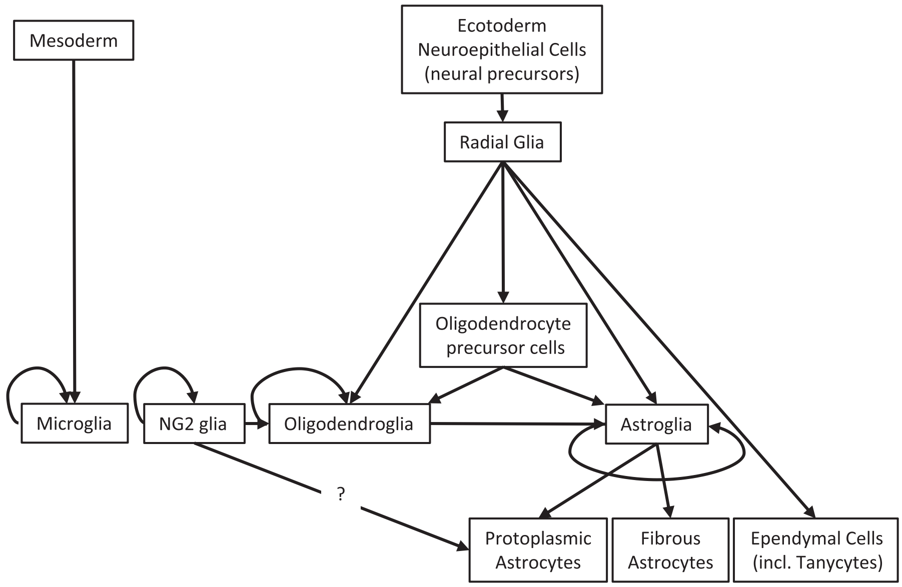

Fig. 1. Classification and origins of CNS neuroglia.

defined simply as "homeostatic cells of the nervous system" (Parpura and Verkhratsky, 2012a,b).

The dominant view of neuroglia for almost the last century was that they serve primarily a supportive role for neurons. Thus, they are not nearly as well studied, or understood, as neurons, despite the fact that in mammals neuroglia greatly outnumber neurons. However, the relatively recent discovery that neuroglia can both release and respond to neuroactive chemicals combined with growing evidence that they participate actively in information processing (Dallerac et al., 2013; Pirttimaki and Parri, 2013) has dramatically increased interest in this class of cells. The purpose of this review is to provide those in the respiratory field with a brief review of: i) the diverse roles played by neuroglia in maintaining CNS homeostasis; ii) the phylogenetic proliferation and diversification of neuroglia and the insight that this might provide about function; iii) the diversity of neuroglia subtypes, their embryonic origins and their functional significance for respiratory networks; and, iv) current views on the role of neuroglia as sensors and processors of chemosensory information important in the homeostatic control of blood gases by the respiratory network. This review is not intended as an exhaustive review but as an introduction to those becoming interested in the field and a guide for those wishing to delve further.

2. Contributions of neuroglia to the maintenance of CNS homeostasis

The concept of neuroglia was first introduced in 1856 by Rudolf Virchow, who described it as a substance "nervenkitt" (the glue between the neurons/nerves) in which nervous system elements are imbedded, and as having a role in supporting neurons and in maintaining stability/structure of the nervous system (Kettenmann and Verkhratsky, 2008; Parpura and Verkhratsky, 2012a; Verkhratsky and Butt, 2013). Subsequent histological analysis by Camillo Golgi in the 1870s revealed contacts between glia and vascular elements, so called "end-feet", and led to the hypothesis that these cells provide metabolic support and exchange substances with neurons. Santiago Ramón y Cajal, observing close apposition between neurons and neuroglia, suggested that they might isolate neighboring neurons from each other, separating different paths of information flow (Navarrete and Araque, 2014). Potential roles in secretory/signaling processes, transmitter uptake and pathological processes were also hypothesized near the turn of the 20th century. However, with the neurocentric view of brain function that emerged out of the neuron doctrine and the ability to measure electrical activity of neurons in the brain, it would be three-quarters of a century before exploration of these hypothesized functions began. It is now clear that neuroglia contribute to the maintenance of homeostasis on multiple levels (Kettenmann and Verkhratsky, 2008; Parpura and Verkhratsky, 2012a; Freeman and Rowitch, 2013; Verkhratsky and Butt, 2013). These include but are not limited to:

Structural homeostasis. Virchow's initial view of neuroglia included that, although passive, neuroglia maintained neuronal/CNS structure and stability (cited in Kettenmann and Verkhratsky, 2008; Parpura and Verkhratsky, 2012a; Verkhratsky and Butt, 2013). The importance of neuroglia in the structural integrity of the CNS is exemplified in the gray matter where protoplasmic astrocytes define the local architecture, by covering neurons within a specific region, essentially dividing the territory into individual domains. In addition, radial glia provide the substrate for neuronal migration during development. Macro and microglia participate in synaptogenesis and synaptic pruning during both development and different types of plasticity (Corty and Freeman, 2013; Ji et al., 2013; Miyamoto et al., 2013; Ota et al., 2013; Schafer and Stevens, 2013; Wake et al., 2013; Bernardinelli et al., 2014a,b). Oligodendrocytes produce myelin, effectively isolating axons from their neighbors and allowing for faster transmission of information (Verkhratsky and Butt, 2013).

Homeostatic control of the extracellular space (ionic, neurochemical, volumetric homeostasis). Astrocytes regulate the volume and composition of the extracellular space. Neuroglia also form (in lower vertebrates) or control the cells that make up the blood brain barrier (endothelial cells in higher vertebrates) that separates the CNS from the rest of the body (Kimelberg, 2004b; Alvarez et al., 2013). They control ionic composition of the cerebrospinal fluid (CSF) (especially K^+), water movement, and transmitter levels, including the removal of extracellular glutamate, degradation of glutamate to glutamine, which is subsequently resupplied to neurons for synthesis of glutamate. Neurons lack the enzyme glutamine synthase, and thus depend on the neuroglial supply of glutamine to synthesize glutamate, the main excitatory amino acid in the brain (Parpura and Verkhratsky, 2012c; Verkhratsky and Butt, 2013).

Metabolic homeostasis occurs on at least two levels. First, unlike neurons, neuroglia can store glycogen, which may be broken down into lactate and utilized by neurons as an energy substrate (Parpura and Verkhratsky, 2012c). This possibility is described in the astrocyte-to-neuron lactate shuttle hypothesis (Pellerin et al., 1998; Baltan,