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Neural Regulation of Endocrine and Autonomic Stress Responses

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Preface

The survival and well-being of all species requires appropriate physiological responses to environmental and homeostatic challenges. The reestablishment and maintenance of homeostasis entails the coordinate activation and control of neuroendocrine and autonomic stress systems. These collective stress responses are mediated via largely overlapping circuits in the limbic forebrain, hypothalamus and brainstem, so that the respective contribution of the neuroendocrine and autonomic systems is tuned in accordance with stressor modality or intensity. Limbic regions that are responsible for regulating stress responses intersect with circuits that are responsible for memory and reward, providing a means to tailor the stress response with respect to prior experience and anticipated outcomes.

Introduction

Adaptation in the face of stress is a major priority for all organisms. Stress can be broadly defined as a real or anticipated disruption of homeostasis or an anticipated threat to well-being. Stressor-related information from all major sensory systems (e.g. interoceptive cues, such as blood volume and osmolarity, and/or exteroceptive cues, such as the smell of a predator) is conveyed to the brain, which recruits neural and neuroendocrine systems (effectors) to minimize the net cost to the animal. The physiological response to stress involves an efficient and highly-conserved set of interlocking systems that aims to maintain physiologic integrity even in the most demanding of circumstances.

The autonomic nervous system (ANS) (Text Box 1) provides the most immediate response to stressor exposure via its sympathetic and parasympathetic arms that provoke rapid alterations in physiological states through neural innervation of end organs. For example, the sympatho-adrenomedullary arm can rapidly increase heart rate and blood pressure (in seconds) by excitation of the cardiovascular system[1]. Importantly, excitation of the ANS wanes quickly — due to reflex parasympathetic activation —, resulting in short-lived responses.

Activation of the hypothalamo-pituitary-adrenocortical (HPA) axis results in elevations in circulating glucocorticoids (Text Box 1). Peak plasma glucocorticoid levels occur tens of minutes after initiation of stress[2]. The two-step hormonal mechanism of HPA induction (Box 1) is sluggish relative to the latency of the synaptic mechanisms driving sympatho-adrenomedullary activation, and ensures an amplified and relatively protracted secretory episode.

The brain triggers stress responses that are commensurate with the nature of the stimulus. Physical stressors — blood loss, infection, pain — require an immediate 'systemic' reaction that is triggered by reflexive mechanisms. The brain also responds to non-physical or 'psychogenic' stressors based on prior experience or innate programs[3]. These responses require processing in forebrain, and can occur in anticipation of or in reaction to stressful events.

This Review addresses the brain circuits that regulate ANS and HPA axis responses to stress. The first section reviews the neurocircuitry, focusing on ascending inputs from the brainstem, descending influences from the limbic forebrain, and hypothalamic mechanisms that integrate limbic and brainstem input with respect to homeostatic feedback (Figure 1). The second section presents a case for reorganization of stress-control circuitry in the chronically stressed brain, involving recruitment of some regions and diminished impact of others. The final section discusses overlap of stress circuits and those controlling memory and reward, an anatomical arrangement that provides opportunity for mutual interaction in the ultimate neural interpretation of stressor significance.

Triggering stress responses: Brainstem/hypothalamic mechanisms

Brainstem systems

The brainstem receives inputs that signal major homeostatic perturbations such as blood loss, respiratory distress, visceral or somatic pain and inflammation[3]. Sympathetic responses to these inputs involve reflex arcs that communicate with areas in the medulla (e.g., rostral ventrolateral medulla) and preganglionic sympathetic neurons in the intermediolateral cell column of the spinal cord[1] (Figure 2). Coordinate alteration of the parasympathetic branch of the ANS also occurs following stress, altering 'vagal tone' to the heart and lungs[1] and helping to control the duration of autonomic responses. This parasympathetic response to stress is mediated by the nucleus ambiguus and dorsal motor nucleus of the vagus nerve, possibly via input from the nucleus of the solitary tract (NTS)[1] (Figure 2). In addition, medullary and spinal cord systems inform higher-order autonomic integrative sites in the hindbrain (e.g., raphe pallidus, lateral parabrachial nucleus and Kölliker-Fuse nucleus), midbrain and forebrain (e.g., dorsomedial hypothalamus)[1], which modulate the autonomic response to stressors in accordance with descending information from hypothalamus and limbic forebrain. Although all of these circuits participate in autonomic integration, their precise role(s) in stress-induced responses is not yet defined.

Signals of homeostatic imbalance in the brainstem also lead to activation of the HPA axis: ascending brainstem (and perhaps spinal) pathways project heavily to the parvocellular divisions of the paraventricular nucleus of the hypothalamus (PVN) (Figure 3). For example, catecholaminergic (e.g., noradrenaline and adrenaline) projections to the hypophysiotrophic zone of the PVN originate in the NTS and C1–C3 regions[4, 5] and participate in HPA activation (see[6]). NTS projections to the same area release additional neuroactive factors (including neuropeptide Y, glucagon-like peptide 1, inhibin β, somatostatin and enkephalin[7–9]) that can regulate HPA activation. In some but not all NTS neurons these factors are co-localized with noradrenaline and adrenaline[8].

Destruction of ascending noradrenaline/adrenaline neurons reduces HPA-axis responses to stimuli that signal homeostatic perturbations (e.g., hypoglycemia or interleukin 1β injection)[10, 11], but does not affect psychogenic responses, leading to the hypothesis that ascending catecholaminergic pathways mediate systemic-stress responses[3]. However, some non-catecholaminergic NTS cell groups (e.g., glucagon-like peptide 1 neurons)[12] are involved in the generation of HPA responses to both psychogenic and systemic stressors, suggesting some degree of functional specialization among NTS-PVN pathways.

The parvocellular PVN also receives serotonergic innervation from the median raphe nuclei in the midbrain. Serotonin activates the HPA axis[13] through activation of serotonin 2A receptors on PVN neurons[14]. Serotonergic fibers project equally to the PVN and surrounding regions[15], raising the possibility that serotonin also influences local circuit neurons projecting into the PVN.

Circumventricular organs: integration of peripheral signals

Components of the lamina terminalis system in the forebrain (i.e. the median preoptic nucleus, the subfornical organ (SFO) and the organum vasculosum of the lamina terminalis) respond to perturbations in fluid and electrolyte balance and blood pressure. This system is essential for the central regulation of blood pressure by angiotensin II. The SFO[16] has direct angiotensin II-containing projections to the medial parvocellular PVN, where it stimulates HPA-axis activity via activation of the angiotensin II type-I receptor[17]. The lamina terminalis also projects to other hypothalamic structures, including the anteroventral preoptic nucleus, DMH and preautonomic PVN[18], through which it can initiate stress-induced changes in cardiovascular activity[19].

Paraventricular and Dorsomedial Nuclei

Among several hypothalamic nuclei directly involved in the regulation of HPA axis and autonomic responses to stressors, the PVN stands out as a principal integrator of stress signals. The PVN houses distinct populations of neurons that project to the median eminence and to autonomic targets in the brainstem and spinal cord, such as the intermediolateral cell column, parabrachial nucleus, dorsal motor nucleus of the vagus and NTS[20]. Transneuronal tracing studies indicate that parasympathetic and sympathetic projection neurons are intermingled in the PVN, suggesting input into both arms of ANS function[21].

The PVN is heavily innervated by GABAergic inputs[22], which provide a substantial inhibitory tone[23, 24] (Figures 3 and 4). Some of the GABAergic innervation to the PVN comes from neurons in the peri-PVN region[25], which in turn is targeted by several limbic brain regions, enabling it to translate limbic information into modulation of HPA axis or autonomic activation[26].

The DMH regulates autonomic and perhaps also HPA-axis responses to psychogenic stimuli. Local stimulation of the DMH increases heart rate, blood pressure and HPA-axis responses to a psychological stressor[27], whereas inhibition attenuates stress-induced increases in heart rate and blood pressure[28]. However, inactivation of the DMH does not affect cardiovascular responses to hemorrhage[28], indicating that hypovolaemic stimuli are

processed elsewhere (most likely through brainstem reflex pathways). The DMH may also be involved in gating PVN activation: local inhibition of the dorsal DMH reduces ACTH release and neural excitation (as reflected by immediate early gene (Fos) activation[29]) in the parvocellular PVN to psychogenic, but not systemic stimuli[30]. Moreover, the ventral DMH inhibits neuronal activity in the PVN[31], indicating that the DMH contains anatomically segregated neuronal populations that activate or inhibit HPA-axis activity (Figure 3).

