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Review

Glia and central cardiorespiratory pathology

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ABSTRACT

Respiration and blood pressure are primarily controlled by somatic and autonomic motor neurones, respectively. Central cardiorespiratory control is critical in moment-to-moment survival, but it also has a role in the development and maintenance of chronic pathological conditions such as hypertension. The glial cells of the brain are non-neuronal cells with metabolic, immune, and developmental functions. Recent evidence shows that glia play an active role in supporting and regulating the neuronal circuitry which drives the cardiorespiratory system. Here we will review the activities of two key types of glial cell, microglia and astrocytes, in assisting normal central cardiorespiratory control and in pathology.

1. Introduction

Cardiorespiratory control involves nervous system substrates that regulate breathing and cardiovascular function. It refers to a network of neurons throughout the midbrain, brainstem, and spinal cord that regulate the functions of the skeletal muscles associated with breathing, the smooth muscle of the airways and blood vessels, and cardiac muscle, pacemakers and conduction system. An understanding of sympathetic nervous control in particular is essential for comprehending the development of many pathologies, including hypertension and heart failure (Lambert and Esler, 2016). Central nervous system (CNS) neurons are maintained and supported by glial cells that populate the entire brain and spinal cord. Microglia are highly motile immune cells with phagocytic and inflammatory functions (Kettenmann et al., 2011). Their processes extend and retract to sample the extracellular space around them (Li et al., 2012). Astrocytes are non-motile supporting cells that deliver oxygen and nutrients to neurons and remove metabolic by-products (Mishra et al., 2016). Astrocytic processes associate closely with neuronal elements and envelop blood vessels to form an integral part of the blood-brain barrier (Ikeshima-Kataoka and Yasui, 2016; Janzer and Raff, 1987).

Glial cells are as complex as neurons, but their diverse functions are often overlooked in the context of autonomic control. Their roles in autoimmune and neurodegenerative disorders are well-known, but they also contribute to synaptic plasticity, brain development, and the maintenance of neuronal homeostasis (Benarroch and Microglia, 2013; Gee and Keller, 2005). Recent evidence shows a strong role for glia in the normal function of the autonomic nervous system, and in the development of related disorders (Shen et al., 2015; Marina et al., 2016). This review will outline the contributions of microglia and astrocytes to central cardiorespiratory control, their mechanistic contribution to physiology and pathology, and the challenges associated with this area of study.

2. Microglia and astrocytes

Microglia, the tissue-resident macrophages of the central nervous system (CNS), are innate immune cells present throughout the brain and spinal cord. Microglia express a range of functional receptors for classical neurotransmitters, and their branching processes survey the surrounding tissue, interacting with neuronal elements to maintain homeostasis. Under physiological conditions in adults, microglia

Abbreviations: 2K1C, two-kidney one-clip; ACE, angiotensin converting enzyme; ADP, adenosine diphosphate; AIH, acute intermittent hypoxia; AngII, angiotensin II; ATP, adenosine triphosphate; CIH, chronic intermittent hypoxia; CNS, central nervous system; CX3CR1, fractalkine receptor; ICV, intracerebroventricular; IFNγ, interferon gamma; IL-1β, interleukin-1 beta; IL-4, IL-6, IL-10, IL-13, interleukin 4, 6, 10, 13; JAM-1, junctional adhesion molecule 1; LPS, lipopolysaccharide; mGluR, metabotropic glutamate receptor; NTS, nucleus tractus solitarius; pLTF, phrenic long-term facilitation; PVN, paraventricular nucleus of the hypothalamus; RSNA, renal sympathetic nerve activity; RVLM, rostral ventrolateral medulla; SHR, spontaneously hypertensive rats; SHR-SP, stroke-prone spontaneously hypertensive rats; TLR4, toll-like receptor 4; TNFα, tumour necrosis factor alpha; UDP, uridine diphosphate; WKY, Wistar-Kyoto rats

