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Review article

# Limbic system mechanisms of stress regulation: Hypothalamo-pituitary-adrenocortical axis

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**Abstract**

Limbic dysfunction and hypothalamo-pituitary-adrenocortical (HPA) axis dysregulation are key features of affective disorders. The following review summarizes our current understanding of the relationship between limbic structures and control of ACTH and glucocorticoid release, focusing on the hippocampus, medial prefrontal cortex and amygdala. In general, the hippocampus and anterior cingulate/prelimbic cortex inhibit stress-induced HPA activation, whereas the amygdala and perhaps the infralimbic cortex may enhance glucocorticoid secretion. Several characteristics of limbic–HPA interaction are notable: first, in all cases, the role of given limbic structures is both region- and stimulus-specific. Second, limbic sites have minimal direct projections to HPA effector neurons of the paraventricular nucleus (PVN); hippocampal, cortical and amygdalar efferents apparently relay with neurons in the bed nucleus of the stria terminalis, hypothalamus and brainstem to access corticotropin releasing hormone neurons. Third, hippocampal, cortical and amygdalar projection pathways show extensive overlap in regions such as the bed nucleus of the stria terminalis, hypothalamus and perhaps brainstem, implying that limbic information may be integrated at subcortical relay sites prior to accessing the PVN. Fourth, these limbic sites also show divergent projections, with the various structures having distinct subcortical targets. Finally, all regions express both glucocorticoid and mineralocorticoid receptors, allowing for glucocorticoid modulation of limbic signaling patterns. Overall, the influence of the limbic system on the HPA axis is likely the end result of the overall patterning of responses to given stimuli and glucocorticoids, with the magnitude of the secretory response determined with respect to the relative contributions of the various structures.


*Keywords:* ACTH; Amygdala; Glucocorticoids; Glucocorticoid receptor; Hippocampus; Infralimbic cortex; Mineralocorticoid receptor; Prelimbic cortex; Stress

**Contents**



*Abbreviations:* (ACTH), adenocorticotropine hormones; (CRH), corticotropin releasing hormone; (GR), glucocorticoid receptor; (HPA), hypothalamo-pituitary-adrenocortical; (MR), mineralocorticoid receptor; (PTSD), post-traumatic stress disorder; (PVN), paraventicular nucleus.

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## 1. Introduction

Limbic system dysfunction plays a major role in numerous neuropsychiatric disease states. Recent advances in neuroimaging have supplemented prior evidence from post-mortem observations and natural/psychosurgical lesion studies to implicate the hippocampus, amygdala and medial prefrontal cortex in affective disorders. For example, depression is accompanied by decreases in hippocampal volume (Sheline et al., 1996) and alterations in prefrontal cortical and amygdalar blood flow (Drevets, 2000). Many of these changes are reversible with antidepressant treatment (Drevets, 2000), suggesting that altered limbic function may reflect the depressive state.

Multiple neuropsychiatric diseases are associated with life stress (see McEwen, 1998). Stress is known to exacerbate depressive states, and post-traumatic stress disorder (PTSD) is clearly triggered by exposure to severe stressors (McEwen, 1998). Importantly, these disorders are accompanied by alterations in glucocorticoid secretion, suggesting that dysfunction of the hypothalamo-pituitary-adrenocortical (HPA) axis may be involved in the deleterious effects of stress on affective state. For example, resistance to glucocorticoid feedback is observed in a substantial proportion of individuals suffering from melancholic depression (c.f., Kathol et al., 1989), implying episodic hyper-secretion and attendant consequences on somatic and cognitive function. In contrast, PTSD patients exhibit decreased basal corticosteroid levels (Yehuda et al., 1991) and decreased responsiveness to stress (Heim et al., 2000). Taken together, the data indicate the importance of maintaining an optimal level of HPA responsiveness, in that mental illness may be associated with either hyper- or hypo-secretion of glucocorticoids.

Given the connection between stress and affective disorders, it is important to note that the hippocampus, amygdala and prefrontal cortex are also implicated in HPA axis regulation. The hippocampus and prefrontal cortex are largely (but not exclusively) inhibitory to HPA axis secretion, whereas the amygdala is implicated in activation of glucocorticoid secretion (c.f., Feldman et al., 1995; Herman and Cullinan, 1997; Jacobson and Sapolsky, 1991). Thus, the very structures implicated in neuropsychiatric disease states also play a major role in stress control. Given the link between limbic regions, stress and psychosis, it is important to determine the role these structures play in stress integration. In the current review, we summarize recent work exploring the role of the hippocampus, amygdala and prefrontal cortex in stress control, in an attempt to understand how malfunction of these prominent stress regulatory 'nodes' in disease states can result in HPA axis dysfunction.

## 2. Regulatory characteristics of the HPA axis

The HPA axis is controlled by a discrete set of hypophysiotrophic neurons in the medial parvocellular division of the hypothalamic paraventricular nucleus (PVN). These neurons synthesize and secrete corticotropin releasing hormone (CRH), the primary secretagogue for ACTH, as well as a cocktail of other factors (e.g., arginine vasopressin (AVP)) that modulate ACTH release. Secretagogues travel by way of the hypophysial portal veins to access anterior pituitary corticotropes, which then stimulate release of ACTH into the systemic circulation. Glucocorticoids are then synthesized and released upon binding of ACTH in the adrenal cortex (Antoni, 1986; Whitnall, 1993) (Fig. 1).

