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

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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.

Keywords

Hypothalamo-pituitary-adrenocortical axis; corticosterone; prefrontal cortex; amygdala; hippocampus; hypothalamus; glucocorticoid receptor; mineralocorticoid receptor

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

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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 releasing factor (CRF) as the primary driver of pituitary ACTH release (Bale and Chen, 2012; C. Rivier et al., 1983; Rivier et al., 1982; J. Rivier et al., 1983; 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., 1983, 1981). 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 Glucocorticoids

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, 2006b, 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 glucocorticoidinducible 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 output from the mPFC (Hill et al., 2011). The effects of corticosterone on mIPSCs were prevented by CB1 antagonism, suggesting that the effect of acute stress on disinhibition of mPFC pyramidal neurons is likely endocannabinoid-dependent (Hill et al., 2011). Overall, the present data suggest that glucocorticoids acutely increase glutamatergic neurotransmission and decrease inhibitory neurotransmission in the mPFC. It remains to be determined whether reduced inhibition contributes to enhanced mPFC excitability.

The synaptic effects of glucocorticoids in the mPFC during chronic stress are not as well established, and the effects on excitatory and inhibitory neurotransmission are largely unknown. Repeated restraint stress, chronic unpredictable stress, or chronic corticosterone treatment decrease apical dendritic complexity of pyramidal neurons (Cerqueira et al., 2007, 2005; Cook and Wellman, 2004; Goldwater et al., 2009; Liston et al., 2006; Radley et al.,

2006, 2004; Wellman, 2001). Conversely, repeated restraint stress increases the complexity and transcriptional activity of prefrontal GABAergic interneurons (Gilabert-Juan et al., 2012). While the functional consequence of these morphologic modifications is unknown, the direction of changes suggests both decreased pyramidal cell excitability and increased capacity for interneuron-mediated inhibition.

In adolescent rats, chronic stress decreases NMDA- and AMPA-mediated currents in the mPFC through increased degradation of postsynaptic glutamate receptors (Yuen et al., 2012). Notably, adolescence is a developmental period marked with pruning of prefrontal glutamatergic synapses, particularly those to the basolateral amygdala (BLA) (Cressman et al., 2010). Therefore, it remains to be determined whether increased degradation of glutamate receptors is due to chronic stress or stress/development interactions (for review on adolescent synaptic plasticity see Selemon, 2013). In adult animals, chronic corticosterone administration decreases expression of NMDA subunit NR2B and AMPA subunits GluR2/GluR3 in the ventral mPFC (Gourley et al., 2009). However, the impact of chronic stress on inhibitory neurotransmission in the mPFC has not been directly tested, further highlighting the need for a better understanding of chronic glucocorticoid effects on synaptic physiology in adult animals.

2.2 Hippocampus

The hippocampus is critical for processes related to memory, particularly spatial and contextual learning and memory retrieval (Roozendaal and McGaugh, 1997a; Roozendaal et al., 2001). The hippocampus consists of multiple subregions, including the CA1 and CA3 regions, the dentate gyrus, and the ventral subiculum (Swanson and Cowan, 1977). The actions of glucocorticoids in the hippocampus have long been recognized (McEwen et al., 1968) and have been studied in great detail. Both MR and GR are abundantly expressed in hippocampus, and memory processing is heavily influenced by circulating levels of glucocorticoids (Fuxe et al., 1987; Meaney et al., 1985; Oitzl and de Kloet, 1992; Reul and de Kloet, 1986). Moreover in addition to a role in memory processes, the hippocampus (specifically the ventral subiculum) inhibits HPA axis responses to psychogenic stressors (Herman et al., 2003, 1998, 1989).

The cellular actions of glucocorticoids in the hippocampus (predominantly CA1 pyramidal neurons) have been very well characterized, particularly by Joëls and colleagues (for review see Joëls et al., 2012). The rapid, non-genomic effects of glucocorticoids (occurring within minutes) are mediated primarily by the membrane-associated MR at the pre- and postsynaptic membrane (Joëls et al., 2008; Karst et al., 2005; Olijslagers et al., 2008; Pasricha et al., 2011). Activation of MR increases neuronal excitability by increasing the probability of glutamate release, suppressing potassium conductance, and increasing glutamate receptor trafficking (Groc et al., 2008; Karst et al., 2005; Olijslagers et al., 2008). Conversely, the delayed effects of glucocorticoids are mediated primarily by GR (Karst and Joëls, 2005). Activation of GR causes delayed suppression of neuronal excitability (due to enhanced calcium influx, decreased calcium efflux, and increased calcium-dependent potassium current) and synaptic plasticity (impaired long-term potentiation (LTP) due to lateral diffusion of glutamate receptors), presumably to normalize hippocampal activity after

stress and protect information acquired during the stressful experience, respectively (Bhargava et al., 2002; Chameau et al., 2007; Groc et al., 2008; Joëls and de Kloet, 1990, 1989; Joëls, 2006; Joëls et al., 2009, 2007; Karst et al., 1994; Kim and Diamond, 2002; Pavlides et al., 1996). The ventral part of the hippocampus responds to glucocorticoids much differently than the dorsal hippocampus. Upon corticosterone application, the ventral hippocampus has reduced firing frequency accommodation and more depolarization-associated spikes (Maggio and Segal, 2009a). Further, unlike CA1, stress does not lead to impaired LTP in the ventral subiculum (Maggio and Segal, 2010, 2009b, 2007). These differential effects in the ventral hippocampus may allow for a longer window of acquisition when this brain region is activated during a stressful experience (Joëls et al., 2012). The prominent role of the ventral hippocampus/subiculum in inhibiting HPA axis stress responses raises the possibility that differential actions of stress/glucocorticoids on synaptic function may be relevant to stress regulation.

The effect of chronic stress on cellular physiology in the hippocampus is fairly well characterized. In chronically stressed animals, LTP in the CA1 hippocampal area and dentate gyrus is impaired at basal levels of corticosterone and is not further impaired in the CA1 hippocampal area or dentate gyrus following corticosterone application (Alfarez et al., 2003). The effects of chronic stress on synaptic plasticity in the CA1 hippocampal area are likely GR-mediated, as blockade of GR during the last 4 days of chronic stress blocks the effects of stress on LTP (Krugers et al., 2006). Further, animals with a history of chronic stress have GR-dependent increases in calcium influx into CA1 neurons at basal levels of corticosterone, which may contribute to impaired synaptic plasticity (Karst and Joëls, 2007). These impairments of synaptic plasticity in the hippocampus following chronic stress likely underlie some of the cognitive impairments observed with chronic stress exposure.

2.3 Amygdala

The amygdala integrates emotional and sensory information for the expression of fear and anxiety (Charney and Deutch, 1996; Davis, 1997; Phelps and LeDoux, 2005; Weiskrantz, 1956). Additionally, the amygdala is involved in the learning and consolidation of emotional memories and has an essential role in conditioned responses (Davis, 1992; LeDoux, 2012). The amygdala is composed of multiple subnuclei that are anatomically and physiologically heterogeneous. Of these subnuclei, the basolateral (BLA), central (CeA), and medial (MeA) cell groups appear to be most closely linked to regulation of stress responses (Sah et al., 2003; Swanson and Petrovich, 1998; Ulrich-Lai and Herman, 2009).