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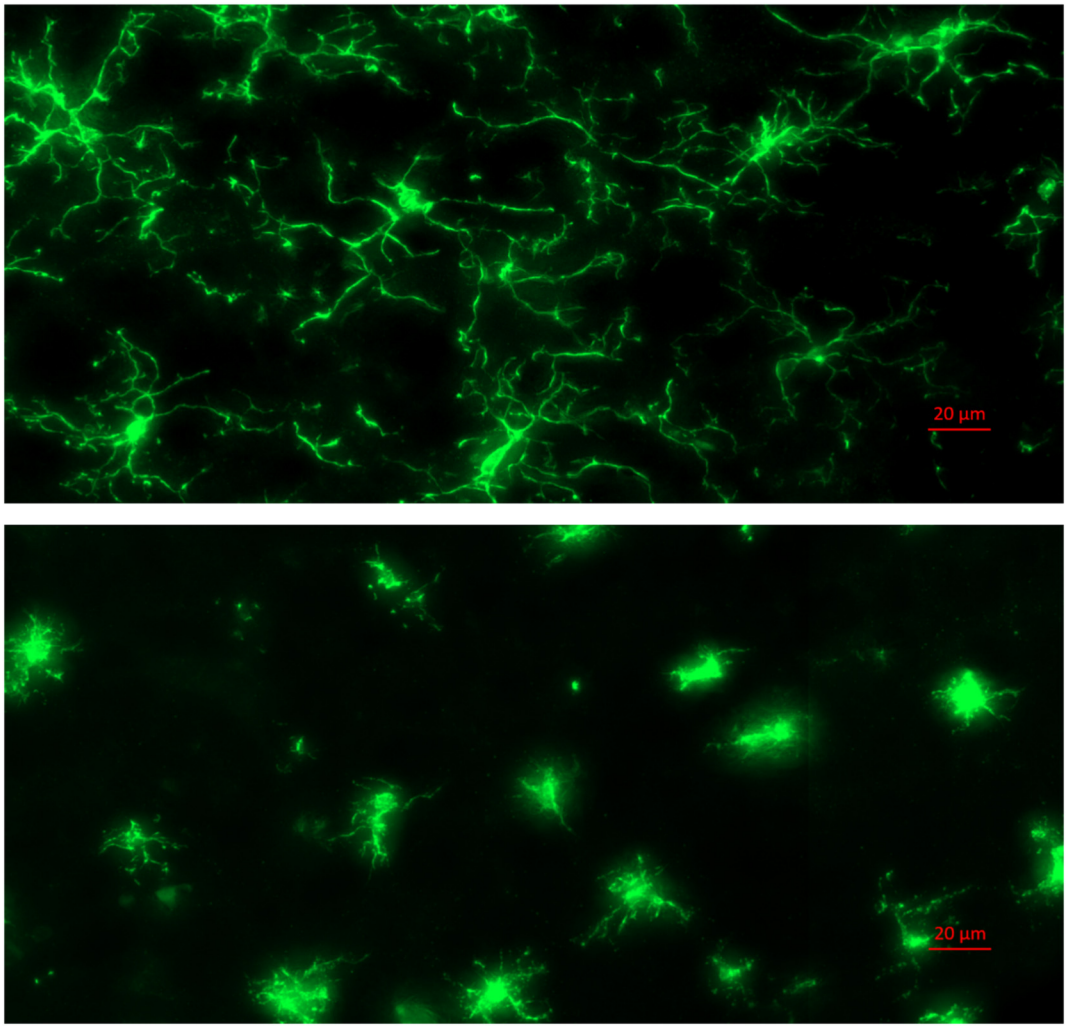

Fig. 1. Microglial cells stained with the microglia/macrophage marker Iba1 in formalin-fixed rat brain tissue. The long, branching processes in the top panel reflect the 'resting' or surveilling state of the microglial cells. The microglia in the bottom panel display an 'activated' or de-ramified morphology. Process retraction and cell soma enlargement indicate an inflammatory response.
Both images were obtained from one experiment, in which a Sprague-Dawley rat under urethane anaesthesia was given an injection of 10 µL of Chicago Blue dye into the 4th ventricle of the brain, followed 30 min later by an intraperitoneal injection of lipopolysaccharide (LPS, 0.5 mg/kg). Two hours after the LPS injection, the rat was perfused transcardially with formalin. The brain was removed and post-fixed in formalin overnight, then sectioned at 40 µm, stained for Iba1 immunoreactivity, and imaged with a Zeiss Z2 microscope. Both images in Fig. 1 are from the same section of tissue, at the level of the RVLM (Bregma −12.24 mm) (Paxinos and Watson, 1986). The top panel is an image taken from an area dorsal to the RVLM, while the bottom panel is taken from the ventral surface of the same tissue section. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

participate in synaptic pruning, phagocytosis of cellular debris, and monitoring of the surrounding parenchyma (Li et al., 2012; Sipe et al., 2016; Chen et al., 2014). During inflammation, injury, or neuronal excitotoxicity, microglia exhibit a range of complex responses to defend against infection, prevent the spread of damage, and initiate tissue repair (Szalay et al., 2016; Kato et al., 2016). Microglia can also affect neuronal excitability during inflammation (Fig. 2) (Moriguchi et al., 2003; Ferrini and De Koninck, 2013; Klapal et al., 2016; Stellwagen and Malenka, 2006; Hayashi et al., 2006). In general, a given stimulus will either increase or decrease microglial chemotaxis, which often coincides with a morphological change (Fig. 1). This visible response may be related to a change in secretory or phagocytic activity, usually involving the release of factors which can be broadly characterised as pro-inflammatory or anti-inflammatory (Soltys et al., 2005; Soltys et al., 2001). Although microglia populate the entire CNS, their phenotype and function may vary according to local neuronal populations (de Haas et al., 2008; De Biase et al., 2017). The heterogeneity of microglia across different brain regions has not been thoroughly explored. Gross brain structures such as the striatum, cortex, or cerebellum are often used in their entirety for gene expression analysis (Grabert et al., 2016), but this method may be too crude to detect differences between cardiorespiratory control centres and surrounding tissue. Although the basic features of defence and repair are likely present in all microglial cells, it is possible that microglia in cardiorespiratory nuclei have distinct patterns of gene expression, morphology, and function.

A currently unresolved question in this area is how the morphology of microglia relates to their activity. As a rule, de-ramification and cell soma enlargement indicates 'activation,' implying a profound change in secretory activity. 'Activated' microglia are characterised as either pro-inflammatory (M1 phenotype) or anti-inflammatory (M2 phenotype). Microglial process extension, motility, and branching is critical for the rapid response to disturbance, but this coincides with a decreased phagocytic capacity. However, microglia extend or retract their processes in response to a variety of stimuli which are not generally considered pro-inflammatory or anti-inflammatory. Therefore, while morphological analysis is useful, it should be used concurrently with physiological data which can assist interpretation of the functional relevance of microglial morphology.