Frontiers in Neuroendocrinology 35 (2014) 180–196

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

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

Review

Glucocorticoid actions on synapses, circuits, and behavior: Implications for the energetics of stress

Brent Myers [1], Jessica M. McKlveen [1], James P. Herman *

Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati, Cincinnati, OH, United States

ARTICLE INFO

Article history:
Available online 18 December 2013

Keywords:
Hypothalamo–pituitary–adrenocortical axis
Corticosterone
Prefrontal cortex
Amygdala
Hippocampus
Hypothalamus
Glucocorticoid receptor
Mineralocorticoid receptor

ABSTRACT

Environmental stimuli that signal real or potential threats to homeostasis lead to glucocorticoid secretion by the hypothalamic–pituitary–adrenocortical (HPA) axis. Glucocorticoids promote energy redistribution and are critical for survival and adaptation. This adaptation requires the integration of multiple systems and engages key limbic-neuroendocrine circuits. Consequently, glucocorticoids have profound effects on synaptic physiology, circuit regulation of stress responsiveness, and, ultimately, behavior. While glucocorticoids initiate adaptive processes that generate energy for coping, prolonged or inappropriate glucocorticoid secretion becomes deleterious. Inappropriate processing of stressful information may lead to energetic drive that does not match environmental demand, resulting in risk factors for pathology. Thus, dysregulation of the HPA axis may promote stress-related illnesses (e.g. depression, PTSD). This review summarizes the latest developments in central glucocorticoid actions on synaptic, neuroendocrine, and behavioral regulation. Additionally, these findings will be discussed in terms of the energetic integration of stress and the importance of context-specific regulation of glucocorticoids.

1. Introduction

The scientific understanding of 'stress' and its ramifications for the organism have continually evolved. Based on Claude Bernard's theory of the internal milieu, Walter Cannon first used the concept of homeostasis to explain the 'fight-or-flight' response of an organism presented with a threat (Cannon, 1932). In a biological sense, Hans Selye coined the term 'stress' as the non-specific response of the body to any homeostatic demand (Selye, 1936). While it is still generally accepted that the physiological role of the stress response is to coordinate autonomic, neuroendocrine, and immune responses to potential homeostatic threats, an emerging concept in stress neurobiology suggests that the primary role of stress responding is to mobilize energy to promote context-specific survival and not necessarily sustain homeostatic systems at levels maintained prior to a challenge (Dallman et al., 2006; Nederhof and Schmidt, 2013). Given this framework, responses to both acute and chronic stress are considered adaptive, up to a point, and prepare the organism for current and future demands. Thus, for the purpose of the current review, stress will be defined as a stimulus that mobilizes energetic systems to respond to an ongoing or anticipated challenge.

Responding to stress involves the concerted activity of multiple, interacting central stress-regulatory systems to mobilize energy for the organism. Activation of the stress response occurs either as a consequence of, or in anticipation of, a challenge (Myers et al., 2012b). Anticipatory responses require the organism to reference prior experiences to predict the need for energy mobilization, primarily mediated by multi-synaptic forebrain projections to the medial parvocellular paraventricular nucleus (PVN) of the hypothalamus. Systemic challenges are largely reflexive responses to physiological disruption generated by direct projections from the hindbrain to the PVN, though there is considerable overlap and integration at various nodes throughout the brain (Herman et al., 2012, 2003; Ulrich-Lai and Herman, 2009). Thus, the neuroendocrine response to stress is a highly-regulated, temporal process, involving the integration of sensory information from multiple modalities to rapidly activate, as well as inhibit the secretion of glucocorticoids.