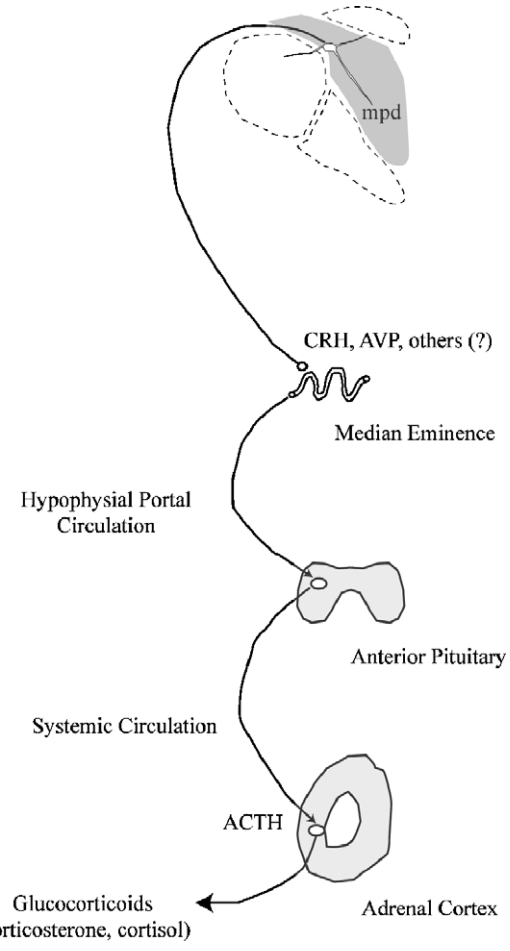


Fig. 1. Diagrammatic representations of the HPA axis of the rat. HPA responses are initiated by neurosecretory neurons of medial parvocellular paraventricular nucleus (mpPVN), which secretes ACTH secretagogues such as corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) in the hypophysial portal circulation at the level of the median eminence. These secretagogues promote release of ACTH into the systemic circulation, whereby it promotes synthesis and release of glucocorticoids at the adrenal cortex.

The HPA axis is activated by both internal and external signals. In most vertebrates there is a pronounced circadian rhythm in glucocorticoid secretion, with peaks corresponding to the onset of the active phase of the diurnal cycle (Keller-Wood and Dallman, 1984). Daily glucocorticoid rhythms are dependent on the suprachiasmatic nucleus, as lesions of this structure flatten the corticosteroid rhythm to levels intermediate those of the circadian peak and nadir (Cascio et al., 1987; Moore and Eichler, 1972).

Glucocorticoid secretion is also driven by internally perceived disruptions of homeostasis, cued by cardiovascular, respiratory or visceral stimuli. These disruptions appear to be relayed to the PVN by way of brainstem neurons, located in the region of the nucleus of the solitary tract and to a lesser extent, the ventrolateral medulla (Swanson and Sawchenko, 1983). A substantial population of these excitatory neurons are noradrenergic or adrenergic (Cunningham et al., 1990, Cunningham and Sawchenko, 1988). In addition, changes in circulating cytokines subsequent to infection/toxic challenge promote PVN excitation, either by activating ascending brainstem afferents (Ericsson et al., 1997; Ericsson et al., 1994) or stimulating local synthesis of nitric oxide (Rivier, 2001) and/or prostaglandins (Rivest, 2001).

Finally, the HPA axis is exquisitely sensitive to perturbations of the external environment. Glucocorticoid responses can be initiated by direct activation of the PVN by nociceptive pathways (e.g., pain (Palkovits et al., 1999), recruitment of innate defensive programs (e.g., aversion to predators (Figueiredo et al., 2003a) or associations cued by multimodal sensory stimuli (e.g., fear conditioning (Van de Kar et al., 1991).

## 3. Glucocorticoid signaling

The catabolic processes initiated by glucocorticoids make it imperative that secretion be restricted to times of overt need (Sapolsky et al., 1986). Accordingly, mechanisms are in place to limit the magnitude and duration of glucocorticoid release. Prominent among these is glucocorticoid negative feedback, whereby secreted glucocorticoids can inhibit further release of ACTH. Importantly, there are at least two mechanisms of negative feedback: 'fast' feedback is sensitive to the rate of glucocorticoid secretion and is likely non-genomic, whereas 'delayed' feedback is sensitive to glucocorticoid levels and appears to involve genomic actions (Keller-Wood and Dallman, 1984). The latter process may be further distinguished into 'intermediate' and 'delayed', as increasing stress duration elicits prolonged changes in pituitary proopiomelanocortin content and ACTH stores (see (Keller-Wood and Dallman, 1984). Thus, glucocorticoids appear to modulate HPA axis function by multiple feedback mechanisms.

Delayed (i.e., genomic) glucocorticoid feedback is likely mediated by endogenous glucocorticoid receptors present in key HPA-regulatory brain regions. These receptors act to modulate gene transcription by either binding cognate response elements or modulating activity of other transcription factors (Gustafsson et al., 1987; McKay and Cidlowski, 1998; Pearce and Yamamoto, 1993; Yang-Yen et al., 1990). There are currently two known glucocorticoid receptors in brain. The glucocorticoid receptor (GR) is highly expressed in numerous brain regions (Ahima and Harlan, 1990; Ahima et al., 1991; Aronsson et al., 1988; Arriza et al., 1988; Fuxe et al., 1985; Reul and deKloet, 1986); this receptor has 5–10 nM affinity and is extensively bound only during periods of intermediate to high glucocorticoid secretion (as occurs during the circadian corticosterone peak and following stress) (Reul and deKloet, 1985). The mineralocorticoid receptor (MR) has an approximately 5–10 fold greater affinity and as a consequence is extensively bound even during periods of basal secretion (Reul and deKloet, 1985). Expression of the MR is considerably more restricted than that of GR (Ahima and Harlan, 1990; Ahima et al., 1991; Aronsson et al., 1988; Arriza et al., 1988; Fuxe et al., 1985; Reul and deKloet, 1986). The binding characteristics of the two receptors have led some to postulate that the GR is important in mediating glucocorticoid feedback following stress, whereas the MR regulates basal HPA tone (De Kloet et al., 1998). There is pharmacological evidence in support of both of these suppositions (Dallman et al., 1989; Ratka et al., 1989).

Numerous studies provide evidence for fast membrane actions of glucocorticoids, mediating the phenomenon known as 'fast feedback'. Membrane glucocorticoid binding has been observed in non-mammalian species (Orchinik et al., 1991), and it is clear that glucocorticoids have rapid effects on glutamate signaling in the PVN (see (Di et al., 2003). In both cases, binding profiles suggest that the membrane receptor is structurally distinct from GR or MR (Di et al., 2003; Orchinik et al., 1991). The receptor responsible for rapid glucocorticoid action remains to be isolated and characterized.

