Stress is commonly defined as a state of real or perceived threat to homeostasis. Maintenance of homeostasis in the presence of aversive stimuli (stressors) requires activation of a complex range of responses involving the endocrine, nervous, and immune systems, collectively known as the stress response. Activation of the stress response initiates a number of behavioral and physiological changes that improve an individual’s chance of survival when faced with homeostatic challenges. Behavioral effects of the stress response include increased awareness, improved cognition, euphoria, and enhanced analgesia. Physiological adaptations initiated by activation of this system include increased cardiovascular tone, respiratory rate, and intermediate metabolism, along with inhibition of general vegetative functions such as feeding, digestion, growth, reproduction, and immunity. Due to the wide array of physiologic and potentially pathogenic effects of the stress response, a number of neuronal and endocrine systems function to tightly regulate this adaptive process.

### Anatomy of the stress response

The anatomical structures that mediate the stress response are found in both the central nervous system and peripheral tissues. The principal effectors of the stress response are localized in the paraventricular...
nucleus (PVN) of the hypothalamus, the anterior lobe of the pituitary gland, and the adrenal gland. This collection of structures is commonly referred to as the hypothalamic-pituitary-adrenal (HPA) axis (Figure 1). In addition to the HPA axis, several other structures play important roles in the regulation of adaptive responses to stress. These include brain stem noradrenergic neurons, sympathetic andrenomedullary circuits, and parasympathetic systems.5,7

### The HPA axis

Hypophysiotropic neurons localized in the medial parvocellular subdivision of the PVN synthesize and secrete corticotropin-releasing factor (CRF), the principle regulator of the HPA axis.8 In response to stress, CRF is released into hypophysial portal vessels that access the anterior pituitary gland. Binding of CRF to its receptor on pituitary corticotropes induces the release of adrenocorticotropic hormone (ACTH) into the systemic circulation. The principal target for circulating ACTH is the adrenal cortex, where it stimulates glucocorticoid synthesis and secretion from the zona fasciculata. Glucocorticoids are the downstream effectors of the HPA axis and regulate physiological changes through ubiquitously distributed intracellular receptors. The biological effects of glucocorticoids are usually adaptive; however, inadequate or excessive activation of the HPA axis may contribute to the development of pathologies.10,12

### The CRF family of peptides

Corticotropin-releasing factor is a 41 amino acid peptide that was originally isolated from ovine hypothalamic tissue in 1981.8 Since this initial identification, CRF has been shown to be the primary regulator of ACTH release from anterior pituitary corticotropes and has also been implicated in the regulation of the autonomic nervous system, learning and memory, feeding, and reproduction-related behaviors.13,19 CRF is widely expressed through-
out the central nervous system (CNS) and in a number of peripheral tissues. In the brain, CRF is concentrated in the medial parvocellular subdivision of the PVN and is also localized in the olfactory bulb, bed nucleus of the stria terminalis (BNST), medial preoptic area, lateral hypothalamus, central nucleus of the amygdala, Barington’s nucleus, dorsal motor complex, and inferior olive.20 In the periphery, CRF has been detected in the adrenal gland, testis, placenta, gastrointestinal tract, thymus, and skin.21-23 Three additional members of the CRF peptide family have recently been identified. These include urocortin (Ucn)24 and the recently cloned Ucn 225 and Ucn 3,26 which are also known as stresscopin-related peptide and stresscopin,27 respectively. In the mammalian brain, Ucn 1 is predominantly expressed in the Edinger-Westphal nucleus24 and Ucn 2 expression is restricted to the PVN and locus coeruleus.25 Ucn 3 has a wider distribution in the brain and is localized in the perifornical area of the hypothalamus, BNST, lateral septum (LS), and amygdala.28 The widespread anatomical distribution of CRF and the urocortins correlates well with the diverse array of physiological functions associated with this peptide family.

