Autonomic Neuroscience: Basic and Clinical 175 (2013) 51–60

Contents lists available at SciVerse ScienceDirect

Autonomic Neuroscience: Basic and Clinical

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

Bidirectional neuro-glial signaling modalities in the hypothalamus: Role in neurohumoral regulation

J.E. Stern *, J.A. Filosa

Department of Physiology, Georgia Health Sciences University, United States

ARTICLE INFO

Article history:
Received 10 September 2012
Received in revised form 17 December 2012
Accepted 26 December 2012

Keywords:
Paraventricular
Supraoptic
Astrocytes
Microglia
Sympathetic
Neuroendocrine
Oxytocin
Vasopressin
Nitric oxide
Glutamate
GABA

ABSTRACT

Maintenance of bodily homeostasis requires concerted interactions between the *neuroendocrine* and the *autonomic nervous systems*, which generate adaptive neurohumoral outflows in response to a variety of sensory inputs. Moreover, an exacerbated neurohumoral activation is recognized to be a critical component in numerous disease conditions, including hypertension, heart failure, stress, and the metabolic syndrome. Thus, the study of neurohumoral regulation in the brain is of critical physiological and pathological relevance. Most of the work in the field over the last decades has been centered on elucidating *neuronal* mechanisms and pathways involved in neurohumoral control. More recently however, it has become increasingly clear that non-neuronal cell types, particularly astrocytes and microglial cells, actively participate in information processing in areas of the brain involved in neuroendocrine and autonomic control. Thus, in this work, we review recent advances in our understanding of neuro-glial interactions within the hypothalamic supraoptic and paraventricular nuclei, and their impact on neurohumoral integration in these nuclei. Major topics reviewed include anatomical and functional properties of the neuro-glial microenvironment, neuron-to-astrocyte signaling, gliotransmitters, and astrocyte regulation of signaling molecules in the extracellular space. We aimed in this review to highlight the importance of neuro-glial bidirectional interactions in information processing within major hypothalamic networks involved in neurohumoral integration.

1. Introduction

Maintenance of bodily homeostasis requires concerted interactions between the *neuroendocrine* and the *autonomic nervous systems*. By controlling these two major information processing systems, specific neuronal networks within the central nervous system (CNS) generate adaptive *neurohumoral* responses, which are necessary for proper cardiovascular, fluid and energy balance system regulation. Neurohumoral activation is not only important within the context of adaptive physiological responses, but it is now also recognized to be a critical pathophysiological component in numerous disease conditions, including hypertension, heart failure, stress, and the metabolic syndrome (Cohn et al., 1981; Haywood et al., 1985; Middlekauff and Mark, 1998; Brook and Julius, 2000; Felder et al., 2001; Perez-Tilve et al., 2006). In the case of heart failure, for example, a compelling correlation between neurohumoral activation, morbidity and mortality in heart failure patients has been established (Cohn et al., 1984). Thus, elucidating precise anatomical pathways and cellular mechanisms underlying the generation of neurohumoral outflows by the brain is of critical physiological and clinical relevance.

Within the central neuronal circuitry involved in autonomic and neuroendocrine regulation, the hypothalamic paraventricular (PVN) and supraoptic (SON) nuclei stand as pivotal centers involved in the generation of coordinated neurohumoral responses (Cohn et al., 1984) (Swanson and Kuypers, 1980; Swanson and Sawchenko, 1983; Guyenet, 2006). Neurons in the PVN and SON are activated in response to a variety of afferent stimuli triggered by disturbances in the internal milieu, including dehydration, changes in blood pressure and blood volume, among others (Lovick and Coote, 1988; Li and Dampney, 1994; McKinley et al., 1994; Badoer et al., 1997; Krukoff et al., 1997; Schiltz et al., 1997; Randolph et al., 1998; Stocker et al., 2006). These afferent stimuli elicit in turn robust autonomic and neuroendocrine responses coordinated by tese nuclei, which include increases in sympathetic outflow to the kidney and vasopressin release (Stricker et al., 2002; Stocker et al., 2004, 2005).