Top-down regulation: limbic stress circuits

Both psychogenic and systemic stimuli are processed in multiple limbic forebrain structures, including the amygdala, hippocampus and prefrontal cortex. These regions receive associational information from subcortical and cortical areas that are involved in higher-order sensory processing (e,g., olfactory nuclei, pirifirm cortex, insular cortex) and memory (medial septum, entorhinal cortex, cingulate cortices), as well as ascending inputs from sites involved in attention and arousal (e.g., locus coeruleus, raphe nuclei). The output from these limbic structures converges on crucial subcortical relay sites, providing for downstream processing of limbic information[3]. These limbic regions work in parallel to influence the activation of the HPA-axis, and likely perform similar functions in the autonomic responses to stress.

Amygdala

The amygdala is structurally complex with numerous downstream targets that modulate autonomic and neuroendocrine stress responses (Figure 4). The central nucleus of the amygdala (CeA) has received considerable attention as a key node for stress integration, given its involvement in autonomic regulation and its association with stress-related behaviors (specifically, fear responses)[32]. The CeA is differentially activated by homeostatic disruption[33, 34] and systemic[35], but not psychogenic[36, 37] stressors. Nonetheless, CeA lesions impair bradycardic responses during exposure to psychological stressors[38, 39], suggesting a role in integrating the autonomic components of psychogenic stress. Overall, the role of the CeA appears specific to stimulus modality, and may be preferentially weighted toward autonomic rather than HPA-axis responses to stress.

The medial (MeA) and basolateral (BLA) amygdala nuclei are preferentially activated by psychological stressors[33, 40, 41]: lesions of the MeA produce selective deficits in HPA axis responses to psychogenic but not homeostatic stressors[36]. and BLA lesions dampen HPA-axis responses to restraint[42]. The impact of the MeA and BLA on HPA responses is likely mediated by extensive interactions with intervening PVN-projecting neurons, as there are few direct connections between the PVN and these amygdala nuclei[43]. The roles of the MeA and BLA in regulation of autonomic stress responses have yet to be definitively tested; however, based on the paucity of MeA and BLA projections to principal autonomic output nuclei, it appears unlikely that these regions directly modulate autonomic stress responses to a significant extent.

Hippocampus

Numerous studies link the hippocampus with inhibition of the HPA axis[3, 44]. Hippocampal stimulation decreases glucocorticoid secretion in rats and humans[45, 46], whereas hippocampal damage increases stress-induced and in some cases, basal glucocorticoid secretion[3, 44]. Notably, lesion effects are most pronounced during the recovery phase of stress-induced glucocorticoid secretion, implicating the hippocampus in regulating the termination of stress-initiated HPA responses.

Hippocampal regulation of the HPA axis is region- and stressor-specific. The inhibitory effects of the hippocampus on the PVN are subserved by a relatively circumscribed population of neurons in the ventral subiculum[47] (Figure 4). Lesions of this area result in increased corticosterone release following psychogenic, but not systemic stressors[47], consistent with context-specific modulation of stress responses by the hippocampus.

The hippocampus also influences autonomic tone. Hippocampal stimulation decreases heart rate, blood pressure and respiratory rate in awake rats, effects that are blocked by lesions of the medial prefrontal cortex (mPFC)[48]. The hippocampus has no major direct projections to the brainstem, but connects with NTS-projecting regions of the mPFC, such as the infralimbic cortex[49], suggesting that hippocampal actions on autonomic function may be routed through the mPFC.

Medial prefrontal cortex (mPFC)

The mPFC is also complex, with different subregions contributing to different aspects of stress output (Figure 4). The prelimbic mPFC preferentially inhibits HPA-axis responses to psychogenic stressors[50–53] and, like the hippocampus, regulates the duration but not the peak levels of glucocorticoid secretion, suggesting involvement in response termination. Inhibition of the prelimbic mPFC or local injection of noradrenaline enhances heart-rate responses to psychological stimuli[54], consistent with a role for the prelimbic PFC in inhibiting autonomic stress responses.

In contrast, the infralimbic PFC is involved in the initiation of autonomic and HPA responses to psychogenic stimuli[52, 55]. Electrical stimulation of the ventromedial mPFC (which encompasses the infralimbic cortex) increases blood pressure in unanesthetized rats, whereas lesion or inactivation of this region inhibits conditioned cardiovascular responses[56, 57]. Inactivation of this area does not affect baseline heart rate or blood pressure, suggesting that the infralimbic cortex is selectively involved in stress-induced cardiovascular regulation, perhaps via modification of the parasympathetic component of the baroreflex[58]. Collectively, the data indicate that the prelimbic and infralimbic cortices have different roles in the coordination of stress responses, with outflow from the dorsal mPFC and the prelimbic cortex conferring inhibition, and that from the infralimbic cortex conferring stimulation. By virtue of its interconnections with the hippocampus and amygdala, the prefrontal cortex is positioned at the top of the response initiation hierarchy, and may be a principal, but not sole, limbic coordinator of physiological reactivity.

Other Limbic Sites

There is also evidence for stress-regulatory roles of other limbic sites, including the lateral septum, supramammillary nucleus and anterior thalamus[40, 59, 60]. For example, the lateral septum inhibits HPA axis and autonomic responses to acute stressors[59], a role it shares with its principal afferent source, the hippocampus.

Top-down integration of glucocorticoid negative feedback

The HPA axis is subject to feedback inhibition by its principal product, glucocorticoids (Text Box 2), which is mediated at least in part by limbic forebrain structures. Both glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs) are abundantly expressed in the hippocampus and are likely co-localized in some neurons[61]. As MRs and GRs have different affinities for corticosterone (see Box 2), this renders the hippocampus responsive to both basal and stress-induced elevations of corticosterone[62]. GRs are also highly expressed in the mPFC, but the expression of MRs is more limited here, suggesting that the mPFC may be less responsive to low glucocorticoid levels. Implants of corticosteroids in the mPFC inhibit HPA-axis responses to restraint but not ether[51], supporting a possible role in feedback inhibition of psychogenic responses. Given that both the hippocampus and mPFC attenuate stress-induced increases in heart rate and blood pressure, it is possible that one or both glucocorticoid receptors influence autonomic outflow in addition to HPA axis activity, but this possibility has yet to be investigated.

Forebrain GRs are involved in regulating both basal HPA tone and termination of the stress response. Mice with selective deletion of the GR in the cortex, hippocampus and BLA have elevated basal glucocorticoids and prolonged corticosterone responses to psychogenic but not systemic stress[63, 64], and are resistant to the inhibitory effect of exogenous glucocorticoids on HPA-axis activation[63]. Overexpression of GR in forebrain leads to reduced peak ACTH and corticosterone levels following stress, suggesting that forebrain GR are sufficient to reduce stress reactivity[65, 66]. Forebrain MRs have a more subtle role in acute HPA-axis feedback regulation. Deletion of MRs in the limbic forebrain has no effect on basal HPA tone or the peak response to restraint (recovery was not assessed)[67]. Overexpression of MR produces a mild suppression of acute stress responding only in female mice[68].

Collectively, the data are consistent with a limbic interface between glucocorticoid signals and feedback regulation of the HPA axis. The relative importance of limbic glucocorticoid signaling depends on the stress modality: it regulates HPA axis responses to psychogenic but not systemic stress and so provides a context-specific feedback signal that modifies HPA axis inhibition.

Middle management of stress responses

Limbic structures have little direct anatomical interaction with primary stress effector systems. Intervening synapses are required to relay information from the amygdala, hippocampus and mPFC to the primary stress effector neurons in the PVN, caudal medulla and spinal cord[3] (Figure 4). In general, output from stress-excitatory structures (such as the CeA, MeA and infralimbic cortex) mixes with that of stress-inhibitory regions

(hippocampus, prelimbic cortex)[3], providing opportunity for local integration of limbic information prior to accessing primary stress effectors.

