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Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamo–pituitary–adrenocortical responsiveness

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Abstract

Appropriate regulatory control of the hypothalamo–pituitary–adrenocortical stress axis is essential to health and survival. The following review documents the principle extrinsic and intrinsic mechanisms responsible for regulating stress-responsive CRH neurons of the hypothalamic paraventricular nucleus, which summate excitatory and inhibitory inputs into a net secretory signal at the pituitary gland. Regions that directly innervate these neurons are primed to relay sensory information, including visceral afferents, nociceptors and circumventricular organs, thereby promoting 'reactive' corticosteroid responses to emergent homeostatic challenges. Indirect inputs from the limbic-associated structures are capable of activating these same cells in the absence of frank physiological challenges; such 'anticipatory' signals regulate glucocorticoid release under conditions in which physical challenges may be predicted, either by innate programs or conditioned stimuli. Importantly, 'anticipatory' circuits are integrated with neural pathways subserving 'reactive' responses at multiple levels. The resultant hierarchical organization of stress-responsive neurocircuitries is capable of comparing information from multiple limbic sources with internally generated and peripherally sensed information, thereby tuning the relative activity of the adrenal cortex. Imbalances among these limbic pathways and homeostatic sensors are likely to underlie hypothalamo–pituitary–adrenocortical dysfunction associated with numerous disease processes.

Keywords: Corticotropin releasing hormone; Glucocorticoids; ACTH; Hypothalamus; Paraventricular nucleus; Nucleus of the solitary tract; Hippocampus; Amygdala

1. Introduction

The hypothalamo–pituitary–adrenocortical (HPA) axis plays a vital role in adaptation of the organism to homeostatic challenge. Activation of the HPA system culminates in secretion of glucocorticoids, which act at multiple levels to redirect bodily energy resources [198,210,262]. These hormones are recognized by glucocorticoid receptor molecules in numerous organ systems, and act by genomic mechanisms to modify transcription of key regulatory proteins [198,210]. Emerging evidence suggests that glucocorticoids also act by non-genomic mechanisms on cell signaling processes [208,217], and in such fashion have rapid actions on homeostatic regulation.

The end effects of glucocorticoid action include energy mobilization (glycogenolysis) in the liver, suppression of innate immunity in immune organs, inhibition of bone and muscle growth, potentiation of sympathetic nervous system-mediated vasoconstriction, proteolysis and lipolysis, suppression of reproductive function along the hypothalamo–pituitary–gonadal axis, and behavioral depression (see [198,210]). The spectrum of effects have led to the hypothesis that glucocorticoids act to restore homeostasis following disruption [210]; for example, increasing glucose can replenish lost energy stores; inhibiting T-cell proliferation will control the inflammatory response; and inhibiting other hormonal systems reduces expenditure of energy on processes unrelated to the immediate challenge. These 'restorative'

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processes are generally catabolic in nature, and naturally if extended in time can take a powerful toll on the organism. Indeed, glucocorticoid hypersecretion is implicated as a major deleterious factor in the aging process [171,172,261], and is known to accompany numerous long-term metabolic, affective, and psychotic disease states (see [111,198], for review).

Accordingly, adequate control of glucocorticoids needs to be accomplished by the organism. Such 'negative feedback' control is efficiently exerted in healthy organisms, and involves both rapid and genomic actions at the pituitary and at multiple sites in the brain (discussed below). Thus, a HPA response is generally characterized by a temporally regulated 'surge' of ACTH release followed by a 'shut-off' signal generated by glucocorticoid as well as neuronal feedback (see Fig. 1, [151]). The ACTH 'surge' is initiated by a discrete population of hypophysiotrophic neurons in the medial parvocellular division of the paraventricular hypothalamic nucleus (PVN) [6,319]. This small population of cells (approximately 4000 in rat [290]) produce a number of ACTH-releasing factors. Of these, corticotropin releasing hormone (CRH) is required for normal ACTH release under both basal and stressed conditions [6,319] and is the defining phenotypic feature of this cell type. The most important co-expressed peptide is arginine vasopressin, which synergizes with CRH to enhance the 'gain' of the ACTH response [6,187,319]. These neurons also produce numerous other peptides and neurotransmitters [155], and may thus have their net activity orchestrated by multiple neuroactive species. Once released by the corticotropes, ACTH travels through the systemic circulation and promotes on-site synthesis and secretion of corticosteroids at the adrenal cortex. While ACTH is the major modulator of corticosteroid release, adrenocortical output can be modulated by neuronal inputs that adjust responsivity to ACTH [304].

The HPA axis operates in two equally important domains of activity. Under relatively unstressed condi-

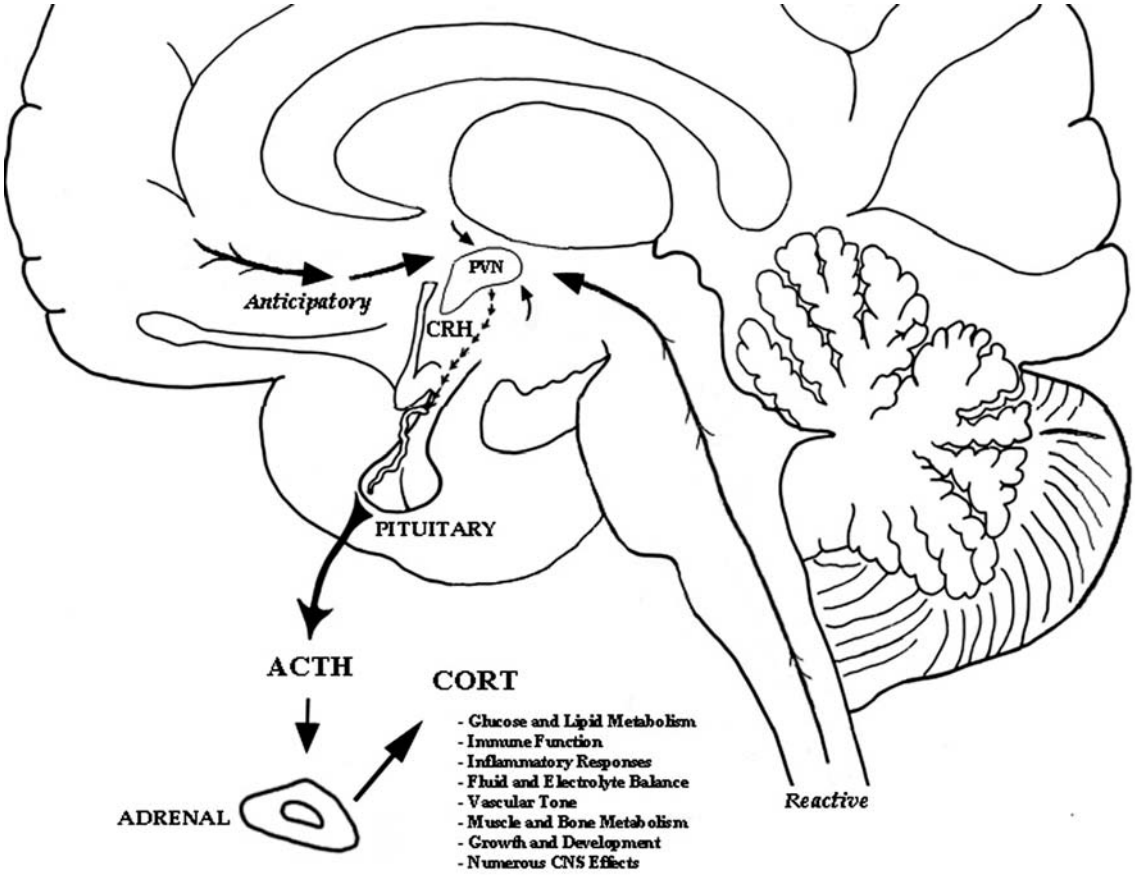


Fig. 1. Overview of the hypothalamo–pituitary–adrenocortical axis, including principal classes of regulatory afferents and corticosteroid actions. CRH neurons located within the hypothalamic paraventricular nucleus (PVN) drive pituitary corticotrophs via the portal vasculature, stimulating the release of ACTH. ACTH, in turn, mediates the synthesis and release of corticosteroids from the adrenal glands. CRH neurons are regulated by sensory afferents which are relayed via brainstem loci, and transmit "reactive' stimuli which are generally excitatory and relatively direct. Conversely, limbic forebrain structures are hypothesized to convey "anticipatory" signals that involve processing within pathways proximal to the level of the PVN, including in the peri-PVN area and several local hypothalamic regions. Integration of "anticipatory' circuits and neural pathways subserving 'reactive' responses occurs at multiple levels (not shown; see text).

tions, glucocorticoid secretion undergoes a daily rhythm, with peak secretion occurring at the initiation of the waking cycle in most vertebrate organisms [151]. Secretion during the waking phase permits circulating glucocorticoids to partially occupy glucocorticoid receptors [238], and is believed to be critical for optimizing functional tone of numerous systems [67]. For example, partial occupation of hippocampal glucocorticoid receptors is required for efficient performance of learning and memory tasks in rats [67,72], suggesting that glucocorticoids may 'set the tone' for information processing in the brain. Control of this rhythmic activity is coordinated by inputs from the suprachiasmatic nucleus [67,72], the critical pacemaker of numerous bodily rhythms.

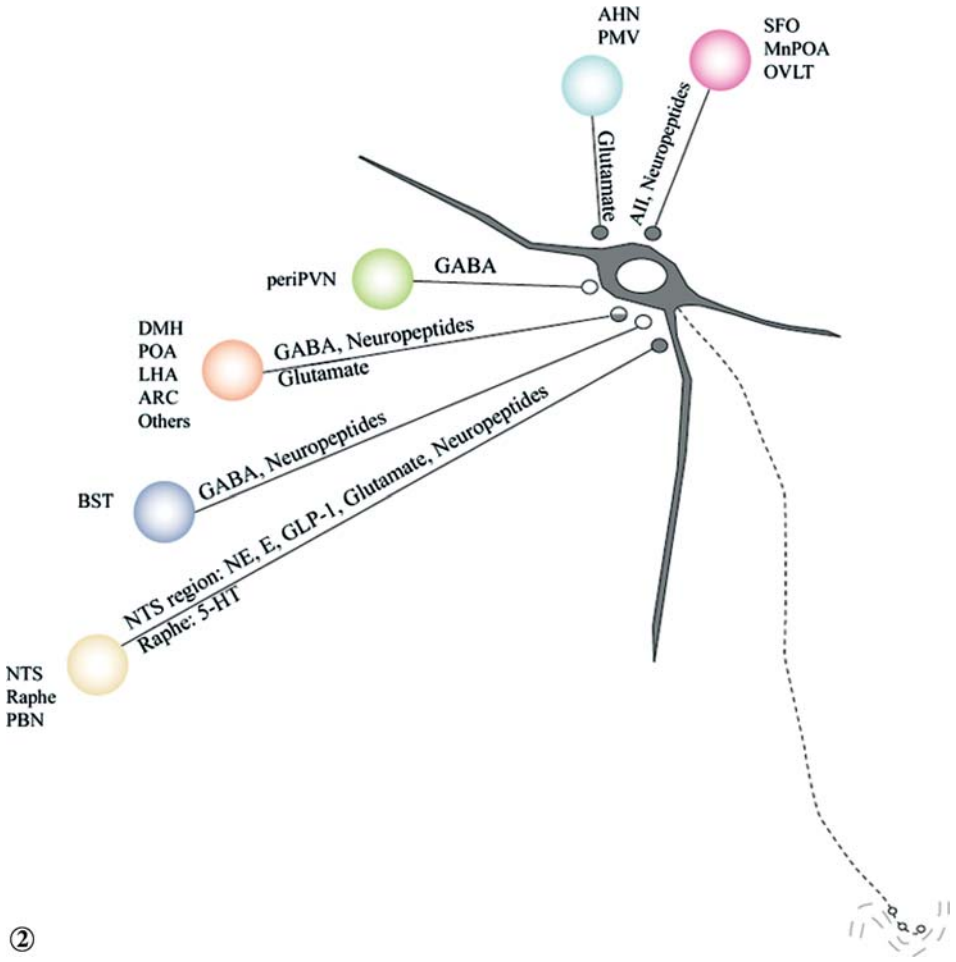
The second domain of HPA action, and the principal topic of this review, is control of corticosteroid secretion following stress. Upon receipt of a 'stressful' stimulus, defined here as a real or predicted threat to homeostasis, the brain initiates an ACTH surge to promote adrenocortical activation. The notion of 'real' or 'predicted' is important, as it highlights what we hypothesize are two distinct realms of stress activation. A 'real' stressor represents a genuine homeostatic challenge that is recognized by somatic, visceral or circumventricular sensory pathways. These stressors would include such things as marked changes in cardiovascular tone, respiratory distress, visceral or somatic pain, and blood-borne cytokine or chemokine factors signaling infection or inflammation (see Table 1). As these represent a response of the body to a very real sensory stimulus, we consider these responses to be 'reactive.' However, HPA activation can also occur in the absence of primary sensory stimuli signaling homeostatic disruption. These responses are centrally generated in the absence of a physiological challenge, and represent an effort of the organism to mount a glucocorticoid response in anticipation of, rather than as a reaction to, homeostatic disruption. These 'anticipatory' responses are either generated by conditioning ('memory') or by innate, species-specific predispositions (e.g., recognition of predators, recognition of danger associated with heights or open spaces) (Table 1). The 'reactive-anticipatory' distinction is experience dependent; the environment associated with a reactive stressor can be itself conditioned, resulting in an 'anticipatory' response when the conditioned stimuli are next encountered.