Despite the clear importance of glucocorticoids in feedback regulation, it is crucial to note that the HPA axis is also susceptible to glucocorticoid-independent inhibition from neuronal sources. The PVN is richly innervated by GABAergic neurons from multiple brain regions, including the bed nucleus of the stria terminalis, medial preoptic area, dorsomedial hypothalamus, lateral hypothalamic area and neurons scattered in the immediate surround of the PVN (Cullinan et al., 1996; Cullinan et al., 1993; Roland and Sawchenko, 1993). The degree to which GABAergic inhibitory circuits respond to neural stimuli vs. glucocorticoid level is not clear. However, it is important to note that animals lacking glucocorticoid feedback signals (subsequent to adrenalectomy) can inhibit ACTH responses (Jacobson et al., 1988), indicating that mechanisms exist to check ACTH secretion in the absence of steroid feedback.

The sensitivity of animals and humans to glucocorticoid feedback is not a constant. In rats, chronic stress can decrease the sensitivity of the HPA axis to dexamethasone (Mizoguchi et al., 2003). These data are similar to effects seen in subpopulations of human depressives (see Carroll et al., 1976a,b; Kathol et al., 1989). The mechanism underlying this adjustment of feedback sensitivity is a subject of considerable attention, and may involve altered glucocorticoid receptivity in central pathways controlling responses of the HPA axis.

When exposed to chronic stress, the HPA axis can show both response 'habituation' and response 'facilitation'. 'Habituation' occurs when the same (homotypic) stressor is delivered repeatedly, and is characterized by progressive diminution of glucocorticoid responses to the stimulus (c.f., Bhatnagar et al., 2002; Cole et al., 2000; Kant et al., 1985). Systemic administration of a mineralocorticoid receptor antagonist is sufficient to block habituation, implying a role for MR signaling in this process (Cole et al., 2000). It should be noted that HPA axis habituation is highly dependent on both the intensity and predictability of the stressful stimulus (see Marti and Armario, 1997; Pitman et al., 1988). 'Facilitation' is observed when animals repeatedly exposed to one stimulus are presented with a novel (heterotypic) stressor (Akana et al., 1992; Kant et al., 1985). In chronically stressed animals, exposure to a novel stimulus results in rise in glucocorticoids that is as large as or greater than that seen in a chronic stress-naïve animal. Importantly, facilitation can occur in the context of chronic stress-induced elevations in resting glucocorticoids levels, suggesting that this process involves a bypass or override of negative feedback signals.

## 4. Role of limbic structures in HPA axis integration

### 4.1. Hippocampus

Numerous studies have connected the hippocampus with inhibition of the HPA axis (see Herman and Cullinan, 1997; Jacobson and Sapolsky, 1991; Sapolsky et al., 1986). Hippocampal stimulation decreases glucocorticoid secretion in rat and human (Dunn and Orr, 1984; Rubin et al., 1966), suggesting that this region is sufficient to inhibit HPA activation. In support of this hypothesis, numerous studies indicate that total hippocampectomy, fimbria-fornix lesion or excitotoxic lesions of the hippocampus increase corticosterone and/or ACTH release (Fendler et al., 1961; Knigge, 1961; Knigge and Hays, 1963; Sapolsky et al., 1984). Damage to the hippocampal system also elevates parvocellular PVN CRH and/or AVP mRNA levels (Herman et al., 1995, 1992, 1989b), indicating that lesions affect ACTH secretagogue biosynthesis in hypophysiotrophic neurons. Lesion effects are most pronounced during the recovery phase of stress-induced glucocorticoid secretion (Herman et al., 1995; Sapolsky et al., 1984); in conjunction with the very high density of glucocorticoid receptors in the hippocampus, these data have led some to posit a critical role for the hippocampus in feedback inhibition of the HPA axis (Jacobson and Sapolsky, 1991; Sapolsky et al., 1986).

Hippocampal regulation of the HPA axis appears to be both region- and stressor-specific. Using a sequential lesion approach, our group has noted that the inhibitory effects of the hippocampus on stress-induced corticosterone release and CRH/AVP mRNA expression are likely subserved by neurons resident in the ventral subiculum-caudotemporal CA1 (Herman et al., 1995). In addition to spatial specificity, hippocampal regulation of the HPA axis also appears to be specific to certain stress modalities; our studies indicate that ventral subiculum lesions cause elevated glucocorticoid secretion following restraint, open field or elevated plus maze exposure, but not to ether inhalation or hypoxia (Herman et al., 1995, 1998; Mueller et al., 2004). These data agree with previous studies that fail to observe altered stress-induced HPA activation following fimbria-fornix lesion or hippocampectomy using ether and hypoxia as the evocative stimuli (Table 1).

There are some data that suggest the hippocampus may also play a stimulatory role in HPA axis regulation under some circumstances (Table 1). For example, stimulation of some

Table 1
Stressor-specificity of limbic–HPA regulation in the rat: hippocampus

| Stressor | Lesion | HPA response to stress |
|---|---|---|
| Restraint | Excitotoxic lesion* | Increase (1–4), no effect (5)† |
| Context/conditioning | Fornix lesion | Increase (6) |
| | Aspiration lesion | Increase (7) |
| Extinction | Aspiration lesion | No effect (8) |
| Novelty | Excitotoxic lesion | Increase (1; 2; 9), no effect (5), decrease (10) |
| Ether | Aspiration lesion | No effect (11–16), increase (17) |
| | Fornix lesion | No effect (males) (18), increase (females) (18) |
| | Excitoxic lesion | No effect (2) |
| Lithium chloride | Aspiration lesion | No effect (19) |
| Hypoxia | Fornix lesion | No effect (20) |
| | Excitoxic lesion | Decrease (9) |

*Excitoxic lesions: destruction of all or part of the hippocampus by single or multiple injections of ibotenic acid or kainic acid; fornix lesion: physical disruption (e.g., knife cut) of fibers traveling in the fimbria/fornix; aspiration lesion: suction ablation of all or part of the hippocampus.
†Effects of lesions on ACTH or corticosterone secretion following stress. For the purposes of this table, no distinctions are made between dorsal and ventral hippocampus; for discussion of regional differences, refer to the text.

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hippocampal regions increase corticosterone release (Dunn and Orr, 1984; Feldman and Weidenfeld, 2001), and lesion studies have demonstrated excitatory actions of (in particular) the dorsal hippocampus on HPA axis activation (Feldman and Weidenfeld, 1993). Our own work has indicated a somewhat paradoxical inhibition of hypoxia-induced corticosterone release following ventral subiculum lesions (Mueller et al., 2004), suggesting that in some cases, lesions may have opposite effects on stressors of different modalities.