Most limbic-PVN connections relay through GABA-rich cell groups in the bed nucleus of the stria terminalis (BST) and hypothalamus[3]. These inhibitory relays provide transsynaptic inhibition, translating excitatory glutamatergic outflow from the hippocampus and prelimbic cortex into inhibition of the PVN[3]. Descending information from the amygdala uses many of the same relay sites, but here the upstream neurons in the CeA and MeA are GABAergic[69]. Thus, activation of the PVN by these amygdala structures likely results from disinhibition[3]. Some degree of bisynaptic integration of stress outflow traverses excitatory networks as well. For example, the CeA and IL project to the NTS, which in turn excites the HPA axis and ANS[70, 71].

Bed nucleus of the stria terminalis (BST)

The BST has numerous subregions that differ markedly in their contributions to stress integration (Figures 3–4). Anteroventral subregions are important in HPA-axis excitation, as lesions there reduce HPA-axis responses and inhibit acute activation of PVN neurons following restraint[72, 73] (Figure 4). The anterolateral BST contains PVN-projecting CRH neurons[74,75], suggesting a mechanism for central excitatory actions of CRH on the HPA axis. In contrast, lesions of the posteromedial BST increase ACTH and corticosterone secretion, PVN Fos activation and PVN CRH mRNA expression[72, 73], consistent with a loss of inhibitory input to the HPA axis (Figure 4). Tracing studies indicate that PVN-projecting neurons in this region are predominantly GABAergic[76], suggesting that, in contrast to the anterolateral PVN, posterior regions inhibit HPA responses to stress.

The precise role of the BST in autonomic regulation remains to be defined. In anesthetized rats, chemical or electrical stimulation of the BST produces predominantly depressor actions, particularly when the stimulation is directed to the anteromedial subregion[77–79]. However, in awake animals, pharmacological activation of this region elicits a rapid pressor response, followed by bradycardia[80, 81], whereas inactivation exacerbates restraint-induced increases in heart rate[82]. This indicates that BST signaling is necessary for inhibiting cardiovascular responses to stress. Modulation of heart rate by BST stimulation or inhibition seems to be mediated by the parasympathetic nervous system[80, 81].

Hypothalamic nuclei

Several hypothalamic regions provide potential interaction between descending limbic input and homeostatic integration. Hypothalamic relays between limbic sites and HPA and ANS output neurons provide a means to gate responses to stressors with respect to ongoing physiological status.

The medial preoptic hypothalamus (mPOA) supplies GABAergic innervation to the PVN (figure 3). mPOA lesions enhance HPA-axis responses to stressors[83] and local inactivation enhances ACTH release, both consistent with a loss of inhibitory input to the PVN[84]. Moreover, mPOA lesions block the excitatory effect of amygdala stimulation on corticosterone release[85], suggesting that the amygdala is an upstream modulator of mPOA neurons controlling the HPA axis response. Indeed, the mPOA is a prominent target of

projections from the hippocampus and medial amygdala and is important in the integration of gonadal steroid signals, body temperature and sleep[86]; it thus provides a site for interaction between limbic inputs and physiological regulatory processes.

Limbic efferents also innervate the mediobasal hypothalamus, including the arcuate nucleus[87] (Figure 3), which is a key regulator of energy balance and uses the PVN as a down-stream effector to regulate feeding and energy expenditure (via neuropeptidergic and GABAergic projections)[88]. The net output from the arcuate to the PVN is complex, communicating both orexigenic (neuropeptide Y, Agouti-related peptide) and anorexic (e.g., alpha-MSH)[88] signals. Notably, many of these peptides activate the HPA axis, implying that both positive and negative energy balance represent homeostatic stressors[89].

Lateral hypothalamic neurons are activated by stressors[40], positioning them to modulate autonomic and/or HPA tone. The lateral hypothalamus is targeted by hippocampal, prefrontal cortical and amygdalar efferents and is important in the coordination of ingestive behaviors[86]. Glutamatergic, GABAergic and peptidergic neurons are highly intermingled in this region, making it difficult to predict its net impact on stress responses[90, 91].

The suprachiasmatic nucleus (SCN) has a substantial impact on basal HPA and autonomic tone and on responses to psychogenic stressors[92–94]. The SCN has few direct projections to the PVN, but heavily innervates the area surrounding the PVN[95], where it can interface with input from limbic sites. The SCN is the primary coordinator of physiologic rhythms, and is thus positioned to modulate HPA axis output in conjunction with time-of-day cues.

Neural control of chronic stress responses

Chronic stress exposure physically alters the structure and function of brain regions involved in controlling HPA and autonomic responses to stress (see Table 1). In the hippocampus and prefrontal cortex, chronic restraint causes retraction of apical dendrites and reduces spine density in pyramidal cells[96, 97]. Conversely, increased dendritic branching is observed in the BLA[98]. Chronic stress also changes PVN function, including increased expression of CRH and vasopressin mRNA[99, 100], reduced GR expression[99, 100] and altered expression of numerous neurotransmitter receptor subunits[101, 102]. Finally, neurochemical changes are seen in numerous stress-regulatory pathways that project to the PVN, including increased glutamic acid decarboxylase expression (implying increased GABA levels) in the hypothalamus and the BST[103].

Sensitization of stress responses

Neurochemical evidence suggests that chronic stress enhances the excitability of the HPA and the sympatho-adrenomedullary systems. Facilitated ACTH and corticosterone responses to novel stressors occur after chronic drive by either homotypical or unpredictable stress regimens[104, 105]. This response facilitation occurs despite clear evidence for ongoing or cumulative elevation in glucocorticoid levels, implying that feedback efficacy is diminished and/or drive is increased.

Chronic stress can recruit pathways that are distinct from those involved in acute responses. For example, lesions of the paraventricular thalamus inhibit the development of chronic-stress induced facilitation of HPA-axis activation, but do not affect responses to acute stress[106], indicating that this region is engaged during repeated, chronic stress exposure. In contrast, lesions of the hippocampus do not affect HPA-axis responses associated with chronic stress[47], suggesting that its role in HPA-axis regulation is diminished upon repeated stress exposure. The BST seems to be differentially involved in acute and chronic-stress responses, as lesions of the anterolateral BST reduce HPA-axis responses to acute stress, but enhance chronic-stress-induced facilitation of HPA axis activation[107].

Repeated exposure to cold enhances stress-induced noradrenaline release in the frontal cortex and sensitizes the firing rate of locus coeruleus neurons following a novel stressor[108–110]. Chronic cold stress also increases the sensitivity of the locus coeruleus to CRH, suggesting that it increases the responsiveness to a factor that is released during stress[109]. Finally, chronic stress increases the expression of tyrosine hydroxylase, the rate-limiting enzyme in noradrenaline synthesis, in the locus coeruleus, as well as that of co-localized neuropeptides (e.g., galanin), which is consistent with an enhanced capacity for noradrenaline release ([111, 112] but see also[113]). The locus coeruleus does not have substantial projections to the PVN[5], suggesting that contributions to HPA-axis regulation are mediated by upstream (e.g., hippocampus, mPFC and amygdala) or downstream (ventrolateral medulla, spinal cord) targets.

The CeA is implicated in chronic stress regulation by virtue of its sensitivity to corticosteroids. High levels of glucocorticoids increase CRH mRNA expression in the CeA[114], an effect that is mimicked by some chronic stress regimens (e.g., chronic immobilization, chronic pain)[115] but not others (e.g., chronic restraint, chronic unpredictable stress, repeated predator exposure)[116]. In sheep, repeated stress (dog exposure) causes CRH release in the CeA, which appears crucial for sensitization of both the CRH response in the PVN and cortisol release upon repeated exposure[117]. The amygdalar CRH response to repeated stress is blocked by pretreatment with a GR antagonist, implying that corticosteroids are required for the enhanced CRH release in the CeA during repeated stress[117, 118].