The mnemonic aspects of anticipatory stressors are important determinants of the HPA response. As noted above, the HPA response is energetically costly and cannot be over-engaged without deleterious consequences [197]. As such, the brain can generate memory-dependent inhibitory and excitatory traces to control glucocorticoid responses. For example, mnemonic circuits can diminish responsiveness to contextual stimuli with repeated exposure (habituation), or activate responses to innocuous cues that are associated with an emergent threat. The wide spectrum of these responses is under exquisite control by limbic brain regions such as the hippocampus, amygdala, and prefrontal cortex.

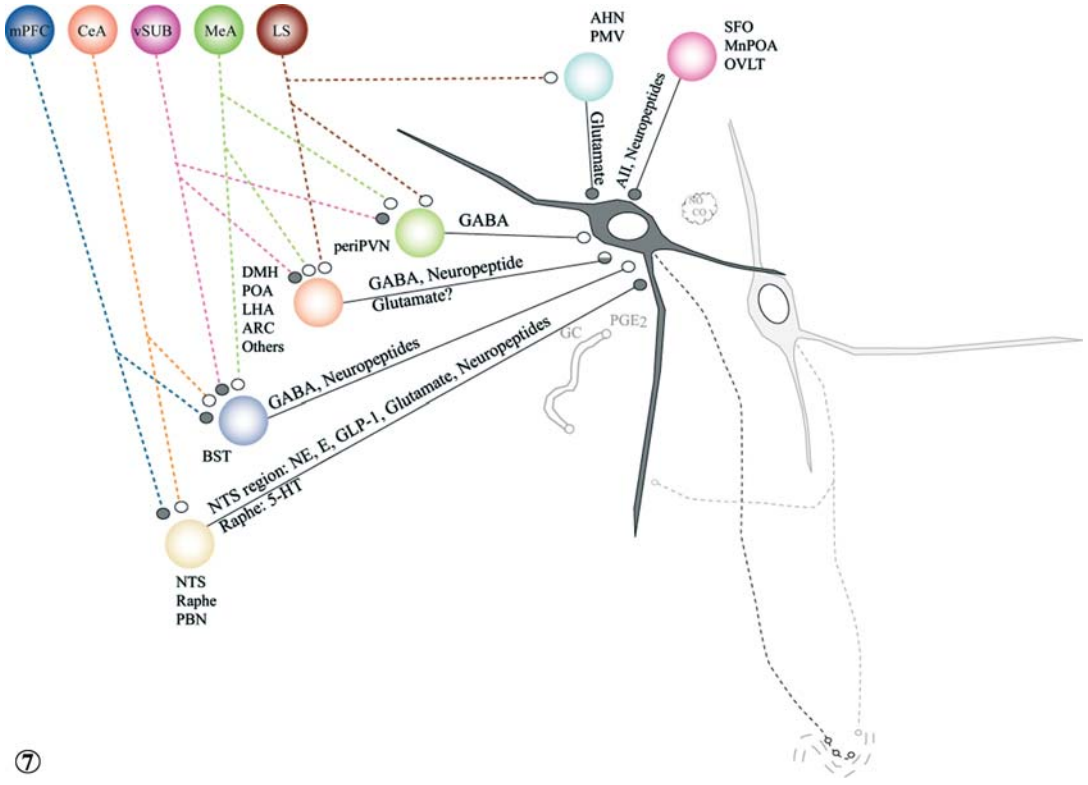
The remainder of this review will be devoted to delineating critical circuits responsible for regulation of the HPA stress response, and developing a framework for understanding the possible role of these hierarchical circuits in stress-related disease states.

Table 1
Stimuli triggering 'reactive' vs. 'anticipatory' HPA stress responses

'Reactive' responses	'Anticipatory' responses
Pain	Innate Programs
Visceral	Predators
Somatic	Unfamiliar environments/situations
Neuronal homeostatic signals	Social challenges
Chemoreceptor stimulation	Species-specific threats (e.g., illuminated spaces for rodents, dark spaces for humans)
Baroreceptor stimulation	Memory programs
'Osmoreceptor' stimulation	Classically conditioned stimuli
Humoral homeostatic signals	Contextually conditioned stimuli
Glucose	Negative reinforcement/frustration
Leptin	
Insulin	
Renin–angiotensin	
Atrial natriuretic peptide	
Others	
Humoral inflammatory signals	
IL-1	
IL-6	
TNF-α	
Others	


AHN
PMV
SFO
MnPOA
OVLT
Glutamate
AII, Neuropeptides
periPVN
GABA
DMH
POA
LHA
ARC
Others
GABA, Neuropeptides
Glutamate
BST
GABA, Neuropeptides
NTS region: NE, E, GLP-1, Glutamate, Neuropeptides
Raphe: 5-HT
NTS
Raphe
PBN

②


mPFC
CeA
vSUB
MeA
LS
AHN
PMV
SFO
MnPOA
OVLT
Glutamate
AII, Neuropeptides
periPVN
GABA
DMH
POA
LHA
ARC
Others
GABA, Neuropeptide
Glutamate?
GC
PGE2
BST
GABA, Neuropeptides
NTS region: NE, E, GLP-1, Glutamate, Neuropeptides
Raphe: 5-HT
NTS
Raphe
PBN

⑦

2. Direct PVN connections

The medial parvocellular PVN is in receipt of synaptic innervation from a relatively circumspect set of central nervous system structures, summarized in Fig. 2. In general, PVN projecting neurons are localized in regions known to receive first- or second-order inputs from somatic nociceptors, visceral afferents or humoral sensory pathways. As such, the majority of PVN-projecting neurons are positioned to evoke rapid, reflexive activation of the HPA axis.

2.1. Nucleus of the solitary tract

Brainstem catecholamine systems play a major role in excitation of the HPA axis. The PVN receives its major norepinephrine (NE) and epinephrine (E) input from the A2/C2 region, originating in the area of the nucleus of the solitary tract (NTS). Fibers from these regions preferentially innervate the medial parvocellular zone of the PVN, at the expense of magnocellular neurosecretory and parvocellular preautonomic neurons, which are innervated by the A1/C1 groups in the rostral ventrolateral medulla [58,59]. General consensus indicates that the NE/E input represents a major HPA excitatory pathway, promoting CRH and ACTH release and CRH gene transcription through activation of α1 adrenergic receptors [230,231,294]. The excitatory nature of NE/E inputs is further supported by evidence documenting stress-induced NE release in the PVN, and by studies indicating that 'reactive' HPA responses can be attenuated by lesions of ascending medullary PVN inputs or by selective lesions of catecholaminergic pathways using 6-hydroxydopamine [108,183,266]. Finally, microdialysis studies indicate that a variety of stressors directly promote norepinephrine release in the PVN region [221]. The latter studies indicate that the relationship between NE release and HPA activation varies with stimulus modality, indicating that NE release is not the sole determinant of the stress response [221].

However, the direct involvement of NE/E pathways in PVN activation is not without some degree of controversy. First, pharmacological studies indicate that high levels of NE may have inhibitory effects on ACTH release mediated by β adrenergic receptors [230]. Second, electrophysiologicial studies indicate that effects of NE on activity of parvocellular neurosecretory neurons can be blocked with tetrodotoxin or glutamate receptor antagonists [60], suggesting that NE effects are mediated by glutamatergic interneurons, rather than acting on CRH neurons directly. Finally, a recent study suggests that stimuli that sensitize HPA stress responses reduce NE/E innervation of the parvocellular PVN [138], suggesting that enhanced excitability is accompanied by withdrawal of catecholaminergic inputs.

Tyrosine hydroxylase-c-fos colocalization studies reveal that catecholaminergic cells represent only a subset of stress-activated, PVN-projecting NTS neurons [31,46,66,223]. Recent evidence indicates that these non-catecholaminergic NTS neurons modulate HPA axis activity. For example, glucagon-like peptide 1 (GLP-1), which is richly expressed in medial parvocellular PVN terminals, is only synthesized in non-tyrosine hydroxylase (i.e., non-catecholaminergic) neurons of the NTS and its immediate environs [177,204]. Exposure to lithium chloride, which produces visceral illness and an attendant HPA response, activates NTS GLP-1 neurons [240]. Importantly, ACTH and corticosterone responses to lithium chloride can be inhibited by central administration of the GLP-1 receptor antagonist des-His_1, Glu_9-exendin-4, indicating that endogenous GLP-1 of NTS origin inhibits HPA activation by this stimulus [154]. In addition, ACTH release can be induced by direct injections of GLP-1 into the PVN (but not amygdala) [154], consistent with direct GLP-1 actions on PVN neurons.

Fig. 2. Major direct projections to a prototypical medial parvocellular PVN neuron. The PVN receives direct innervation from several extrahypothalamic pathways regulating homeostatic functions, including: (1) the subfornical organ (SFO)-median preoptic nucleus (mnPOA)-organum vasculosum of the lamine terminalis (OVLT), regulating fluid and electrolyte balance; (2) norepinephrine (NE), epinephrine (E), glucagon-like peptide 1 (GLP-1) and other neuropeptidergic neurons in the nucleus of the solitary tract (NTS) and parabrachial nucleus (PBN), subserving relay of autonomic and immune system afferents; and (3) hypothalamic nuclei subserving autonomic/metabolic/immune/arousal signals, including the dorsomedial hypothalamus (DMH), medial preoptic area (mPOA), lateral hypothalamic area (LHA), arcuate nucleus (ARC), peri-PVN zone, anterior hypothalamic nucleus (AHN) and ventral premammillary nucleus (PMV), among others. Some of these projections are largely GABAergic (open circles), some are predominantly glutamatergic (closed circles), whereas as others contain mixed populations of cells. The bed nucleus of the stria terminalis (BST) is predominantly GABAergic, suggesting a largely inhibitory influence on the PVN.

Fig. 7. Hierarchical limbic projections to reactive stress pathways. The medial prefrontal cortex (mPFC), central amygdaloid nucleus (CeA), ventral subiculum (vSUB), medial amygdaloid nucleus (MeA), and lateral septum (LS) are limbic system regions known to affect HPA axis activation. None of these regions send direct projections to the PVN; however, all project to select brainstem, hypothalamic, and BST regions that in turn innervate the medial parvocellular PVN. Limbic structures subserving 'anticipatory' stress responses can therefore modulate PVN activation through interactions with 'reactive' stress circuits. Superimpostion of limbic input onto brainstem and hypothalamic stress effectors forms a hierarchical system that uses direct PVN projections to mediate both reflexive (reactive) and 'voluntary' (anticipatory) stress responses. Note that the projections of these limbic regions have considerable, but incomplete overlap with one another, implying that the net impact of the stress response is dependent on the ensemble activity of these structures. Symbols and other abbreviations are defined in the legend of Fig. 2; grayed-in details summarizes intrinsic PVN regulatory mechanisms, noted in Fig. 6.

In addition to GLP-1, non-aminergic PVN-projecting NTS neurons may also synthesize additional neuropeptidergic species, including somatostatin, substance P, and enkephalin [267,268]. Of these, substance P is known to inhibit stress-induced HPA activation [141,175,259], whereas enkephalin analogs can promote corticosterone release [136]. However, all the above peptides are produced in other PVN-projecting regions as well, and it is not completely clear whether specific NTS peptidergic populations specifically modulate PVN activitation.