The hippocampus may also be involved in interpretation of stressor intensity. Work performed in hippocampectomized rats indicates a greater sensitivity to the mild stress of cage relocation (Kant et al., 1984). In addition, ventral subiculum lesion rats show the most robust augmentation of HPA axis activity following open field exposure, a stimulus which produces a relatively mild corticosterone response in intact rats (Herman et al., 1998).

The role of the hippocampus in negative feedback processes is far from clear. The hippocampus expresses high levels of both glucocorticoid and mineralocorticoid receptors (Aronsson et al., 1988; Arriza et al., 1988; Herman, 1993; Herman et al., 1989a,b; Reul and deKloet, 1985, 1986), and as noted above, is involved in inhibiting HPA axis responses to at least some classes of stressor. In addition, numerous studies provide circumstantial evidence for feedback actions. For example, chronic stress, long-term high dose corticosteroid treatment and aging are all associated with hippocampal neuroimpairment, decreased levels of hippocampal corticosteroid receptors and prolonged stress responses, suggesting a connection between decreased hippocampal glucocorticoid signaling and HPA inhibition (Issa et al., 1990; Sapolsky et al., 1986). In addition, systemic administration of a MR antagonist abolishes habituation of the HPA axis to repeated stress (Cole et al., 2000), whereas central infusions of the GR antagonist RU486 retards shut-off of the corticosterone response to novelty (Ratka et al., 1989). Nonetheless, direct tests of feedback have yielded at best mixed results: the ability of the synthetic glucocorticoid dexamethasone to block HPA axis responses to ether stress is impaired by hippocampectomy (Feldman and Confronti, 1980; Magarinos et al., 1987); however, neither fimbria-fornix section nor hippocampal lesions impair fast or delayed feedback effects of high doses of the endogenous ligand (corticosterone) on ACTH release following restraint or hypoxia (Bradbury et al., 1993; Herman et al., 1998).

### 4.2. Medial prefrontal cortex

The medial prefrontal cortex is also implicated in stress regulation. Lesions of the anterior cingulate and prelimbic divisions of the medial prefrontal cortex enhance ACTH and corticosterone secretion and PVN c-*fos* mRNA induction following restraint but not ether (Diorio et al., 1993; Figueiredo et al., 2003a,b), implying a stressor-specific role in HPA inhibition. However, recent studies indicate that the role of the medial prefrontal cortex is considerably more complex; for example, large lesions restricted to the right infralimbic cortex decrease, rather than increase, corticosterone responses to restraint stress, whereas left-sided lesions do not affect glucocorticoid secretion (Sullivan and Gratton, 1999). In addition, the infralimbic cortex may differentially affect responses to inflammatory stimuli, as a recent study indicates that lesions of this region attenuate ACTH secretion following interleukin-1 beta injection but not noise (Crane et al., 2003b). Taken together, these observations suggest an intricate topographical organization of prefrontal cortex output to HPA-regulatory circuits. The anatomy of medial prefrontal cortex efferents may illuminate this issue. The infralimbic cortex projects extensively to the anterior bed nucleus of the stria terminalis, medial and central amygdala and the nucleus of the solitary tract, all of which are implicated in stress excitation (below) (Hurley et al., 1991; Sesack et al., 1989; Takagishi and Chiba, 1991). In contrast, the prelimbic cortex has minimal input to these structures, but projects to the ventrolateral preoptic area, dorsomedial hypothalamus and peri-PVN region, areas implicated in stress inhibition (Hurley et al., 1991; Sesack et al., 1989). Thus, the infralimbic and prelimbic/anterior cingulate components of the prefrontal cortex may play very different roles in HPA axis regulation.

Like the hippocampus, the medial prefrontal cortex expresses large numbers of glucocorticoid receptor positive neurons (Ahima and Harlan, 1990; Fuxe et al., 1985). A sizable proportion of these neurons co-localizes c-*fos* following restraint, suggesting that stressful stimuli target these neurons (Ostrander et al., 2003). Implants of corticosterone in this region attenuate HPA axis responses to restraint (Akana et al., 2001; Diorio et al., 1993) but not ether (Diorio et al., 1993), suggesting that this region may be a site for glucocorticoid negative feedback regulation of responses to defined stress modalities.

### 4.3. Amygdala

The amygdala is believed to activate the HPA axis. The influence of the amygdala on the HPA system is largely mediated by the medial and central amygdaloid nuclei, representing the principle amygdalar projection neurons to basal forebrain, hypothalamic and brainstem structures (c.f., Swanson and Petrovich, 1998). Large amygdaloid lesions or lesions of the central or medial amygdaloid nuclei reduce ACTH and/or corticosterone secretion following stress (see Allen and Allen, 1974; Beaulieu et al., 1986; Dayas and Day, 2002; Feldman et al., 1994; Van de Kar et al., 1991), whereas stimulation increases HPA axis output (Dunn and Whitener, 1986; Matheson et al., 1971; Redgate and Fahringer, 1973). Positive effects of the amygdaloid nuclei on the HPA axis are consistent with other known functions of these regions, including activation of autonomic responses (Gray, 1993) and involvement in fear and anxiety (Davis, 1992).

Like other limbic regions, the influence of the amygdala on the HPA axis is stressor- and region-specific. The medial amygdala shows intense c-*fos* induction following stressors such as restraint, swimming, predator exposure and social interaction (Cullinan et al., 1995; Figueiredo et al., 2003a,b;

Kollack-Walker et al., 1997), but considerably less activation following interleukin-1 beta injection, hypoxia or hemorrhage (Figueiredo et al., 2003a,b; Sawchenko et al., 1996; Thrivikraman et al., 1997). Lesions of this structure reduce HPA axis responses to restraint (Dayas et al., 1999). In contrast, the central amygdaloid nucleus is preferentially responsive to inflammatory/hemodynamic stimuli (Sawchenko et al., 1996; Thrivikraman et al., 1997), and lesions of this region attenuate HPA activation following system interleukin-1 beta (Xu et al., 1999) but not restraint (Dayas et al., 1999; Prewitt and Herman, 1997) (however, see also (Beaulieu et al., 1986).