Although glucocorticoid secretion could be important for stress sensitization of the amygdala, chronic stress produces marked reductions in glucocorticoid signaling in other brain regions. Numerous chronic-stress regimens cause down-regulation of GR (and to a lesser extent, MR) mRNA, binding and protein levels in the mPFC and the hippocampus[99, 119–121]. This down-regulation could be associated with a loss of glucocorticoid negative-feedback sensitivity, at least in terms of inhibiting the circadian rise in corticosterone levels[120, 121]. Thus, chronic stress seems to be sufficient to both dampen negative-feedback signaling by stress-inhibitory pathways and to enhance positive drive through regions such as the CeA, which, together or alone, could contribute to an enhanced drive of the PVN.

Sensitization of autonomic responses is observed in some chronic stress models. In rats, chronic mild stress produces exaggerated heart rate and pressor responses to a novel stressor[122]. However, the neural substrates of ANS sensitization are not known.

Habituation of stress responses

Response habituation has been observed upon repeated exposure to mild stressors. In this case, the magnitude of the response diminishes with each exposure, even as responses to novel stressors are facilitated[104, 123]. The decreased physiological responses are paralleled by a decrement in central stress-induced Fos activation[124]. The habituation process seems to involve MRs, as systemic treatment with MR antagonists reverses the reduced corticosterone responses to repeated restraint[125]. Lesions of the paraventricular thalamus inhibit habituation of corticosterone responses to repeated restraint[126] (however, see[127]) without affecting acute responding. In combination with the effects of lesions of this region on facilitation[106], the paraventricular thalamus seems to be important in transducing information regarding the chronicity of stress exposure. Notably, this region receives heavy projections from the ventral subiculum and the mPFC[76, 128, 129] and projects heavily to the CeA[130, 131], providing a possible intermediary relay between stress-inhibitory and stress-excitatory brain regions.

Habituation of autonomic responses is highly dependent on the stress regimen. In mice, chronic social stress causes limited habituation of heart-rate responses to attack in submissive, but not dominant mice[132]. Chronic stress produces long-term changes in autonomic function, including increased heart rate, decreased heart rate variability (rats)[122] and decreased blood pressure variability (mice)[133]. As was the case for response facilitation, the neural mechanisms underlying habituation of autonomic changes by chronic stress have yet to be explored.

Memory, reward and stress responses

Emotional learning and memory

Interpretating the predictive significance of environmental stimuli is crucial for appropriate control of physiological responses to stressors: the response to stimuli associated with a highly salient negative (or positive) outcome should produce a physiological response that is appropriate for coping with those stimuli, whereas a response generated to innocuous stimuli would be inefficient and metabolically costly. Thus, certain memories encourage responses to situations that predict an adverse outcome and discourage responses to irrelevant or habituated stimuli.

Limbic sites that regulate HPA and ANS responses — including the amygdala, hippocampus and mPFC — are involved in the conditioning of behavioral responses to emotional stimuli (reviewed in[134,135–137]) and are thus also poised to mediate conditioning of HPA and ANS activity. In support of this, conditioned HPA activation after conditioned taste aversion (Text Box 3) is blocked by hippocampectomy[138], and the expression of conditioned HPA responses after contextual or tone-footshock conditioning is blocked by CeA lesions[139]. Conditioned pressor and tachycardia responses to contextual footshock conditioning are also

reduced by pretreatment of the ventral mPFC with $CoCl_2$ (a nonselective synapse blocker), an NMDA receptor antagonist, or nNOS inhibitors[57,140].

There is also evidence for conditioning of stress responses at the level of the relay areas to HPA and autonomic effectors. Lesions of the BST block corticosterone responses to contextual, but not tone, conditioning, purportedly due to connections between the BST and hippocampus[139]. Lesions of the perifornical hypothalamus and lateral hypothalamus disrupt some types of conditioned stress responses[141–144], raising the possibility that conditioned HPA and ANS activation might also be integrated at the level of limbic-hypothalamic relay areas, which in turn suggests that both limbic and homeostatic signals are involved in the generation of learned responses.

Stress and reward

There seems to be a reciprocal relationship between reward and stress processing in the brain. Exposure to natural rewards buffers the effect of stressors on HPA activity, and stress increases reward-seeking behavior (e.g., intake of palatable food, reinstatement of drug-taking behavior). Experiences with rewarding stimuli generally evoke stress-like HPA and ANS responses (see Text Box 4). The effects vary depending on whether the reward is ‘natural’ (e.g., sexual behavior, voluntary wheel running, palatable food intake) or ‘pharmacological’ (e.g., drugs of abuse), and on whether the experiences were self-administered (e.g, contingent on level pressing, self-choice) or investigator-delivered.

The primary brain reward circuit consists of dopaminergic projections from the ventral tegmental area to the nucleus accumbens (NAc) and has extensive connections with the BLA and mPFC (reviewed in[145–147]). The NAc, BLA and mPFC are widely recognized as key mediators of responses to natural rewards and drugs of abuse[145–147]. As the mPFC and BLA regulate stress responses and are involved in conditioning to salient emotional stimuli, these structures are likely to regulate HPA and ANS responses to both unconditioned and conditioned reward exposure. It is not clear whether the NAc also regulates HPA axis and ANS activity, but projections from the NAc core and shell to brain regions such as the lateral hypothalamus, BST, lateral preoptic area and parabrachial nucleus[148, 149] provide an anatomical substrate for potential physiological effects on the HPA axis and ANS. Thus, there is considerable anatomical overlap among the brain regions subserving reward processing, emotional learning and stress responses.

Overlapping circuits mediating stress, memory and reward: functional significance

Stress responses allow the animal to cope with aversive stimuli that represent real or anticipated threats to homeostasis, but mounting a stress response is energetically demanding. Thus, there is an advantage to learning when a particular situation is not a threat and to preemptively reducing an ensuing stress response; moreover, it is advantageous to be able to associate specific environmental cues with a particular stressor so that stress responses can be mounted in anticipation of predicted stressors, thereby minimizing homeostatic disruption.

Rewarding stimuli (particularly those that are novel, unpredicted and/or not self-administered) can be considered stressful because they disrupt homeostasis. In particular,

drugs of abuse elicit strong unconditioned and conditioned activation of the HPA axis and ANS that are linked to the addiction process[150, 151]. However, rewarding stimuli provide fundamentally different experiences from other types of stressors because animals are motivated to obtain them. In fact, chronic voluntary engagement in naturally rewarding behaviors, such as palatable food intake, reduces stress responses; these fundamentally 'pleasurable' experiences seem to have anti-stress effects. In this manner, the brain can tailor stress responses based on the collective experiences of an individual.

Conclusions and future directions

The neural control of stress is a complex process that requires integration of information regarding both real and potential outcomes. Higher-order processing of stress involves weighing the potential value of a given stimulus against potential negative outcomes. The polysynaptic organization of stress pathways further suggests that inputs relaying information on the physiological status of the animal can contribute to the eventual endocrine or autonomic response to the stressor. The vast majority of 'decisions' regarding the initiation of physiological stress responses seem to be made at the level of limbic structures, which communicate information to subcortical sites positioned to interface with ongoing homeostatic feedback.

Emerging functional studies suggest a considerable division of labor among limbic sites. Connections between the infralimbic cortex, CeA, ventrolateral BST, PVN and NTS with autonomic effectors suggest a means by which the important immediate effector — the sympatho-adrenomedullary system — is brought on line. Responses of the other effector — the HPA axis — involve a network that connects the prelimbic cortex, MeA, hippocampus, posterior BST, preoptic area and other hypothalamic nuclei with hypophysiotrophic neurons of the PVN; these connections serve to initiate as well as terminate glucocorticoid release in response to neural and hormonal feedback. The physical separation of autonomic and HPA stress effector circuits promotes some degree of independence of the two stress-modulatory cascades, allowing for appropriate tuning of neural and hormonal responses to specific demand characteristics of the real or anticipated event. However, these two physiological systems also work together, both in terms of overlap in their underlying neural circuitry and their physiological functions. Future growth of the stress physiology field will need to include more work that crosses over the proverbial HPA vs. ANS divide, thereby providing a more complete picture of how an individual learns to anticipate and otherwise cope with stress.