Similar to the hippocampus, glucocorticoids rapidly increase mEPSCs in the BLA via the membrane associated-MR (Karst et al., 2010). In contrast to the suppressive and normalizing effects of glucocorticoids on cellular responses in the hippocampus following acute stress, glucocorticoids in the BLA prolong excitatory synaptic responses via GR (Duvarci and Paré, 2007; Karst et al., 2002; Liebmann et al., 2008; Rainnie et al., 2004). Further, subsequent corticosterone application or acute stress prior to slice preparation decreases mEPSC frequency in the BLA via the GR and CB1 receptor (Karst et al., 2010). Thus, the cellular responses of BLA neurons to glucocorticoids depend on the recent history of stress exposure, an effect known as metaplasticity (Joëls et al., 2012; Karst et al., 2010). In

response to acute noise stress, amygdalar c-fos mRNA expression increases only during the rising phase of pulsatile glucocorticoid infusion in adrenalectomized animals, as opposed to the falling phase or during constant infusion of corticosterone, further suggesting that rapid reactivity of the amygdala to glucocorticoids is highly dependent on recent changes in glucocorticoid status (Sarabdjitsingh et al., 2010a). Stress also impairs LTP in projections from the BLA to the plPFC and in the ventral hippocampus-mPFC pathway (Maroun and Richter-Levin, 2003; Richter-Levin and Maroun, 2010). The stress-induced impairment of LTP in the ventral hippocampus-mPFC pathway does not occur in previously stressed animals if the BLA is stimulated or if animals receive a second bout of stress (Richter-Levin and Maroun, 2010), another example of metaplasticity. While stress impairs LTP in BLA projections, LTP in afferents to the BLA is strengthened, including input from the entorhinal cortex, external capsule, and plPFC (Kavushansky et al., 2006; Maroun, 2006; Rodríguez Manzanares et al., 2005; Vouimba et al., 2004). Further, unpredictable footshock facilitates LTP in the BLA, which may be due to a stress-induced increase in GluR1 in spines from dendritic stores (Li et al., 2011; Hubert et al., 2013). The effects of stress on LTP in the BLA appear to be primarily mediated by GR as MR is involved in the maintenance of LTP, regardless of circulating glucocorticoid levels (Sarabdjitsingh et al., 2012b).

3. Connectivity and Integration of Glucocorticoid-Responsive Circuits

Stress integrative functions are regulated by forebrain circuits, primarily involving the above mentioned regions (mPFC, hippocampus, and amygdala) (Ulrich-Lai and Herman, 2009) (Table 2). Notably, these interconnected limbic forebrain sites do not send substantial projections to stress-effector neurons in the PVN. Thus, their influence on HPA axis output is communicated through intervening PVN-projecting neurons. Inhibitory GABAergic inputs to the PVN emanate from several structures in the basal forebrain and hypothalamus, including the BST, preoptic area (POA), and dorsomedial hypothalamus (DMH) (Boudaba et al., 1996; Radley et al., 2009; Roland and Sawchenko, 1993). In contrast, glutamatergic inputs to the PVN originate predominantly from hypothalamic nuclei, including the ventromedial hypothalamus (VMH), posterior hypothalamus (PH), as well as DMH (Ulrich-Lai et al., 2011). Neurons in these regions, including those that project to the PVN, show pronounced activation by stressful stimuli (Cullinan et al., 1996, 1995), consistent with a role in stress regulation. All hypothalamic PVN-projecting regions receive mixed GABAergic and glutamatergic input from other hypothalamic nuclei (Myers et al., 2013), which may be responsible for intrahypothalamic mechanisms governing the integration of forebrain limbic inputs and stress responsiveness based on metabolic demand.

Importantly, GR is expressed in numerous hypothalamic PVN-projecting neurons, including the POA, DMH, and arcuate nucleus (Fuxe et al., 1987). In the PVN, glucocorticoids signal by non-genomic mechanisms to rapidly inhibit activation of parvocellular neurons and consequent drive on the HPA axis (Evanson et al., 2010; Tasker and Herman, 2011). These ‘fast feedback’ glucocorticoid effects are non-genomic in nature, acting through an endocannabinoid-dependent mechanism to inhibit glutamatergic drive (Tasker and Herman, 2011). Fast inhibitory effects of glucocorticoids are attenuated in animals with PVN GR deletion, consistent with action via GR (Haam et al., 2010). However, the role of GR in other PVN-projecting hypothalamic cell groups remains to be determined.

3.1 Medial Prefrontal Cortex

Previous studies determined that glucocorticoids act at the mPFC to inhibit HPA axis responses to psychogenic stress (e.g. restraint) (Akana et al., 2001; Diorio et al., 1993). More recently, we established that glucocorticoids bind specifically to GR in the plPFC or ilPFC to regulate glucocorticoid responses to acute psychogenic stress (McKlveen et al., 2013). Glucocorticoids also mobilize endocannabinoids in the mPFC in response to acute stress, and cannabinoid receptor 1 (CB1) antagonism disinhibits the HPA axis (Hill et al., 2011). Thus, glucocorticoids acutely inhibit the HPA axis via GR and consequent effects on endocannabinoid signaling. Our lab has also demonstrated that chronic stress selectively recruits ilPFC glucocorticoid signaling to inhibit the HPA axis stress response during chronic stress, while the plPFC appears to be involved in maintaining basal glucocorticoid levels during chronic stress (McKlveen et al., 2013). Thus, glucocorticoids in the mPFC play a region- and context-specific role in HPA axis regulation during acute and chronic stress. Prefrontal output neurons are almost exclusively glutamatergic, and projections from the plPFC to GABAergic neurons in the anterior BST mediate inhibition of HPA responses to acute stress (Radley et al., 2009). The intervening structures relaying the influence of the ilPFC to the PVN have yet to be determined. Preliminary studies from our group indicate the PH may be important for integrating ilPFC output with HPA responses (Myers et al., 2012a).

3.2 Hippocampus

The hippocampus is involved in terminating HPA axis responses to acute psychogenic stress, consistent with a role in memory and emotion processing (Cullinan et al., 1993; Herman et al., 1989; Mueller et al., 2004; Radley and Sawchenko, 2011). The importance of the hippocampus for glucocorticoid negative feedback is highlighted by the dense expression of GR and MR in this area (Reul and de Kloet, 1985), as well as functional studies demonstrating diminished feedback efficacy following hippocampal lesions (Herman and Mueller, 2006; Mueller et al., 2006). Surprisingly, feedback effects of glucocorticoids in the hippocampus may be mediated by MR, as multiple studies indicate that MR antagonists in the hippocampus increase HPA axis output (Feldman and Weidenfeld, 1999; van Haarst et al., 1997). The role of hippocampal GR in glucocorticoid negative feedback is more equivocal. Although GR antagonism has been shown to increase HPA axis activation in response to psychogenic stress (Feldman and Weidenfeld, 1999), other studies indicate that local GR inactivation actually decreases ACTH release at the diurnal peak of glucocorticoid secretion (van Haarst et al., 1997). Further, recent studies employing viral knockdown of GR in the hippocampus found no effect on either basal or stress-induced levels of glucocorticoids (Fitzsimons et al., 2013). As was the case for the mPFC, the output of the hippocampus is largely glutamatergic, and therefore excitatory. Consequently, numerous studies suggest that hippocampal inhibition of responses to psychogenic stress is mediated by activation of PVN-projecting GABAergic neurons in the BST, POA, DMH, and possibly the peri-PVN region (Cullinan et al., 1993; Herman et al., 2002; Mueller et al., 2006; Myers et al., 2013; Radley and Sawchenko, 2011).