The amygdala is also a potential target for glucocorticoids. Both the central and medial amygdaloid nuclei express GR (Ahima and Harlan, 1990; Aronsson et al., 1988; Arriza et al., 1988; Fuxe et al., 1985); Fig. 2) and MR (Arriza et al., 1988) (Fig. 2). Expression of MR is notably weaker than GR, especially in the medial nucleus; nonetheless, the presence of both GR and MR suggests that the central and medial amygdaloid nuclei are able to process signals related to both basal and stress levels of glucocorticoids. Thus, these amygdaloid nuclei are well-positioned to influence multiple domains of central glucocorticoid signaling.

The role of the CeA and perhaps MeA in glucocorticoid signaling may differ substantially from that of the hippocampus/prefrontal cortex, commonly thought of as 'feedback inhibition' sites. Regulatory studies indicate that glucocorticoids positively increase CRH expression in the CeA (Makino et al., 1994), in marked contrast with known inhibitory effects of glucocorticoids on CRH production in the PVN (Beyer et al., 1988; Schafer et al., 1989). Implants of glucocorticoids into the CeA do not affect acute stress responsiveness, but appear to potentiate autonomic responses to chronic stress exposure (Akana et al., 2001). In addition, the CeA appears to be selectively activated by heterotypic stressors given in conjunction with chronic stress, suggesting that this structure plays a role in the facilitation process (Bhatnagar and Dallman, 1998). Overall, the data have led to the intriguing hypothesis that amygdalar glucocorticoid receptors play a 'feed forward' role in stress regulation, serving to potentiate rather than inhibit HPA responses (Dallman et al., 2003).

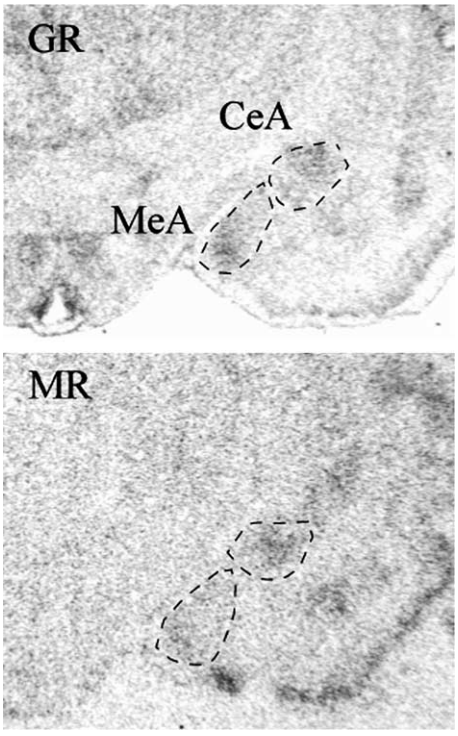


Fig. 2. Expression of glucocorticoid receptor (GR, top) and mineralocorticoid receptor (MR, bottom) mRNAs in the rat amygdala. Both GR and MR mRNAs are present in the central amygdaloid (CeA) and medial amygdaloid (MeA) nuclei.

## 5. Neurocircuitry of limbic–HPA interactions: subcortical relay systems

Despite the prominent involvement of the hippocampus, medial prefrontal cortex and amygdala in HPA axis regulation, there is limited evidence of direct innervation of the PVN by these structures (Herman et al., 2003). Rather, these regions appear to project to a number of basal forebrain, hypothalamic and brainstem cell populations that in turn innervate the medial parvocellular PVN. Thus, in order to access principle stress effector neurons, information from the limbic system requires an intermediary synapse.

In the bed nucleus of the stria terminalis and hypothalamus, the majority of these intermediary neurons are GABAergic. For example, the bed nucleus of the stria terminalis, ventrolateral preoptic area, dorsomedial hypothalamic nucleus and peri-PVN region all contain rich populations of neurons expressing the GABA marker glutamatic acid decarboxylase (GAD) 65/67. (Bowers et al., 1998; Okamura et al., 1990). Combined in situ hybridization/retrograde tracing studies indicate that most of the PVN projection neurons in these regions are GABAergic (Cullinan et al., 1993; Roland and Sawchenko, 1993). GABA neurons in PVN-projecting zones of these regions express c-*fos* immunoreactivity following swim stress (Cullinan et al., 1996), suggesting that these cells are involved in regulation of HPA responses. Finally, HPA axis responses are inhibited by direct infusion of the GABA-A receptor agonist muscimol into the PVN region (Cullinan, 1998), consistent with an important role for GABA in regulation of hypophysiotrophic PVN neurons.

The bed nucleus of the stria terminalis is in receipt of information from all stress-regulatory limbic regions noted above. In some cases, there is considerable overlap of projections from various limbic sources; for example, the medial amygdala, medial prefrontal cortex and ventral subiculum all send afferents to anteromedial subdivisions of the bed nucleus of the stria terminalis (Canteras et al., 1995; Crane et al., 2003a; Cullinan et al., 1993). However, it is not currently known whether these projections contact the same neurons. Lesion and stimulation studies also suggest that the role of the bed nucleus of the stria terminalis in stress integration is site-dependent; posterior/medial regions are involved in HPA axis inhibition (Dunn, 1987; Herman et al., 1994), whereas anterior/lateral regions appear HPA excitatory (Crane et al., 2003a; Dunn, 1987; Gray et al.,

1993; Herman et al., 1994). Site-dependent effects of the bed nucleus of the stria terminalis on HPA responses may be associated with the topography of amygdalar vs. hippocampal inputs; for example, the PVN-projecting fusiform subdivision in the anterolateral region is preferentially innervated by the central amygdalaoid nucleus (Dong et al., 2001a,b; Prewitt and Herman, 1998), whereas the posteriorly situated interfascicular and transverse nuclei receive rich input from the ventral subiculum (Cullinan et al., 1993).

There are numerous hypothalamic connections to the medial parvocellular PVN, only a few of which have been systematically studied with respect to HPA axis regulation. The literature suggests that at least two of these PVN-projecting regions, the medial preoptic area and dorsomedial hypothalamic nucleus, have a role in HPA axis integration. Lesions of both of these nuclei increase corticosteroid secretion (Bealer, 1986; Herman et al., 2003; Viau and Meaney, 1996). Conversely, stimulation of dorsomedial nucleus or medial preoptic area can inhibit PVN neurons (Boudaba et al., 1996), and stimulation of medial regions of the medial preoptic area can reverse the excitatory effects of amygdalar stimulation on HPA activation (Feldman et al., 1990). In addition, induction of c-*fos* occurs in GABAergic cell populations of these nuclei following stress exposure (Cullinan et al., 1996). Overall, these data are consistent with an inhibitory role for the medial preoptic area and dorsomedial nucleus in HPA regulation, and indicate the potential for these hypothalamic structures to serve as relays for limbic stress-modulatory circuitry.