CRF receptors

The physiological actions of the CRF family of peptides are mediated through two distinct receptor subtypes belonging to the class B family of G-protein coupled receptors.29 The CRF type 1 receptor (CRFR1) gene encodes one functional variant (α) in humans and rodents along with several nonfunctional splice variants.30-32 The CRF type 2 receptor (CRFR2) has three functional splice variants in human (α, β, and γ) and two in rodents (α and β) resulting from the use of alternate 5’ starting exons.33,34 CRFR1 is expressed at high levels in the brain and pituitary and low levels in peripheral tissues. The highest levels of CRFR1 expression are found in the anterior pituitary, olfactory bulb, cerebral cortex, hippocampus, and cerebellum. In peripheral tissues, low levels of CRFR1 are found in the adrenal gland, testis, and ovary.35-38 In contrast, CRFR2 is highly expressed in peripheral tissues and localized in a limited number of nuclei in the brain.37 In rodents, the CRF type 2α splice variant is preferentially expressed in the mammalian brain and is localized in the lateral septum, BNST, ventral medial hypothalamus, and mesencephalic raphe nuclei.34 The CRF type 2β variant is expressed in the periphery and is concentrated in the heart, skeletal muscle, skin, and the gastrointestinal tract.29,38,39 Radioligand binding and functional assays have revealed that CRFR1 and CRFR2 have different pharmacological profiles. CRF binds to the CRFR1 with higher affinity than to CRFR2.29,33 Ucn 1 has high affinity for both CRFR1 and CRFR2 and is more potent than CRF on CRFR2.24,33 Ucn 2 and Ucn 3 are highly selective for CRFR2 and exhibit low affinities for CRFR1. In addition, Ucn 2 and Ucn 3 minimally induce cyclic adenosine monophosphate (cAMP) production in cells expressing either endogenous or transfected CRFR1.25-27 The neuroendocrine properties of CRF are mediated through CRFR1 in the anterior pituitary. Binding of CRF to the type 1 receptor results in the stimulation of adenylate cyclase and a subsequent activation of cAMP pathway events that culminate with the release of ACTH from pituitary corticotropes.29,39,40 The integral role of CRFR1 in the regulation of ACTH release was confirmed by the phenotype of CRFR1-deficient mice. Mice deficient for CRFR1 have a severely attenuated HPA response to stress and display decreased anxiety-like behaviors.41,42 The role of CRFR2 in the regulation of the HPA axis and adaptive responses to stress is less clear. Mice deficient for CRFR2 have an amplified HPA response to stress and display increased anxiety-like behaviors.43-45 However, administration of CRFR2 agonists and antagonists into discrete brain regions reveal both anxiolytic and anxiogenic roles for CRFR2.45

Vasopressin

Vasopressin (AVP) is a nonapeptide that is highly expressed in the PVN, supraoptic (SON), and suprachiasmatic nuclei of the hypothalamus.46,47 Magnocellular neurons of the PVN and SON project to the posterior lobe of the pituitary and release AVP directly into the systemic circulation to regulate osmotic homeostasis.48,49 In addition to magnocellular neurons, parvocellular neurons of the PVN synthesize and release AVP into the portal circulation, where this peptide potentiates the effects of CRF on ACTH release from the anterior pituitary.7,50,51 The synergistic effects of AVP on ACTH release are mediated through the vasopressin V1b (also known as V3) receptor on pituitary corticotropes.52 Binding of AVP to
the V₁b receptor activates phospholipase C by coupling to Gq proteins. Activation of the phospholipase C stimulates protein kinase C, resulting in the potentiation of ACTH release. Several investigators have reported that the expression of AVP in parvocellular neurons of the PVN and V₁b receptor density in pituitary corticotropes is significantly increased in response to chronic stress. These findings support the hypothesis that AVP plays an important role in the stress response by maintaining ACTH responsiveness to novel stressors during periods of chronic stress.

**Adrenocorticotropic hormone**

Pro-opiomelanocortin (POMC) is a prohormone that is highly expressed in the pituitary and the hypothalamus. POMC is processed into a number of bioactive peptides including ACTH, β-endorphin, β-lipotropic hormone, and the melanocortins. In response to CRF, ACTH is released from pituitary corticotropes into the systemic circulation where it binds to its specific receptor in the adrenal cortex. ACTH binds to the melanocortin type 2 receptor (MC2-R) in parenchymal cells of the adrenocortical zona fasciculata. Activation of the MC2-R induces stimulation of cAMP pathway events that induce steroidogenesis and the secretion of glucorticoids, mineralcorticoids, and androgenic steroids. Specifically, ACTH promotes the conversion of cholesterol into δ-5 pregnenolone during the initial step of glucocorticoid biosynthesis.