3.3 Amygdala

The BLA is an activator of acute HPA axis stress responses, as excitotoxic lesions of the BLA dampen ACTH and corticosterone secretion following acute but not repeated restraint (Bhatnagar et al., 2004). Furthermore, BLA inhibition induced by potassium channel overexpression inhibits glucocorticoid responses to restraint (Mitra et al., 2009a). Overexpression of MR in the BLA is sufficient to attenuate corticosterone responses to restraint (Mitra et al., 2009b), suggesting that as in the hippocampus, BLA MR serves a role in feedback inhibition. As with the mPFC, endocannabinoid signaling in the BLA is involved in HPA axis regulation. The CB1 receptor may be acting as a 'gatekeeper' for BLA-driven glucocorticoid responses after acute stress, as stress decreases inhibitory endocannabinoid signaling specifically in the BLA (Hill et al., 2009). Thus, the data suggest the BLA increases the magnitude of HPA axis responses to acute psychogenic stress. Projection neurons of the BLA are largely glutamatergic, and heavily innervate down-stream GABAergic neurons in the CeA and MeA (Bienkowski and Rinaman, 2012; Pare et al., 1995). The BLA also innervates the BST (Myers et al., 2013), which may link BLA activation with HPA modulation.

Anatomical studies indicate that the CeA provides major output to regions that mediate not only fear and anxiety-related behaviors but also HPA axis responses (LeDoux et al., 1988; Myers et al., 2013; Swanson and Petrovich, 1998). PVN projecting GABAergic neurons of the POA receive inhibitory input from the CeA (Prewitt and Herman, 1998), suggesting the CeA disinhibits HPA axis responses. However, there are somewhat divergent reports on regulation of glucocorticoid release by the CeA. Bilateral lesions of the CeA inhibit ACTH responses to immobilization (Beaulieu et al., 1987, 1986) and corticosterone responses to footshock (Roozendaal et al., 1991), but do not affect responses to acute restraint (Prewitt and Herman, 1997). Other lesion studies have suggested that the CeA activates the HPA axis in response to systemic but not psychogenic stressors (Dayas et al., 1999; Xu et al., 1999). Importantly, corticosterone implanted on the CeA potentiates HPA axis responses to acute psychogenic stress (Shepard et al., 2003). Further, glucocorticoid responses to repeated psychogenic stress can be inhibited by GR or MR antagonism in the CeA (Myers and Greenwood-Van Meerveld, 2012), suggesting that the CeA has feed-forward effects on the HPA axis that may be linked to context-specific enhanced stress excitability. The MeA appears to be selectively involved in generating HPA responses to acute, but not chronic, psychogenic stress (Dayas et al., 1999; Ma and Morilak, 2005; Solomon et al., 2010). Although very little is known about the actions of glucocorticoids in the MeA, this region provides mixed glutamatergic and GABAergic innervation of the BST and hypothalamus, indicating the potential for subregional differences in the effects of the MeA on stress responding (Myers et al., 2013; Poulin et al., 2008).

3.4 Bed Nucleus of the Stria Terminalis

The BST provides direct input to the PVN and is a hub for forebrain inputs and trans-synaptic input to the PVN. Regulation of the HPA axis occurs at the level of the BST in a regional- and context-specific manner. The anterolateral BST receives projections from the plPFC and the ventral subiculum and sends GABAergic projections to the PVN that inhibit HPA axis responses to acute stress (Radley and Sawchenko, 2011). Additionally, lesions of

the principal nucleus in the posterior BST increase glucocorticoid responses to acute and chronic stress, suggesting an inhibitory role of this region in HPA axis regulation (Choi et al., 2008b, 2007). Lesions of the dorsomedial/fusiform nuclei in the anteroventral BST decrease HPA axis responses to acute stress, whereas lesions to this same region under chronic stress increase HPA axis responses (Choi et al., 2008a, 2007). Thus, the anteroventral BST appears to be sensitive to circulating glucocorticoid levels such that this region is involved in promotion and inhibition of HPA axis responses to acute and chronic stress, respectively. Moreover, the functional 'switch' in anteroventral BST suggests stress-induced metaplasticity at the physiologic level, as prior experience alters the role this nucleus from excitation to inhibition.

3.5 Hindbrain

Hindbrain monosynaptic inputs to the PVN are also modulated by glucocorticoids and interact with forebrain stress-regulatory circuits. The PVN receives dense input from brainstem noradrenergic and adrenergic neurons primarily from the NTS, as well as C1–C3 (Cunningham Jr. and Sawchenko, 1988; Cunningham Jr. et al., 1990). Lesions of these neurons attenuate HPA axis responses to systemic stressors, while adrenergic receptor stimulation activates CRF and ACTH secretion, indicating that catecholamines are necessary and sufficient for HPA axis activation (Plotsky, 1987; Plotsky et al., 1989). PVN-projecting neurons in the NTS also contain peptidergic neuromodulators (e.g., glucagon-like peptide-1 (GLP-1), neuropeptide Y) that are HPA axis excitatory (Harfstrand, 1987; Merchenthaler et al., 1999; Sawchenko et al., 1985; Tauchi et al., 2008). The NTS receives descending projections from forebrain limbic stress-regulatory regions, including the mPFC and CeA (Schwaber et al., 1982; van der Kooy et al., 1984), indicating possible involvement of the NTS in emotional and cognitive stress responses. In agreement with this hypothesis, GR activation in the NTS facilitates memory consolidation through involvement of the BLA (Roozendaal et al., 1999).

In the NTS, expression of preproglucagon (PPG) mRNA, which encodes the stress-excitatory GLP-1, is suppressed following acute and chronic stress in a glucocorticoid-dependent manner (Ghosal et al., 2013; Zhang et al., 2009). Loss of PPG mRNA is correlated with a reduction in GLP-1 fiber density in the PVN, indicative of reduced capacity for NTS neurons to release GLP-1 and stimulate ACTH secretion (Tauchi et al., 2008; Zhang et al., 2009). Glucocorticoid-induced reductions in PPG mRNA occur within 30 min and are not accompanied by reduced PPG gene transcription, indicating that glucocorticoid effects are likely mediated by destabilization of existing RNA pools (Zhang et al., 2009). Glucocorticoids decrease RNA stability *in vitro*, and this may represent an adaptive mechanism for limiting PVN excitation following stress (Stellato, 2004).

Serotonin (5-HT) participates in HPA axis activation by way of projections from the midbrain and pontine raphe nuclei (Lowry, 2002; Sawchenko et al., 1983). Lesion studies indicate serotonin provides excitation of the HPA axis (Jorgensen et al., 1998). However, direct serotonin input to the PVN is somewhat limited as the majority of serotoninergic fibers terminate in the peri-PVN (Sawchenko et al., 1983). In addition, 5-HT heavily innervates most limbic regions that project to the PVN (Kosofsky and Molliver, 1987;

Palkovits et al., 1977), and may modulate HPA axis responses indirectly. Additionally, glucocorticoids regulate the expression of tryptophan hydroxylase-2 (TPH2), an enzyme involved in 5-HT synthesis (Clark et al., 2005). Dexamethasone reduces TPH2 mRNA and protein in the raphe leading to reduced 5-HT synthesis in the mPFC, all of which is blocked by co-administration of a GR antagonist (Clark et al., 2008, 2005). Furthermore, daily rhythms in TPH2 mRNA are dependent on fluctuations in circulating glucocorticoids (Malek et al., 2007). Together, these studies indicate the importance of glucocorticoids for 5-HT activity throughout the brain.