The organization of the peri-PVN cell groups is particularly interesting. In the case of the ventral subiculum and to a lesser extent, the medial prefrontal cortex, terminal fields can be observed in the immediate surround of the PVN (Cullinan et al., 1993; Hurley et al., 1991; Oldfield et al., 1985; Sesack et al., 1989), corresponding to areas containing substantial numbers of GABA neurons (Bowers et al., 1998; Roland and Sawchenko, 1993). Importantly, dendrites of PVN neurons are largely confined within the nucleus proper (van den Pol, 1982), indicating that limbic afferents are unlikely to interact directly with the PVN neurons themselves. The peri-PVN GABA neurons are activated by glutamate (Cole and Sawchenko, 2002), and likely express glutamate receptor subunits (Herman et al., 2000). These neurons also up-regulate GAD65 mRNA following chronic stress (Bowers et al., 1998), commensurate with involvement in long-term HPA regulation. Injections of a general ionotroptic glutamate receptor antagonist into the PVN surround potentiates glucocorticoid responses to restraint (Ziegler and Herman, 2000), consistent with blockade of glutamate excitation of these GABA neurons. The data are consistent with an interaction between the excitatory limbic structures and inhibitory PVN-regulatory cells at the level of the PVN surround.

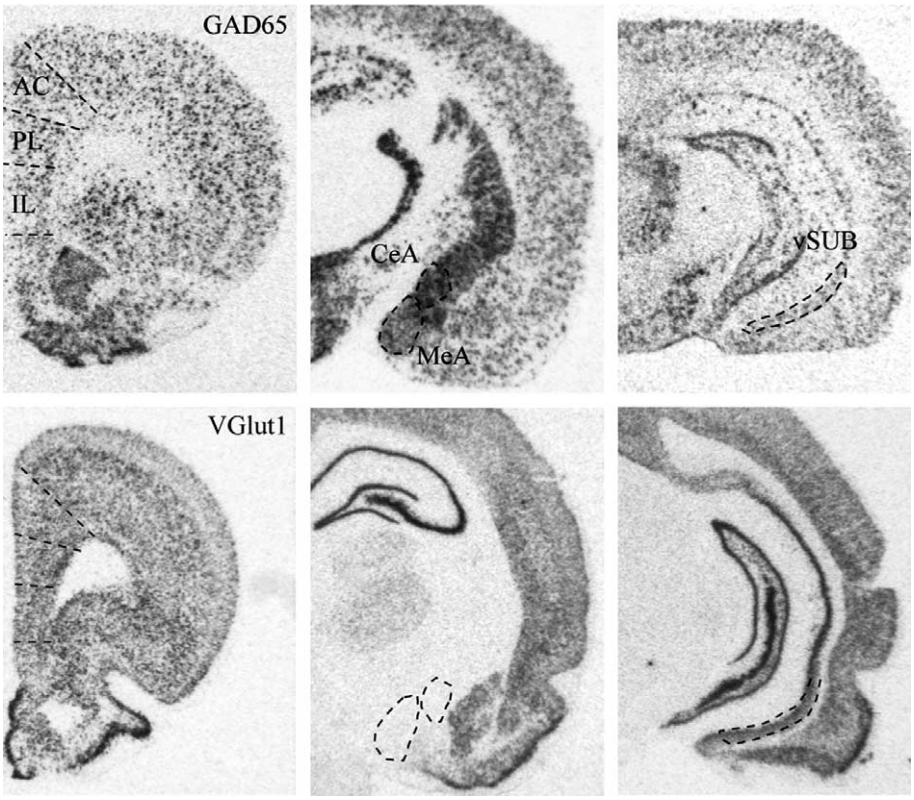


Fig. 3. Expression of GABA (glutamic acid decarboxylase (GAD)65) and glutamate (vesicular glutamate transporter 1) mRNAs in the prefrontal cortex (left panels), amygdala (middle panels) and ventral subiculum (right panels) of the rat. GAD65 mRNA is localized to interneurons of the anterior cingulate (ac), prelimbic (pl), and infralimbic (il) cortices as well as the ventral subiculum (vSUB). In contrast, the majority of neurons in primary projection regions of the amygdala (central amygdaloid (CeA) and medial amygdala (MeA) nuclei) are GABAergic. VGlut1 is present in pyramidal cell layers of the medial prefrontal cortices and ventral subiculum, in agreement with the known glutamate phenotype of neurons in these regions; in contrast, the CeA and MeA express little or no VGlut1 mRNA.

Brainstem stress-modulatory pathways likely relay excitatory information to the PVN. For example, the nucleus of the solitary tract provides both catecholaminergic (norepinephrine) and non-catecholaminergic (e.g., glucagon-like peptide-1 (GLP-1) input to the medial parvocellular PVN (Cunningham et al., 1990; Cunningham and Sawchenko, 1988; Rinaman, 1999). Norepinephrine is released into the PVN following stress (Pacak et al., 1995) and is believed to activate CRH neurons via alpha-1 adrenergic receptors (Plotsky et al., 1989). The role of this pathway is thought to be associated with systemic stressors, as selective destruction of PVN norepinephrine input using anti-dopamine beta hydroxylase-saporin conjugate blocks responses to 2-deoxy-glucose but not restraint (Ritter et al., 2003). In contrast, blockade of central GLP-1 receptors using exendin 9–36 markedly inhibits responsiveness to both lithium chloride and novelty (Kinzig et al., 2003), suggesting that this non-catecholaminergic cell population may play a more general role in stress integration.

