Neuroscience and Biobehavioral Reviews 74 (2017) 366–375

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review article

Ascending mechanisms of stress integration: Implications for brainstem regulation of neuroendocrine and behavioral stress responses

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ARTICLE INFO

Article history:
Received 20 February 2016
Received in revised form 12 May 2016
Accepted 17 May 2016
Available online 18 May 2016

Keywords:
Hypothalamic-pituitary-adrenocortical axis
Paraventricular hypothalamic nucleus
Nucleus of the solitary tract
Glucocorticoid

ABSTRACT

In response to stress, defined as a real or perceived threat to homeostasis or well-being, brain systems initiate divergent physiological and behavioral processes that mobilize energy and promote adaptation. The brainstem contains multiple nuclei that engage in autonomic control and reflexive responses to systemic stressors. However, brainstem nuclei also play an important role in neuroendocrine responses to psychogenic stressors mediated by the hypothalamic-pituitary-adrenocortical axis. Further, these nuclei integrate neuroendocrine responses with stress-related behaviors, significantly impacting mood and anxiety. The current review focuses on the prominent brainstem monosynaptic inputs to the endocrine paraventricular hypothalamic nucleus (PVN), including the periaqueductal gray, raphe nuclei, parabrachial nuclei, locus coeruleus, and nucleus of the solitary tract (NTS). The NTS is a particularly intriguing area, as the region contains multiple cell groups that provide neurochemically-distinct inputs to the PVN. Furthermore, the NTS, under regulatory control by glucocorticoid-mediated feedback, integrates affective processes with physiological status to regulate stress responding. Collectively, these brainstem circuits represent an important avenue for delineating interactions between stress and health.

Contents

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http://dx.doi.org/10.1016/j.neubiorev.2016.05.011
0149-7634/

1. Introduction

In response to real or perceived threats to homeostasis or well-being, an organism generates multiple integrated stress responses that provide resources for physiological and behavioral adaptation (De Kloet et al., 2005; Myers et al., 2014b). Physiological stress responses promote energy mobilization and redistribution through two primary systems, the autonomic nervous system and the hypothalamic-pituitary-adrenocortical (HPA) axis (for review see Ulrich-Lai and Herman, 2009). Autonomic responses to stress increase heart rate, blood pressure, and glucose availability, providing energetic substrates for stress adaptation (Ulrich-Lai and Herman, 2009). The neuroendocrine HPA axis causes the secretion of glucocorticoids (principally corticosterone in rodents and cortisol in humans) from the adrenal cortex (Keller-Wood and Dallman, 1984). Activity of the HPA axis is initiated by parvocellular corticotropin-releasing hormone (CRH) neurons of the paraventricular nucleus of the hypothalamus (PVN). At the level of the anterior pituitary, CRH leads to the systemic release of adrenocorticotropic hormone (ACTH), the primary stimulus for glucocorticoid secretion (Ulrich-Lai and Herman, 2009). Glucocorticoids then signal throughout the body to regulate many systemic and neural functions, including hepatic glycogenolysis and neuronal metabolism (Herman, 2013; Herman et al., 2003). Behavioral stress responses depend on a large network of brain systems involved in appraisal, emotion, and memory (Joëls and Baram, 2009; Sousa and Almeida, 2012). Behavioral-regulatory circuits include forebrain sites such as the amygdala, prefrontal cortex, and hippocampus; importantly, these networks also interact with the hypothalamus and brainstem to integrate behavioral responses with HPA axis and autonomic activity (Joëls and Baram, 2009; McKlveen et al., 2015; Ulrich-Lai and Herman, 2009).

Aberrant activation of the HPA axis plays a role in many psychiatric illnesses including depression, anxiety, and post-traumatic stress disorder (for review see Refs. Jacobson, 2014; Ströhle and Holsboer, 2003). Glucocorticoids also exert profound effects on somatic health, particularly cardio-metabolic processes (Vogelzangs et al., 2010). In fact, cardiomyocyte glucocorticoid signaling is essential for maintaining cardiac function and survival (Oakley et al., 2013). Glucocorticoids also act in the hindbrain to increase arterial pressure and modulate baroreflex control (Bechtold and Scheuer, 2006; Scheuer et al., 2007). Therefore, the ascending brainstem circuits that regulate HPA axis activity and stress-related behaviors represent an important avenue for delineating the complex relationships between stress, behavior, and health.