3.6 Limbic Integration of Glucocorticoid Signaling

Based on the substantial interconnectedness of limbic forebrain regions and hypothalamic PVN-projecting nuclei, it is highly likely that glucocorticoid actions in a given cell population or brain region can have pronounced effects on the function and output of other regions. Few studies have investigated how GR signaling is integrated at a circuit level, largely focusing on downstream effects in the PVN. For instance, glucocorticoids in the CeA increase CRF expression in the PVN (Shepard et al., 2000). Although glucocorticoids in the CeA have been shown to increase CRF mRNA in the anterior BST (Shepard et al., 2006), in-depth studies of glucocorticoid interactions within the forebrain are lacking. A recent study employing selective deletions of GR within the mesolimbic dopaminergic system supports this hypothesis of integrated GR signaling. In these experiments, GR knockout in neurons of the nucleus accumbens decreased the firing rate of ventral tegmental dopamine-releasing neurons, resulting in social aversion (Barik et al., 2013). Interestingly, these effects could not be produced by deleting GR directly within the tegmental dopamine-releasing neurons. More studies focused on the integrative actions of glucocorticoids within the limbic forebrain are necessary to decipher the mechanisms of central stress regulation.

4. Behavioral Effects of Glucocorticoids

Activation of glucocorticoid responsive pathways, particularly within the limbic system, can lead to pronounced changes in behavior that have long-term implications for organismal well-being (Arnett et al., 2011) (Table 3). Functional changes at the synaptic and circuit levels affect a variety of neurobehavioral systems. For instance, mice with deletion of GR in the forebrain (mPFC, hippocampus, and BLA) exhibit increased despair-like behavior in the forced swim test (FST) and tail-suspension test (TST), as well as anhedonia in the sucrose preference test (SPT) (Boyle et al., 2005). In addition, mice overexpressing MR in the forebrain exhibit decreased anxiety-like behavior in the open field test (OFT) and elevated-plus maze (EPM) (Rozeboom et al., 2007). These studies support a role for forebrain glucocorticoid signaling in inhibiting behavioral responses indicative of depression and anxiety. Although numerous psychiatric disorders are associated with dysregulation of stress systems, the precise role of glucocorticoid dyshomeostasis in pathology remains to be determined.

4.1 Medial Prefrontal Cortex

Glucocorticoids have profound effects on prefrontal-mediated behaviors, including working memory, executive function, behavioral flexibility, and affect. Acutely, glucocorticoids act

through the cAMP pathway in the plPFC to impair working memory and enhance memory consolidation (Barsegyan et al., 2010; Roozendaal et al., 2004). Thus, glucocorticoid signaling reinforces consolidation of emotionally salient events while minimizing competing information, underscoring the context-specific actions of glucocorticoids. Chronically, glucocorticoids also impair performance in working memory tasks (Mizoguchi et al., 2004, 2000). Acute restraint stress impairs the ability of animals to execute the delayed spatial win-shift task, a prefrontal-mediated task, which relies on the ability to use information acquired prior to a delay to prospectively plan where to retrieve food in a radial arm maze (Butts et al., 2011). Chronic unpredictable stress or repeated restraint stress also impair behavioral flexibility (set-shifting and/or reversal learning) in the extra-dimensional set-shifting task, which requires animals to inhibit a previously learned response (Birrell and Brown, 2000; Bondi et al., 2008; Liston et al., 2006). Further, chronic stress favors habitual strategies in two instrumental operant tasks involving evaluation of outcome value and action-outcome contingency, reducing the ability of animals to employ flexible, goal-directed decision-making (Dias-Ferreira et al., 2009). Glucocorticoids in the mPFC also play a major role in affect. Knockdown of GR in the ilPFC increases immobility in the forced swim test, indicative of increased depression-like behavior (McKlveen et al., 2013). These behaviors share a common ‘prefrontal-related’ feature, in that the organism must coordinate an appropriate context-specific response by maintaining attention and flexibly inhibiting inappropriate responses.

4.2 Hippocampus

As with the cellular effects of glucocorticoids in the hippocampus, the role of glucocorticoids in hippocampal-dependent behaviors (e.g. learning and memory) has been extensively studied. Similar to glucocorticoid actions at the synapse, the effects of glucocorticoids on learning and memory are temporally- and context-dependent (Diamond et al., 1994). In the short term, stress can facilitate the formation of emotionally salient memories, that are important for adaptation (de Kloet et al., 1999; Smeets et al., 2009). In line with this, MR is important for initial appraisal and strategy selection in a novel spatial orientation task and for acquisition of fear memory (Khaksari et al., 2007; Oitzl and de Kloet, 1992). Conversely, the GR mediates consolidation of context-relevant information to optimize adaptation and survival in a variety of spatial and fear-related memory tasks (Abrari et al., 2009; Chen et al., 2012; Conrad et al., 1999; Donley et al., 2005; Fitzsimons et al., 2013; Gutièrrez-Mecinas et al., 2011; Oitzl and de Kloet, 1992; Pugh et al., 1997; Revest et al., 2010; Sandi et al., 1997). Thus, elevated glucocorticoid levels are important for the acquisition and consolidation of affectively relevant information and the disruption of memory processes that are less relevant for adaptation. Conversely, acute levels of glucocorticoids disrupt memory retrieval in tasks that have already been acquired (Roozendaal, 2002), including spatial memory in a radial arm task or Morris water maze (de Quervain et al., 1998; Diamond and Rose, 1994; Diamond et al., 1999; Ferguson and Sapolsky, 2008), novel object recognition (Baker and Kim, 2002), inhibitory avoidance (Schutsky et al., 2011) and contextual fear conditioning (Atsak et al., 2012a). Chronic stress exposure impairs hippocampal-dependent tasks as well (Conrad et al., 1996; Kleen et al., 2006; Krugers et al., 1997; Luine et al., 1994). For instance, chronic stress disrupts spectral coherence (matching of temporal structure in signals recorded from the hippocampus and

the mPFC) in the projection from the ventral hippocampus to the mPFC, which may contribute to stress-induced deficits in spatial reference memory (Oliveira et al., 2013). Therefore, the timing of enhanced glucocorticoid levels must be appropriate for the context. Thus, glucocorticoids act within specific time domains in the hippocampus to facilitate the acquisition and consolidation of spatial and emotionally salient information relevant to adaptation and disrupt memory processes less essential for survival.

4.3 Amygdala

The amygdala organizes fear and anxiety responses (Adamec, 1990; Davis et al., 2010; Kopchia et al., 1992; LeDoux, 2012; Shepard et al., 2000). Roozendaal and colleagues indicate that glucocorticoids in the BLA play a prominent role in promoting learning and memory of aversive stimuli (Roozendaal et al., 1996). Specifically, injections of GR agonists and antagonists in the BLA immediately after training in an inhibitory avoidance task point to the necessity and sufficiency of GR activation for long-term retention (Roozendaal and McGaugh, 1997b; Roozendaal, 2000). GR antagonist injection in the BLA prior to training also impairs inhibitory avoidance learning (Roozendaal and McGaugh, 1997b). In addition, blockade of GR prior to contextual fear conditioning decreases freezing in a 24 hour retention test (Donley et al., 2005). Glucocorticoids in the BLA are also involved in memory consolidation and reconsolidation of auditory fear conditioning as GR antagonism disrupts both of these memory processes (Jin et al., 2007). Ipsilateral lesions of the BLA block the memory enhancing effects of GR agonist infusion into the mPFC after inhibitory avoidance training (Roozendaal et al., 2009), suggesting that the effects of GR on memory consolidation depend on bidirectional communication between the BLA and the mPFC. The BLA is also necessary for glucocorticoid modulation of memory functions primarily mediated by the hippocampus and mPFC, such as memory retrieval and working memory, respectively (Nathan et al., 2004; Roozendaal and McGaugh, 1997a; Roozendaal et al., 2004, 2003). The effects of glucocorticoids on learning and memory may be mediated by endocannabinoids, as intra-BLA CB1 antagonism blocks glucocorticoid-mediated post-training enhancement of memory consolidation (Akirav, 2013; Atsak et al., 2012b; Campolongo et al., 2009).