The NTS appears to be a common site for integration of reactive HPA responses. The NTS shows c-fos activation following most stressors we classify as 'reactive,' including visceral illness (lithium chloride) [170,240], cytokine/inflammatory challenge (e.g., interleukin 1-β or lipopolysaccharide injection) [83,168], hypovolemia [302], hypoxia [297], and hypotension [167]). These responses are in keeping with the known role of the NTS in relaying reflexive or sensorial information to the PVN and other forebrain structures [299]. However, the NTS is also activated by numerous stressors having mixed reactive and anticipatory attributes, such as restraint, swim, and immobilization [56,270], and can be activated during conditioning paradigms [228], suggesting that the NTS also plays a role in anticipatory stress integration. This hypothesis is supported by recent studies indicating that central injection of a GLP-1 receptor antagonist (des-His_1, Glu_9-exendin-4) blocks ACTH and corticosterone release following elevated plus maze exposure [154]. As noted above, GLP-1 is only expressed in the NTS; thus, these data indicate that ascending NTS input is required for optimal elaboration of internally generated, anticipatory HPA axis responses.

The role of the NTS in the reactive or reflexive stress pathway may be related to its position as a relay for both visceral and somatic sensory information. For the former, it is clear that the NTS is in receipt of ascending cardiovascular afferents and plays a major role in the baroreceptor reflex [299]. The NTS also receives inputs from brainstem regions integrally involved in respiration and from rostroventral medullary neurons controlling autonomic outflow [299]. Notably, somatic pain stimuli also appear to activate PVN NE release via ascending NTS neurons, presumably via direct or indirect input from the spinoreticular [224]. In addition, the NTS is densely innervated by the area postrema [299], which is a blood–brain barrier deficient region that is at least in part responsible for cytokine-initiated HPA axis activation [83]. There is also evidence for a role of the local NTS microvasculature in HPA integration, as studies indicate that vessels in this region can activate neurons through local synthesis of prostaglandins [82], as noted above.

Importantly, the NTS also receives afferents from limbic forebrain stress circuits, including the medial prefrontal cortex, central amygdaloid nucleus, and several hypothalamic nuclei [273,308]. As such, the NTS may not only serve as a relay for reflexive inputs, but may respond to descending information as well; these connections likely subserve the influence of this cell group on anticipatory stress responses.

2.2. *Raphe nuclei*

Serotonergic systems are known to modulate HPA axis activity. The majority of studies indicate that serotonin (5-HT) stimulates ACTH and corticosterone secretion by way of PVN 5HT2A and perhaps 5HT1A receptors [225,305] (although the latter is somewhat controversial [318]). In addition, depletion of serotonin inhibits c-fos induction and CRH heteronuclear RNA expression in the PVN following lipopolysaccharide injection [169]. Given this stimulatory role, it is somewhat surprising that direct serotonin input to the PVN is limited to a small number of fibers derived from the dorsal and median raphe nucleus [272]. Indeed, the vast majority of serotonin positive fibers are seen in the immediate PVN surround, raising the possibility for prominent interactions with GABAergic neurons occupying the PVN shell (see below). Given the potential for injected pharmacological agents to spread to these local interneurons, the exact locus of serotonergic involvement in stress integration is difficult to pinpoint.

Lesion studies lend further support for a stimulatory role of 5-HT in HPA axis regulation. Lesions of the raphe nuclei (either electrolytic or neurochemical (5,7-dihydroxytryptamine (DHT)) elicit decreased HPA responses to restraint stress [143], photic stimuli [87], local PVN glutamate administration [93], and stimulation of the dorsal hippocampus or central amygdaloid nucleus [87,94]. The latter study demonstrates that local PVN injections of 5,7-DHT can block stimulation-induced HPA activation, indicating that the effects of 5-HT may be exerted directly at the PVN and/or its surround.

Notably, 5-HT heavily innervates forebrain stress-integrative structures, including the hippocampus, prefrontal cortex, amygdala, and hypothalamus (see [186]). Thus, in addition to direct actions at the PVN, systemic or intracerebroventricular injections of serotonergic drugs may also influence HPA activity indirectly. For example, administration of 5HT2 receptor antagonist into the amygdala inhibits the ACTH response to photic stress [90], suggesting that 5-HT may also modulate HPA axis activity via upstream stress effectors.

The PVN is also in receipt of information from ascending pontine and midbrain pathways relevant to reflexive stress integration. These include the parabrachial nucleus and periaqueductal gray, which are intimately involved in autonomic function [255]. Evidence supporting a role for the parabrachial nucleus in stress responses centers primarily on several tract tracing studies

establishing widespread connections with many thalamic nuclei (including paraventricular thalamic nucleus), hypothalamic nuclei (including PVN), amygdala, bed nucleus of the stria terminalis (BST), NTS, ventrolateral medulla, raphe nuclei, and periaqueductal gray [165,166,256]. The ventrolateral periaqueductal gray sends projections to the medial parvocellular PVN [105], consistent with a role in endocrine integration, and this region shows c-fos induction in numerous stress paradigms [56,205,270]. While the parabrachial nucleus and ventrolateral periaqueductal gray relay information on cardiovascular tone and pain perception to the PVN, the precise role of these structures in HPA integration remains to be determined.

2.3. Subfornical organ/lamina terminalis system

The PVN is in direct receipt of information on fluid and electrolyte status by way of the subfornical organ/lamina terminalis system. Signals are relayed through direct projections of the subfornical organ, median preoptic nucleus, and the organum vasculosum of the lamina terminalis to medial parvocellular PVN neurons [17,271]. These regions are critically involved in control of osmoregulation and drinking behavior, as lesions along this pathway can result in adipsia and dehydration [142]. Notably, like the area postrema, both the subfornical organ and organum vasculosum of the lamina terminalis are blood–brain barrier deficient regions [215], providing another mechanism by which blood-borne signals may be communicated to the PVN. Accordingly, previous work indicates that angiotensinergic neurons of the subfornical organ directly activate CRH secretion [232]. This response may itself be mediated by direct interaction of circulating angiotensin II with angiotensin II-receptive neurons in the blood–brain barrier deficient subfornical organ (see [104]). The subfornical organ is also enriched in atrial natriuretic peptide and its cognate receptor (natriuretic peptide receptor-A) [124,173], suggesting that other osmoregulatory peptides may also signal via this mechanism.

2.4. Hypothalamus

The PVN receives massive input from numerous regions of the hypothalamus. Dual-label tract tracing studies indicate that the lion's share of this input emanates from GABAergic neurons [57,246]. Parvocellular CRH neurons are directly innervated by GABAergic boutons (Fig. 3) and express multiple GABA-A receptor subunits [54], consistent with the importance of GABA in central HPA integration. Notably, PVN injection of the GABA-A agonist muscimol inhibits corticosterone secretion following restraint [53], validating the physiological relevance of GABA in PVN stress integration.

The PVN is richly innervated by GABAergic neurons located in its immediate proximity [23,57,246]. Numerous studies indicate a prominent role for these neurons in stress integration. For example, acute stress exposure induces c-fos expression in the peri-PVN region [122], while GAD65 mRNA is up-regulated in these neurons following chronic stress exposure [24]. Importantly, the peri-PVN region preferentially expresses select kainate-preferring glutamate receptor subunits [125], and injection of a pan-ionotropic glutamate receptor antagonist (kynurenic acid) into this region exacerbates corticosterone responses to restraint [330]. In addition, microinjection of glutamate in this region induces c-fos expression in GAD neurons present in the immediate surround of the PVN (peri-PVN zone), but does not activate hypophysiotrophic PVN neurons [50]. Thus, the peri-PVN appears highly receptive to glutamatergic

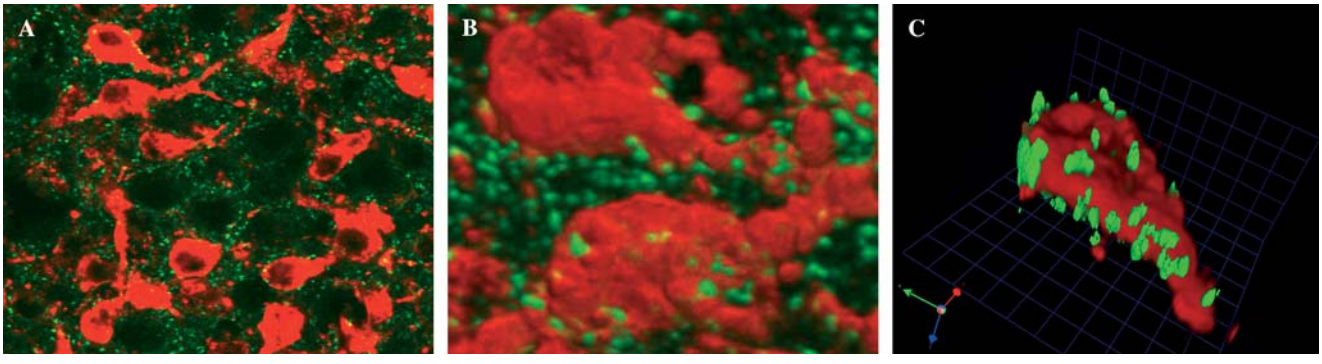


Fig. 3. Confocal microscopic images illustrating direct innervation of PVN CRH neurons by glutamate (vesicular glutamate transporter 2 immunoreactivity, VGlut2) (A,B) and GABA (glutamic acid decarboxylase immunoreactivity) (GAD) (C). (A) Image from a single 0.5 μm section, depicting VGlut2 immunoreactive boutons (green) in apparent apposition to individual CRH neurons (red). (B) Three-dimensional reconstruction of VGlut2 bouton appositions to CRH neurons, using image stacks merged and rotated (Volocity software). Note close appositions of boutons to cell somata and dendrites. (C) Processed three-dimensional image (Volocity software), illustrating GAD bouton appositions to a CRH neuron. The processed image employs an algorithm that determines overlap of red- and green-channel fluorescence in three-dimensional space. The indicated boutons are those that have >10 voxel overlap with the CRH immunoreactive cell.

inputs, and affords a means whereby excitatory inputs to the peri-PVN region can elicit inhibition of the HPA axis.

Medial parvocellular PVN neurons are also richly innervated by GABAergic cell populations from the dorsomedial hypothalamic nucleus [57]. GABAergic neurons in the dorsomedial nucleus (particularly its ventrolateral part) show c-fos activation following swim stress ([55], Fig. 4A), consistent with a role in inhibition of the stress response. Accordingly, lesions of this region exacerbate HPA axis responses to stress [14,312], whereas pharmacological stimulation of neurons in the dorsomedial nucleus generates GABAergic inhibitory post-synaptic potentials in PVN neurosecretory neurons [23]. Recent data from our laboratory indicate that local infusion of kynurenic acid into this region prolongs stress-induced glucocorticoid secretion (Fig. 4B), indicating that blockade of glutamate in PVN-projecting dorsomedial nucleus neurons disinhibits the HPA axis.

However, it should be noted that the role of the dorsomedial nucleus in HPA integration may be subregion or cell-type specific; for example, data from Tasker's group indicate that this region supplies excitatory as well as inhibitory input to PVN neurons [295], and glutamate stimulation of neurons in the dorsal extent of the dorsomedial nucleus promote rather than inhibit ACTH secretion [11]. Electrophysiological studies indicate that intrahypothalamic excitation of the PVN by the dorsomedial nucleus (as well as other local PVN projecting regions) involves glutamatergic neurotransmission [22]. Electron microscopic studies have demonstrated the presence of glutamate-immunoreactive synapses on parvocellular PVN neurons [69], and our recent studies indicate direct innervation of CRH neurons by vesicular glutamate transporter 2 (VGlut2)-immunoreactive terminals (Figs. 3A and B). VGlut2 is a specific marker for glutamatergic cell populations, and is highly expressed in a number of hypothalamic PVN-projecting regions, including neurons scattered throughout the dorsomedial hypothalamic nucleus (Fig. 5) [329]. In addition, local infusion of the ionotropic glutamate receptor antagonist kynurenic acid directly into the medial parvocellular PVN inhibits ACTH and corticosterone responses to stress, consistent with an excitatory action of PVN glutamate release on CRH secretion [330]. These results complement previous studies showing that systemic injection of a NMDA and AMPA/kainate receptor antagonist cocktail inhibits ACTH responses to immobilization, but not footshock or ether [326]. Importantly, NMDA and kainate receptor subunits are indeed expressed in the parvocellular PVN [8,125], and are regulated by acute and chronic stressors [13], consistent with a role in processing of stressful information.

While the dorsomedial nucleus contains VGlut2 neurons and projects to the PVN, combined tract-tracing/in situ hybridization data confirming PVN-projecting glutamate cells in the dorsomedial nucleus or other hypothalamic regions has yet to be advanced. Alternative attempts to demonstrate this projection have been made, but have not allowed definitive conclusions to be drawn. For example, light-microscopic glutamate immunohistochemistry has proved unsuitable in allowing confirmation of a glutamatergic phenotype, and the method of retrograde transport of [^{3}H]D-aspartate [52] has several limitations, including the difficulty in limiting injections to the PVN proper, as well as questions concerning its ability to specifically mark glutamatergic neuronal populations.