Whereas the effector circuits that control stress are likely hard-wired, the overall weighting of information is subject to considerable individual variation. It is likely that dysfunctions of information processing across these circuits, as a result of environmental adversity and/or genetic factors, lie at the root of maladaptive stress reactions that can culminate in affective disease (e.g., depression, post-traumatic stress disorder) and physical infirmities. Importantly, stress research generally focuses on the use of 'negative' stimuli as stressors (i.e., situations that individuals would avoid if possible). However, 'positive' stimuli (such as novel rewards) can cause comparable physiological stress responses despite the fact that individuals are motivated to obtain them. An understanding of how and why this apparent

contradiction occurs is necessary to appreciate why individuals make the choices that they do, and how the brain and body cope with the consequences of their actions.

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Glossary

Bradycardic response	slowing of heart rate
Brainstem	portion of brain including the pons, medulla and midbrain
Chronic stress	Ongoing or repeated exposure to one or more types of stress stimuli over a period ranging from days to months
Depressor response	decrease in blood pressure
Effector	final common pathway controlling autonomic or neuroendocrine responses
Fos	immediate early gene product whose expression is tightly linked to recent cellular excitation
Glutamic Acid Decarboxylase (GAD)	enzyme responsible of synthesis of GABA. Exists in two isoforms (GAD65, GAD67)
Limbic System	Collection of highly-interconnected forebrain structures involved in processing emotion and memory
Postganglionic	Second neuron in the two-neuron chain mediating autonomic responses
Preautonomic neurons	CNS neurons involved in regulation of preganglionic sympathetic or parasympathetic neurons in the spinal cord and/or brainstem
Preganglionic	First neuron in the two-neuron chain mediating autonomic responses
Pressor response	increase in blood pressure
Subfornical organ	forebrain blood-brain barrier deficient circumventricular organ
Visceral afferent	ascending sensory nerves from thoracic and abdominal organs

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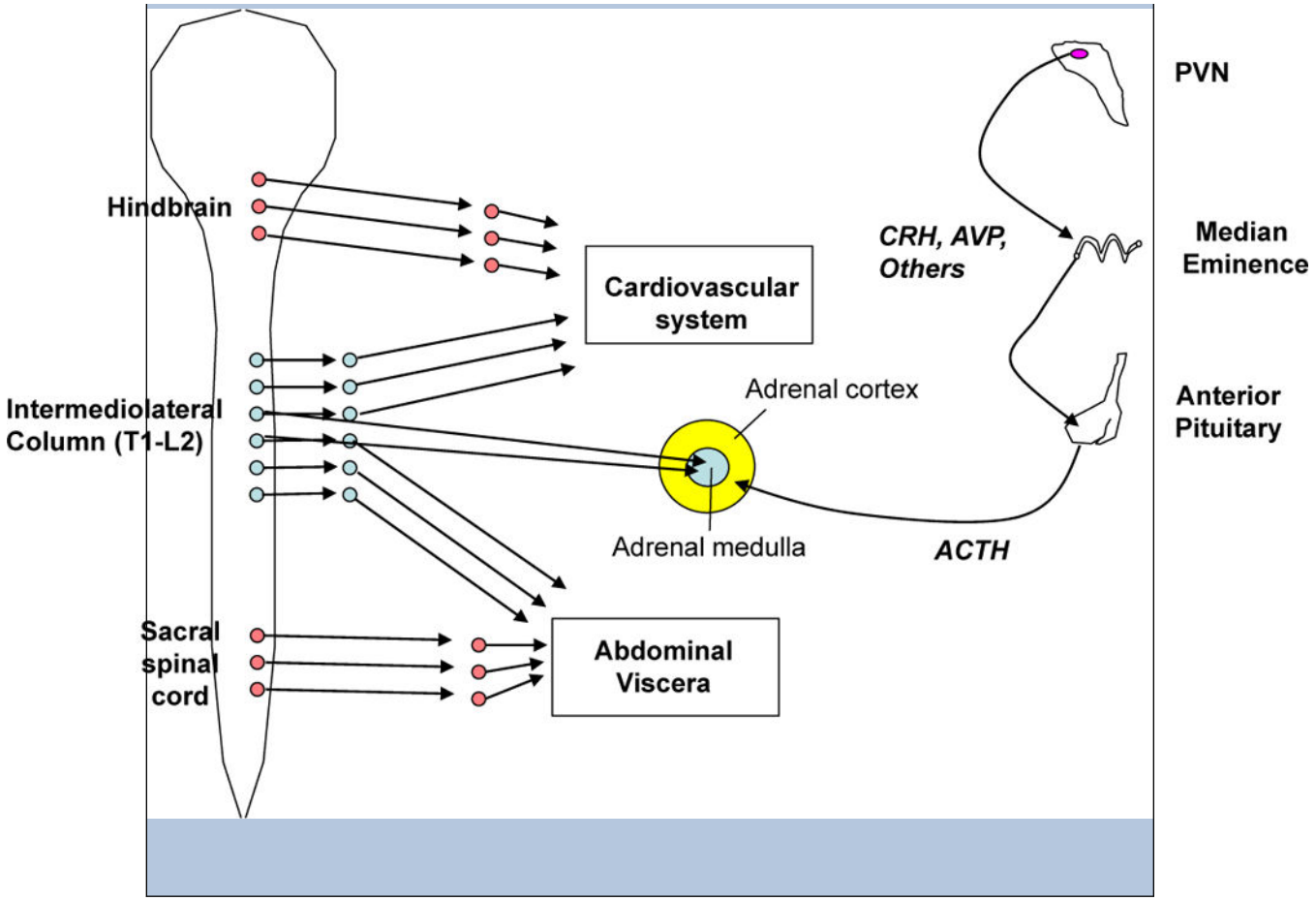
Box 1

HPA axis and autonomic nervous system responses to stress

The sympatho-adrenal medullary (see figure, left) and hypothalamic-pituitary-adrenocortical (HPA, see figure, right) axes are the primary systems for the maintenance or reinstatement of homeostasis during stress. Stressor exposure results in activation of preganglionic sympathetic neurons in the intermediolateral cell column of the thoracolumber spinal cord (shown in blue). These preganglionic neurons project to pre- or para-vertebral ganglia that in turn project to end organs, and to chromaffin cells of the adrenal medulla. This sympathetic activation represents the classic 'fight or flight' response that was first characterized by Walter Cannon and colleagues in the early 20th century[152]; it generally increases circulating levels of adrenaline (primarily from the adrenal medulla) and noradrenaline (primarily from sympathetic nerves), heart rate and force of contraction, peripheral vasoconstriction, and energy mobilization. Parasympathetic tone can also be modulated during stress. In the parasympathetic system (shown in red), activation of craniosacral preganglionic nuclei activates postganglionic nuclei located in or near the end organs they innervate; parasympathetic actions are generally opposite those of the sympathetic system.

For the HPA axis, stressor exposure activates hypophysiotropic neurons in the PVN that secrete releasing hormones, such as corticotrophin releasing hormone and vasopressin, into the portal circulation of the median eminence. These releasing hormones act on the anterior pituitary to promote the secretion of adrenocorticotropic hormone, which in turn acts on the inner adrenal cortex (i.e. the zona fasciculata) to initiate the synthesis and release of glucocorticoid hormones (e.g. corticosterone in rats and cortisol in humans). Circulating glucocorticoids then promote the mobilization of stored energy and potentiate numerous sympathetically-mediated effects, such as peripheral vasoconstriction. Moreover, the adrenal cortex is directly innervated by the sympathetic nervous system, which can facilitate corticosteroid release[153]. Thus, the HPA axis and sympathetic system have largely complementary actions throughout the body, including energy mobilization and maintenance of blood pressure during stress.