The lateral portion of the BLA targets the CeA, which is considered the output nucleus for the behavioral expression of conditioned fear responses (Amorapanth et al., 2000). Growing evidence suggests that the CeA is also necessary for learning and consolidation of conditioned fear (Nader et al., 2001; Wilensky et al., 2006). However, recent studies have defined an amygdala microcircuit wherein BLA projections activate inhibitory neurons within the CeA that gate behavioral output (Ciocchi et al., 2010; Haubensak et al., 2010; Tye et al., 2011), suggesting the amygdala has the ability to both facilitate and inhibit behaviors indicative of fear and anxiety. Viral cre recombinase injections into the CeA of GR floxed mice produce a CeA-specifc GR knockout that exhibits deficits in conditioned fear (Kolber et al., 2008). Glucocorticoids localized to the CeA increase anxiety-like behavior in the EPM (Shepard et al., 2000), an effect that can be prevented by GR or MR antagonists in the CeA (Myers and Greenwood-Van Meerveld, 2007). In addition, specific GR or MR agonists injected in the CeA promote anxiety-like behavior (Myers and Greenwood-Van Meerveld, 2010a). The long-term anxiogenic effects of glucocorticoid signaling in the CeA are thought

to be mediated by transcriptional interactions with CRF, perhaps driving synaptic plasticity (Kolber et al., 2010; Laryea et al., 2013; Myers and Greenwood-Van Meerveld, 2010b; Shekhar et al., 2005). In addition, downstream activation of the BST may play a role in behavioral responses to stress (Poulos et al., 2010; Singewald et al., 2003; Sullivan et al., 2004). Chronic glucocorticoid signaling in the BST appears to induce a shift toward anxiogenic behavior and enhance unconditioned fear and stress-induced learning (Bangasser et al., 2005; Shepard et al., 2009; Ventura-Silva et al., 2012). However, more work delineating the actions of glucocorticoids underlying BST-mediated behaviors during stress exposure is needed.

5. Clinical Relevance of Glucocorticoid Signaling

Recent technological advances have allowed for more in-depth analysis of glucocorticoid effects in humans. In healthy controls, glucocorticoids have profound time-dependent effects on memory and decision-making. For instance, the synthetic glucocorticoid hydrocortisone given 30 min prior to a memory encoding task impairs memory contextualization performance, while hydrocortisone given 210 min prior to the task has the opposite effect (van Ast et al., 2013). These findings suggest that the rapid effects of glucocorticoids promote memory of the most emotionally salient aspects of an experience, whereas the delayed effects of glucocorticoids may enhance cognitive function. Similarly, hydrocortisone given before sleep in the evening after the presentation of emotional imagery enhances memory consolidation of emotional information and suppresses amygdalar activation during retrieval (van Marle et al., 2013). Acute stress also shifts hippocampal-dependent learning toward habitual striatum-dependent learning, an effect that can be prevented by pretreatment with an oral MR antagonist (Schwabe et al., 2013). Additionally, this stress-induced shift in memory processing correlates with altered coupling of the amygdala with the hippocampus and dorsal striatum, marked by decoupling of amygdala-hippocampal connectivity and strengthening of amygdala-putamen connectivity. The effects of stress on alterations in amygdala connectivity with the hippocampus and dorsal striatum are also prevented by MR antagonist pretreatment (Schwabe et al., 2013). Thus, the importance of glucocorticoids for regulating cognitive function and the brain regions mediating glucocorticoid activity during these processes are beginning to be characterized in humans. While there has been a recent increase in the number of studies assessing the central actions of glucocorticoids in humans, there is still a vital need to establish the mechanistic effects of glucocorticoids in health as well as psychopathology.

Glucocorticoid signaling is essential for adaptation to stress and alterations in glucocorticoid activity may underlie transitions to pathology in humans. In fact, several polymorphisms of the glucocorticoid receptor gene have been reported in individuals with posttraumatic stress disorder (PTSD), as well as major depression. For instance, the single nucleotide polymorphism (SNP) Bcl-1 (C to G nucleotide change involving a restriction site in intron 2) is associated with glucocorticoid hypersensitivity and lower cortisol levels (Derijk et al., 2008; Hauer et al., 2011; Huizenga et al., 1998; Kumsta et al., 2008; van Rossum et al., 2006, 2003). Further, homozygous carriers of the Bcl-1 SNP(G allele) have more traumatic memories 6 months after intensive care unit care than heterozygous or non-carriers of the SNP (Hauer et al., 2011). Similarly SNPs in the steroid receptor chaperone FK506 binding

protein 5 (FKBP5) increase glucocorticoid receptor sensitivity leading to lower basal cortisol levels and increased risk for PTSD following traumatic experience (Binder et al., 2008; Klengel et al., 2013; Wüst et al., 2004; Yehuda et al., 2009). Further, stress-level doses of hydrocortisone reduce PTSD symptomtology in patients following traumatic experience (Aerni et al., 2004; Delahanty et al., 2013; Schelling et al., 2003, 2001, 1999; Weis et al., 2006; Zohar et al., 2011). In healthy controls, stress enhances the consolidation of emotionally salient information (Andreano and Cahill, 2006; Buchanan and Lovallo, 2001), while also impairing memory retrieval (de Quervain et al., 2009, 2007). Therefore, hydrocortisone has been proposed to impair the retrieval of traumatic memories resulting in decreased PTSD symptoms following a traumatic experience (Hauer et al., 2013). Glucocorticoids also reduce local oxygen metabolism selectively in the amygdala and parahippocampal gyrus immediately following stress-level hydrocortisone exposure (Lovallo et al., 2010). Collectively, these studies suggest that stress-level doses of hydrocortisone may prove useful, particularly in patients with polymorphisms of the GR gene or genes affecting glucocorticoid sensitivity (Hauer et al., 2013; Schelling et al., 2013). In contrast to the low levels of cortisol generally associated with PTSD, patients with major depression typically display hypercortisolemia (Yehuda et al., 2004). Hypometabolism (decreased uptake of fluorine deoxyglucose) as well as hypermetabolism (increased regional cerebral blood flow) have been reported in the subgenual anterior cingulate cortex (Brodmann area 25) of patients with major depression (Drevets, 2000; Mayberg et al., 2005). Additionally, hydrocortisone decreases subgenual cingulate oxygen utilization evoked by sad stimuli, suggesting that this region is a key target for glucocorticoid-mediated effects on emotional processes (Sudheimer et al., 2013). Thus, the aggregate data suggest that glucocorticoids have pronounced effects on local metabolic activity within forebrain limbic circuits and alterations in glucocorticoid signaling within these areas may play a prominent role in stress-related neuropsychiatric disorders.

6. Stress, Energetics, and Adaptation

Responses to stress occur at the level of the individual, requiring both appraisal systems (limbic forebrain) and effector sites (hypothalamus and hindbrain) in the brain, as well as peripheral physiological systems. Consequently, regulation of the HPA axis is a distributed process integrated by multiple sites with considerable overlap and redundancy to permit compensation. For instance, both the plPFC and the ventral hippocampus provide inhibition of the HPA axis via convergent projections onto PVN-projecting neurons in the aBST (Radley and Sawchenko, 2011). Neuroendocrine responses to stress are initiated by the brain and result in the secretion of glucocorticoids to promote energy mobilization for current or anticipated needs. In turn, glucocorticoids act as a signal that influences cellular function, gene transcription, circuit activity, and, ultimately, behavior. Thus, responses to both acute and chronic stress promote context-specific adaptation based on the real or perceived needs of the individual. Although responses to chronic stress may promote adaptation, there is a cost of adaptation. Consequently, the adaptive cost may be deleterious for the organism when stress effector systems are repeatedly activated to meet the energetic demands of severe or prolonged stress. The physiological and behavioral consequences of driving energetic systems may encompass both stress resilience, as well the transition to pathology.