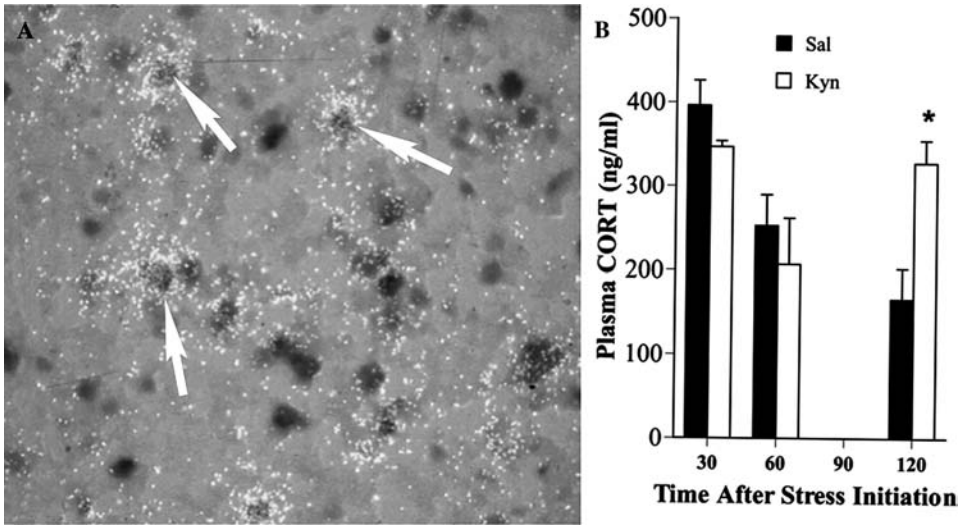


Fig. 4. Dorsomedial hypothalamic nucleus (DMH) involvement in stress integration. (A) Dual in situ hybridization image, showing co-localization of GAD65 mRNA (dark cell bodies) with c-fos mRNA (white grains) in the ventromedial DMH following 30 min of swim stress. (B) Inhibition of DMH ionotropic glutamate receptors by microinjection of kynurenic acid (Kyn) prolongs corticosterone (CORT) secretion following restraint stress, consistent with loss of glutamate excitation to neurons inhibiting the PVN.

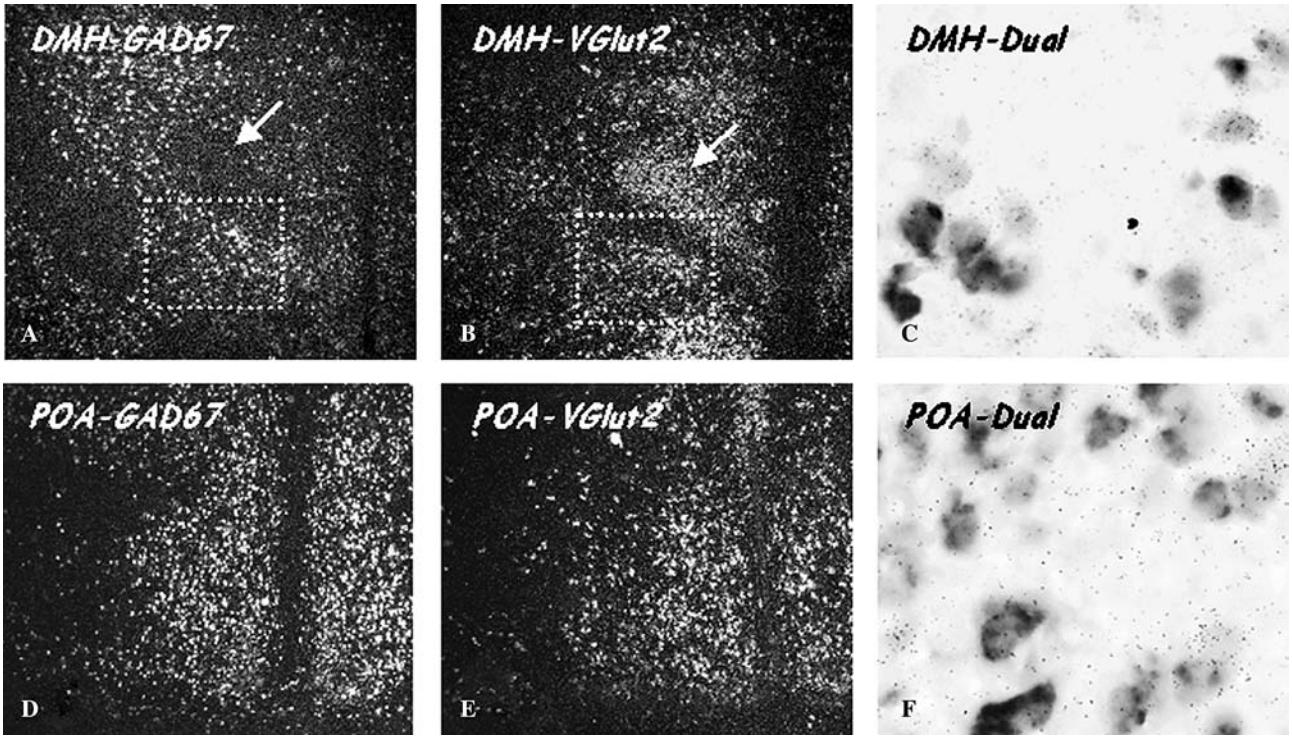


Fig. 5. Mixed populations of GABA and glutamate neurons are present in the dorsomedial hypothalamic nucleus (DMH) and preoptic area (POA). In situ hybridization indicates that both GABA (glutamic acid decarboxylase 67 mRNA-expressing) and glutamate (VGlut2 mRNA-expressing) neurons are present in the DMH (A–C) and POA (D–F). Note that GAD67 and VGlut2 populations are extensively intermingled in both regions; however, dual in situ hybridization does not reveal VGlut2 associated grains over dark GAD67-positive neurons (C,F), indicating that these represent two distinct cell populations.

Notably, the dorsomedial nucleus possesses mutually exclusive populations of GABA and glutamate neurons ([329], Figs. 5A–C). As such, this nucleus may supply both inhibitory and excitatory projections to the parvocellular PVN, perhaps depending on which sets of neurons are activated by an incoming stimulus and/or the sequence/timing of synaptic activity.

The medial preoptic area also sends stress-activated, GABAergic projections to the PVN [55]. Lesions of this region enhance stress-induced ACTH secretion [312], whereas stimulation can block the excitatory effects of medial amygdalar stimulation on corticosterone release in anesthetized rats [88]. Notably, electrophysiological studies suggest differential involvement of preoptic area subregions in PVN regulation; stimulation of the medial portion, including the highly GABAergic medial preoptic nucleus [213], decreases PVN neuronal activity, whereas stimulation of more laterally situated cell groups increases firing rate [257]. As was the case for the dorsomedial nucleus, the lateral regions of the medial preoptic area contain intermingled GABA and glutamate neurons (Figs. 5D–F).

The medial preoptic area stands out as a potential interface between gonadal steroids and the HPA axis. This region, along with subdivisions of the bed nucleus of the stria terminalis (see below), express extremely high levels of androgen, estrogen receptor α, estrogen receptor β, and progesterone receptors [9,114,279,282], and is a major target for gonadal steroid modulation of reproductive function. While it is not known whether steroid-receptive cells project to the PVN, it is clear that the HPA axis is keenly sensitive to gonadal steroids. Early studies showed that female rats display HPA axis hyperactivity relative to males, predominantly during proestrus [41,51,178], a phenomenon that was linked with variations in gonadal hormone levels [156,157]. Indeed, administration of estrogen to ovariectomized females enhances corticosterone secretion following stress [41,100,311]. The increase in stress-induced corticosterone release is not normalized by corticosterone-binding globulin [109], verifying that females have greater free corticosterone levels as well. In contrast, testosterone inhibits HPA responses to stress when injected systemically [310] or directly into the preoptic area [312], consistent with an opposite role for androgens in PVN regulation.

The importance of PVN gonadal steroid-receptive regions such as the medial preoptic area and perhaps the bed nucleus of the stria terminalis is highlighted by the dearth of gonadal steroid receptor expression in the medial parvocellular PVN proper. Thus, although CRH and arginine vasopressin (AVP) mRNA levels in the

PVN are elevated in proestrus [20,283] and in estrogen-replaced OVX animals [227,249], these effects are likely mediated by transynaptic mechanisms, as the CRH secreting PVN neurons do not express substantial levels of estrogen receptor α or β (the latter receptor is, however, expressed in magnocellular oxytocin and vasopressin neurons [5,130]). Similarly, PVN androgen receptor expression appears to be limited to spinal cord and brainstem projecting cell groups [327], suggesting that testosterone acts transsynaptically as well [116]. Expression of progesterone receptor in the PVN is limited to isolated cells in rat [107]. Thus, in all cases it appears likely that centrally mediated effects of gonadal steroids on the HPA axis are mediated predominantly by afferent projection systems, of which the medial preoptic area and related PVN projecting structures (BST, anteroventral periventricular nucleus) are prime candidates.

Signals relevant to energy balance may be transmitted by direct innervation of PVN neurons by the arcuate nucleus and perhaps the lateral hypothalamus. Arcuate nucleus neurons are sensitive to circulating glucose, leptin, and insulin [322]. Neuropeptidergic systems resident in the arcuate nucleus have complementary roles in food intake; neuropeptide Y and agouti related peptide (AGRP) neurons promote food intake, whereas proopiomelanocortin peptides have anorectic actions [322]. Hypothalamic neuropeptide Y (NPY) and AGRP infusions increase HPA axis activation [71,181,315] and stimulate CRH release [71]. However, injections of α-melunocyte stimulating hormone (α-MSH) also elevate ACTH and corticosterone secretion, induce rapid cyclic AMP response element binding protein phosphorylation in CRH neurons [264] and enhance CRH release in vitro [71]. These data indicate that the HPA axis is activated by negative as well as positive energy balance. Thus, both signals may be interpreted as stressors by the organism.

Given the largely excitatory actions of both the NPY and α-MSH systems, it is somewhat surprising to note that neonatal monosodium glutamate lesions of the arcuate, which destroy both systems [2,152], enhance both basal and stress-induced corticosterone release [176,189]. These data suggest a role for the arcuate nucleus in HPA inhibition, which is not in keeping with the known role of its PVN-projecting peptidergic subpopulations. However, it is important to note that lesions performed early in postnatal development may trigger compensation by other regulatory pathways.

Tracing studies indicate that a sizable proportion of PVN-projecting arcuate nucleus neurons are GABAergic [12]. These GABAergic neurons tend to be concentrated in the medial region of the nucleus, corresponding with the location of NPY/AGRP neurons [12], and at least a subpopulation of these neurons co-express GABA and NPY [236]. However, the specific role of GABA in arcuate nucleus control of HPA axis activation has yet to be evaluated.

The PVN also receives input from nuclei of the posterior hypothalamus, with the densest innervation supplied by the ventral premammillary nucleus. The function of these regions is ill-defined with respect to either reactive or anticipatory stress responses; however, it should be noted that the mammillary nuclei all receive considerable input from limbic forebrain structures [235], and are thus in good position to relay stress-related information from these structures to the PVN.

2.5. Bed nucleus of the stria terminalis

Direct non-hypothalamic forebrain inputs to the parvocellular PVN are largely confined to discrete subnuclei of the bed nucleus of the stria terminalis (BST) and the neighboring parastrial nucleus [271,290]. The densest PVN projections emanate from the intrafascicular, transverse, and anterodorsal nuclei of Ju and Swanson [144], which contain predominantly GABAergic neurons [57,145]. As such, like hypothalamic inputs, the majority of these BST inputs to the PVN appear to be inhibitory. In addition, the PVN is also innervated by ventrolateral regions of the BST, including the fusiform nucleus [76]. This pathway may be of importance in relaying information from the central amygdaloid nucleus to the PVN.

The valence of BST action on HPA secretory activity appears to be location-specific. Our group has shown that lesions of the posterior BST, which include the intrafascicular and transverse subnuclei, enhance expression of CRH mRNA in the PVN, consistent with an inhibitory role in HPA regulation [120]. In contrast, lesions of the anterior BST, including the anterodorsal and fusiform subnuclei, decrease CRH mRNA expression [120]. These results largely agree with studies of Gray et al. [113], which demonstrate an excitatory role for anterolateral BST regions in conditioned corticosterone responses. In addition, stimulation of anterior BST structures, including PVN projecting regions in the anterodorsal and fusiform subnuclei, increase corticosterone secretion, whereas stimulation in regions corresponding to the intrafascicular and transverse subnuclei reduce circulating glucocorticoids [78]. Importantly, the anterolateral BST is positioned to modulate behavioral stress responses as well, as restraint stress and lateral BST stimulation produce similar changes in stress-related behaviors (home cage immobility, aggressive behavior) [42].

