Neural regulation of the stress response: The many faces of feedback

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Abstract

The mammalian stress response is an integrated physiological and psychological reaction to real or perceived adversity. Glucocorticoids (GCs) are an important component of this response, acting to redistribute energy resources to both optimize survival in the face of challenge and restore homeostasis after the immediate threat has subsided. Release of GCs is mediated by the hypothalamo-pituitary-adrenocortical (HPA) axis, driven by a neural signal originating in the paraventricular nucleus (PVN). Stress levels of GCs bind to glucocorticoid receptors (GRs) in multiple body compartments, including brain, and consequently have wide-reaching actions. For this reason, GCs serve a vital function in feedback inhibition of their own secretion. Fast, non-genomic feedback inhibition of the HPA axis is mediated at least in part by GC signaling in the PVN, acting by a cannabinoid-dependent mechanism to rapidly reduce both neural activity and GC release. Delayed feedback termination of the HPA axis response is mediated by forebrain GRs, presumably by genomic mechanisms. Glucocorticoids also act in the brainstem to attenuate neuropeptidergic excitatory input to the PVN via acceleration of mRNA degradation, providing a mechanism to attenuate future responses to stressors. Thus, rather than having a single defined feedback switch, GCs work through multiple neurocircuits and signaling mechanisms to coordinate HPA axis activity to suit the overall needs of multiple body systems.

Keywords

Hypothalamo-pituitary-adrenocortical axis; Corticotropin-releasing hormone; Corticosterone; Glucocorticoid receptor; Hypothalamus; Amygdala; Prefrontal cortex

Stress and the Hypothalamo-Pituitary-Adrenocortical axis

The organismal response to stress (defined as a real or perceived threat to homeostasis or well-being) promotes survival via adjustments to ongoing physiological processes and behavior. The activation of multiple interacting processes, including the behavioral, autonomic, endocrine, and immune systems, acts to produce an integrated stress response. This article focuses on the neuroregulatory processes governing activity of the primary endocrine stress response, initiated by the hypothalamo-pituitary-adrenocortical (HPA) axis. Stimulation of the HPA axis occurs in reaction to or in anticipation of stress. Physiological threats (systemic stressors) initiate largely reflexive responses that can be triggered without conscious perception. However, the ability to anticipate threat requires the organism to interpret the significance of multi-modal sensory information with respect to previous experience. Thus, stimuli that predict adversity (psychogenic stressors) can generate an HPA

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response in the absence of an existing physiologic insult. The relevance of the anticipatory glucocorticoid (GC) response hinges on the predicted need for adaptive hormonal secretion in order to redistribute resources (e.g., energy) to meet the challenge. Glucocorticoid hormones (corticosterone in rodents, cortisol in humans), which are the ultimate product of HPA axis activation, act on multiple bodily systems to maintain homeostasis. Appropriate activation of the HPA axis by acute stress is critical, as impaired reactivity hinders physiological resilience and cognitive processes (e.g., learning and memory). However, many of the effects of GCs that are beneficial for short-term survival can be counterproductive or even deleterious if prolonged. Therefore, the activation and inhibition of GC release is a temporally regulated process involving rapid neuronal activation and efficient inhibition.

The hypothalamic paraventricular nucleus (PVN) is responsible for initiating HPA axis stress responses. Activation of the HPA axis is mediated by neurosecretory neurons localized in the medial parvocellular portion of the PVN (Figure 1). These neurons project to blood vessels in the median eminence, where they release adrenocorticotropin (ACTH) secretagogues, the most potent of which are corticotropin-releasing hormone (CRH) and arginine vasopressin (Vale et al., 1981; Swanson et al., 1983). Adrenocorticotropin secretion from the anterior pituitary then leads to the synthesis and release of GCs from the adrenal cortex (Dallman and Jones, 1973; Dallman et al., 1987). Paraventricular CRH neurons are activated by neural inputs from a number of sources. Stressors signaling systemic challenge are communicated by neurons providing direct excitation of the PVN via sensory input from sources detecting neural or humoral homeostatic imbalance (e.g., the nucleus of the solitary tract (NTS), circumventricular organs) (Ulrich-Lai and Herman, 2009). In contrast, anticipatory HPA-axis responses are mediated by multisynaptic limbic forebrain circuits. These brain structures have no direct inputs to the PVN and require synaptic relays in subcortical structures (Herman et al., 2003). In many cases, subcortical relay sites also receive homeostatic information, providing a means for integrating descending limbic input with the ongoing physiological state. Given the need to temporally constrain secretion, activity of the HPA axis is controlled by negative feedback, a process wherein end-products of the stress response (GCs) inhibit their own release.