Thus, the stress response leads to a redistribution of energy resources to meet emergent or anticipated needs driven by a glucocorticoid signal that influences cellular function, neurocircuits, and behavior. This signal pushes physiological systems to adapt until the adaptive cost becomes greater than the adaptive capacity of the individual. In this framework, the adaptive capacity can be defined as the degree to which the organism can deploy energy mobilizing systems (e.g. HPA axis) to successfully meet current or anticipated needs.

The relationship between stress and energetics can be summarized by examining the relationship between systems performance, environmental demand, and energy input (Figure 1). The performance of the individual is largely dependent on energetic status, environmental demand (i.e. context), adaptive capacity, and adaptive cost. Glucocorticoids regulate the energetic status of the individual and are a crucial determinant of both adaptive capacity and cost. In turn, the adaptive capacity and cost directly influence the performance of the individual across varying ranges of environmental demand. The actions of glucocorticoids have been proposed to follow an inverted U-shape, such that high or low levels of glucocorticoids can impair systems performance (de Kloet et al., 1999; Herman, 2013). This is especially true for processes dependent on the hippocampus (Joëls, 2006). For example, a high dose of corticosterone or adrenalectomy increases behavioral reactivity to novel versus familiar objects, whereas a low dose of corticosterone normalizes this behavior (Oitzl et al., 1994). Glucocorticoid secretion must also be context appropriate. Hypersecreting glucocorticoids under conditions of low demand can be detrimental, but so can hyposecretion in the face of high demand. Therefore, the same concentration of glucocorticoids could be considered deleterious or beneficial depending on the energetic status of the individual. For instance, the same dose of exogenous corticosterone improves performance in a water maze task when animals are trained in warm water, but not cold water (Sandi et al., 1997). Thus, an optimal context-specific amount of glucocorticoid secretion is necessary for maintaining optimal performance (de Kloet et al., 1999; Herman, 2013; Joëls, 2006).

Energy regulatory systems must work in concert to meet the needs of the individual and use overlapping mechanisms to control and fine-tune energy reallocation (multiple feedback sites and pathways). As a result, the individual is able to maintain adaptive capacity across a broad range of environmental demand. For example, the behavioral and physiological changes accompanying responses to chronic stress are typically considered maladaptive. However, if these changes are interpreted based on the environmental context of the individual experiencing chronic stress, many responses could be considered adaptive for organismal survival. Chronic stress can be a time of high energetic need and glucocorticoids activate glycogen metabolism and glucose synthesis. Glucocorticoids also inhibit energy utilization by systems that are not necessary for immediate survival, including growth, immune, and reproductive processes (Munck et al., 1984). These steps in energy redistribution and reallocation are essential for increasing the adaptive capacity of the individual. In terms of behavior, the effects of chronic glucocorticoids on measures of anxiety, depression, and behavioral flexibility may be deleterious in some environmental contexts; however, in the face of chronic stress, diminished behavioral output could be considered beneficial. For instance, the neophobia and behavioral withdrawal assessed by

many tests of anxiety- and depression-like behavior may serve to minimize risk exposure and energy expenditure in contexts of prolonged challenge. Further, a switch to habitual strategies under chronic stress may lead to greater efficiency in predictable tasks by allowing the individual to respond instinctually and bypass the appraisal process (Dias-Ferreira et al., 2009; Schwabe et al., 2013). Thus, limiting risky or energy-demanding behaviors and energy-intensive physiologic processes (e.g. growth, reproduction, immune responses, etc) represent major components of the organismal adaptive capacity. However, when these responses are inappropriate to environmental demand or are sustained of prolonged time periods, the individual generates an adaptive cost that can decrease overall performance.

Glucocorticoid responses promote survival during periods of environmental demand but, over longer time frames, glucocorticoid secretion can impair behavioral and physiological health. There is a certain cost of adaptation that is likely dependent on how the individual's genetic background and life history interact with their appraisal of environmental demand. Thus, inappropriate regulatory balance in stress systems may comprise a risk factor for pathology (increasing adaptive cost). Adaptive cost may be further increased by energy depletion due to overdrive of energetic systems, physiological energy ‘sinks’ (e.g. infection, inflammation, metabolic disease, etc), design faults (inefficient energy redistribution systems, genetic polymorphisms), or poor decision making (misinterpretation of energetic need). As mentioned previously, habitual strategies are beneficial under chronic stress when the task and environment remain the same. However, if the environment changes to a context that requires appraisal and flexible strategies, individuals that have adopted habitual strategies may be at a disadvantage. For example, a recent study found that chronically stressed humans are unable to appropriately appraise outcome values. Further, this behavior is associated with a shift from activation of associative areas to increased activation of sensorimotor areas, mPFC and caudate atrophy, and increased putamen volume (Soares et al., 2013). In this case, misappraisal and energy depletion likely increase the adaptive cost. Depression and PTSD are stress-related disorders characterized by cognitive, affective, and physiological responses that are inappropriate to environmental context. Thus, psychopathologies may emerge when adaptive costs outweigh adaptive capacity, leading to a ‘break point’ in the process of adaptation.

6. Conclusions

A substantial and evolving body of work indicates that glucocorticoids are vital for central stress integration. Accordingly, we propose that the actions of glucocorticoids on neural systems from synapses to circuits generate the energetic resources to promote behavioral stress adaptation. These actions also illustrate the importance of appropriate context appraisal for successful adaptive responses. Misappraisal and/or inadequate adaptive capacity increase the risk for stress-related disorders, including depression and PTSD. Future studies addressing the mechanisms by which glucocorticoid signaling is integrated across multiple brain regions and peripheral sites will improve our understanding of the etiology of stress-related illness. In order to meet this challenge we must consider the sensitivity of current models and endpoints for determining the transition from adaptive to deleterious stress responses, as well as ways to increase translation of these findings into improved clinical outcomes.

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Highlights

- Glucocorticoids primarily mobilize energy in response to homeostatic challenge
- The forebrain receives glucocorticoid feedback and mediates stress responsiveness
- Glucocorticoid actions on synapses, circuits, and behavior promote adaptation
- Adaptive capacity and adaptive cost interact to determine risk for pathology