Like the medial preoptic area, the principle encapsulated, intrafascicular and transverse subnuclei robustly express gonadal steroid receptors [279,282]. Thus, effects of gonadal steroids on the HPA axis may be also be modulated by receptive neurons in these regions. Analysis of the respective roles of these BST regions in HPA integration remains to be evaluated.

As several subdivisions of the BST are heavily populated with CRH neurons [145], it is important to comment on the potential involvement of CRH neurons in regulation of the HPA axis. Several lines of evidence implicate CRH as a positive modulator of PVN stress responses. Electron microscopic studies indicate the presence of axodendritic and axosomatic CRH-positive contacts on PVN CRH neurons [185,281], and it is well established that intracerebroventricular injections of CRH can promote immediate early gene induction [133,226] and CRH gene transcription [226] in medial parvocellular PVN neurons. While CRH receptor expression in the PVN is minimal, CRHR1 expression is rapidly potentiated in response to either stress or CRH [132,191], implying a possible role in prolonged or chronic stress conditions. The fusiform nucleus of the BST is known to send a CRHergic projection to the PVN [76], and is a possible candidate for BST-mediated excitation of the PVN. However, as was the case for glutamate, CRH innervation of the PVN may emanate from several regions, including several hypothalamic nuclei (perifornical, dorsal hypothalamic nucleus, and dorsal hypothalamic area), dorsal raphe or Barrington's nucleus [45]. In addition, it is also possible that axodendritic CRH–CRH contacts may be axon collaterals of PVN neurons [185].

2.6. Thalamus

Recent evidence suggests that the PVN may receive inputs from thalamic sensory nuclei as well. Notably, neurons in auditory-responsive posterior thalamic nuclei, including the subparafascicular and posterior intralaminar regions, send direct projections to the medial parvocellular PVN [36], and are likely involved in pathways mediating activation of the HPA axis by audiogenic stressors [33,35]. These regions are known to be responsive to cardiovascular stimuli and may play a role in noise-induced sympathetic activation [180]. It remains to be determined whether other sensory modalities (e.g., somatosensory/pain input via the spinothalamic pathway [49]) can connect with the PVN through the same or parallel thalamic circuitry.

The parvocellular PVN is also innervated by neurons of the anteromedial zona incerta [271,314], many of which are dopaminergic [47]. Zona incerta neurons show minimal stress-induced c-fos expression, but do show rapid induction of other immediate early genes (e.g., NGFI-A) following restraint or swim [56], suggesting that activity of these neurons is modulated during stress exposure. Dopamine is known to activate the HPA axis [21]; however, it is not known whether effects are exerted directly at the PVN (possibly via local zona incerta projections) or via actions on upstream PVN projections.

3. Intrinsic PVN information processing

The PVN is well positioned to receive direct input from blood- and CSF-borne factors (Fig. 6). This nucleus is endowed with a dense capillary plexus [200,307]; while there is no evidence that these vessels are fenestrated, it is clear that this plexus can allow ready access of blood–brain barrier permeable factors, including steroid hormones. Indeed, there is ample evidence that glucocorticoids exert local feedback effects in the region of the PVN, inhibiting CRH gene expression and adrenalectomy-induced ACTH hypersecretion [163,265]. This capacity for local action suggests that enhanced vascularity may play a role in direct feedback processes. In addition, aldosterone and gonadal steroid hormones also pass readily through the blood-brain barrier, and as noted above, there is evidence for androgen and estrogen receptors in the PVN, though not necessarily in medial parvocellular neurons [116,279,282]. Finally, recent data indicate that brain microvessels may play a major role in communicating cytokine signals to the CNS, through activation of prostaglandin biosynthesis [243]. Notably, the medial parvocellular PVN richly expresses prostaglandin receptors [243], suggesting a capacity for local integration of immune signals within the PVN proper.

Dendrites of PVN neurons may also contact the cerebrospinal fluid under some conditions. For example, studies performed in fish, amphibians, and reptiles reveal that dendrites of PVN neurons contact the third ventricle [313]. Such contacts are not observed in normal mammalian hypothalami [313]. However, axonal projections to the ventricular wall are noted in long-term dehydrated rats [70], suggesting that neuronal contacts with the ventricular system may be physiologically regulated. The significance of these findings remains to be evaluated.

The intrinsic organization of the PVN is positioned to allow considerable cross-talk among hypophysial, neurohypophysial, and preautonomic cell populations. Morphological studies using Golgi impregnation or intracellular fills indicate that the dendrites of PVN neurons ramify freely among various PVN subnuclei [239,307]. Notably, previous EM studies demonstrate CRH synapses on non-CRH containing PVN dendrites [185,281], consistent with anatomical interactions among the various PVN cell phenotypes. In addition to axosomatic interactions, there is evidence for dendritic release of neurohypophysial peptides [188], indicating an additional avenue for intranuclear communication. Finally, recent studies indicate that PVN neurons, particularly those in magnocellular subdivisions, contain neuronal nitric oxide synthase and heme oxygenases 1 and 2 [244,245,324]. These neurons may therefore modulate medial parvocellular activation through release of nitric oxide and carbon monoxide. Consistent

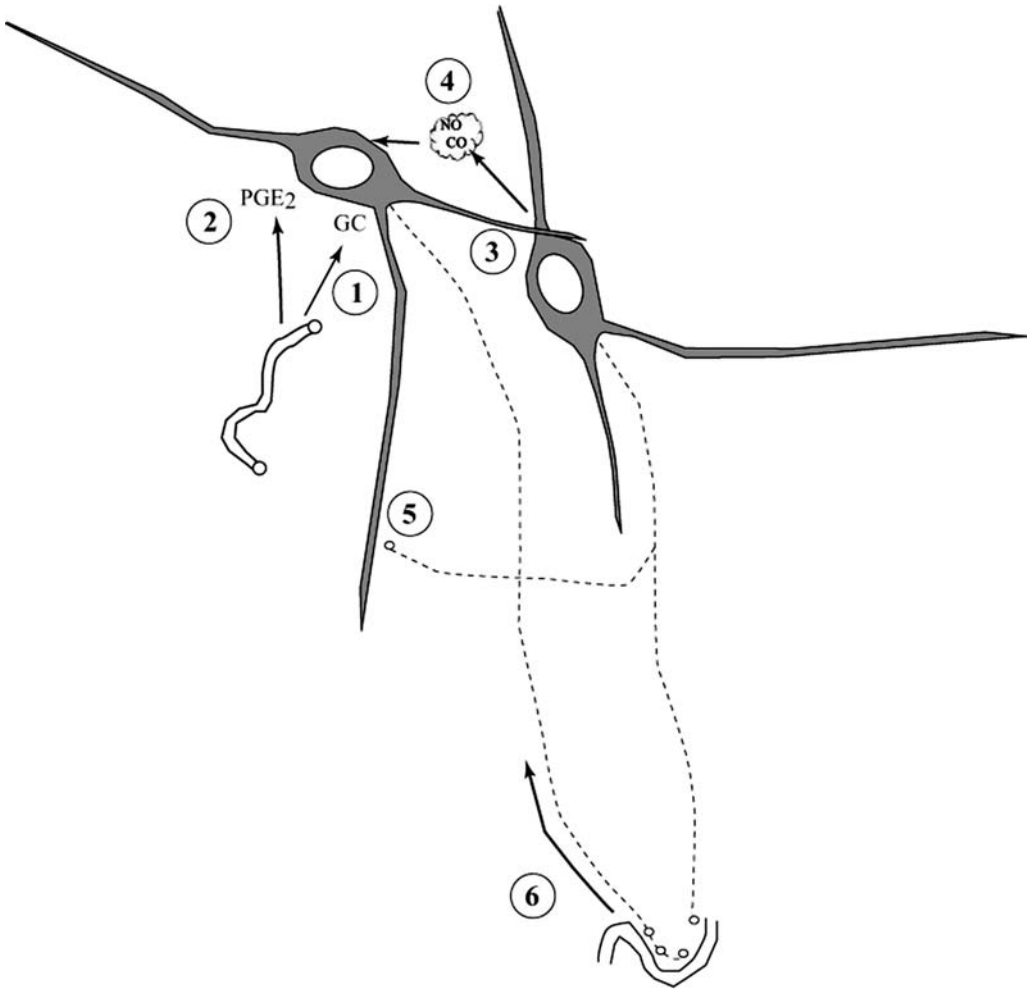


Fig. 6. Intrinsic PVN-regulatory pathways. PVN neurons may be influenced by several processes effected within the PVN proper. First (1) the PVN contains a dense capillary plexus, affording ready access to steroid hormones, such as glucocorticoids (GC). Second (2) PVN capillaries also synthesize prostaglandin E_2, which can interact with receptors on parvocellular PVN neurons to provide a mechanism for local cytokine signaling. Third (3) though dendrites do not extend outside the nucleus, they ramify extensively within the nucleus, affording interaction with other cell populations. Fourth (4) neurons within the parvocellular and/or magnocellular subdivisions contain the cellular machinery to synthesize the gaseous neurotransmitters nitric oxide (NO) and carbon monoxide (CO), both of which affect HPA axis activation. Fifth (5) there is evidence for local lateral innervation of parvocellular neurons by intra-PVN axons, suggesting an opportunity for synaptic interactions within and across PVN cell groups. Finally (6) terminals in the median eminence have access to blood-borne and glial constituents that can be retrogradely transported to affect growth and plasticity.

with this hypothesis, studies from Rivier's laboratory indicate that nitric oxide promotes synthesis of CRH and AVP in parvocellular neurons, suggesting an activational role within the PVN. However, additional data suggest that nitric oxide can inhibit ACTH release to mild stressors, perhaps at the level of the pituitary; thus, the net effect on the HPA axis may depend on the locus of nitric oxide biosynthesis [244,245].

Morphometric analyses indicate that dendrites of PVN axons are largely contained within the PVN proper [239,307]. While there is evidence for contacts between limbic afferents and dendrites of magnocellular neurons in the peri-PVN zone [214], the extent of extra-PVN dendritic ramifications is quite limited, and has not been demonstrated for CRH-containing neurons. As such, PVN neurons have a limited capacity to sample the fiber-rich peri-PVN region directly. The importance of this distinction cannot be overestimated, as a wealth of fibers from limbic forebrain structures terminate (see below) in this peri-PVN zone.

Finally, HPA activation by medial parvocellular CRH neurons may be modulated by non-neuronal factors. For example, the median eminence is a blood–brain barrien deficient region, and as such may allow blood-borne factors access to PVN terminal arbors. In addition, specialized glial elements in the hypothalamus and median eminence produce receptors for growth-associated neuregulin molecules and insulin-like growth factor-1, which may promote neurite outgrowth and thus affect secretory potential [98,212,233].

4. Indirect paths to the PVN

Previous work reveals rich interactions between limbic brain structures and HPA activation. These structures, including regions such as the hippocampus, prefrontal cortex, amygdala, septum, and midline thalamus, are critical for emotional responses and memory, and are thus logical candidates for modulating pituitary–adrenal secretions with respect to previous experience. As such, these structures likely play a major role in anticipatory stress responses. Importantly, all of the above regions have very limited opportunities to interact directly with medial parvocellular PVN neurons, requiring intermediary neurons to relay their influence on ACTH secretagog release (see Fig. 7).

4.1. Hippocampus

Numerous studies indicate that hippocampal lesions promote basal hypersecretion of glucocorticoids [97,158,159]. Hippocampectomy or fornix transection can increase basal glucocorticoid levels [97,263], presumably by altering circadian rhythms [102,103,206,321]. In addition, hippocampal lesions enhance basal CRH and AVP mRNA expression [119,121,127] and elevate basal AVP (but not CRH) in portal blood [260], consistent with increased ACTH secretagog capacity in PVN neurons. Alterations in secretory patterns may be due to loss of mineralocorticoid receptor signaling through this structure, which is believed to play a major role in inhibiting basal HPA tone during the trough of the diurnal corticosterone rhythm [61,67]. However, it should be noted that basal HPA hypersecretion following hippocampal damage is not observed in all studies [25,121,135,174]; inconsistencies among experiments may be related to time of day or experimental design issues (see Section 5).

The hippocampus is also involved in terminating HPA axis responses to stress. Several laboratories have noted that hippocampal lesions prolong corticosterone and/or ACTH release following exposure to a number of stressors, including restraint [119,261], contextual conditioning [148], acoustic stimulation [211], and open field exposure [123]. However, hippocampal lesions are without effect on HPA axis responses to ether ([123,190]; however see also [321]) or hypoxia [25], indicating that involvement of the hippocampus in HPA integration is stressor-specific. It is notable that stressors that are unresponsive to lesions of the hippocampus involve stimuli that rapidly activate the 'reactive' response pathway, indicating they are refractory to hippocampal inhibition.