The PVN is a highly heterogeneous nucleus, containing functionally diverse groups of neurons (Swanson and Sawchenko, 1983). These include: a) magnocellular neurosecretory cells (MNCs), which synthesize the neuropeptides vasopressin (VP) and oxytocin (OT). These neurons project to the posterior pituitary, from where VP and OT are released in response to a variety of stimuli, including hyperosmolarity and lactation; b) parvocellular neuroendocrine neurons, which project to the median eminence and secrete hypophysiotropic hormones, including corticotropin-releasing factor, thyrotropin-releasing hormone, and somatostatin; and c) parvocellular preautonomic neurons, which

* Corresponding author at: Georgia Health Sciences University, Department of Physiology, 1120 15th street, Augusta, GA 30912, United States. Tel.: +1 706 721 2180; fax: +1 706 721 7299.
E-mail address: jstern@georgiahealth.edu (J.E. Stern).

1566-0702/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.autneu.2012.12.009

send long descending projections to autonomic centers in the brainstem and spinal cord, and participate in autonomic control (Saper et al., 1976; Swanson and Sawchenko, 1980; van den Pol, 1982). The SON on the other hand, is a "purely" neurosecretory center, containing only OT and VP MNCs.

Neurohumoral outflow from these centers is directly dependent on the degree and pattern of neuronal activity of both neurosecretory and preautonomic neurons (Poulain and Wakerley, 1982; Cazalis et al., 1985; Allen, 2002; Akine et al., 2003; Stocker et al., 2004). Thus, elucidating precise mechanisms that regulate firing activity in these centers has been a major focus of work in this field. Over the last two decades, we have gain significant insights on intrinsic membrane properties and synaptic physiology of magnocellular and preautonomic PVN/SON neurons, and we refer the readers to excellent reviews and articles on this topic (Armstrong and Stern, 1998; Luther and Tasker, 2000; Stern, 2001; Akine et al., 2003; Brown, 2004; Sonner and Stern, 2007; Bourque, 2008; Iremonger and Bains, 2008; Chen and Toney, 2009). More recently however, it has become increasingly clear that non-neuronal cell types, particularly astrocytes and microglial cells, actively participate in information processing in the brain (Volterra and Meldolesi, 2005; Perea et al., 2009; Araque and Navarrete, 2010). Thus, the focus of the present review will be on recent advances in our understanding of neuro-glial interactions within the hypothalamic SON/PVN, with particular emphasis on astrocytes, and to a lesser extent microglial cells, and their impact on neurohumoral integration by these nuclei.

2. Bidirectional neuro-glia communication in the brain

While for many years astrocytes were regarded as passive supportive cells, the use of Ca^{2+} imaging technology (Tsien, 1980, 1981) unraveled their contribution in numerous processes including: development (Rakic, 2003), synaptic transmission (Volterra and Meldolesi, 2005; Perea and Araque, 2010), modulation of neuronal networks (Araque and Navarrete, 2010; Giaume et al., 2010) and the control of cerebral blood flow (Zonta et al., 2003; Mulligan and MacVicar, 2004; Filosa et al., 2006; Takano et al., 2006; Attwell et al., 2010), to name a few. The finding that astrocytes express a plethora of receptors and respond to numerous neurotransmitters gave name to the tripartite synapse model (Araque et al., 1999), which defines the ability of astrocytes not only to listen to neurons, but also to talk back. Astrocytes are equipped with the machinery to release gliotransmitters (Parpura et al., 1994, 2010) (e.g. glutamate, D-serine, ATP), and also express specialized transporters, which aid in the modulation of synaptic activity by altering the milieu at the synaptic/peri-synaptic space. Moreover, astrocytes play an important role in the buffering of extracellular glutamate and K^+ (Walz, 2000). Anatomically, a single astrocyte can enwrap thousands of synapses and create a physical barrier allowing direct interaction with neurons as well as neural networks (Giaume et al., 2010). Although controversial (Agulhon et al., 2008), a role for astrocytes in synaptic plasticity has been demonstrated, including both long term potentiation (LTP) and long term depression (LTD) (Henneberger et al., 2010; Pascual et al., 2005; Panatier et al., 2006a; Perea and Araque, 2007; Zhang et al., 2008). For example, astrocytes in the SON, via the release of the aminoacid D-serine (see more below) modulate the efficacy of NMDA-mediated long-term synaptic plasticity in MNNs (Panatier et al., 2006b).