Box 2

Corticosteroid receptors and negative feedback

Glucocorticoids have both genomic and nongenomic actions thoughout the body. Genomic actions occur following binding to glucocorticoid receptor (GR) and, in the case of some tissues, mineralocorticoid receptors (MR), which act as ligand-activated transcription factors to affect broad, long-latency and biologically long-acting changes in gene transcription[62]. The MR has a high affinity for endogenous glucocorticoids and is extensively bound even during the circadian nadir of corticosteroid secretion. The GR has a lower affinity and is extensively bound only at relatively high levels of corticosteroids, such as during stress responses[121]. The GR appears to be the primary mediator of 'delayed' glucocorticoid inhibition of stress responses. In contrast, non-genomic effects occur within minutes of glucocorticoid release and likely involve action at the target cell membrane. Non-genomic signaling accounts for 'fast' negative feedback inhibition of the HPA axis, which occurs within minutes of the rise in circulating glucocorticoids (far too fast to be mediated by genomic actions in any traditional sense). It is currently unclear whether this mechanism involves membrane actions of the known nuclear receptors (GR and MR), or a novel, as yet to be identified membrane corticosteroid receptor.

Box 3

Conditioning of stress responses

During exposure to aversive or stress-invoking stimuli, animals learn to associate predictive cues, whether they are contextual (e.g. environmental conditions) or discrete stimuli (e.g. auditory tones) with the onset of stress exposure. During this conditioning process, the predictive stimuli (or conditioned stimuli, CS) become capable of eliciting conditioned responses of the hypothalamus-pituitary-adrenal (HPA) and/or autonomic nervous system responses, presumably in anticipation of the forthcoming stressor.

HPA axis

Some of the earliest work on conditioned activation of the HPA axis used a conditioned taste aversion paradigm. In this model, rats are exposed to a tastant (e.g. a saccharin drink) that is followed by administration of a drug that induces visceral illness (e.g. lithium chloride). When these rats are subsequently given the tastant again, there is a conditioned increase in plasma corticosterone[154, 155]. Conditioned HPA activation is also observed with the conditioned fear paradigm, in which rats receive a footshock in a unique environment (contextual conditioning) or are given a discrete signal (tone or light) paired with a footshock. Upon re-exposure to either the context or the cue there is a conditioned increase in plasma corticosterone[139].

Autonomic nervous system

Conditioned autonomic responses also occur, however the particular nature of the conditioned response varies with the experimental paradigm. Conditioned increases in heart rate, blood pressure, plasma catecholamines (i.e. adrenaline and noradrenaline), and/or sympathetic nerve activity have been shown to occur upon re-exposure to a tone previously paired with shock receipt[142, 156, 157], the unique environment after contextual footshock conditioning[158–160], a non-electrified probe after previously receiving shock from the probe[160, 161], a cage after contextual airjet stress conditioning[162], and a tone predicting tail pinch or shock[163].

Box 4

Reward and stress effectors

Acute exposure to rewarding stimuli

When naïve rats are first given acute noncontingent administration of rewarding drugs (i.e. drugs of abuse) there typically is a robust activation of the HPA axis and an increase in sympatho-vagal activity (reflected by increased heart rate, blood pressure and/or circulating catecholamines) (cocaine[164–166], amphetamine[164, 167, 168], nicotine[169, 170], morphine[171, 172], ethanol[173–177]). Many of these drugs can have direct actions, both in the periphery and at central sites (for example, activation of the reward system), that can contribute to altered activity of the hypothalamus-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS)[178, 179]. In addition, contingent (i.e. self) administration of drugs can reduce HPA and ANS responses[169176, 180, 181]. Importantly, acute experiences with naturally rewarding stimuli do not always evoke stress-like responses[182–185186, 187].

Chronic exposure to rewarding stimuli

Chronic drug exposure generally induces a chronic stress-like state in which basal tone of the HPA axis and ANS and/or their responses to stress are facilitated[188–191192–196]. The effects of chronic exposure to natural rewards have been little investigated, with the exception of chronic intake of palatable foods: in no-choice paradigms (e.g. rats given sucrose drink instead of water, or lard mixed with chow), chronic intake of palatable food generally increases sympathetic and/or HPA axis tone[197198199200–203]. In contrast, in choice paradigms (e.g. rats are offered sucrose drink and/or lard in addition to water and chow), chronic intake of palatable food reduces HPA and sympathetic activation after stress[105, 202, 204–206]. Moreover, the artificial sweetener saccharin reproduces some of these effects[105, 206], suggesting that palatability or reward, rather than the calories contained in the food, is sufficient to evoke these responses. Thus, the nature of the effect of repeated exposure to natural rewards on the HPA axis and ANS seems to depend largely on whether the rats chose to engage in the natural reward.

Conditioned responses to rewarding stimuli

Cues that predict exposure to drugs of abuse elicit conditioned activation of the HPA axis and ANS[207, 208]. However, when the appetitive stimuli are natural rewards the conditioned response is more complex; cues generally evoke anticipatory HPA axis and ANS activation with a rapid inactivation upon receipt of the reward[209–211]. Moreover, if the natural reward is not provided as expected, then there is a further increase in HPA axis activation (“frustration”)[209–213].

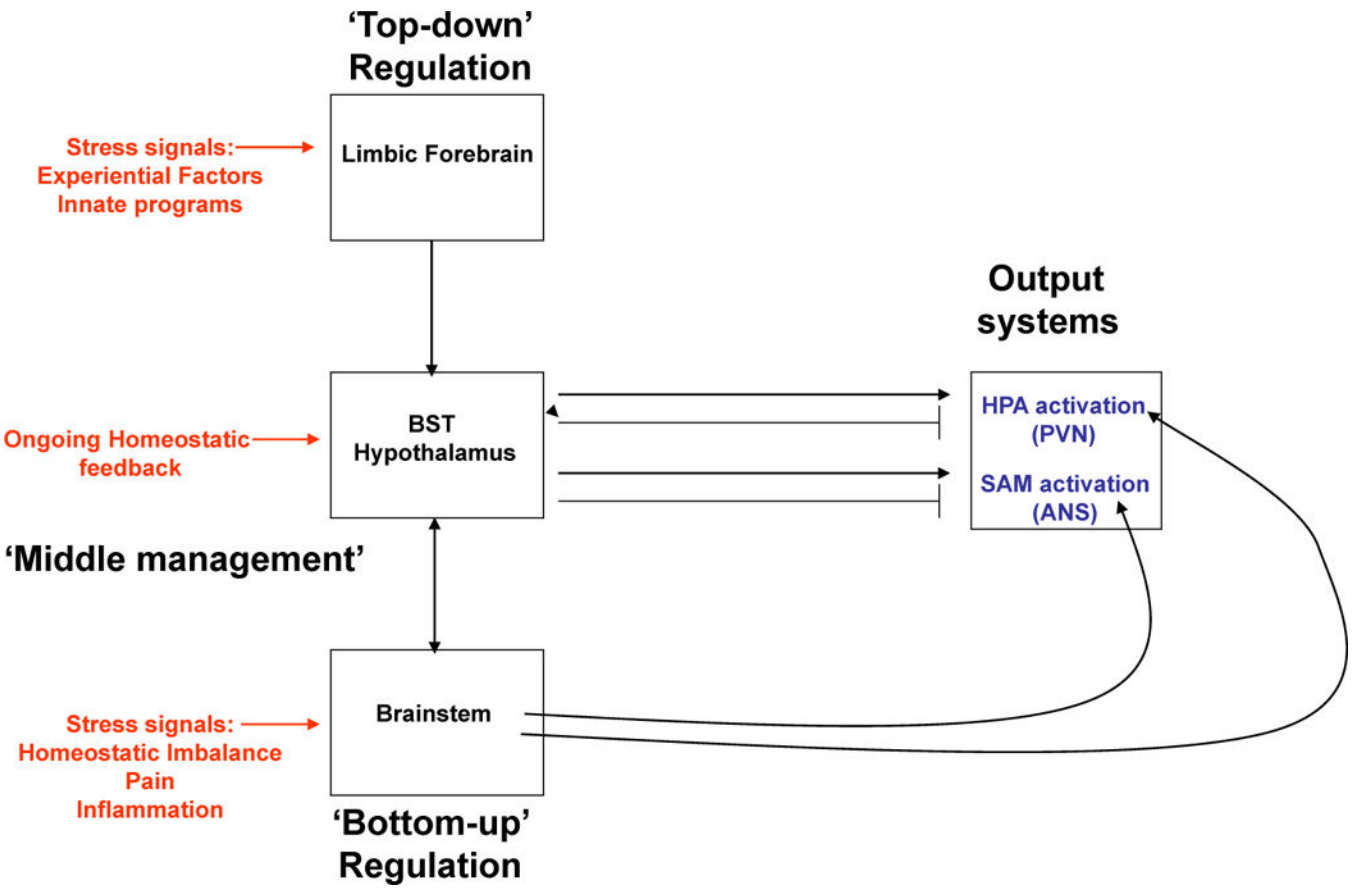


Figure 1. General scheme of brain acute stress-regulatory pathways

Stressors activate brainstem and/or forebrain limbic structures. The brainstem is able to generate rapid hypothalamus-pituitary-adrenal (HPA) axis and autonomic nervous system (ANS) responses via direct projections to hypophysiotrophic neurons in the paraventricular nucleus of the hypothalamus (PVN) or to preganglionic autonomic neurons (bottom-up regulation). In contrast, forebrain limbic regions have no direct connections with the HPA axis or the ANS and thus require intervening synapses prior to accessing autonomic or neuroendocrine neurons (top-down regulation). A high proportion of these intervening neurons are located in hypothalamic nuclei that are also responsive to homeostatic status, providing a mechanism by which the descending limbic information can be modulated according to the physiological status of the animal (middle management).