Glucocorticoid-mediated feedback involves both genomic and nongenomic mechanisms (de Kloet et al., 2005; Groeneweg et al., 2011). Fast feedback inhibition occurs within minutes, resulting in rapid termination of PVN activation and ACTH release following stress. Delayed feedback occurs over a longer time frame, and is mediated in part by genomic actions of the nuclear corticosteroid receptors (glucocorticoid receptor (GR) and mineralocorticoid receptor (MR)). Both GR and MR act as ligand-activated transcription factors, modifying the expression of a large number of genes. The MR has a very high affinity for endogenous GCs and regulates circadian secretory rhythms and ultradian pulsatility (de Kloet et al., 1998; de Kloet and Sarabdjitsingh, 2008). Although the permissive actions of MR maintain cellular responses to GCs, only stress levels of GCs extensively bind GR, which is necessary for the inhibition of HPA stress responses (Reul and de Kloet, 1985; de Kloet and Reul, 1987; Boyle et al., 2005; de Kloet et al., 2005). The GR is densely expressed in the PVN as well as numerous brain regions implicated in HPA axis regulation, all of which may contribute to feedback regulation (Reul and de Kloet, 1985; de Kloet and Reul, 1987; Jankord and Herman, 2008).

Local fast feedback regulation at the PVN

The rapid effects of GCs were observed as early as the 1960’s. However, the mechanisms underlying nongenomic feedback were not understood until recently (Dallman and Yates, 1969; Dallman, 2005). The PVN is well positioned to receive direct input from blood–brain

barrier permeable factors and appears to be a primary site for GC negative feedback of the HPA axis. Glucocorticoids rapidly inhibit PVN CRH neurons by way of a membrane-associated GR (mGR) that suppresses excitatory synaptic inputs to the PVN (Di et al., 2003; Di et al., 2005; Tasker and Herman, 2011). Rapid GC feedback is mediated by glucocorticoid-induced suppression of excitation (GSE), occurring as a result of postsynaptic G-protein activation and release of retrograde messengers that provide presynaptic inhibition of glutamate release (Di et al., 2003). Interestingly, GR antagonists do not completely block GSE, suggesting that GSE may be mediated by a novel membrane receptor or modification of the nuclear GR. There is electron microscopy and neurochemical evidence for GR localization to neuronal membranes, in particular postsynaptic membranes, supporting an alternative role for the so-called 'nuclear' receptor (Johnson et al., 2005; Komatsuzaki et al., 2005; Wang and Wang, 2009; Prager et al., 2010). This is further supported by recent data demonstrating that GSE is not present in animals bearing GR deletion in PVN neurons (Nahar et al., submitted). Moreover, GCs conjugated to bovine serum albumin, which prevents the steroids from crossing the cell membrane, suppress restraint-induced HPA axis activation in the PVN *in vivo* (Evanson et al., 2010).

Nongenomic regulation of PVN neurons is mediated by intracellular signaling networks promoting the synthesis of endocannabinoids (eCBs) in the PVN (Di et al., 2009) (Figure 2). Endocannabinoids are synthesized from lipid precursors in the membrane and bind the type 1 cannabinoid receptor (CB1) (Breivogel and Childers, 1998; Malcher-Lopes et al., 2008). Arachidonoyl ethanolamide (also known as anandamide) and 2-arachidonoylglycerol, eCBs rapidly produced in the PVN following GC exposure, act as dendritic retrograde messengers to mediate GSE (Di et al., 2003; Malcher-Lopes et al., 2006; Evanson et al., 2010). Cannabinoid receptors are predominately localized in presynaptic terminals, and CB1 antagonism or knockout leads to elevated CRH expression in the PVN and increased plasma ACTH and CORT (Patel et al., 2004; Cota et al., 2007; Ginsberg et al., 2010; Hill and McEwen, 2010). Furthermore, co-application of GCs and a CB1 inverse agonist block the GC-induced suppression of HPA axis responses to acute stress (Evanson et al., 2010). Collectively these findings suggest GCs act nongenomically to provide rapid feedback inhibition of the PVN via GC actions at mGR and subsequent dendritic synthesis and release of eCBs.