Work from our group indicates that hippocampal inhibition of the HPA axis is mediated by a relatively restricted set of neurons in the ventral subiculum [119,123]. These neurons appear responsible for inhibiting responses to anticipatory stressors, as lesion of this region enhances responsiveness to restraint and open field exposure, but not to ether vapors [119,123,209]. This region projects extensively to BST and hypothalamic neurons relaying information to the PVN, as well as to the peri-PVN zone [57], and as such are well-positioned to mediate hippocampal HPA inhibition.

Overall, the observation that hippocampal damage can delay termination of corticosterone release is consistent with a role in glucocorticoid negative feedback inhibition of the HPA axis (reviewed in [137,261]). This hypothesis is supported by rich localization of glucocorticoid receptors in the hippocampus [199,238], and by lesion studies demonstrating that (1) hippocampal damage can reduce the ability of dexamethasone to inhibit corticosterone release following ether stress [190] or photic stimulation [92], and (2) fimbria–fornix lesions inhibit the ability of dexamethasone to block hypotension-induced CRH and AVP release into hypophysial portal blood [260]. Implants of glucocorticoids into the ventral hippocampus flatten the circadian corticosteroid rhythm [284], and dorsal hippocampal implants of corticosterone (but not dexamethasone) decrease adrenalectomy-induced ACTH release [164]. Hippocampal implants of glucocorticoid and mineralocorticoid antagonists attenuate, but do not block HPA responses to novel photic or acoustic stimuli [95]. However, a comprehensive study from Dallman's group found no effect of fimbria–fornix lesion on glucocorticoid feedback responses following hypoxia [25], and our group has been unable to demonstrate that ventral subiculum lesions reverse corticosteroid feedback inhibition of an ACTH response to restraint [123]. As such, it is currently unclear whether hippocampal inhibition of HPA responses to anticipatory stressors involves glucocorticoid receptor activation and signaling.

Hippocampal stimulation reduces HPA axis activity in human subjects [250], inhibits the circadian rise in corticosterone in freely moving animals [43], and reduces 'resting' corticosterone levels in anesthetized preparations [79]. Likewise, dorsal hippocampal stimulation inhibits median eminence-projecting PVN neurons [258]. The effects of hippocampal stimulation appear to be dependent on subfield, as stimulation of CA1 stimulates, rather than inhibits corticosterone secretion in anesthetized rats [79]. However, it should be noted that much of the stimulation work is complicated by use of anesthesia; for example, studies from the Feldman group indicate that dorsal hippocampal stimulation can increase corticosterone release in anesthetized rats [85,91], whereas similar stimulation produces long-lasting inhibition of ACTH and corticosterone secretion following light exposure in freely moving animals [96].

It is notable that both glucocorticoid and mineralocorticoid receptors are richly expressed throughout the hippocampus and subiculum [7,117]. Since inhibition of

the HPA axis represents a minor subset of hippocampal function, it is clear that the vast majority of hippocampal steroid receptors have other physiological actions. Given the well-documented, inverted-U shaped relationship between glucocorticoids and memory [67,72], these receptors are probably relevant to encoding the significance of stressful stimuli viz. memory consolidation.

The impact of the hippocampus on the HPA axis may also be mitigated by up-stream factors mediating hippocampal function. For example, lesions of the septo-hippocampal cholinergic pathway effectively enhance responses to restraint stress, suggesting that cholinergic tone is critical for normal hippocampal inhibition of HPA stress responsiveness [115]. In addition, the deleterious effects of aging on the hippocampal neurons are highly correlated with prolonged corticosterone responses to restraint stress [134,261], suggesting that loss of hippocampal function results in HPA axis hypersecretion.

Anatomical tracing studies reveal that the principal hypothalamic outflow of the hippocampus originates in the ventral subiculum and ventral CA1 [37,57,160,203]. These neurons densely innervate the peri-PVN zone, but not the PVN proper [39,40,57,242], and send rich projections to numerous PVN-projecting nuclei in the BST and hypothalamus [37,57,160,203]. As noted above, parvocellular PVN dendrites show quite limited ramification outside the nucleus, and thus ventral subiculum terminal boutons likely contact somata and processes of neurons populating the PVN surround. The lack of direct innervation indicates that hippocampal regulation of the PVN is mediated by intervening neurons.

Combined retrograde–anterograde tracing studies reveal several regions where ventral subicular efferents contact PVN-projecting cell populations, including the anterodorsal, intrafascicular, and transverse subnuclei of the BST, medial preoptic area, and to a lesser extent, the dorsomedial hypothalamic nucleus [57]. These regions contain rich populations of GABAergic neurons [24,213], and indeed the vast majority of PVN-projecting neurons in the BST co-express the GABAergic marker glutamic acid decarboxylase [57]. There are also substantial populations of GABAergic neurons in the peri-PVN region [24,213] that may serve to relay inhibitory information to hypophysiotrophic PVN neurons. The implications of this synaptic arrangement is clear: rather than projecting directly to CRH neurons, subicular neurons connect with the PVN through at least one intervening synapse.

Subicular afferents to PVN-projecting regions are predominantly glutamatergic. Neurochemical studies indicate a marked depletion of hypothalamic glutamate following fimbria–fornix lesions [316]. More recent work from our group indicates that ventral subicular neurons innervating PVN-projecting regions of BST and medial preoptic area are nearly all positive for VGlut1 (Fig. 8), a specific phenotypic marker for corticolimbic glutamate neurons [147,329]. When combined, the tracing data indicate that hippocampal inhibition of the PVN is likely mediated by a two-neuron relay, involving contacts between glutamatergic neurons in the subiculum and GABAergic neurons in the BST and hypothalamus (Fig. 7).

The hippocampus may also interact with the PVN by multi-synaptic connections. For example, the lateral septum is a major target of efferents from the entire septotemporal axis of the hippocampus [292], and innervates numerous PVN-projecting hypothalamic nuclei as well as the peri-PVN region [242]. There is also evidence that the inhibitory effects of hippocampal stimulation on the HPA axis may be in part relayed through the brainstem [85,91].

4.2. Prefrontal cortex

The medial prefrontal cortex also modulates HPA axis activation. The medial prefrontal cortex manifests robust c-fos induction following numerous stress modalities (cf. [56,161,193]), and dopamine/norepinephrine release is markedly elevated in this region following acute or chronic stress [101,140]. Lesion studies indicate that bilateral lesions of the anterior cingulate or prelimbic components of the medial prefrontal cortex enhance ACTH and corticosterone responses and PVN c-fos induction following restraint stress, but not ether inhalation [26,73,99]. These data are consistent with the hypothesis that, like the hippocampus, dorsal subregions of the medial prefrontal cortex selectively inhibit HPA axis responses to anticipatory stressors. Interestingly, inhibitory effects do not generalize to the entire structure; only lesions of ventral regions of the rat prefrontal cortex (infralimbic cortex) reduce corticosterone secretion following restraint [289]. The influence of medial prefrontal cortex on stress habituation may be lateralized; bilateral or right prefrontal cortex lesions suppress corticosterone secretion, whereas unilateral, left-sided lesions do not [289]. Unlike the hippocampus, dorsal or ventral medial prefrontal cortex lesions have no effect on basal morning or evening ACTH and corticosterone levels [73,99], indicating that the prefrontal cortex selectively modulates stress-induced HPA axis activity.

Like the hippocampus, the prefrontal cortex has been implicated in negative feedback regulation of the HPA axis. Direct implants of corticosterone into the medial prefrontal region decrease stress-induced ACTH and corticosterone secretion following acute or repeated restraint, but like hippocampal lesions, have no effect on responses to ether [1,73]. These results are consistent with stress- or modality-specific modulation of feedback efficacy.

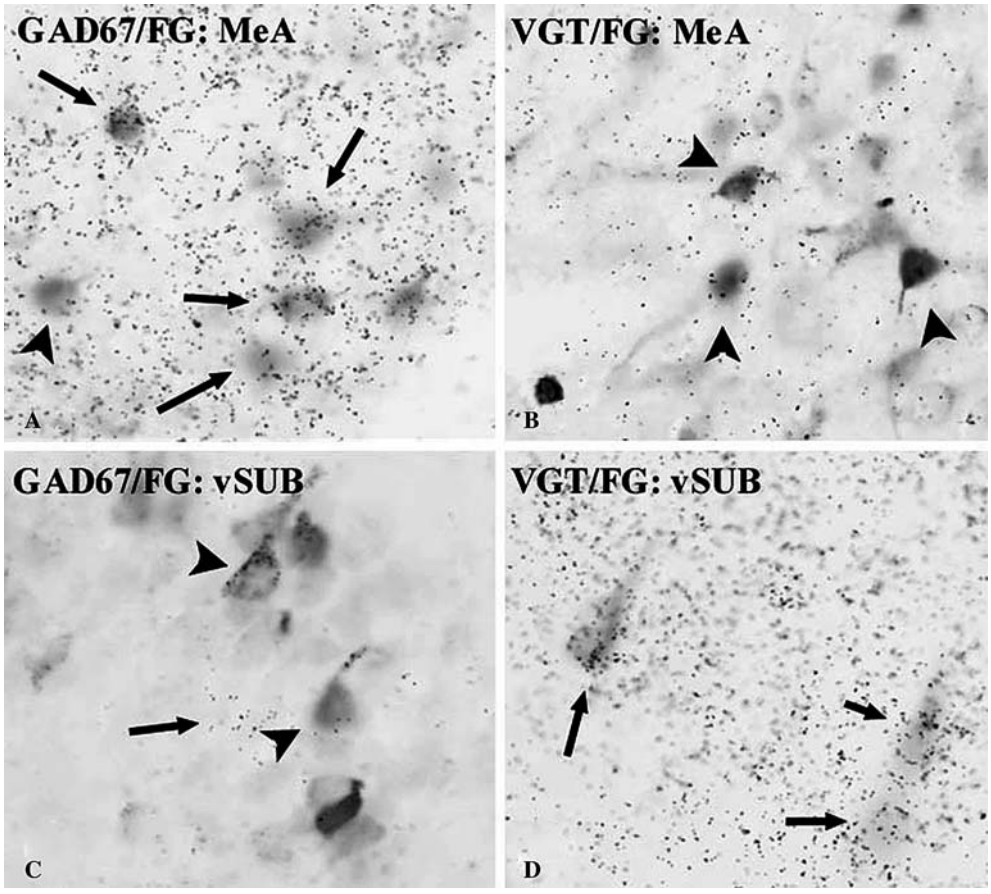


Fig. 8. Innervation of the PVN-projecting region of the bed nucleus of the stria terminalis (BST) by GABAergic and glutamatergic limbic regions. Combined tract tracing/immunohistochemistry (Fluorogold, FG) and in situ hybridization was used to establish the neurochemical identity of medial amygdalar (MeA) (A,B) and ventral subicular (vSUB) (C,D) neurons innervating the PVN-projecting interfascicular 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.

Anatomical studies indicate that the prefrontal cortex does not innervate the PVN to any substantial degree. However, fibers from the infralimbic cortex and to a lesser extent, prelimbic and anterior cingulate cortex innervate several predominantly GABAergic PVN-projecting regions, including the BST, perifornical nucleus, lateral hypothalamus and dorsomedial nucleus [131,277], and prominently innervate the nucleus of the solitary tract [300,308]. The infralimbic and prelimbic cortices also project to the amygdaloid complex and raphe nuclei, and may thereby modulate HPA activation mediated by these structures (see below) [196,277]. Finally, the medial prefrontal cortex projects heavily to the paraventricular thalamic nucleus [131,277] (below), a structure that is intimately involved in tuning HPA axis responses to chronic stress [18].

Activation of the prefrontal cortex may itself be modulated by afferent input. The medial prefrontal cortex receives heavy noradrenergic input from the locus coeruleus, a stress-activated region that is involved in HPA axis integration [328]. Dopaminergic input to the medial prefrontal region is exquisitely stress-sensitive [129], and may be sufficient to alter HPA-relevant output. Finally, NTS-projecting neurons in the prefrontal cortex receive direct innervation from the ventral hippocampus [251], suggesting that these regions may act in concert to modulate multiple down-stream stress regulatory circuits.

4.3. Amygdala

In contrast with the hippocampus and prefrontal cortex, the amygdala appears to activate the HPA axis. Gross stimulation of the amygdala promotes corticosteroid biosynthesis [150,252] and secretion [194,195,237,296] in rats, rabbits and monkeys, and elicits ACTH secretion in humans [110]. Conversely, lesions of large portions of the amygdala reduce

glucocorticoid secretion following stressful stimuli, including ether inhalation [158,159], leg break [3] and sensory stimulation [84]. Large amygdaloid regions also reduce adrenalectomy-induced ACTH hypersecretion [4], suggestive of a role in feedback integration.