The neuroendocrine stress cascade, comprising the hypothalamic–pituitary–adrenocortical (HPA) axis, begins with the release of adrencorticotropic hormone (ACTH) secretagogues from neurosecretory neurons in the medial parvocellular PVN, which project to hypophysial portal vessels in the external zone of the median eminance (Bruhn et al., 1984). Secretagogues travel via the portal veins to the anterior pituitary, where they can access corticotropes (De Wied et al., 1957; Gibbs and Vale, 1982; McCann and Fruit, 1957; Saffran and Schally, 1956). The pioneering work of Wylie Vale and colleagues provided initial identification of corticotropin

* Corresponding author. Address: Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati, Metabolic Diseases Institute, 2170 East Galbraith Road, Cincinnati, OH 45237, United States. Fax: +1 513 558 9104.
E-mail address: james.herman@uc.edu (J.P. Herman).
[1] Authors contributed equally.

0091-3022/$ - see front matter © 2014 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.yfrne.2013.12.003

releasing factor (CRF) as the primary driver of pituitary ACTH release (Bale and Chen, 2012; Rivier et al., 1983a,b; Rivier et al., 1982; Spiess et al., 1981; Swanson et al., 1983; Vale et al., 1981). Subsequent studies, also by Vale and colleagues, revealed the existence of several co-secretagogues that synergize with CRF, including arginine vasopressin (AVP) (Rivier and Vale, 1983a, 1983b; Sawchenko et al., 1984; Vale et al., 1981, 1983). By way of the systemic circulation, ACTH acts at the level of the adrenal cortex to induce the release of glucocorticoids, cortisol in some species (e.g., humans, non-human primates) and corticosterone in others (e.g., rats, mice) (Dallman and Jones, 1973; Dallman et al., 1987). At the adrenal, cortisol/corticosterone is released in pulses, the timing of which dictates the overall magnitude of both baseline activity and stress responses (Lightman et al., 2008; Young et al., 2004). Pulsatile patterns of glucocorticoid release are dictated by ultradian rhythms (for review see de Kloet and Sarabdjitsingh, 2008; Sarabdjitsingh et al., 2012a). This rhythmicity of glucocorticoid release is essential for maintaining cellular responsiveness and promotes wide-ranging glucocorticoid actions from gene transcription to behavior (Conway-Campbell et al., 2010; Sarabdjitsingh et al., 2010b). Glucocorticoids then travel throughout the body, exerting a multitude of effects in the periphery including glycogen breakdown and gluconeogenesis (Coderre et al., 1991; Exton, 1979; Munck et al., 1984; for detailed reviews of brain circuits regulating glucose homeostasis see Schwartz et al., 2000; Seeley and Woods, 2003; Woods et al., 1998). Glucocorticoids cross the blood–brain-barrier, and primarily bind to mineralocorticoid (MR) and glucocorticoid receptors (GR) in neurons and/or glia. In the brain, MR has high-binding affinity for corticosteroids and, consequently, is activated at basal levels (de Kloet and Sarabdjitsingh, 2008; de Kloet et al., 1998). Thus, MR is thought to sense resting levels of glucocorticoids and promote key functions associated with low glucocorticoid levels, including circadian drive of the HPA axis and mnemonic function (de Kloet et al., 2005). Conversely, GR has a lower binding affinity for glucocorticoids and is largely unoccupied at basal levels. Thus, GR is thought to be particularly important in signaling mediated by stress levels of glucocorticoids (Boyle et al., 2005; de Kloet and Reul, 1987; de Kloet et al., 2005; Reul and de Kloet, 1985). GR is abundantly expressed throughout the brain, including the primary stress-regulatory sites discussed in this review: medial prefrontal cortex (mPFC), hippocampus, amygdala, bed nucleus of the stria terminalis (BST), hypothalamus, and hindbrain (Fuxe et al., 1987; Meaney et al., 1985; Reul and de Kloet, 1986). MR has a more restricted distribution that overlaps with that of GR in several key regions, including the mPFC, hippocampus, and amygdala (de Kloet and Reul, 1987; Reul and de Kloet, 1985).