Monosynaptic feedback inputs to the PVN

The medial parvocellular PVN receives synaptic innervation from a relatively circumscribed set of central nervous system structures. In general, PVN afferent neurons are localized to regions known to receive inputs from somatic nociceptors, visceral afferents, and/or humoral sensory pathways (Kiss et al., 1996; Li et al., 1996). Thus, the majority of excitatory PVN-projecting neurons are positioned to evoke rapid, reflexive activation of the HPA axis. Importantly, these PVN-projecting neurons can be influenced by inputs from the forebrain, a process that may integrate anticipatory activation with physiological demand. The PVN receives a large input from brainstem noradrenergic and adrenergic neurons of the NTS and C1–C3 (Cunningham and Sawchenko, 1988; Cunningham et al., 1990). Lesions of these neurons attenuate reflexive HPA axis responses to stressors, while adrenergic receptor stimulation activates CRH and ACTH secretion, indicating that norepinephrine and epinephrine are necessary and sufficient for HPA axis activation (Plotsky, 1987; Plotsky et al., 1989). Paraventricular nucleus-projecting neurons in the NTS also contain peptide neuromodulators (e.g., glucagon-like peptide-1 (GLP-1), neuropeptide Y) that are HPA axis excitatory (Sawchenko et al., 1985; Harfstrand, 1987; Merchenthaler et al., 1999; Tauchi et al., 2008). In addition, serotonin participates in HPA axis activation by way of projections from the midbrain and pontine raphe nuclei (Sawchenko et al., 1983; Lowry, 2002). 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). The raphe nuclei also heavily innervate limbic structures including the hippocampus, prefrontal cortex, and amygdala (Lowry, 2002), suggesting that serotonin has both direct and indirect effects on HPA axis regulation.

The PVN receives heavy input from numerous regions of the hypothalamus, a large portion of which is inhibitory (Cullinan et al., 1993; Roland and Sawchenko, 1993). GABAergic inputs to the PVN originate in hypothalamic nuclei involved in homeostatic regulation, including the dorsomedial hypothalamus (DMH), preoptic area (POA), arcuate nucleus, and lateral hypothalamus (Roland and Sawchenko, 1993). The PVN also receives input from hypothalamic neuropeptide (e.g., CRH, alpha-melanoctye stimulation hormone) and glutamate expressing neurons (Ziegler and Herman, 2000; Zhang and Felder, 2004; Rinaman, 2007; Ulrich-Lai et al., 2011). These inputs are predominately excitatory and serve to activate the HPA axis in response to homeostatic imbalance (Ziegler and Herman, 2000; Bartanusz et al., 2004). The peri-PVN region contains large numbers of GABAergic neurons, some of which project into the PVN proper (Boudaba et al., 1996). This region also receives rich input from hypothalamic cell groups, serotonin neurons, and limbic structures, suggesting that this area may play a role in limiting information coming into the PVN (Cole and Sawchenko, 2002; Herman et al., 2002). Thus, hypothalamic inputs both excite and inhibit the PVN, consistent with a role in the maintenance of systemic homeostasis.

Direct forebrain inputs to the parvocellular PVN are largely confined to discrete subnuclei of the bed nucleus of the stria terminalis (BST) (Sawchenko and Swanson, 1983). Generally, posterior regions of the BST inhibit HPA axis responses to stress whereas anterior BST neurons provide excitatory input to the PVN, a heterogeneity that may be related to differential limbic innervation of these regions (Herman et al., 1994; Dong et al., 2001b; Dong and Swanson, 2004b, 2006; Choi et al., 2007). However, regional heterogeneity of BST effects on the HPA axis may be limited to acute stress as both the anterior and posterior BST provide inhibition of GC responses following chronic stress (Choi et al., 2008a; Choi et al., 2008b).

Recent evidence suggests that monosynaptic PVN inputs may be targets of GC feedback. In the NTS, expression of mRNA encoding the stress-excitatory neuropeptide GLP-1 (preproglucagon (PPG)) is effectively suppressed by acute and chronic stress in a GC-dependent manner (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 peptide and thereby stimulate ACTH release (Tauchi et al., 2008; Zhang et al., 2009). Stress/glucocorticoid-induced reductions in PPG mRNA occur within 30 minutes and are not accompanied by reduced PPG gene transcription, indicating that GC effects are likely mediated by destabilization of existing RNA pools (Zhang et al., 2009). Glucocorticoids are known to have effects on RNA stability *in vitro*, and may utilize this mechanism to limit excitation of the PVN following stress (Stellato, 2004). Importantly, GRs are also localized in numerous hypothalamic PVN-projecting neurons, including the arcuate nucleus, POA, and DMH (Fuxe et al., 1987). It remains to be determined whether GCs can alter this largely GABAergic input to PVN neurons.

Forebrain feedback (and feedforward?) regulation of HPA axis

Limbic brain structures including the hippocampus, prefrontal cortex, amygdala, septum, and midline thalamus are critical for emotional responses and memory, making them prime candidates for modulating GC secretion with respect to prior experience. However, these regions have little or no direct interactions with medial parvocellular PVN neurons,

requiring intermediary neurons to relay their influence on CRH release (Sawchenko and Swanson, 1983; Ulrich-Lai and Herman, 2009). Multiple limbic brain regions express GR and contribute to feedback integration (McEwen et al., 1968; Reul and de Kloet, 1985; Boyle et al., 2005). While hippocampal and medial prefrontal cortical GRs are required for inhibition of the HPA axis (Diorio et al., 1993; Boyle et al., 2005) (Figure 3), amygdaloid GRs can stimulate HPA responses (Beaulieu et al., 1986; Beaulieu et al., 1987; Shepard et al., 2003; Myers and Greenwood-Van Meerveld, 2011). Regulation of the HPA axis by forebrain limbic sites appears to be mediated by synapses onto neurons of the BST, hypothalamic nuclei, and brainstem nuclei that innervate the PVN directly.