**Glucocorticoids**

Glucocorticoids, cortisol in humans and corticosterone in rodents, are a major subclass of steroid hormones that regulate metabolic, cardiovascular, immune, and behavioral processes. The physiological effects of glucocorticoids are mediated by a 94kD cytosolic protein, the glucocorticoid receptor (GR). The GR is widely distributed throughout the brain and peripheral tissues. In the inactive state, the GR is part of a multiprotein complex consisting of several different molecules of heat shock proteins (HSP) that undergo repeated cycles of dissociation and ATP-dependent reassociation. Ligand binding induces a conformational change in the GR, resulting in the dissociation of the receptor from the HSP complex and translocation into the nucleus. Following translocation, the GR homodimer binds to specific DNA motifs termed glucocorticoid response elements (GREs) in the promoter region of glucocorticoid responsive genes and regulates expression through interaction with transcription factors. The GR has also been shown to regulate activation of target genes independent of GRE-binding through direct protein-protein interactions with transcription factors including activating protein 1 (AP-1) and nuclear factor-κB (NF-κB).

**Endocrine regulation of the HPA axis**

Activation of the HPA axis is a tightly controlled process that involves a wide array of neuronal and endocrine systems. Glucocorticoids play a prominent role in regulating the magnitude and duration of HPA axis activation. Following exposure to stress, elevated levels of circulating glucocorticoids inhibit HPA activity at the level of the hypothalamus and pituitary. The HPA axis is also subject to glucocorticoid independent regulation. The neuroendocrine effects of CRF are also modulated by CRF binding proteins that are found at high levels in the systemic circulation and in the pituitary gland.

**Glucocorticoid negative feedback**

The HPA axis is subject to feedback inhibition from circulating glucocorticoids. Glucocorticoids modulate the HPA axis through at least two distinct mechanisms of negative feedback. Glucocorticoids have traditionally been thought to inhibit activation of the HPA axis through a delayed feedback system that is responsive to glucocorticoid levels and involves genomic alterations. There is increasing evidence for an additional fast nongenomic feedback system that is sensitive to the rate of glucocorticoid secretion; however, the exact mechanism that mediates rapid feedback effects has not yet been characterized.

The delayed feedback system acts via transcriptional alterations and is regulated by GR localized in a number of stress-responsive brain regions. Following binding of glucocorticoids, GRs modulate transcription of HPA components by binding to GREs or through interactions with transcription factors. Glucocorticoids have a low nanomolar affinity for the GR and extensively occupy GRs during periods of elevated glucocorticoid secretion that occur following stress. Mineralocorticoid receptors (MRs) have a subnanomolar affinity for glucocorticoids, a restricted expression pattern in the brain, and bind glu-
corticoids during periods of basal secretion. The distinctive pharmacologies of these two receptors suggest that MRs regulate basal HPA tone while GRs mediate glucocorticoid negative feedback following stress. GRs are widely expressed in the brain, and thus the precise anatomical locus of glucocorticoid negative feedback remains poorly defined. However, two regions of the brain appear to be key sites for glucocorticoid feedback inhibition of the HPA axis. High levels of GR are expressed in hypophysiotropic neurons of the PVN, and local administration of glucocorticoids reduce PVN neuronal activity and attenuate adrenalectomy-induced ACTH hypersecretion. These findings suggest that the PVN is an important site for glucocorticoid feedback regulation of the HPA axis. The hippocampus has been implicated as a second site for glucocorticoid negative feedback regulation of the HPA axis. The hippocampus contains a high concentration of both GR and MR, and infusion of glucocorticoids into this structure reduces basal and stress induced glucocorticoid release.

CRF binding proteins

Two soluble proteins have been identified that bind the members of the CRF family of peptides with high affinity. The CRF binding protein (CRF-BP) is a highly conserved 37kD glycoprotein that binds both CRF and Ucn 1 with high affinity. The CRF-BP was originally identified in maternal plasma where it functions to inhibit HPA axis activation stemming from the elevated circulating levels of placenta-derived CRF. The CRF-BP is highly expressed in the pituitary, and recombinant CRF-BP attenuates CRF-induced ACTH release from dispersed anterior pituitary cells in culture. These findings suggest the CRF-BP may function to sequester CRF at the level of the pituitary and reduce CRFR activity. Our laboratory has recently identified a transcript that encodes a soluble splice variant of the CRFR2 receptor (sCRFR2α) in the mouse brain. Soluble CRFR2α is a predicted 143 amino acid protein generated from a predicted 143 amino acid protein generated from exons 3-5 of the extracellular domain of CRFR2α gene and a unique 38 amino acid hydrophilic C-terminal tail. High levels of sCRFR2α expression are found in the olfactory bulb, cortex, and midbrain regions that have been shown to express CRFR1. Recombinant sCRFR2α binds CRF with low nanomolar affinity and inhibits cellular responses to both CRF and Ucn 1 in signal transduction assays, suggesting that sCRFR2α may function as a decoy receptor for the CRF family of peptides.