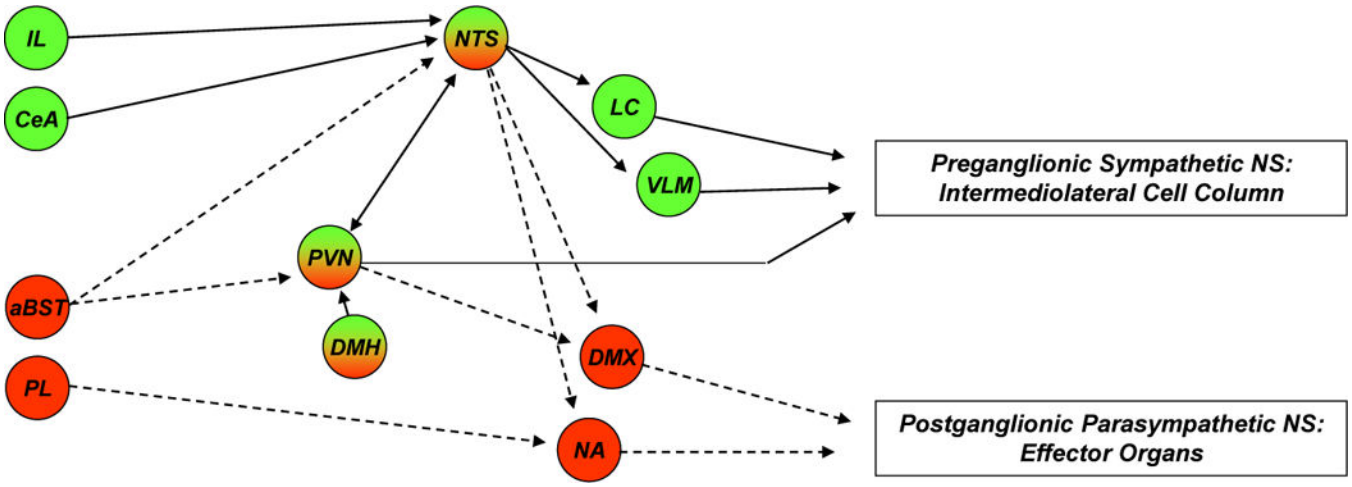


Figure 2. Brain circuitry regulating autonomic stress responses

Stress-induced pre-autonomic outflow originates in multiple brain areas. Colors denote brain regions that are implicated in sympathetic activation (blue), parasympathetic activation (red) or both (bicolored). The paraventricular nucleus of the hypothalamus (PVN) has substantial projections to both sympathetic and parasympathetic nuclei, including the nucleus of the solitary tract (NTS), dorsal motor nucleus of the vagus nerve (DMX), intermediolateral cell column (IML), locus coeruleus (LC) and ventrolateral medulla (VLM) (latter two not shown for clarity). The rostral VLM, LC, and PVN provide direct innervation of the IML and are thought to initiate sympathetic responses. These NTS in turn receive direct input from neurons in the infralimbic cortex (IL), central amygdala (CeA) and PVN. Other hypothalamic regions, most notably the dorsomedial hypothalamus (DMH), modulate ANS activation via connections with the PVN (and possibly other descending pathways) (see text). Parasympathetic outflow is mediated largely by descending outflow from the DMX and nucleus ambiguous (NA) (colored red) and is under the direct influence of the prelimbic cortex (PL), PVN and possibly other descending relays (see text). Parasympathetic effects of the anterior bed nucleus of the stria terminalis (aBST) are likely mediated by relays in the PVN or the NTS. The anatomical complexity of ANS integration is underscored by the mixing of sympathetic and parasympathetic projection neurons in individual nuclei.