The hippocampus is involved in terminating anticipatory HPA axis responses, consistent with its role in memory and emotion processing (Herman et al., 1989; Cullinan et al., 1993; Mueller et al., 2004; Radley and Sawchenko, 2011). A role for the hippocampus in GC negative feedback is supported by the dense expression of GRs in the hippocampus (Reul and de Kloet, 1985), as well as functional studies demonstrating diminished feedback efficacy following hippocampal lesions or local GR inactivation (van Haarst et al., 1997; Herman and Mueller, 2006; Mueller et al., 2006). Forebrain GR knockout mice, which sustain GR deletion in the hippocampus (as well as prefrontal cortex and basolateral amygdala), also show delayed inhibition of the HPA axis response to psychogenic (but not systemic) stressors, further suggesting a role for the hippocampal GR in feedback (Furay et al., 2008). The output of the hippocampus is largely glutamatergic, and therefore excitatory. Hence, inhibition is thought to be mediated by activation of PVN-projecting GABAergic neurons in the BST, POA, DMH, and peri-PVN region (Cullinan et al., 1993; Choi et al., 2007; Radley and Sawchenko, 2011).

The medial prefrontal cortex (mPFC) also modulates HPA axis activation, albeit in a more complex fashion. Numerous studies indicate that dorsal components of the mPFC (prelimbic (pl) PFC) inhibit HPA axis responses (Diorio et al., 1993; Figueiredo et al., 2003; Boyle et al., 2005; Radley et al., 2006; Radley et al., 2009). Indeed, anatomical studies suggest that plPFC activates inhibitory relays in the BST (Radley et al., 2009). Acute activation of the plPFC reduces GC secretion after psychogenic stress (Jones et al., 2011) and restraint-activated neurons of the plPFC express GR (Ostrander et al., 2003), suggesting that GC-sensitive neurons are engaged by stressors. Moreover, GC implants in the dorsal mPFC decrease GC release following acute restraint (Diorio et al., 1993), indicating that the inhibitory effect of the plPFC is at least in part GR-dependent.

Lesion studies indicate that the more ventral components of the mPFC (infralimbic (il) PFC) may be involved in stress excitation (Sullivan and Gratton, 1998, 1999; Radley et al., 2006). Neurons of the ilPFC also appear to process GC information as they co-express c-Fos and GR after acute restraint (Ostrander et al., 2003). Notably, subcortical ilPFC projections differ substantially from those of the plPFC, targeting known stress-excitatory regions such as the central nucleus of the amygdala (CeA) and NTS (Hurley et al., 1991; Vertes, 2004). Taken together, these studies suggest that the ilPFC may be involved in conveying GC feedforward rather than feedback information to subcortical HPA axis effector pathways.

Similar to ilPFC, the amygdala provides excitation of HPA axis responses (Roozendaal et al., 1991; Van de Kar et al., 1991; Roozendaal et al., 1992; Feldman et al., 1994; Feldman and Weidenfeld, 1998; Shepard et al., 2003), although there is considerable functional differentiation among individual amygdalar regions (Dunn and Whitener, 1986; Swanson and Petrovich, 1998; Sah et al., 2003; Ulrich-Lai and Herman, 2009). The CeA appears to be involved in activation of the HPA axis in response to systemic but not psychogenic stressors (Dayas et al., 1999; Xu et al., 1999; Dayas et al., 2001). Conversely, the medial amygdala may be selectively involved in generating anticipatory responses (Dayas et al., 1999; Dayas

et al., 2001; Ma and Morilak, 2005; Solomon et al., 2010). Although the basolateral amygdala (BLA) is activated by both psychogenic and systemic stressors (Cullinan et al., 1995; Jones et al., 2011), relatively few studies have examined the role of this area in GC secretion. However, lesions of the BLA dampen HPA axis responses to psychogenic stress (Bhatnagar et al., 2004) while intra-BLA administration of CRH increases GC secretion (Daniels et al., 2004), indicating this area may also provide feedforward regulation of the HPA axis. The output of the basolateral amygdala is predominantly glutamatergic, suggesting that modulation of GC responses is mediated by excitatory PVN-projecting neurons as well as extensive interactions with other regions of the amygdala (Krettek and Price, 1977; Pare et al., 1995; Dong et al., 2001a).