There is a vital need for glucocorticoid activity to be tightly regulated, requiring systems coordination from cellular to behavioral levels. In response to stress, glucocorticoid signaling promotes organismal adaptation to environmental conditions and helps to meet the resulting energetic demands. This adaptation requires the integration of multiple systems and engages key limbic-neuroendocrine circuits. Forebrain, hypothalamic, and hindbrain circuits are activated by glucocorticoids and participate in the coordination of physiological and behavioral output. However, when energetic drive does not appropriately match environmental demand, or the organism is chronically activating these systems, risk factors emerge for a variety of stress-related pathologies. The present article will review the actions of glucocorticoids in central stress-regulatory circuits, focusing on the rodent literature, in the context of the adaptive role of the stress response for the organism. The review will summarize the role of central glucocorticoid actions on synaptic, neuroendocrine, and behavioral regulation, highlighted by a discussion of the energetic integration of stress and the importance of context-specific regulation of glucocorticoids. The energy mobilizing effects of glucocorticoids require integration of cellular activity, circuit connectivity, and behavioral output to coordinate context-appropriate adaptation. We propose that glucocorticoid-mediated energetic drive generates an adaptive capacity in response to environmental demand; however, the cost of repeatedly or excessively driving adaptive systems may compromise performance under conditions of elevated environmental pressure. Thus, we will examine the integrative actions of glucocorticoids on the primary limbic sites mediating organismal stress responsiveness within the framework of context-specific adaptation.

2. Synaptic actions of clucocorticoids

The cellular actions of glucocorticoids are largely dependent on brain site and the relative expression of GR and MR (de Kloet, 2013a) (Table 1). Glucocorticoids also act in concert with monoaminergic and peptide neurotransmitters, particularly noradrenergic (Quirarte et al., 1997; Roozendaal et al., 2008, 2006a,b, 2002) and CRF systems (Bale and Vale, 2004; Bale, 2005; Meng et al., 2011), which have been reviewed elsewhere (de Kloet, 2013b; Ferry and McGaugh, 2000; Heinrichs and Koob, 2004; Roozendaal, 2000). Further, the synaptic actions of glucocorticoids are critically affected by the recent stress history of the organism, a concept known as 'metaplasticity', which will be expanded on in the following section (for review see: Schmidt et al., 2013). Acute and chronic stress often yield different effects on cellular function to meet context-specific energetic demands placed on the organism. Thus, we will discuss the effects of glucocorticoids on cellular function in light of these considerations.

2.1. Medial prefrontal cortex

The mPFC is the executive control center of the brain, providing top-down regulation of behavioral function. Thus, it is a key site for glucocorticoid actions and regulation of the HPA axis (Akana et al., 2001; Diorio et al., 1993; McKlveen et al., 2013). The rodent mPFC is comprised of three subdivisions, based on connectivity and cytoarchitecture: the anterior cingulate, prelimbic (plPFC), and infralimbic (ilPFC) cortices (Uylings et al., 2003; Vertes, 2004). On the basis of structure and function, these regions are thought to be homologous to human Brodmann areas 24b, 32, and 25, respectively (Gabbott et al., 2005; Uylings et al., 2003).

Molecular and functional studies indicate that glucocorticoids acutely increase glutamatergic output from the mPFC (Popoli et al., 2012). Microdialysis and microelectrode sampling experiments indicate increased extracellular glutamate *in vivo* in the mPFC following acute stress (Bagley and Moghaddam, 1997; Hascup et al., 2010; Moghaddam, 1993). Acute foot shock increases depolarization-evoked release of glutamate in isolated synaptosomes via a GR-dependent mechanism and increases the amplitude of excitatory postsynaptic currents (EPSCs) in mPFC pyramidal neurons (Musazzi et al., 2010). In adolescent rats, acute stress also increases NMDA- and AMPA-mediated excitatory currents by up-regulating the expression of these receptors on the postsynaptic membrane (via serum- and glucocorticoid-inducible kinases) (Yuen et al., 2011, 2009). Thus, existing data suggest that acute stress activates mPFC neurons, permitting down-stream activation of target regions (see below).

Very few studies have assayed inhibitory neurotransmission after acute corticosterone application. A recent study in mice found that corticosterone decreased miniature inhibitory postsynaptic currents (mIPSCs) and increased paired pulse inhibition, suggesting that acute glucocorticoid exposure disinhibits glutamatergic