Subsequent studies using more localized stimulation/lesion paradigms implicate the central (CeA), medial (MeA) and basolateral (BLA) subnuclei in control of ACTH release. While all subnuclei are implicated in HPA activation, they appear to respond preferentially to different stimulus modalities, and therefore have distinct roles in HPA integration.

The central amygdaloid nucleus (CeA) is involved in integration of behavioral responses to fear and/or anxiety provoking behaviors [62,179]. Accordingly, the CeA appears to regulate HPA axis activation in a number of stress paradigms. Lesion studies indicate that selective damage of the CeA decreases ACTH and corticosterone release following immobilization stress [15], photic/olfactory stimuli [86] and importantly, fear conditioning [306]. Lesions of the CeA cause depletion of CRH from the median eminence under basal conditions [16], and block stress-induced decreases in median eminence CRH stores [86], suggesting that the CeA promotes both CRH synthesis and release. Lesions of the CeA also reduce the number of c-fos positive PVN CRH neurons following interleukin-1 injection [323], consistent with an interaction between this region and cytokine-mediated activation of PVN neurons.

However, other reports have failed to find a significant impact of CeA lesions on HPA axis regulation. Lesions of the CeA fail to reduce either ACTH release or PVN c-fos induction following restraint stress [65,234]. In combination with data showing clear involvement of the CeA in cytokine-mediated PVN c-fos induction by the same group [323], these data have lead to the conclusion that the CeA is selectively involved in generating what we have termed 'reactive' responses [64,118,270]. This hypothesis is supported by c-fos mapping data showing preferential induction of the CeA by stressors such as hemorrhage, cytokine infusions and lithium chloride injection [269,302,325], while stimuli such as novelty, restraint, footshock or air-puff startle [56,81,269,301] show a minimal CeA c-fos response. Moreover, CeA c-fos responses can be conditioned by stimuli eliciting 'reactive' responses (e.g., lithium chloride) [170,325], but are not induced in conjunction with 'anticipatory' stress responses (e.g., fear conditioning) [34,229].

The CeA has little direct interaction with the PVN, limited to scattered fibers present in preautonomic cell groups [112,192,234]. However, the CeA has rich connections with brainstem structures innervating the PVN, including most notably the NTS and lateral parabrachial nucleus [273,308]. In addition, there is evidence for a relatively circumspect forebrain relay in the BST, encompassing groups of cells in the region of the fusiform, subcommissural and anterodorsal subnuclei [76,234]. The latter subgroups contain large populations of GABAergic neurons; in combination with the predominantly GABAergic phenotype of CeA projection neurons, the CeA–BST–PVN circuit may utilize two GABA synapses, and thus activate the PVN by disinhibition (Fig. 7).

The MeA also plays a role in HPA axis integration. Selective stimulation of the MeA increases corticosterone release in anesthetized rats [80] and may increase adrenal sensitivity to ACTH [253]. In agreement with these data, lesions of the medial amygdala decrease ACTH and corticosterone secretion and inhibit median eminence CRH depletion following photic and olfactory stimulation [86]. However, in contrast to the CeA, lesions of the MeA reduce c-fos activation in the PVN by restraint [65]. Furthermore, MeA c-fos induction can be observed following stimuli that activate of 'anticipatory' pathways, including restraint [56,64], novelty [81] and fear conditioning [229], but is far less pronounced in conjunction with 'reactive' responses to stimuli such as hypovolemia [302], cytokine stimulation [269] or ether inhalation [81].

Like the CeA, the MeA has very few direct projections to the PVN [39,112,216,234]. However, the MeA has an extensive network of projections to PVN-projecting regions, including the intrafascicular, transverse, anterodorsal and ventral subnuclei of the BST, medial preoptic nucleus, medial preoptic area, anterior hypothalamus, ventral premammillary nucleus and peri-PVN zone [39]. Combined anterograde-retrograde tracing studies indicate that PVN-projecting neurons of the aforementioned BST subnuclei and the medial preoptic nucleus are contacted by boutons labeled following posteroventral MeA injections of the anterograde tracer PHA-L [234]. With the possible exception of the ventral premammillary nucleus, PVN-projecting neurons in these MeA-receptive regions are predominantly GABAergic [55,57], thus suggesting that MeA–PVN relays are composed of sequential GABA neurons. Accordingly, combined retrograde tracing-in situ hybridization studies reveal that majority of MeA neurons projecting to the posterior BST express glutamic acid decarboxylase (but not VGlut1) mRNA, consistent with a largely GABAergic phenotype (Fig. 8). The stimulatory effect of the MeA on corticosterone release can be blocked by lesions of the BST or medial preoptic area [88], supporting the importance of these putative relays in HPA integration. Therefore, the MeA likely activates the PVN by disinhibition, using relays distinct from those of the CeA.

The BLA has received considerable attention as a stress-regulatory structure. This region is robustly activated by 'anticipatory' stressors, including restraint, swim and footshock, but shows a substantially lower response to cytokine stimulation [56,270]. Stimulation of

the BLA in anesthetized rats can decrease [80] or increase [89] corticosterone secretion, perhaps due to complex interactions between stimulation parameters and anesthesia. Lesions of the BLA are ineffective in modulating ACTH, corticosterone or CRH release following photic or olfactory stimuli [86], and do not affect corticosterone release following social interaction [201], novelty, restraint, ether stress or cold [274]. However, it is important to note that this region may indeed play a more complex role in stress regulation; for example, the BLA appears to be critical for integrating the effects of glucocorticoids on memory consolidation [247,248], suggesting involvement in memory of stressful stimuli. Similarly, this region is selectively activated by novel stressors presented during a chronic stress protocol, consistent with a role in HPA axis sensitization [18].

Projections of the BLA are to a large extent intra-amygdalar. Indeed, the anterior BLA extensively innervates the CeA and MeA, suggesting that output from this region of the amygdala are funneled through these principle amygdalar output nuclei. Nonetheless, the posterior BLA does have limited projections to the anterodorsal BST and several medial hypothalamic nuclei (excluding the PVN), suggesting the capacity for this region to act via non-amygdalar circuitry as well [75,293].

4.4. Lateral septum

Lateral septal lesions are known to produce a constellation of behavioral and autonomic symptoms consistent with extreme anxiety ('septal rage') [242]. Accordingly, the lateral septum seems well-positioned to modulate neuroendocrine stress responses. Indeed, numerous c-fos mapping studies provide circumstantial evidence for a role of the ventrolateral septal region in stress regulation. Neurons in this area are robustly induced by a variety of 'anticipatory' stressors, such as novelty, predator exposure and social interaction [34,38,81,162], but show little induction following activation of the 'reactive' stress pathway [81,270,301].

In agreement with the c-fos mapping data, lesion studies suggest that the septum has an inhibitory influence on the HPA axis. Large lesions of the septum, encompassing both lateral and medial divisions, do not affect basal or circadian corticosterone rhythms [74,275,320], but prolong corticosterone responses to immobilization [74]. Septal lesion animals also show enhanced susceptibility to mild stress [27,276,303]. However, these early studies of septal function used large electrolytic lesions, which did extensive damage to both the medial septum and descending fimbria–fornix system. Thus, the results of these early studies are difficult to interpret with regard to the lateral septum per se, and refined lesion and stimulation studies of this region are lacking.

The anatomy of the septal region predicts prominent interactions between the ventrally situated septal cell groups (ventrolateral septal (LSv) or ventral regions of the rostral subdivision (LSr)) and PVN-projecting forebrain regions. As is the pattern for limbic stress integrative regions, ventrolateral septal neurons do not project directly to the PVN, but innervate the peri-PVN zone and numerous hypothalamic PVN relays, including the anterior hypothalamus, medial preoptic area and lateral hypothalamus [242]. The vast majority of neurons in this region of the septal complex express GABAergic markers [241], thus suggesting an inhibitory influence on PVN-projecting cell groups. Notably, lateral septal neurons innervate PVN-projecting regions that contain both GABAergic and glutamatergic neurons [68,213,329], and thus the lateral septum is well-positioned to modulate either inhibition or excitation of the PVN.

4.5. Thalamus

Several recent reports implicate limbic thalamic nuclei in processes related to HPA axis regulation. The midline thalamus shows robust c-fos induction following psychogenic stimuli in several subregions, including the paraventricular, subparafascicular, posterior intralaminar, anteroventral, anteromedial, paratenial, centromedial and rhomboid nuclei (cf. [10,18,28,56, 81,280]).

Of the known stress-activated thalamic nuclei, the paraventricular thalamus appears to play a major role in integrating HPA axis responses to repeated stressors. The paraventricular thalamus is among a handful of regions that is selectively activated by novel stressors presented after a repeated stress regimen [18]. This regimen produces a phenomenon known as 'facilitation', whereby the HPA axis response to the novel stressor is markedly potentiated in previously stressed animals, despite the presence of elevated glucocorticoid feedback. Notably, lesions of the paraventricular thalamus (in particular, its posterior subdivision) effectively block chronic stress facilitation of ACTH release [18], and can indeed inhibit habituation of the HPA axis to repeated exposure to the same stressor [19]. Overall, these data suggest that this region plays a prominent role in controlling HPA responsiveness following repeated stimulation [19].

The connectivity of the paraventricular thalamus places it in prime position to mediate HPA responsiveness. Combined c-fos-retrograde tracing studies indicate that the paraventricular thalamus receives extensive input from numerous stress-activated regions, including the ventral subiculum, infralimbic/prelimbic cortex, BST, NTS, rostrolateral medulla, locus coeruleus, dorsal raphe and parabrachial nuclei [218]. In addition, the paraventricular thalamus heavily innervates several

PVN-projecting and PVN-interactive regions, including the medial prefrontal cortex and the basolateral and central amygdaloid nuclei [207,219].

Recent work also suggests that the anterodorsal thalamic nucleus can modulate both basal and stress-induced HPA activation. Small lesions of this nucleus elevate basal ACTH levels while inhibiting stress-induced release [287]. This region has extensive reciprocal connections with the subiculum [291,309], which may account for its impact on HPA axis regulation.

4.6. Hypothalamus

There are several hypothalamic regions that appear able to interact with the PVN through intrahypothalamic relays. Prominent among these is the suprachiasmatic nucleus, which is the major integrator of circadian HPA rhythmicity [44]. While having minimal direct projections to the medial parvocellular PVN per se, the SCN projects heavily to GABA-rich, PVN-projecting hypothalamic regions, including the subparaventricular zone of the peri-PVN region and dorsomedial hypothalamus [29,317]. The SCN inhibits circadian corticosterone release by way of these nuclei, apparently via vasopressinergic neurons [30,146]. In addition to its circadian influence, the SCN has inhibitory actions on corticosterone responses to novelty stress that appears to involve actions at both the hypothalamus and adrenal cortex [30].

The PVN also receives transsynaptic innervation from the ventromedial nucleus of the hypothalamus (VMH). In this case, interconnectivity is likely achieved through intervening neurons in the dorsomedial and lateral hypothalamic nuclei [298]. Electrolytic lesions of the ventromedial nucleus disrupt circadian corticosterone secretion, resulting in a net elevation in secretory activity across the day-night period [153,288]. However, colchicine inactivation of the VMH in fact reduces corticosterone secretion at the circadian peak and inhibits stress-induced corticosterone secretion [48].

5. Synthesis

5.1. Methodological considerations in stress research: sources of disagreements?

Before generalities can be drawn concerning the voluminous literature on neurocircuit regulation, sources for some of the disagreements among studies need to be considered. Disagreements are most pronounced among limbic-HPA studies, where conflicting data exist regarding the effects of hippocampal and central amygdalar lesions on ACTH secretion (see above). While some of the conflict can be resolved by consideration of stress modality, there are some instances where very similar experiments yield divergent results. We feel there are at least four possible explanations for such discrepancies. First, the environment surrounding stress experiments represents an important and largely uncontrolled experimental variable. A considerable amount has been learned about HPA secretory time courses, circadian secretory patterns, stress sensitization, and response habituation in recent years. This knowledge emphasizes the necessity for careful control of conditions surrounding stress exposure. Whereas a rigorous level of experimental control (e.g., time of day, limited housing/procedure room access, rapid sampling, etc) is now fairly standard, it is not known how tightly such control was exerted in earlier studies of this system. Indeed, many of the early findings on limbic modulation of the stress response occurs against a backdrop of 'elevated' (i.e., suprabasal) glucocorticoids, and makes it difficult to interpret the data with regard to effects on basal secretion vs. stress-induced release.