Amygdalar excitation of the HPA axis may be mediated by either transsynaptic disinhibition or excitation. Most projection neurons of the central and medial amygdala are primarily GABAergic, and both regions project heavily to the BST and POA, which contain populations of GABAergic PVN-projecting neurons (Prewitt and Herman, 1998; Sah et al., 2003). Therefore, excitatory effects on HPA axis stress responses may be mediated by inhibition of GABAergic neurons in the hypothalamus or BST, effectively resulting in activation by disinhibition. There is also a specific projection from the CeA to the anterolateral BST, a stress excitatory region that innervates the PVN (Dong et al., 2001a; Dong and Swanson, 2004a; Choi et al., 2007). Glucocorticoids localized to the CeA increase CRH mRNA in the CeA, anterolateral BST, and PVN (Shepard et al., 2000, 2003; Shepard et al., 2006). Thus, in addition to GABAergic outflow, the CeA may provide peptidergic innervation of PVN-projecting, CRH-containing neurons in the BST that are in position to mediate trans-synaptic excitation from the CeA as well as excitatory outflow from regions such as the BLA.

Stress-regulatory amygdalar subnuclei also express GRs. Unlike the plPFC and hippocampus, amygdalar GRs appear to have excitatory effects on stress responses (Figure 4). For example, systemic GCs increase CRH mRNA expression in the CeA (Schulkin et al., 1998) and stress-induced CeA CRH release is blocked by pretreatment with a GR antagonist (Cook, 2002). Thus, GCs may have feedforward effects in the amygdala that can be linked to enhanced stress excitability. Dallman and colleagues (Dallman et al., 2003) propose that recruitment of amygdalar CRH may be a deleterious consequence of elevated GC release during chronic stress or stress-related diseases. Furthermore, the GR appears vital for normal function of amygdala circuits, as mice with specific disruption of the CeA GR have deficiencies in fear conditioning (Kolber et al., 2008).

The lateral septum inhibits HPA axis stress responses, and the anatomy of the septal region suggests interactions with hypothalamic and brainstem regions projecting to the PVN (Staiger and Nurnberger, 1991; Singewald et al., 2011). As the majority of lateral septal neurons express GABA as their transmitter, the HPA inhibitory effects of this region are likely mediated by inhibition of excitatory projections to the PVN (Stevens et al., 1987). Expression of the MR is particularly pronounced in the lateral septum (Grillo et al., 1990), suggesting that this site may be highly sensitive to modulatory effects of low physiological GCs, perhaps as a means to set the tone of this stress-regulatory region.

Several reports implicate midline thalamic nuclei in HPA axis regulation, likely communicated via hypothalamic nuclei (Jaferi et al., 2003). Of the known stress-responsive thalamic nuclei, the paraventricular thalamus appears to play a major role in integrating HPA axis responses, mediating both habituation to familiar stressors and sensitization to novel stressors (Bhatnagar et al., 2002; Jaferi and Bhatnagar, 2006). Once again, the paraventricular thalamus is rich in GRs (Fuxe et al., 1987), suggesting that GCs are capable of tuning the overall influence of this region on stress responses.

Consequences of impaired negative (or enhanced positive) feedback

In the short term, GC release is essential for mobilizing energy stores and suppressing non-essential processes to promote survival of the organism. However, chronic activation of the HPA axis can be directly detrimental (e.g., catabolic effects in muscle and bone). In addition, abnormally elevated or suppressed GCs can increase susceptibility to multiple pathological conditions including neuropsychiatric disorders and metabolic dysregulation. Major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) are two of the most prevalent psychiatric conditions attributed to dysregulation of GC feedback. MDD is commonly associated with hypercortisolemia, whereas PTSD is frequently linked to GC hyposecretion (Yehuda et al., 2004; Radley et al., 2011; Yehuda and Seckl, 2011). Both affective states correlate with altered activation or volume of the prefrontal cortex, amygdala, and hippocampus, suggesting that the disease processes involve the anticipatory stress response (Drevets, 1999; Mayberg et al., 2005; Yehuda and LeDoux, 2007; Krishnan and Nestler, 2010; Myers-Schulz and Koenigs, 2011). Additionally, sensitization of reward pathways due to aberrant HPA axis activity has been proposed to drive vulnerability to addictive disorders, as GCs promote perseverance of addictive behavior (de Jong and de Kloet, 2004; Uhart and Wand, 2009; Frank et al., 2011)

Although GCs acutely enhance cognitive performance and improve memory consolidation, high circulating levels of GCs impair memory retrieval (Roozendaal, 2002). Further, GCs can negatively affect processes governing dendritic plasticity, neurogenesis, and neuronal viability (Sapolsky et al., 1986; Pham et al., 2003; Radley et al., 2008). Stress is also a prominent risk factor for neurological conditions including epilepsy, Parkinson's disease, Alzheimer's disease, and chronic pain, suggesting that GCs play a role in the onset and progression of these disorders (Smith et al., 2002; Myers et al., 2007; Sotiropoulos et al., 2008; Kanner, 2009; McEwen and Kalia, 2010). Dysregulation of the HPA axis is also related to metabolic and cardiovascular disorders. Accumulating evidence suggests that heightened GCs contribute to visceral obesity, especially in the propensity to consume rewarding foods (Adam and Epel, 2007). Cushing's syndrome (characterized by hypercortisolemia) further illustrates the physiological consequences of prolonged GC exposure. The vast majority of these patients exhibit obesity, hypertension, impaired glucose tolerance, diabetes, and dyslipidemia (Sharma and Nieman, 2011). Thus, appropriate initiation and cessation of HPA axis responses is essential for maintaining homeostatic balance and promoting adaptation in the face of adversity.