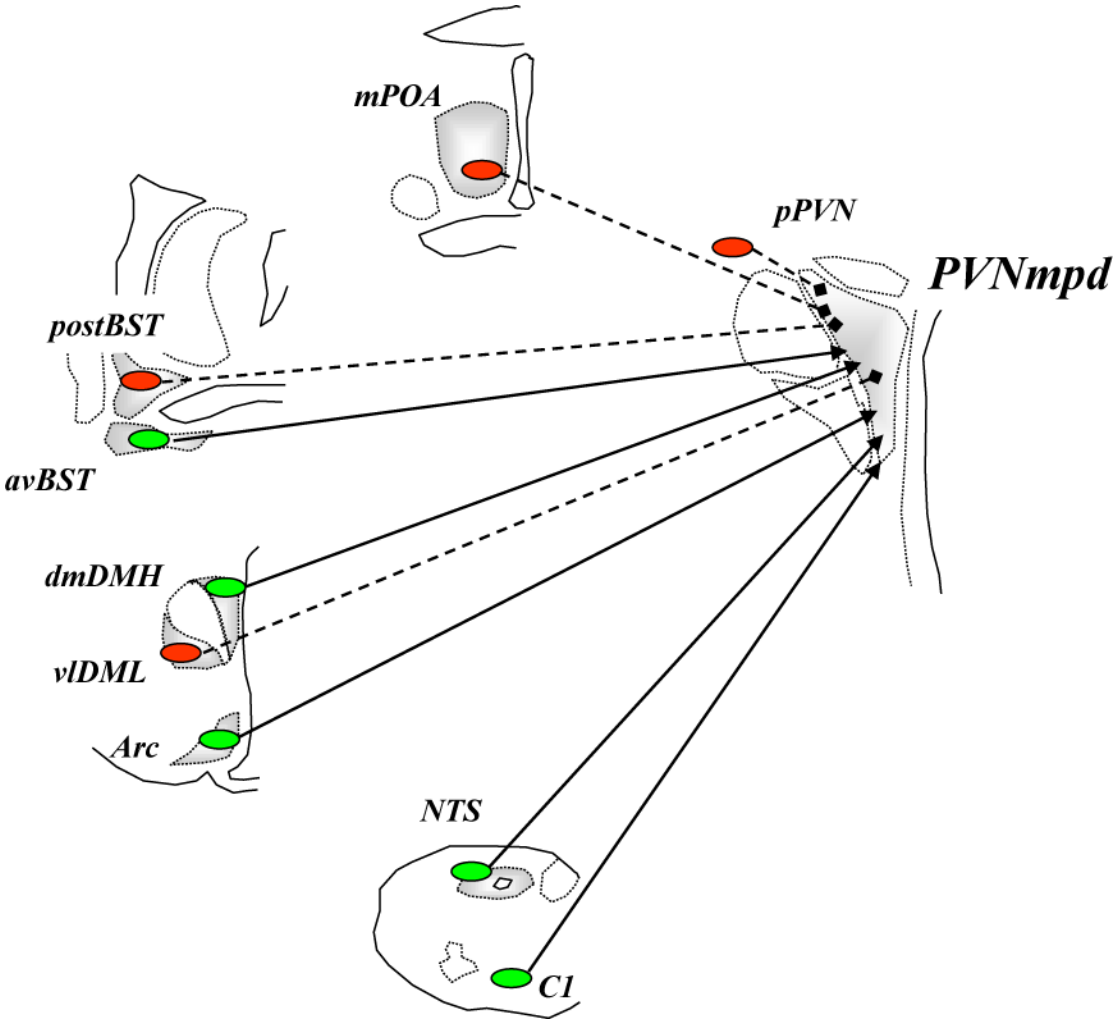


Figure 3. Brain circuitry regulating HPA axis stress responses

Stress-induced activation of the dorsal part of medial parvocellular paraventricular nucleus of the hypothalamus (PVNmpd) originates in several brain regions (excitatory inputs colored blue with solid lines and inhibitory inputs (GABA) colored red with dashed lines). The paraventricular nucleus of the hypothalamus (PVN) receives direct noradrenergic, adrenergic and peptidergic innervation from the nucleus of the solitary tract (NTS). The dorsomedial component of dorsomedial hypothalamus (dmDMH) and arcuate nucleus (Arc) provide intrahypothalamic stress excitation. The anterior part of the bed nucleus of the stria terminalis (BST), particularly the anteroventral nucleus of the BST (avBST), activates HPA axis stress responses. The PVN also receives stress-excitatory drive from the avBST, dorsal raphe, tuberomammillary nucleus, supramammillary nucleus, and spinal cord, among others (omitted in the interest of space). Activation of the PVNmpd is inhibited by numerous hypothalamic circuits, including the medial preoptic area (mPOA), ventrolateral component of dorsomedial hypothalamus (vlDMH) and local neurons in the peri-PVN region (pPVN), encompassing the PVN surround and the subparaventricular zone. The posterior subregions of the bed nucleus of the stria terminalis (pBST) provides a prominent forebrain inhibition of HPA axis responses; the majority of these inputs are GABAergic.

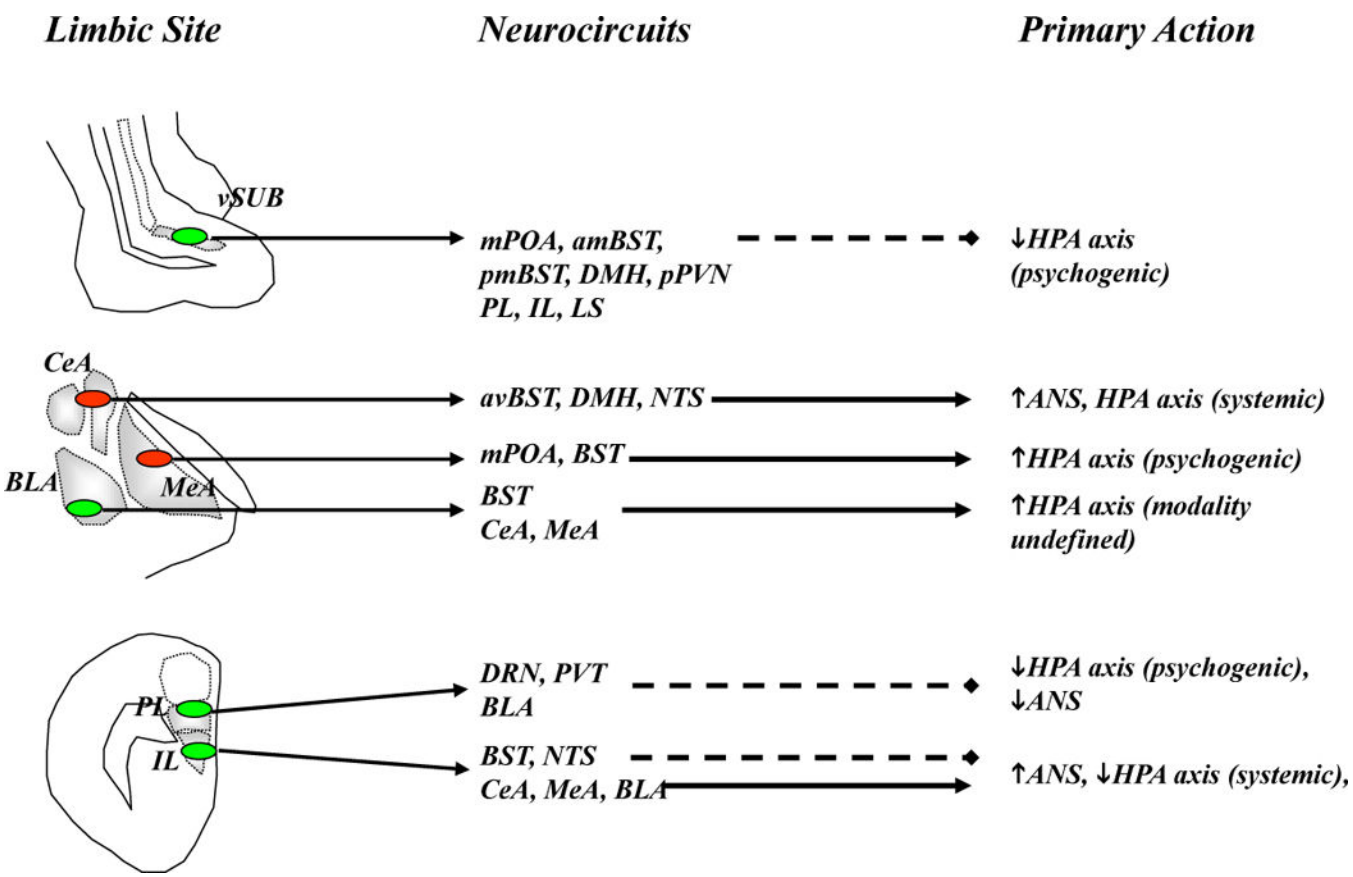


Figure 4. Organization of limbic outputs

Limbic modulation of stress responses occurs predominantly via oligosynaptic inputs to the in the paraventricular nucleus of the hypothalamus (PVN) and other preautonomic brain regions. Excitatory inputs are colored blue with solid lines and inhibitory inputs (GABA) are colored red with dashed lines. Top: The ventral subiculum (vSUB) coordinates hippocampal stress output by providing glutamatergic input to primarily inhibitory PVN relays, thereby limiting psychogenic stress responses. Middle: GABAergic projections from the central amygdala (CeA) regulate responses to systemic stressors, whereas those from the medial amygdala (MeA) preferentially modulate responses to psychogenic stressors. Through glutamatergic projections within and outside the amygdala, the basolateral amygdala (BLA) plays a role in both the acute response to psychogenic stress and in chronic stress regulation. Bottom: The prelimbic cortex (PL) inhibits responses to psychogenic stress, and this inhibition is mediated predominantly by glutamatergic projections to inhibitory PVN relays. In contrast, the infralimbic cortex (IL) activates autonomic and possibly HPA axis responses to psychogenic stress, perhaps via direct (nucleus of the solitary tract, NTS) or indirect (CeA) projections. Abbreviations: anteriomedial BST (amBST), anteroventral BST (avBST), bed nucleus of the stria terminalis (BST), dorsal raphe nucleus (DRN), dorsomedial hypothalamus (DMH), lateral septum (LS), medial preoptic area (mPOA), thalamic paraventricular nucleus (PVT), peri-PVN (pPVN), posteromedial BST (pmBST), ventral subiculum (vSub).

Table 1

Neuroplastic Responses to Chronic Stress

Site	Chronic Stress Plasticity	Process Impacted
HPC	Dendritic atrophy ↓GR expression	↓HPA Glucocorticoid feedback ↓Memory
mPFC	Dendritic atrophy ↓GR expression	↓HPA Glucocorticoid feedback ↓Extinction, ↓Reward
CeA	↑CRH expression ↑CRH release	↑Autonomic and HPA excitability ↑Anxiety
BLA	↑dendritic branching ↑stress excitability	↑Autonomic and HPA excitability ↓Emotional memory, ↓Reward
PVT	↑stress excitability	↑HPA excitability (novel stress) ↓HPA excitability (familiar stress)
LC	↑neurotransmitter/NP ↑stress excitability (mPFC)	↑HPA excitability (novel stress)
PVN	↑secretagogue synthesis ↑stress receptivity ↓GR expression	↑stress excitability (novel stress)