Animal housing represents a second area of concern. Over the last 10–15 years, laboratory animal husbandry has improved dramatically. Even non-SPF (Specific Pathogen Free) rooms have high minimum standards for sanitization, and infections that were largely ignored in previous decades (e.g., pinworm infections) are now aggressively monitored, treated and eradicated. Thus, to the extent that such subchronic infections are now obviated, the 'background level of stress' encountered under current conditions may differ substantially from prior studies. As the existence of background 'stress' can potentially sensitize or habituate HPA responses, and both of these processes are likely modulated by limbic structures, differences in housing may constitute a substantial contribution to the observed experimental discrepancies.

A third source of error concerns the early-life environment of the experimental subjects. Considerable data are emerging to indicate that the quality of maternal care can have a life-long impact on the responsiveness of the HPA axis; good maternal care predisposes efficient HPA axis responses to stress, whereas maternal deprivation elicits stress hyper-responsivity (cf. [32,182,254]). Thus, substantial individual differences may be encountered in studies using animals from different commercial vendors or breeding-colony environments.

A final factor is the animal itself. There is considerable evidence for strain differences in HPA reactivity. The Lewis strain exhibits substantially lower basal CRH mRNA levels in the PVN relative to Fischer 344 strains, and exhibits attentuated neuroendocrine responses to stress [285,286]. Strains also differ in responsiveness to chronic stimulation; for example, our group has noted that the Sprague–Dawley strain exhibits lower levels of chronic stress-induced corticosterone hypersecretion

than Fischer 344 animals [128] or Fisher 344× Brown Norway F1 hybrids [126]. Thus, variation in response predispositions may be present within different strains of rats, generating different baselines against which the experience of stress is perceived.

5.2. Principles governing neurocircuit regulation of the HPA axis

Numerous attempts have been made to distill the stress circuitry literature summarized above into a general theory of stress integration. Perhaps the most durable hypotheses propose a dichotomy between 'neurogenic/psychogenic/processive/exteroceptive' responses and 'systemic/interoceptive' responses [64,118,184,270]. This notion was first presented by Fortier in 1951 to explain why some stressors (epinephrine, cold, and histamine) could elicit corticosteroid release when the pituitary was removed and placed in the anterior chamber of the eye, while others required an intact pituitary for elaboration (immobilization, sound) [106]. The theoretical basis for these distinctions has changed over the years to encompass a very different concept, namely, that the 'neurogenic' class of stimuli requires some form of forebrain processing and integration prior to an HPA response, whereas the 'systemic' class is elaborated by reflexive pathways (spinal cord, brainstem, lamina terminalis continuum) [118,270]. Perhaps nowhere is this better demonstrated than in the seminal study by Sawchenko's group in 1996, demonstrating that ascending medullary systems are required for PVN c-fos activation by interleukin-1β, a 'systemic/interoceptive' stimulus, but do not affect c-fos induction following footshock [183]. Our own work demonstrated that lesions of the ventral subiculum impair corticosterone responsiveness to novelty, but have no impact on responses to ether [123]. Trevor Day's group has subsequently contributed a substantial body of data documenting an amygdalar dissociation of 'emotional' from 'systemic' stress, implicating the medial amygdala in the former, and the central amygdaloid nucleus in the latter [64]. Their work also supports a role for the brainstem in both 'emotional' and 'systemic' stress modalities [66], and has been important in revising how we envision the overall organization of HPA integration by the PVN.

Despite a common unifying theme that runs through the above lines of thought, there is a considerable body of data to suggest that this dichotomy may be an oversimplification. This is particularly evident in the work of Pacak, Goldstein, Palkovits, and colleagues, who have performed numerous studies demonstrating quite unique HPA and sympathomedullary responses to different stressors (see [220,222]). Indeed, these authors use these data to revise the notion of the 'general adaptation syndrome' proposed by Selye, in essence arguing that the road to adaptation may well have many neurochemical and humoral forks.

Our attempt to discern a set of principles defining HPA axis regulation relies heavily on the diversity of the data. In this view, central stress integration relies on hierarchical rather than dichotomous pathways. The output of the stress response is dependent on the overall 'set' of central sensorial input, which places a different weight on the various central structures projecting onto PVN stress integrators. This hypothesis is based on the following premises:

1. Stressors considered to be 'reactive' invoke direct input pathways to the PVN, as PVN activation and glucocorticoid responses are poorly elaborated when these circuits are damaged. Induction of these systems occurs the first time the stimulus is presented, and does not require input from the forebrain.
2. The influence of the forebrain on the stress system is most keenly engaged following stressors that require either initiation of innate 'anxiety' or 'defense' programs (e.g., presence of a predator, high places, social conflict, etc.) or conditioned responses to sensory stimuli associated with previous stressful events.
3. Forebrain influences on the PVN are polysynaptic, and relay through structures that, while engaged in cases of anticipatory stress, may also mediate 'reactive' responses. These include regions such as the NTS, dorsomedial hypothalamus, preoptic area, and PVN surround.
4. Unlike the 'reactive' pathways, forebrain regions such as the prefrontal cortex, hippocampus, and amygdala are in receipt of polysensorial and associational input, rather than primary sensory modalities.
5. The influence of forebrain structures on down-stream stress effectors varies with region and the nature of the stimulus. For example, the hippocampus (ventral subiculum) has a wealth of interactions with the BST and hypothalamus, but very little with the NTS; the prefrontal cortex has limited input to the hypothalamus, but innervates the lateral BST and NTS more extensively; and so on.

All of these data agree in large part with the diverse role of limbic pathways in HPA integration, while conserving the notion of direct, 'reactive' pathways, atop which the hierarchical 'anticipatory' responses can be built.

Hierarchical organization of brain stress integration is in keeping with theories of brain evolution, whereby increasingly complex functions are layered atop simpler reflex pathways. The reflex pathways operate as the default mode, and are subsequently modified by the influence of prior experience or innate programs. The circuitries underlying these internally generated neural programs adjust the stress response with respect to their net actions at the PVN. The outflow of the HPA axis is therefore a summation of integrated inputs from several

forebrain regions, including the hippocampus, prefrontal cortex, amygdala, and septum. Evidence of this summation may be appreciated from the fact that many stressors produce parallel activation among numerous HPA-regulatory limbic regions (e.g. [56,270]), and lesions of different regions can produce similar effects on stress responses (for example [73,99,123]). It stands to reason that these diverse regions will be influenced in accordance with their polysensorial inputs; thus, a medial amygdala-loaded stimulus (e.g., responses to conspecific aggression) is likely to exhibit a stress–response signature that is funneled primarily through the BST and preoptic area, representing its primary terminal fields. Whereas other limbic regions can participate in tuning the response, the heavy emphasis on the medial amygdala gives this PVN input channel priority, and the net HPA outflow is adjusted accordingly.

Preferential weighting of different limbic regions may also be elaborated at the interface between the anticipatory and reflexive pathways. For example, our GLP-1 studies indicate a prominent role for the NTS in initiating HPA responses to the elevated plus maze [154]. The elevated plus maze generates a fear response that is controlled in part by neurons of the CeA [63]. The CeA has considerable projections to NTS–PVN relays, and may thus be involved in generating the HPA response to the fear-evoking stimulus. In contrast, Sawchenko's group noted that the PVN c-fos response to footshock was not blocked by medullary knife cuts, suggesting this 'pain' stimulus does not require NTS input to the PVN [183]. In this study animals were pre-habituated to the testing chamber for several days prior to testing; the brainstem-independent response may have been generated exclusively in limbic sites processing contextual information related to the test environment, such as the hippocampus or perhaps the prefrontal cortex. Thus, the nature of the limbic circuits activated by specific constellations of polysensory input may in large part dictate the down-stream PVN relays controlling HPA axis activation.

Anatomical data also support coordination of descending limbic efferents distal to the PVN proper. Limbic connectivity can overlap in several PVN projecting regions; for example, the medial amygdala, ventral subiculum and medial prefrontal cortex all project to posterior subnuclei of the BST and the peri-PVN region (see Fig. 7), suggesting a convergence of inputs in these areas. While it has yet to be determined whether these regions project to the same neurons, the proximity of efferent targets is consistent with local integration within PVN-projecting cell populations. In addition, there is considerable cross-talk within limbic pathways; for example, in addition to BST and septal outflow, the ventral subiculum also projects to the medial amygdala and medial prefrontal cortex [40,139]; likewise, the medial prefrontal cortex sends projections to the medial and central amygdaloid nuclei [196,277]. Recent work from our group demonstrates that medial prefrontal cortex lesions inhibit medial amygdalar c-fos induction following restraint stress [99], suggesting that such interconnections may be functionally meaningful.

Thus, initiation and cessation of stress responses appears to be choreographed by sets of hierarchical circuits converting mono- or polysensorial information into an integrated PVN response. The simplest form is a novel physiological challenge, which is rapidly communicated by reflex pathways from surveillance sites in the periphery (nociceptors, visceral efferents) or circumventricular organs (subfornical organ, and area postrema). This requires no limbic inputs and is relatively hard-wired. A second-level response involves innate defense programs that 'anticipate' a physiological challenge, in essence driving a glucocorticoid response to obviate a 'predicted' homeostatic disruption. Due to the necessity of comparing polysensory stimuli with these internal programs, these pathways involve limbic outflow. The valence of this outflow will likely be regulated in accordance with the relative sensory and associational load to respective limbic forebrain regions, with the net limbic outflow determining which PVN effector pathways are activated or inhibited. Finally, the third-level response involves learning; responses are keyed to recollection of the significance of prior experience, colored itself by the glucocorticoid response. These responses probably involve mnemonic processing regions such as the hippocampus and medial prefrontal cortex. Again, the strength of the PVN response will be modulated by the relative strength of the respective limbic signals.

Many of the PVN-projecting hypothalamic and brainstem circuits used by limbic inputs govern basic homeostatic regulatory functions. Descending forebrain inputs relayed through these circuits thus interface with information traversing primary somatic, visceral or humoral sensory pathways. This arrangement provides a signaling context with which limbic information can interact; as such, the HPA response to an 'anticipatory' stressor will depend on the homeostatic state of the individual. An inhibitory signal cued by contextual information may be overridden by peripheral stimuli conveying energy imbalance, cardiovascular depression, infection, or thirst; conversely, an excitatory signal originating in the periphery may be modulated by descending contextual information. This arrangement affords the tone of the HPA axis to be set by both polysynaptic forebrain activity and reflexive information, much analogous to layered sensory–motor loops regulating reflexive and voluntary movement.

The teleological implications of hierarchical stress-integrative pathways are clear—the circuitry can weigh the importance of a stimulus to survival, and use the

resulting information to tune an appropriate hormonal response. In most organisms, the system efficiently modulates the HPA axis in accordance with need, assuring that glucocorticoids are present only when required. However, as is the case with all biological processes, there is considerable individual variation in HPA response dispositions. Recent studies reveal that genetics, early-life experience or even trauma in adult life can modulate response characteristics of the HPA axis. In rats, HPA hyperresponsiveness induced by early-life maternal separation/neglect can be correlated with neurochemical changes in key limbic stress circuits, including reduced glucocorticoid receptor expression in the hippocampus, elevated central amygdaloid nucleus CRH expression and reduced GABA-A receptor expression in the basolateral amygdala (see [32,149,202]). This spectrum of changes implies reduced hippocampal inhibition and enhanced amygdalar excitation, and together these results suggest that a coordinate disruption of hierarchical stress circuitry underlies HPA axis dysfunction. The data imply that the configuration of stress circuitry, being subject to considerable influence by environmental factors, is malleable even within an organism. Thus, changes in limbic integration patterns with experience may play a major role in HPA axis dysfunction.

The relationship between affective disease states and HPA hyperactivity may lie in the linkage between descending limbic pathways stress effectors and the PVN. For example, major depression is associated with enhanced blood flow and glucose utilization signal in the prefrontal cortex and amygdala (see [77]) and shrinkage of the hippocampal formation [278]. As noted above, all of these regions are implicated in HPA regulation in animal studies. The characteristics of depression-induced HPA dysfunction, including stress hyperresponsiveness, disrupted circadian secretory pattern, and glucocorticoid negative feedback resistance, can be replicated in some (but not all) animal lesion studies, and are consistent with the changes in regional 'activity' and structure revealed by neuroimaging. Importantly, the HPA symptoms are paralleled by other manifestations of homeostatic disruption—sleep, metabolism, cardiovascular regulation—that are also within the efferent trajectory of these key limbic circuits. Thus, it appears that modulation of the 'anticipatory' pathway—initiated by innate or learned response predispositions—may form a critical neuroendocrine effector component of these human disease processes.

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