Mechanisms underlying HPA axis dysfunction in disease prominently involve alterations in GC feedback mechanisms. For example, a high proportion of depressed individuals fail to suppress HPA axis secretory activity following exogenous GC (dexamethasone) treatment, indicating a loss of feedback sensitivity (Carroll et al., 1980). Moreover, treatment with a GR antagonist can ameliorate symptoms in patients with psychotic depression (Belanoff et al., 2001), suggesting that the GR may be a viable therapeutic target for MDD. In contrast, HPA axis activity is often decreased in individuals with PTSD (Radley et al., 2011). In this case, GC negative feedback is enhanced, resulting in pathologically low HPA axis responsiveness to stress (Yehuda et al., 2004). Despite GC hyposecretion, PTSD patients may actually have prolonged GC exposure following stress due to reduced activity of GC-metabolizing enzymes (Yehuda et al., 2009; Yehuda and Seckl, 2011). Notably, reduced HPA axis activity is thought to be a trait, rather than state variable, placing individuals that hyposecrete GCs at risk for development of disease.

Conclusion

Overall, the data suggest that GC feedback regulation of the HPA axis employs all realms of GC signaling: fast membrane-mediated inhibition of PVN excitation; trans-synaptic delayed feedback, involving genomic signaling; and even actions on RNA stability, effectively taking excitatory stress afferents 'offline'. In some brain regions, such as the amygdala and perhaps ilPFC, GCs may even have positive feedback effects, promoting the actions of CRH. Furthermore, feedback is a distributed process, involving local signaling in hypothalamus, regulation of limbic inhibitory (and perhaps excitatory) outflow, and control of ascending brainstem projections to the PVN. In addition, it is important to consider that GC feedback is not the exclusive province of the brain. There are known inhibitory actions of GCs (albeit at high physiologic levels) on ACTH release by the pituitary (Miller et al., 1992). Numerous other organ systems with the capacity to signal into the CNS (e.g., adipose tissue) express GR (Bronnegard et al., 1990). Thus, GC feedback is best thought of as an integrative process involving central and peripheral compartments.

Control of the GC stress response is of substantial health significance, as dysregulation of GC secretion can lead to affective disease states and impaired metabolic and cardiovascular function. However, only a subset of stressed individuals develops these disorders, suggesting that genetic, social, and/or experiential factors determine individual vulnerability to HPA axis dysfunction. Additional research is needed to elucidate the factors that are responsible for vulnerability in some individuals and resistance in others.

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Abbreviations

ACTH	adrenocorticotropin
BLA	basolateral amygdala
BST	bed nucleus of the stria terminalis
CB1	type 1 cannabinoid receptor
CeA	central nucleus of the amygdala
CRH	corticotropin-releasing hormone
DMH	dorsomedial hypothalamus
eCB	endocannabinoid
GC	glucocorticoid
GLP-1	glucagon-like peptide-1
GR	glucocorticoid receptor
GSE	glucocorticoid-induced suppression of excitation
HPA	hypothalamo-pituitary-adrenocortical
ilPFC	infralimbic prefrontal cortex
MDD	major depressive disorder

mGR	membrane-associated GR
mPFC	medial prefrontal cortex
MR	mineralocorticoid receptor
NTS	nucleus of the solitary tract
plPFC	prelimbic prefrontal cortex
POA	preoptic area
PPG	preproglucagon
PTSD	post-traumatic stress disorder
PVN	paraventricular nucleus