Neuronal regulation of the HPA axis

Hypophysiotropic neurons in the PVN are innervated by a diverse constellation of afferent projections from multiple brain regions. The majority of afferent inputs to the PVN originate from four distinct regions: brain stem neurons, cell groups of the lamina terminalis, extra-PVN hypothalamic nuclei, and forebrain limbic structures. These cell groups integrate and relay information regarding a wide array of sensory modalities to influence CRF expression and release from hypophysiotropic neurons of the PVN (Figure 2).

Brain stem neurons

Brain stem catecholaminergic centers play an important role in the regulation of the HPA axis. Neurons of the nucleus of the solitary tract (NTS) relay sensory information to the PVN from cranial nerves that innervate large areas of thoracic and abdominal viscera. The NTS also receives projections from limbic structures that regulate behavioral responses to stress including the medial prefrontal cortex and the central nucleus of the amygdala. Accordingly, neuronal populations in the NTS are activated following lipopolysaccharide injection, hypotension, forced swim, and immobilization stress paradigms. Stress-receptive neurons in the A2/C2 region of the NTS densely innervate the medial parvocellular subdivision of the PVN. Findings from both in vivo and in vitro studies demonstrate that catecholaminergic input represents a major excitatory drive on the HPA axis and induces CRF expression and protein release through an α-1 adrenergic receptor-dependent mechanism. Nonaminergic NTS neurons also innervate the PVN and contribute to HPA axis regulation. Glucagon-like peptide 1 containing neurons in the NTS are activated by physiological stressors and have been shown to induce ACTH release in vivo. The neuropeptides somatostatin, substance P, and enkephalin are also expressed in NTS neurons that innervate the PVN and have been shown to have regulatory effects on the HPA axis.
The lamina terminalis

A series of interconnected cell groups including the subfornical organ (SFO), median preoptic nucleus (MePO), and the vascular organ of the lamina terminalis are localized on the rostral border of the third ventricle and make up the lamina terminalis.\textsuperscript{107} Cell groups of the lamina terminalis lie outside of the blood-brain barrier and relay information concerning the osmotic composition of blood to the PVN.\textsuperscript{108} The medial parvocellular subdivision of the PVN receives rich innervation from the SFO and to a lesser extent from the OVLT and MePO.\textsuperscript{109} Neurons in the SFO that project to the PVN are angiotensinergic, and promote CRF secretion and biosynthesis.\textsuperscript{110,111} This afferent pathway has parallel input to the magnocellular division of the PVN, and has been hypothesized to serve as a link between HPA and neurohypophysial activation.\textsuperscript{112-114}

Hypothalamus

The medial parvocellular subdivision of the PVN receives afferent projections from $\gamma$-aminobutyric acid (GABA)-ergic neurons of the hypothalamus.\textsuperscript{115} Hypophysiotropic neurons of the PVN express GABA-A receptor subunits\textsuperscript{116} and hypothalamic injection of the GABA-A receptor agonists inhibit glucocorticoid secretion following exposure to stressors.\textsuperscript{117,118} These studies suggest that GABA plays a prominent role in hypothalamic stress integration.

Hypothalamus: DMH and POA

GABAergic neurons in the dorsomedial hypothalamic nucleus (DMH) and preoptic area (POA) project to the medial parvocellular division of the PVN, and are activated following exposure to stressors.\textsuperscript{115,117} Lesions of

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Figure 2. Depiction of the major brain regions and neurotransmitter groups that supply afferent innervation to the medial parvocellular zone of the paraventricular nucleus (PVN). Cell groups of the nucleus of the solitary tract (NTS) and ventral medulla (C1) relay visceral information to the PVN through noradrenergic (NE), adrenergic (Epi), and glucagon-like peptide 1 (GLP-1)-containing neurons. Hypothalamic nuclei (HYPO) encode information from endocrine systems and send mainly $\gamma$-aminobutyric acid (GABA)-ergic (GABA) projections to the PVN. Cell groups of the lamina terminalis relay information concerning the osmotic composition of blood to the PVN through glutamatergic (Glu) and angiotensinergic (Ang) neurons. Limbic structures including the hippocampus, prefrontal cortex, and the amygdala contribute to the regulation of PVN neurons through intermediary neurons of the bed nucleus of the stria terminalis (BNST). PIT, pituitary