The existence of these putative two-neuron circuits lends important insight into the nature of stress information processing. Anatomical data support the hypothesis that the vast majority of medial prefrontal cortex and ventral subicular inputs to subcortical stress relays are glutamate-containing. As can be appreciated in Fig. 3, pyramidal cells of the medial prefrontal cortex and subiculum richly express mRNA encoding vesicular glutamate transporter-1 (VGlut1), a specific marker of glutamate neurons (c.f., Fremeau et al., 2001). Combined retrograde tracing/in situ hybridization studies performed in our lab indicate that the vast majority of cortical and hippocampal afferents to PVN-projecting regions (e.g., bed nucleus of the stria terminalis, dorsomedial hypothalamus, ventrolateral medial preoptic area) indeed contain VGlut1 (Fig. 4), verifying a glutamatergic input to these areas. In contrast, the majority of amygdalar areas implicated in stress regulation express glutamic acid decarboxylase (GAD) 65 or 67 mRNA (Fig. 3), suggesting a GABAergic phenotype; indeed, the vast majority of medial and central amygdaloid projections to PVN relays are GABAergic (Fig. 4).

Given the largely GABAergic phenotype of basal forebrain/hypothalamic PVN projections, it is likely that limbic information is relayed to the PVN in accordance with the scenario presented in Fig. 5. In forebrain, descending limbic information appears to interface with the largely GABAergic cell populations projecting to the medial parvocellular PVN. At least a portion of this regulatory input may be mediated by local cell populations in the PVN surround, which project into the PVN proper. Glutamate inputs (ventral subiculum, medial prefrontal cortex) are thus positioned to inhibit PVN neurons via activation of these GABA cells, whereas GABAergic circuits of the medial and central amygdaloid nuclei may in fact promote CRH release by way of disinhibition (i.e., sequential GABA synapses).

Limbic-brainstem PVN relays present a very different set of possibilities. The NTS is intimately involved in excitation of PVN neurons, via catecholamines and/or neuropeptides (e.g., GLP-1) (Kinzig et al., 2003; Ritter et al., 2003). Thus, stimulation of this structure by descending excitatory (glutamate) signals would be expected to transsynaptically activate the HPA axis, whereas GABAergic inputs may decrease PVN activation.

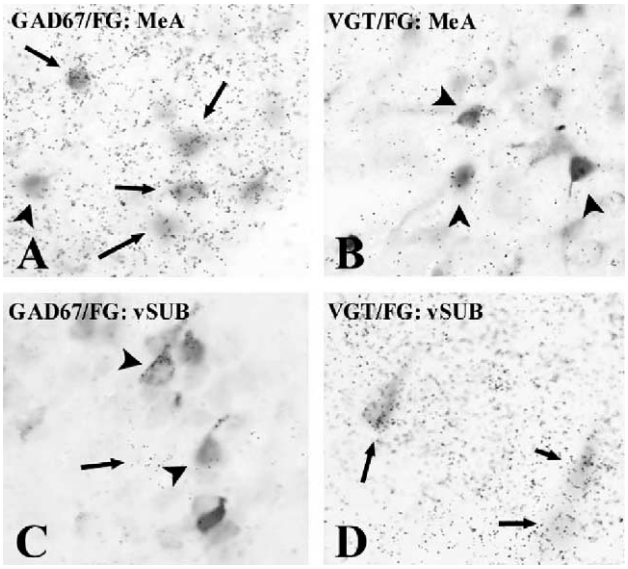


Fig. 4. Innervation of the PVN-projecting region of the bed nucleus of the stria terminalis (BST) by GABAergic and glutamatergic limbic regions. Combined tract tracing/immunohistochemistry (Fluorogold (FG) and in situ hybridization was used to establish the neurochemical identity of medial amygdalar (MeA) (A, B) and ventral subicular (vSUB) (C, D) neurons innervating the PVN-projecting interfascicular (posterior) region of the BST. In situ hybridization-positive neurons are indicated with arrows, unlabeled neurons with arrowheads. In the MeA, the vast majority of FG labeled neurons (dark) contained the GABAergic marker GAD67 (grains) (A), whereas there were very few neurons expressing vesicular glutamate transporter 1 (VGT) (B), a corticolimbic glutamate marker. In contrast, the vast majority of FG-labeled neurons in the vSUB were negative for GAD67 (C), but positive for VGT (D). The arrow in C illustrates a non-FG labeled GAD67 neuron, probably reflecting a subicular GABAergic interneuron. Figure reprinted from (Herman et al., 2003), with permission.

In most cases, the anatomy of these limbic-PVN relays predicts the HPA outcomes observed in lesion and stimulation studies. For example, lesions of largely glutamate cell populations in the hippocampus enhance HPA axis responses, implying loss of transsynaptic inhibition (Herman and Cullinan, 1997). In contrast, lesions of the predominantly GABAergic medial amygdala reduce stress-induced ACTH release and PVN activation (Dayas et al., 1999), and stress-excitatory effects of medial amygdalar stimulation can be blocked by lesions of the similarly GABA-rich medial bed nucleus of the stria terminalis or preoptic area (Feldman et al., 1990), consistent with disinhibition of the PVN via sequential GABA synapses.

Whereas the above scenarios are plausible for relays in hypothalamus and the bed nucleus of the stria terminalis, limbic-nucleus of the solitary tract (NTS) relays may be more complicated. Infralimbic cortical innervation of the NTS would suggest glutamate–noradrenergic or glutamate–peptidergic (e.g., GLP-1) interactions, which should be excitatory in nature. However, projection neurons of central amygdaloid nucleus are predominantly GABAergic, predicting that the amygdala-NTS relay would inhibit the HPA axis. However, it