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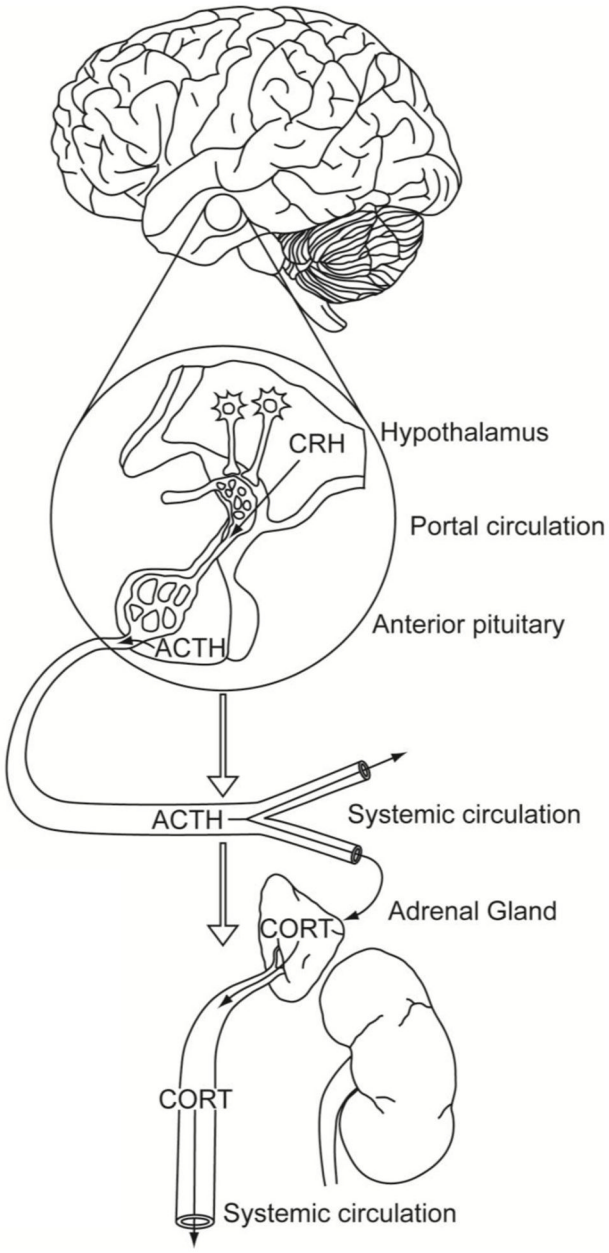

Figure 1.
The HPA axis regulates the endocrine stress response with activation mediated by CRH containing neurons in the hypothalamic PVN. The release of CRH onto cells of the anterior pituitary induces the secretion of ACTH into systemic circulation. At the adrenal cortex, ACTH stimulates synthesis and release of GCs (cortisol in humans and corticosterone in rodents). Glucocorticoids then activate MRs and GRs providing a feedback signal to regulate HPA axis activity.

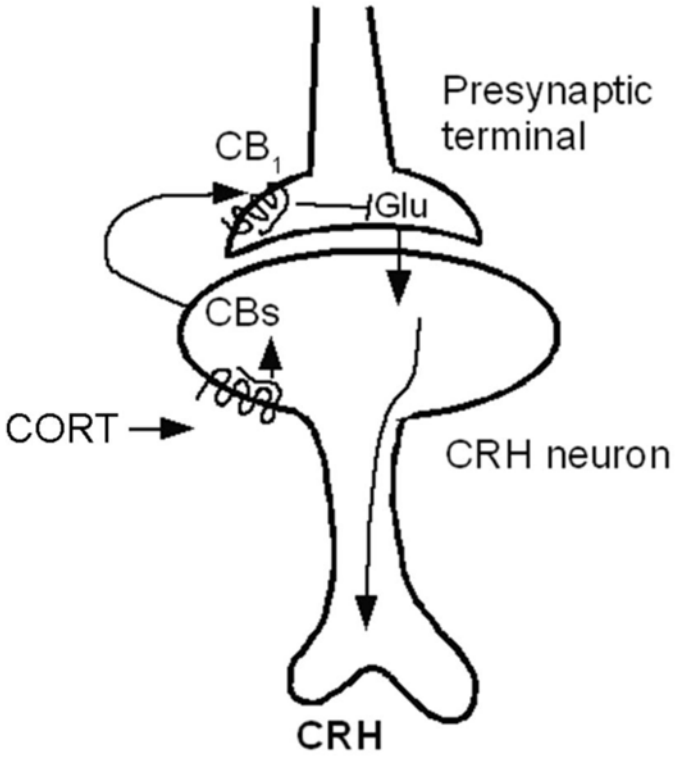

Figure 2.
Glucocorticoids can rapidly inhibit CRH release from PVN neurons by acting on membrane-associated receptors. Receptor activation leads to retrograde eCB signaling at CB1 receptors which suppresses excitation of presynaptic glutamatergic neurons.