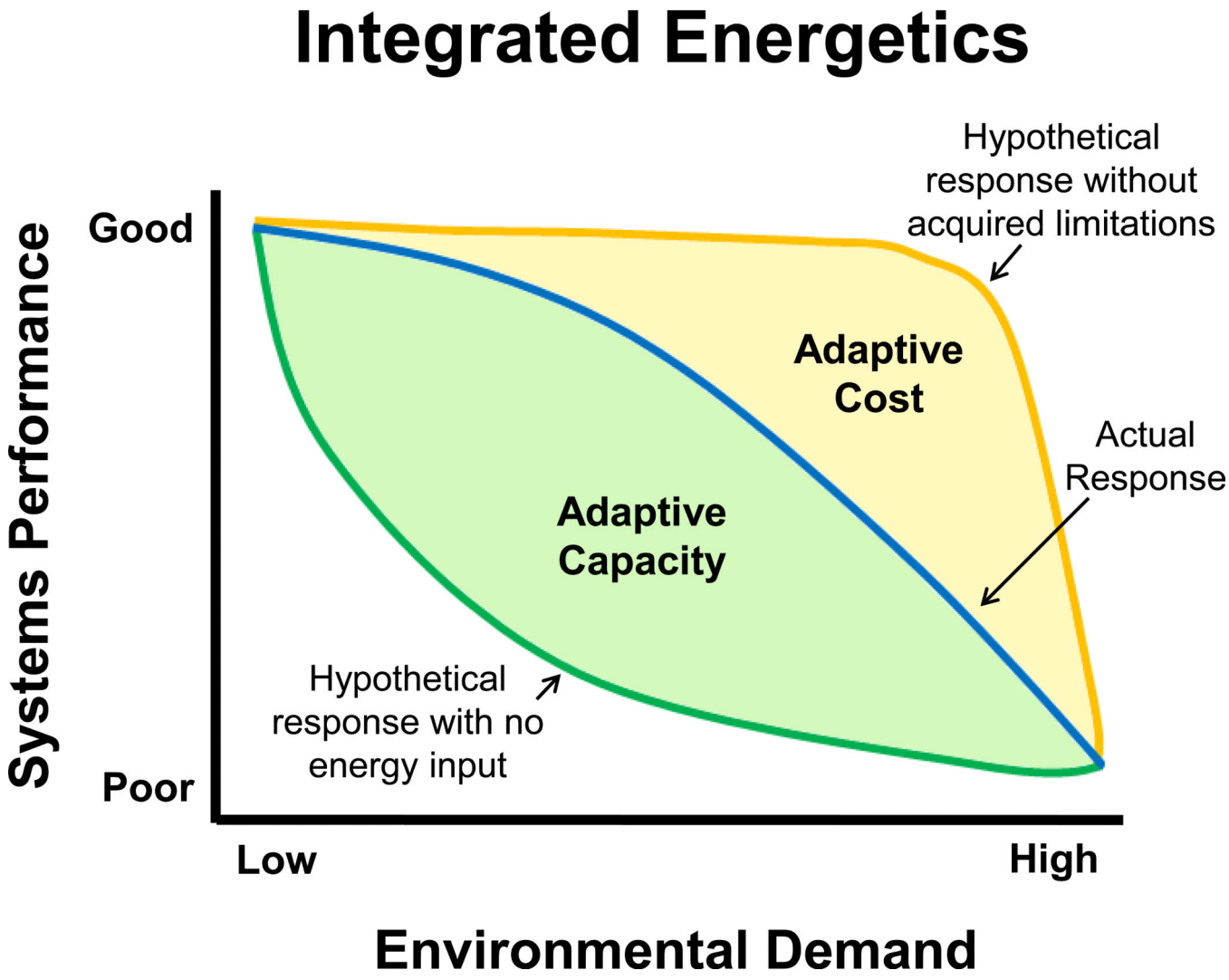

Figure 1.

Stress, energetics, and adaptation. The relationship between stress and energetic can be explained visually by examining the relationship between systems performance and environmental demand. Under conditions of low environmental demand, high levels of systems performance can be achieved without an energetic cost to the individual. With increasing demand, maintaining systems performance requires energetic input to generate an adaptive capacity (indicated by green shaded area), which is opposed by the adaptive cost (yellow shaded area). Without the acquired limitations that generate the adaptive cost, organismal performance could hypothetically be maintained at high levels across a wide range of environmental demand (depicted by the yellow line). Conversely, the absence of energy input would lead to poor performance even under conditions of moderate environmental pressure (depicted by the green line). The actual response (depicted by the blue line) falls between these two theoretical extremes and is determined for each individual as a function of their adaptive capacity and adaptive cost. With optimal energy redistribution and appropriate appraisal of context, the organism is able to maintain systems performance across a wide range of demand. As the adaptive cost of the organism grows, greater energy

input will be required to generate systems performance over a more narrow range of demand. Ultimately, the adaptive cost may be greater than the adaptive capacity, leading to a breaking point where systems performance is compromised and risk factors for pathology emerge.

Table 1

Site-specific effects of glucocorticoids on synaptic transmission and plasticity

Reference	Brain Site	GR/MR Manipulation	Stress Condition	Rapid Effects	Delayed Effects
Yuen et al. 2009	mPFC	CORT	Restraint or Platform or CORT i.p.		↑ eEPSC ampl
		GR Antagonist i.p.	Forced Swimming		↔ eEPSC ampl
Musazzi et al. 2010	mPFC	None	Acute Foot Shock	↑ sEPSC amplitude	
Hill et al. 2011	plPFC	CORT	20 min Slice Incubation		↓ mIPSC freq
		CORT + CB1 Antagonist	20 min Slice Incubation		↔ mIPSC freq
Yuen et al. 2012	mPFC	None	Chronic Stress		↓ mEPSC ampl and freq, ↓ eEPSC ampl
		CORT i.c.	Chronic CORT mPFC		↓ eEPSC ampl
		GR Antagonist i.p. or mPFC	Chronic Stress		↔ eEPSC ampl
	PFC cultures	CORT	7 d CORT Incubation		↓ mEPSC ampl and freq
		CORT + GR Antagonist	7 d CORT Incubation		↔ mEPSC ampl and freq
Karst et al. 2005	CA1	CORT or CORT:BSA	Bath Application	↑ mEPSC freq	
		GR Agonist	Bath Application	↔ mEPSC freq	
		CORT + GR Antagonist or CORT + GR KO	Bath Application	↑ mEPSC freq	
		MR Agonist + GR Antagonist	Bath Application	↑ mEPSC freq	
		MR KO + CORT	Bath Application	↔ mEPSC freq	
Karst and Joels 2005	CA1	CORT	20 min Slice Incubation		↑ mEPSC ampl, ↑ eEPSC ampl
		GR Agonist	20 min Slice Incubation		↑ mEPSC ampl
Oligslagers et al. 2008	CA1	CORT + MR Antagonist	Bath Application	↔ mEPSC freq and ampl	
		CORT	Bath Application	↔ mIPSC freq and ampl	
Pavlides et al. 1996	CA1	GR Agonist s.c.	None		↓ LTP
		MR Agonist s.c.	None		↑ LTP
Alfarez et al. 2002	CA1	CORT	20 min Slice Incubation		↓ LTP
Alfarez et al. 2003	CA1	None	Chronic Stress		↓ LTP
Yang et al. 2004	CA1	None	Inescapable Shock		↓ LTP, ↑ LTD
		GR Antagonist i.p.	Inescapable Shock		↔ LTP, ↔ LTD
Krugers et al. 2006	CA1	None	Chronic Stress		↓ LTP
		GR Antagonist (oral)	Chronic Stress		↔ LTP
		CORT	20 min Slice Incubation		↓ LTP