Adapted from reference 20: Sawchenko PE, Imaki T, Potter E, Kovacs K, Imaki J, Vale W. The functional neuroanatomy of corticotropin-releasing factor. Ciba Found Symp. 1993;172:5-21; discussion 21-29. Copyright © John Wiley and Sons 1993.
hypothalamic regions encompassing the DMH and the POA amplify HPA responses to stress. Furthermore, glutamate microstimulation of DMH neurons produces inhibitory postsynaptic potentials in hypophysiotropic neurons of the PVN, and stimulation of the POA attenuates the excitatory effects of medial amygdalar stimulation of glucocorticoid release. The POA is a potential site of integration between gonadal steroids and the HPA axis. Accordingly, neurons of the POA are activated by gonadal steroids and express high levels of androgen, estrogen, and progesterone receptors.

Hypothalamic centers involved in the regulation of energy homeostasis directly innervate PVN neurons. Neurons in the arcuate nucleus are sensitive to circulating levels of glucose, insulin, and leptin. These cells also synthesize neuropeptide Y (NPY), agouti-related peptide (AGRP), α-melanocyte stimulating hormone (αMSH), and cocaine-and amphetamine-regulated transcript (CART) which play critical roles in the regulation of feeding behaviors. Central injection of the orexigenic factor NPY results in HPA axis activation and infusion of AGRP significantly increases CRF release from hypothalamic explants. The anorectic peptides αMSH and CART have been reported to increase circulating levels of ACTH and corticosterone, induce cAMP binding protein phosphorylation in CRF neurons, and stimulate CRF release from hypothalamic neurons. These studies suggest that the HPA axis is activated in response to positive and negative states of energy balance.

Limbic system: hippocampus

The hippocampus plays an important role in the terminating HPA axis responses to stress. Stimulation of the hypothalamus originates in the ventricle subiculum and CA1 regions of the hippocampus. These regions send afferent projections to GABAergic neurons of the BNST and the peri-PVN region of the hypothalamus that directly innervate the parvocellular division of the PVN. Hippocampal lesions encompassing the ventral subiculum produce exaggerated HPA responses to restraint and open field exposure, but not to hypoxia or ether exposure, suggesting that hippocampal neurons respond to distinct stress modalities.

Limbic system: prefrontal cortex

The prefrontal cortex also regulates HPA responses to stress. Neurons of the medial prefrontal cortex are activated and release catecholamines following exposure to acute and chronic stressors. Bilateral lesions of the anterior cingulate and prelimbic cortex increase ACTH and glucocorticoid responses to stress, demonstrating that the prefrontal cortex has inhibitory effects on the HPA axis. Anatomic tracing studies reveal that the there is an intricate topographic organization of prefrontal cortex output to HPA regulatory circuits. Afferents from the infralimbic cortex project extensively to the BNST, amygdala, and the NTS. In contrast, the prelimbic/anterior cingulate cortex projects to the POA and the DMH but fails to synapse with the BNST, NTS, or amygdalar neurons.

The prefrontal cortex may also play a role in glucocorticoid feedback inhibition of the HPA axis. High densities of GR are expressed in layers II, III, and VI of the...
prefrontal cortex. Infusion of glucocorticoids into the medial prefrontal cortex attenuates ACTH and corticosterone responses to restraint stress, but has no significant effect on HPA responses to ether. Similarly to the hippocampus, it appears that neurons of the prefrontal cortex are subject to modality-specific regulation of glucocorticoid feedback inhibition of the HPA axis.