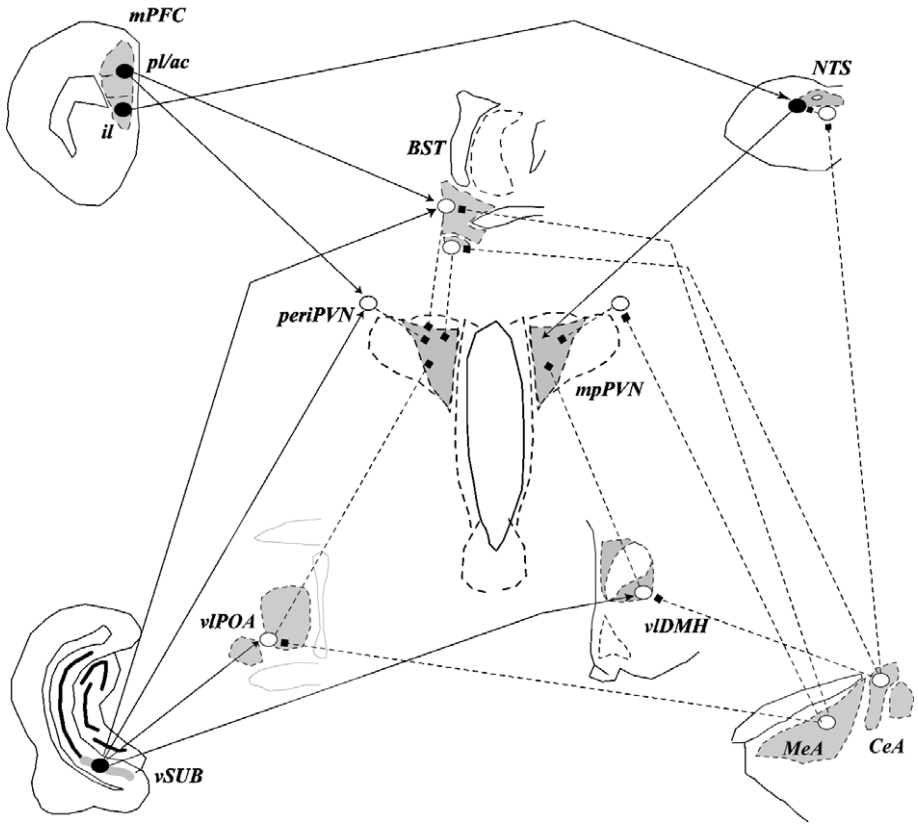


Fig. 5. Diagrammatic representations of limbic stress-integrative pathways from the prefrontal cortex, amygdala and hippocampus. The medial prefrontal cortex (mPFC) subsumes neurons of the prelimbic (pl), anterior cingulate (ac) and infralimbic cortices (il), which appear to have different actions on the HPA axis stress response. The pl/ac send excitatory projections (designated as dark circles, filled line with arrows) to regions such as the peri-PVN zone and bed nucleus of the stria terminalis (BST), both of which send direct GABAergic projections to the medial parvocellular PVN (delineated as open circles, dotted lines ending in squares). This two-neuron chain is likely to be inhibitory in nature. In contrast, the infralimbic cortex projects to regions such as the nucleus of the solitary tract (NTS), which sends excitatory projections to the PVN, implying a means of PVN excitation from this cortical region. The ventral subiculum (vSUB) sends excitatory projections to numerous subcortical regions, including the posterior BST, peri-PVN region, ventrolateral region of the medial preoptic area (vlPOA) and ventrolateral region of the dorsomedial hypothalamic nucleus (vlDMH), all of which send GABAergic projections to the PVN and are likely to communicate transsynaptic inhibition. The medial amygdaloid nucleus (MeA) sends inhibitory projections to GABAergic PVN-projecting populations, such as the BST, vlPOA and peri-PVN, eliciting a transsynaptic disinhibition. A similar arrangement likely exists for the central amygdaloid nucleus (CeA), which sends GABAergic outflow to the ventrolateral BST and to a lesser extent, the vlDMH. The CeA also projects to GABAergic neurons in the NTS, which may disinhibit ascending projections to the PVN.

is important to note that the synaptology of the central amygdala-NTS connections is not worked out; thus, it is possible that this structure may relay through inhibitory interneurons in the NTS itself. There is some evidence to support this supposition, as anterogradely labeled terminals from the central amygdala appear to synapse on GABAergic neurons within the NTS (Pickel et al., 1996). In addition, while the projections of the central amygdala are largely GABAergic, there are some cell populations in these regions that express alternative phenotypes. For example, the central amygdala contains a population of CRH neurons in its lateral region (Gray, 1993); selective activation of NTS-projecting cells of these regions may account for amygdalar excitation of ascending PVN input.

Finally, it is important to note that many of the above structures show considerable microheterogeneity. For example, while the major output of the central amygdaloid nucleus appears to be GABA, the nucleus itself has multiple intrinsic and extrinsic connections (Swanson and Petrovich, 1998) and expresses multiple different types of neuropeptidergic neurons (Cassell et al., 1986). Thus, it is highly possible that point-to-point information from upstream sites or even intrinsic synaptic systems can mediate stimulus-specific actions of given stress-regulatory structures on stress responses. The possible contribution of such microheterogeneity on stressor specificity has yet to be addressed.

## 6. Limbic stress circuits and HPA dysfunction

The association of HPA-regulatory regions of the limbic system with disorders of mood suggests that functional alterations in areas such as the hippocampus, prefrontal cortex and amygdala may be responsible for glucocorticoid hyper- or hyposecretion seen in these affective states. As summarized above, it is clear that the involvement of the limbic system in HPA regulation is a complex issue, with topographical organization and stimulus attributes playing a major role in determining how a given region will affect stress responses. Whereas the animal data are not yet sufficient to provide detailed models of affective disease-related neuroendocrine

dysfunction, they do provide several key clues as to how limbic structures may act in this process. First, it is clear that all limbic structures act through subcortical intermediaries, indicating that effects on the HPA axis are indirect and dependent on the functional integrity of these subcortical relays. Second, there is considerable opportunity for integration of limbic information and intermediary sites; in many regions (e.g., bed nucleus of the stria terminalis), there is considerable overlap of innervation fields from 'inhibitory' (e.g., hippocampus, prelimbic cortex) and 'excitatory' (e.g., medial amygdala) structures. This implies that limbic information may be summated at subcortical sites. Third, there are also important differences in projectional characteristics of limbic stress-regulatory regions; thus, the contribution of a given region to the stress response may be weighted differentially in association with the sensory attributes of stressful stimuli (e.g., central amygdala and infralimbic cortex may be selectively tuned to 'interoceptive' or 'visceral' stimuli). Finally, the hippocampus, amygdala and medial prefrontal cortex express both GR and MR, making them likely targets for glucocorticoid action. Accordingly, 'glucocorticoid feedback' is likely a complex process that involves actions at multiple sites, and probably summates with stimulus induced neuronal activation of the respective regions to negatively or positively modulate HPA output. Overall, the connection between limbic structures, affective disorders and HPA axis dysfunction is likely associated with impaired integration of hippocampal, amygdalar and/or prefrontal cortical information at one or more of these key regulatory nodes.

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