Reference	Brain Site	GR/MR Manipulation	Stress Condition	Rapid Effects	Delayed Effects
Wiegert et al. 2006	CA1	CORT	Bath Application	↑ LTP	
Alfarez et al. 2003	DG	None	Chronic Stress		↓ LTP
Pasricha et al. 2011	DG	CORT	Bath Application	↑ mEPSC freq	
Maggio and Segal 2009a	Dorsal Hipp	CORT or GR Agonist	Bath Application		↑ sIPSC Ampl
		CORT + MR Antagonist	Bath Application		↑ sIPSC Ampl
	Ventral Hipp	CORT	Bath Application		↓ sIPSC Freq
		GR Agonist or CORT + MR Antagonist	Bath Application		↑ sIPSC Ampl
Maggio and Segal 2009a	Ventral Hipp	MR Agonist or CORT + GR Antagonist	Bath Application		↓ sIPSC Freq
Maggio and Segal 2007	Dorsal Hipp	CORT	1 h Slice Incubation		↓ LTP
		CORT + GR Antagonist	1 h Slice Incubation		↑ LTP
	Ventral Hipp	CORT	1 h Slice Incubation		↑ LTP
		CORT + MR Antagonist	1 h Slice Incubation		↔ LTP
Maggio and Segal 2009b	Dorsal or Ventral Hipp	GR Agonist	1 h Bath Application		↑ LTD
	Dorsal Hipp	GR Antagonist s.c.	Forced Swimming		LTD converted to LTP
	Dorsal or Ventral Hipp	MR Agonist	1 h Bath Application		LTD converted to LTP
	Ventral Hipp	MR Antagonist s.c.	Forced Swimming		↑ LTD
		GR Antagonist s.c.	Forced Swimming		LTD converted to LTP
Duvarci and Pare 2007	BLA	CORT	20 min Incubation		↓ eIPSPs
Karst et al. 2010	BLA	CORT	Bath Application	↑mEPSC Freq	
		CORT	20 min Pulse		↑ mEPSC Freq (several hours later)
		GR KO + CORT	Bath Application	↑ mEPSC Freq	↔ mEPSC Freq
		MR KO + CORT	Bath Application	↔ mEPSC Freq	↔ mEPSC Freq
		MR Agonist + GR Antagonist	Bath Application	↑ mEPSC Freq	↔ mEPSC Freq
		GR Agonist	Bath Application	↓ mEPSC Freq	↓ mEPSC Freq
Karst et al. 2010	BLA	CORT + Cycloheximide	Bath Application	↑ mEPSC Freq	↔ mEPSC Freq
		CORT	2 Pulse Application	↓ mEPSC Freq	
		CORT	Acute Restraint + Bath Application	↓ mEPSC Freq	↓ mEPSC Freq
		GR KO + CORT	Acute Restraint + Bath Application	↔ mEPSC Freq	↔ mEPSC Freq
		GR Agonist	Acute Restraint + Bath Application	↓ mEPSC Freq	↔ mEPSC Freq
		GR Antagonist + MR Agonist	Acute Restraint + Bath Application	↔ mEPSC Freq	↔ mEPSC Freq

Reference	Brain Site	GR/MR Manipulation	Stress Condition	Rapid Effects	Delayed Effects
		CORT + Cyclohexamide	Acute Restraint + Bath Application	↓ mEPSC Freq	↓ mEPSC Freq
		CB1 Antagonist	Acute Restraint + Bath Application	↔ mEPSC Freq	↔ mEPSC Freq
Hubert et al. 2013	BLA	None	Chronic Stress		↑ mEPSC Freq
Vouimba et al. 2004	BLA	None	Platform Stress		↑ LTP
		None	Chronic Stress		↓ LTP
Maroun 2006	BLA	None	Elevated Platform		↑ LTP, ↔ LTD
Sarabdjitsingh et al. 2012	BLA	GR Antagonist i.p.	Acute Restraint	↓ LTP	↓ LTP
		MR Antagonist i.p.	Acute Restraint	↔ LTP	↓ LTP (Gradual)
		GR Antagonist i.p.	None	↔ LTP	↔ LTP
		MR Antagonist i.p.	None	↔ LTP	↓ LTP (Gradual)
Karst et al. 2010	CeA	CORT	Bath Application	↔ mEPSC Freq	↔ mEPSC Freq

Table 2

Site-specific effects of glucocorticoids on limbic circuits regulating HPA axis activity

Reference	Brain Site	GR/MR Manipulation	Stress Condition	HPA Outcome
Diorio et al. 1993	mPFC	CORT	Acute Restraint	↓ ACTH, ↓ CORT
			Ether	↔ ACTH, ↔ CORT
Akana et al. 2001	mPFC	CORT	Acute Restraint	↓ ACTH, ↔ CORT
			Repeated Cold	↓ ACTH, ↔ CORT
McKlveen et al. 2013	plPFC	GR Knockdown	Acute Restraint	↑ ACTH, ↑ CORT
			Chronic Variable Stress	↑ Basal CORT
	ilPFC	GR Knockdown	Acute Restraint	↑ CORT
			Chronic Variable Stress	↑ CORT
Van Haarst et al. 1997	Hipp	GR Antagonist	Diurnal Peak	↓ ACTH, ↔ CORT
		MR Antagonist	Diurnal Peak	↑ ACTH, ↑ CORT
Feldman and Weidenfeld 1999		GR Antagonist	Audiogenic or Phototic	↑ ACTH, ↑ CORT
		MR Antagonist	Audiogenic or Phototic	↑ ACTH, ↑ CORT
Fitzsimons et al. 2013	Hipp	GR Knockdown	Basal (AM & PM)	↔ CORT
			Conditioned Fear	↔ CORT
Mitra et al. 2009	BLA	MR Overexpression	Acute Restraint	↓ CORT
Akana et al. 2001	CeA	CORT	Acute Restraint	↔ ACTH, ↔ CORT
			Repeated Cold	↔ ACTH, ↔ CORT
Shepard et al. 2003	CeA	CORT	Elevated Plus Maze	↑ CRF, ↑ CORT
Kolber et al. 2008	CeA	GR KO	Conditioned Fear	↔ CRF
Myers and Greenwood-Van Meerveld 2012	CeA	GR Antagonist	Repeated Water Avoidance	↓ CORT
		MR Antagonist	Repeated Water Avoidance	↓ CORT

Table 3

Site-specific effects of glucocorticoids on limbic circuits regulating depression-, anxiety-, and fear-related behaviors

Reference	Brain Site	GR/MR Manipulation	Behavioral Paradigm	Behavioral Outcome
Roozendaal et al. 2004	plPFC	GR Agonist	Delayed Alternation T-Maze	↑ Error Rate
Barsegyan et al. 2010	plPFC	GR Agonist	Inhibitory Avoidance	↑ Shock Avoidance
		CORT:BSA	Delayed Alternation T-Maze	↑ Error Rate
			Inhibitory Avoidance	↑ Shock Avoidance
McKlveen et al. 2013	plPFC	GR Knockdown	Forced Swim Test	↔ Immobility
			Open Field	↔ Center Time
	ilPFC	GR Knockdown	Forced Swim Test	↓ Immobility
			Open Field	↔ Center Time
Donley et al. 2005	Dorsal Hipp	GR Antagonist	Conditioned Fear	↔ Freezing
	Ventral Hipp	GR Antagonist	Conditioned Fear	↓ Freezing
Fitzsimons et al. 2013	Hipp	GR Knockdown	Conditioned Fear	↓ Freezing
Roozendaal and McGaugh 1997	BLA	GR Agonist	Inhibitory Avoidance	↑ Shock Avoidance
Donley et al. 2005	BLA	GR Antagonist	Conditioned Fear	↓ Freezing
Mitra et al. 2009	BLA	MR Overexpression	Elevated Plus Maze	↑ Open Arm Time
Shepard et al. 2000	CeA	CORT	Elevated Plus Maze	↓ Open Arm Time
Kolber et al. 2008	CeA	GR KO	Conditioned Fear	↓ Freezing
Myers and Greenwood-Van Meerveld 2007	CeA	CORT + GR Antagonist	Elevated Plus Maze	↔ Open Arm Time
		CORT + MR Antagonist	Elevated Plus Maze	↔ Open Arm Time
Myers and Greenwood-Van Meerveld 2010	CeA	GR Agonist	Elevated Plus Maze	↓ Open Arm Time
		MR Agonist	Elevated Plus Maze	↓ Open Arm Time