Importantly, numerous developments of our current understanding of neuro-glial interactions in the brain emerged from pioneering work in hypothalamic centers involved in neurosecretory and autonomic control, including the SON and PVN. This has been the topic of excellent previous reviews (Hatton, 2004; Theodosis et al., 2008; Oliet et al., 2008b; Tasker et al., 2012), and an account of some of the most salient and recent developments in this area are summarized and discussed here.

3. Unique anatomical characteristics of the neuro-glial microenvironment in the SON and PVN

When considering functional interactions among neurons and glial cells in the SON/PVN, it is important to take into consideration several distinctive aspects of these centers. For example, detailed anatomical studies obtained from the magnocellular neurosecretory system in the SON/PVN revealed a highly "compact" neuro-glial microenvironment, in which the surface membrane of principal neurons is largely surrounded by astrocyte processes. Thus, under normal physiological conditions, astrocytes act as a physical and chemical barrier, limiting neuron–neuron interactions, as well as the diffusion of neurotransmitters in the extracellular space. Remarkably however, during conditions known to stimulate SON/PVN neuronal activity, such as dehydration and lactation, in the case of VP and OT neurons, respectively, the neuro-glial microenvironment undergoes a dramatic structural remodeling (Theodosis and Poulain, 1989, 1999; Hatton, 2004; Piet et al., 2004; Oliet et al., 2008a; Tasker et al., 2012). This plasticity involves rapid and reversible glial retraction from between neighboring neurons, unwrapping their synaptic contacts as well. This activity-dependent structural remodeling results in increased neuron-to-neuron juxtapositions, accumulation of extracellular K^+, and build up of neurotransmitter levels in the extracellular space (see more below), all of which facilitate homeostatic responses in order to properly cope with these physiological challenges. A caveat to be taken into consideration, however, is that most of these studies relate to the magnocellular neurosecretory system. Thus, whether a similar neuro-glial organization and plasticity can be extrapolated to other neuronal types in the PVN, particularly preautonomic neurons, is at present unknown. Nonetheless, the SON/PVN has already proven to be a unique experimental model to investigate neuro-glial interactions in the brain.

4. Neuron-to-astrocyte signaling

In addition to classical neurotransmitters, such as glutamate and GABA (Decavel and Van den Pol, 1990; van den Pol, et al., 1990), an abundance of functionally-relevant neuropeptides, including VP, OT, a-MSH, NPY, AGRP, dynorphin, galanin and endothelins, among others (Hokfelt et al., 2000; Landgraf and Neumann, 2004; Ludwig and Leng, 2006) is pivotal signaling molecules within hypothalamic neuronal networks.

Here, we summarize recent studies supporting communication from neurons to astrocytes in the SON and PVN, via classical neurotransmitters as well as neuropeptides.

4.1. Noradrenaline and glutamate

In an elegant study, Gordon et al. (2005) showed that noradrenaline binds on α_1-adrenoceptors on PVN astrocytes to stimulate ATP release (Gordon et al., 2005), which then acting on neighboring MNCs, leads to the Ca^{2+}-dependent insertion of AMPA receptors, increasing neuronal sensitivity to synaptically-released glutamate. In another study, the same group showed that the activation of mGLUR1,5 receptors by synaptically released glutamate was also capable of evoking ATP release from PVN astrocytes (Gordon et al., 2009). Along these lines, Espallergues et al. showed that NE and ATP acted synergistically to increase $[Ca^{2+}]i$ on SON astrocytes. However, the functional consequences of the evoked changes in astrocytes $[Ca^{2+}]i$ were not further assessed (Espallergues et al., 2007).

Results from these experiments provide noteworthy insights into the potential contribution of neuro-glial communication to the generation of integrative neurohumoral homeostatic responses by the PVN. Catecholaminergic afferent inputs originating from A1 caudal medulla neurons and from A2 neurons in the nucleus of the tractus solitarious (Cunningham et al., 2004; Renaud and Bourque,