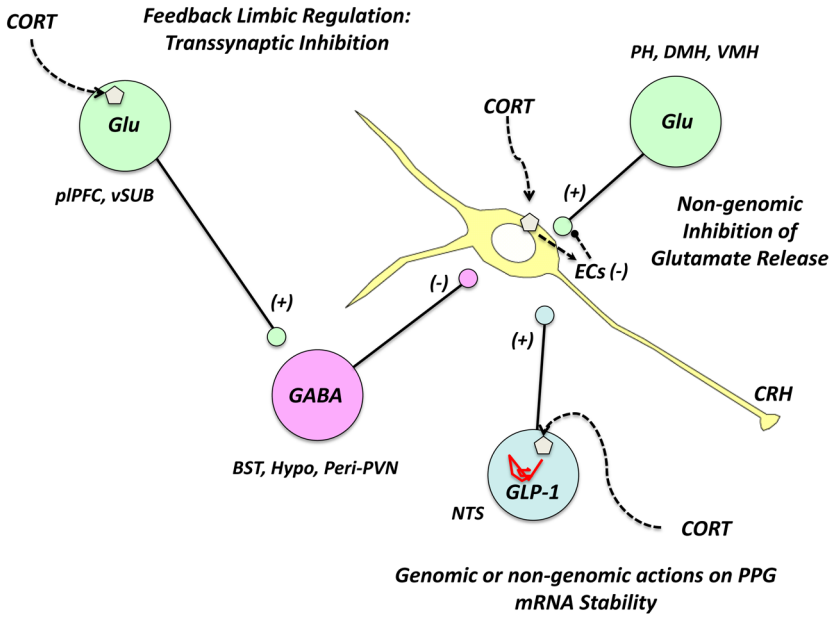

Figure 3.

Glucocorticoid negative feedback can generally be divided into three interacting domains. First, GCs provide rapid, nongenomic inhibition of excitatory inputs to the PVN. Additionally, GCs affect RNA stability in brain structures with direct, excitatory innervation of the PVN. Forebrain genomic GC signaling is also a key component of feedback regulation. Importantly, these structures have little or no direct interactions with the PVN and require intermediary synapses in PVN-projecting cell groups. Specifically, GCs act in the plPFC and the ventral subiculum to inhibit the PVN via GABAergic synaptic relays. BST: bed nucleus of stria terminalis, DMH: dorsomedial hypothalamus, EC: endocannabinoid, GLP-1: glucagon-like peptide-1, Glu: glutamate, NTS: nucleus of the solitary tract, PH: posterior hypothalamus, plPFC: prelimbic prefrontal cortex, VMH: ventromedial hypothalamus, vSub: ventral subiculum, + denotes excitation and − inhibition.

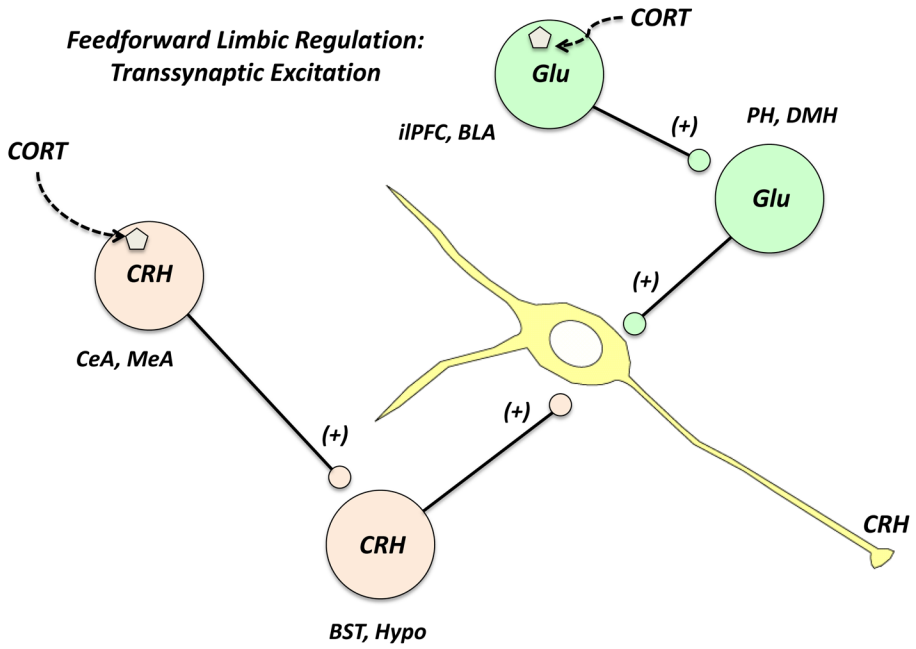

Figure 4.

Depending on physiological demand and anticipatory signals from the forebrain, GCs may provide feedforward excitation of the HPA axis. Glucocorticoids can upregulate CRH signaling in the amygdala and BST, potentially prolonging GC secretion. Glucocorticoids may also act on glutamatergic neurons in the ilPFC and BLA to excite PVN CRH neurons via synaptic relays in the hypothalamus. BLA: basolateral amygdala, CeA: central amygdala, ilPFC: infralimbic prefrontal cortex, MeA: medial amygdala, NE: norepinephrine. + denotes excitation and − inhibition.