**Limbic system: amygdala**

In contrast to the hippocampus and the prefrontal cortex, the amygdala is thought to activate the HPA axis. Stimulation of amygdalar neurons promotes glucocorticoid synthesis and release into the systemic circulation. The medial (MeA) and central (CeA) nuclei of the amygdala play a key role in HPA axis activity and contribute the majority of afferent projections from the amygdala to cortical, midbrain, and brain stem regions that regulate adaptive responses to stress. The MeA and CeA respond to distinct stress modalities and are thought to have divergent roles in HPA regulation. Neurons in the MeA are activated following exposure to “emotional” stressors including predator, forced swim, social interaction, and restraint stress paradigms. In contrast, the CeA appears to be preferentially activated by “physiological” stressors, including hemorrhage and immune challenge. The CeA exerts its regulatory effects on the HPA axis through intermediary neurons in the brain stem. Afferent projections from the CeA densely innervate the NTS and parabrachial nucleus. The MeA sends a limited number of direct projections to the parvocellular division of the PVN; however, this subnucleus innervates a number of nuclei that directly innervate the PVN. Neurons of the MeA project to the BNST, MePO, and ventral premammillary nucleus. The amygdala is a target for circulating glucocorticoids and the CeA and MeA express both GR and MR. In contrast to the effects on hippocampal and cortical neurons, glucocorticoids increase expression of CRF in the CeA and potentiate autonomic responses to chronic stressors. Glucocorticoid infusion into the CeA does not acutely effect HPA activation but may play a feed-forward role to potentiate HPA responses to stress.

**Sympathetic circuits and the stress response**

Activation of brain stem noradrenergic neurons and sympathetic adrenomedullary circuits further contribute to the body’s response to stressful stimuli. Similarly to the HPA axis, stress-evoked activation of these systems promotes the mobilization of resources to compensate for adverse effects of stressful stimuli. The locus coeruleus (LC) contains the largest cluster of noradrenergic neurons in the brain and innervates large segments of the neuroaxis. The LC has been implicated in a wide array of physiological and behavioral functions including emotion, vigilance, memory, and adaptive responses to stress. A wide array of stressful stimuli activate LC neurons, alter their electrophysiological activity, and induce norepinephrine release. Stimulation of the LC elicits several stress-associated responses including ACTH release, anxiogenic-like behaviors, and suppression of immune functions. In addition, there are interactions between CRF and NE neurons in the CNS. Central administration of CRF alters activity of LC neurons and NE catabolism in terminal regions. Finally, dysfunction of catecholaminergic neurons in the LC has been implicated in the pathophysiology of affective and stress-related disorders.

**Conclusions**

Maintenance of homeostasis in the presence of real or perceived challenges requires activation of a complex range of responses involving the endocrine, nervous, and immune systems, collectively known as the stress response. Inappropriate regulation of the stress response has been linked to a wide array of pathologies including autoimmune disease, hypertension, affective disorders, and major depression. In this review we briefly discussed the major neuronal and endocrine systems that contribute to maintenance of homeostasis in the presence of stress. Clearly deciphering the role of each of these systems and their regulatory mechanisms may provide new therapeutic targets for treatment and prophylaxis of stress-related disorders including anxiety, feeding, addiction, and energy metabolism.

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Los animales responden al estrés, activando una amplia gama de respuestas comportamentales y fisiológicas que se conocen, de forma genérica, como respuesta al estrés. El factor liberador de corticotropina (CRF) desempeña una misión cardinal en la respuesta al estrés, al regular el eje hipotálamo-hipófisis-suprarrenal (HHS). En respuesta al estrés, el CRF inicia una cascada de acontecimientos que culminan con la liberación de glucocorticoídes por la corteza suprarrenal. Como consecuencia del elevado número de efectos fisiológicos y conductuales inducidos por los glucocorticoídes, han surgido varios mecanismos para controlar la activación del eje HHS e integrar la respuesta al estrés. La inhibición por retroalimentación de los glucocorticoídes contribuye decisivamente a regular la magnitud y la duración de su liberación. Además de esta retroalimentación glucocorticoidea, el eje HHS está regulado en el hipotálamo por un grupo diverso de proyecciones aferentes de los núcleos límbicos, mesencefálicos y del tronco cerebral. La respuesta al estrés está mediada también, en parte, por las neuronas noradrenérgicas del tronco cerebral, los circuitos adrenomedulares simpáticos y los sistemas parasimpáticos. En resumen, el objetivo de esta revisión es exponer la importancia del eje HHS en la integración de las respuestas adaptativas al estrés. Asimismo, se señalan y describen brevemente los principales sistemas neuronales y endocrinos que contribuyen a la regulación del eje HHS y al mantenimiento de la homeostasis frente a los estímulos adversos.

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