The current review considers the key brainstem nuclei providing direct input to the PVN, circuits that have predominantly been mapped in rodents. We discuss their connectivity, chemistry, and role in HPA axis and behavioral stress responses, principally anxiety-, fear-, and depression-related behaviors. Although the autonomic nervous system mediates many important aspects of stress responsiveness, the role of the brainstem in autonomic regulation has been described elsewhere (see Refs. Ally, 1998; Bandler et al., 2000; Scislo and O'Leary, 2005 for review). Therefore, the current review will focus on the ascending pathways to the endocrine hypothalamus and their effects on behavior. The brainstem also gives rise to neuromodulatory projections that collateralize throughout the brain. These primarily aminergic systems regulate neural and behavioral function throughout the limbic system and cortex. Cataloging the diversity of these functions is beyond the scope of a single review; thus, we will provide references, where applicable, to reviews that focus on specific messenger systems and their effects on behavior mediated through interactions with the forebrain. Brainstem projections to the forebrain also have indirect effects on HPA axis stress responses via neuromodulation within limbic structures (Radley et al., 2008). These multisynaptic network-level mechanisms have yet to be unraveled; consequently, we will focus on the monosynaptic brainstem inputs to the PVN. Our review outlines brainstem nuclei that directly regulate the HPA axis, from rostral to caudal these are the periaqueductal gray (PAG), raphe nuclei, parabrachial nuclei (PBN), and locus coeruleus (LC). Additionally, we will explore the nucleus of the solitary tract (NTS) in detail and its rich collection of messengers that interact with glucocorticoids, including norepinephrine, glucagon-like peptide-1 (GLP-1), and glutamate. Finally, we will discuss how recent advances have expanded our understanding of the role of ascending brainstem projections, suggesting that these circuits form a critical hub for integrating interoceptive input with descending limbic information to coordinate endocrine and behavioral stress responses.

2. Brainstem inputs to the paraventricular hypothalamus (PVN)

The PVN is composed of a relatively small number of neuropeptide-containing cells that regulate many aspects of endocrine and homeostatic function (for reviews see Refs. Herman et al., 2002a,b). Although some PVN neurons project within the central nervous system and act in a pre-autonomic fashion, other PVN cell groups are neuroendocrine (Biag et al., 2012; Hallbeck and Blomqvist, 1999). Thus, multiple subregions of the PVN are defined based on neurochemistry and connectivity (for reviews see Refs. Herman et al., 2008; Swanson and Sawchenko, 1983). Generally, the PVN is divided into magnocellular and parvocellular regions. For instance, the anterior, medial, and posterior magnocellular portions of the PVN contain neurons that synthesize oxytocin and vasopressin for release from neurosecretory terminals in the posterior pituitary (Van Leeuwen et al., 1979). Within parvocellular regions, the lateral, dorsal, and ventromedial areas give rise to central projections that target the basal forebrain, brainstem, and spinal cord (Swanson and Sawchenko, 1983). These central circuits regulate numerous autonomic and behavioral processes through the release of oxytocin, vasopressin, and other transmitters (Knobloch and Grinevich, 2014). Importantly, the dorsomedial and anterior divisions of parvocellular neurosecretory cells project to the median eminence where they secrete CRH, the primary ACTH secretagogue, as well as vasopressin, which acts synergistically with CRH to promote HPA axis activity (Sawchenko et al., 1984; Vale et al., 1981). Thus, the HPA axis response to stress originates in a circumscribed collection of neurosecretory cells in the PVN (Ulrich-Lai and Herman, 2009). These cells express a multitude of neurotransmitter and peptide receptors that integrate signals from PVN-projecting circuits. Importantly, the PVN only receives direct synaptic input from a restricted number of brain regions (for review see Ref. Herman et al., 2003). These PVN-projecting afferents arise from other hypothalamic nuclei, the bed nucleus of the stria terminalis (BST), and importantly, the brainstem (Fig. 1). The intra-hypothalamic interactions have been described in detail (Cullinan et al., 1996; Myers et al., 2014a; Ulrich-Lai et al., 2011), as have projections from the BST (Choi et al., 2007; Cullinan et al., 1996; Dong and Swanson, 2006; Dong et al., 2001; Radley and Sawchenko, 2011). Briefly, these circuits have been proposed to form a hierarchy for mediating limbic stress integration and regulating HPA axis responses to psychogenic stressors (Herman et al., 2005; Myers et al., 2012). In contrast, brainstem projections have been postulated to mediate reflexive responses to systemic stressors. However, the multiple brainstem nuclei innervating the PVN represent a substantial proportion of stress-regulatory input to CRH neurons (Larsen and Mikkelsen, 1995; Ziegler et al., 2012). Accordingly, these structures are well-positioned to regulate endocrine