J. Chem Neuroanat
Special issue devoted to W. Vale
Submitted: February, 2013.

CRH: the link between hormonal- metabolic- and behavioral responses to stress

Krisztina J. Kovács

Laboratory of Molecular Neuroendocrinology

Institute of Experimental Medicine

Budapest, Hungary

Correspondence:
Krisztina J. Kovács
Laboratory of Molecular Neuroendocrinology
Institute of Experimental Medicine
Szigony utca 43.
H-1083 Budapest, Hungary
Phone: +36-1-210-9952
Fax: +36-1-210-9423
E-mail: kovacs@koki.hu

ABSTRACT

Two major and mutually interconnected brain systems are recruited during stress reaction. One is the hypothalamic paraventricular nucleus (PVH) and the second is the extended amygdala. PVH governs the neuroendocrine stress response while CeA regulates most of the autonomic and behavioral stress reactions. The common neurohormonal mediator of these responses is the corticotropin-releasing hormone, CRH, which is expressed in both centers. CRH belongs to a larger family of neuropeptides that also includes urocortins 1, 2, and 3 all have different affinity towards the two types of CRHR receptors and have been implicated in regulation of stress and HPA axis activity. One functionally relevant aspect of CRH systems is their differential regulation by glucocorticoids. While corticosterone inhibits CRH transcription in the PVH, stress-induced glucocorticoids stimulate CRH expression in the extended amygdala. This review summarizes past and recent findings related to CRH gene regulation and its involvement in the neuroendocrine, autonomic and behavioral stress reaction.

Key words: Corticotropin-releasing hormone, paraventricular nucleus, central amygdala, bed nucleus of stria terminalis, corticosterone, cAMP-response element.

Abbreviations

ADX	adrenalectomy
BAT	brown adipose tissue
cAMP	cyclic AMP
CNS	central nervous system
CREB	cAMP response element binding protein
CRH	corticotropin-releasing hormone
CRH1R	type 1 corticotropin-releasing hormone receptor
CRH2R	type 2 corticotropin-releasing hormone receptor
DAG	diacylglycerol
GABA	gamma-aminobutyric acid
GR	glucocorticoid receptor
icv	intracerebroventricular (injection)
LC	locus ceruleus
LTP	long-term potentiation
PVH	paraventricular nucleus of the hypothalamus
mpd	medial parvocellular dorsal subdivision of PVH
dp	dorsal parvocellular subdivision of PVH
mpv	medial parvocellular ventral subdivision of PVH
lp	lateral parvocellular subdivision of PVH
SNS	sympathetic nervous system
TORC	transducer of regulated CREB activity

Introduction

With the discovery of **corticotropin-releasing hormone**, CRH in 1981, Wylie Vale (Spiess et al 1981, Vale et al 1981) launched a wave of discoveries that resulted in the significant achievement of what we know about stress physiology and stress-related pathologies.

CRH-41 is synthesized by the hypophyseotropic neurons in the medial dorsal parvocellular subdivision of the hypothalamic paraventricular nucleus (PVH) (Swanson et al 1983). The axons of these cells run laterally and caudally and terminate in the outer zone of the median eminence to release CRH into the portal vasculature of the anterior pituitary to initiate the neuroendocrine stress response (Gibbs & Vale 1982, Lennard et al 1993, Merchenthaler et al 1984, Plotsky et al 1985, Swanson et al 1983, Vale et al 1983).

Additional cell groups within the lateral-, dorsal- and ventral medial parvocellular subdivisions of the rat PVH also capable to synthesize CRH, however these cells project to preganglionic neurons of medulla and spinal cord and have been implicated in the control of autonomic stress responses (Sawchenko et al 1984, Swanson & Sawchenko 1983).

Since the beginning it has been shown that CRH is widely distributed within the nervous system (Merchenthaler 1984, Palkovits et al 1985, Swanson et al 1983) and at the periphery where it acts as neurotransmitter or neuromodulator. Foremost among these are the central nucleus of amygdala (CeA) and the bed nucleus of stria terminalis (BNST) which comprise functionally the "extended amygdala". CRH expression at these sites is related to wide range of stress-adaptive responses, including autonomic- immune- and behavioral changes. Additionally, there are CRH synthesizing neuron populations in the lateral hypothalamus, prefrontal and cingulate cortex and

in the hippocampus. CRH cells have also been found in the Barrington's nucleus, parabrachial complex and in the nucleus of the solitary tract (NTS). Central CRH has been implicated in regulation of arousal, cognitive and executive functions, reward, fear, anxiety and depression, affects sleep-wake cycles, interacts with growth and reproductive regulatory axes and affects cardiorespiratory-, metabolic- and gastrointestinal functions.

CRH is regulated in site-, stress- and glucocorticoid-specific manner (see Table 1). Acute stress challenges generally increase CRH mRNA and peptide levels both in hypothalamic (Imaki et al 1995, Kovacs & Sawchenko 1996a, Kovacs & Sawchenko 1996b, Lightman & Young 1988, Makino et al 1995, Watts 1996) and extrahypothalamic sites, whereas acute and chronic stress exposure reduces CRH transcription in the olfactory bulb (Imaki et al 1991).

1. Regulation of Hypothalamic CRH Transcription

In response to acute stress challenges there is a robust and immediate release of CRH from the hypothalamic parvocellular neurosecretory neurons into the hypophyseal portal circulation that depletes neuropeptide stores at the axon terminals (Plotsky 1985). However, it remains still unknown if the depletion of CRH at the neurovascular interface and/or excitation by neural inputs triggers CRH synthesis in response to stress.

Hypophyseotropic CRH neurons receive stress-related afferents from various brain sites. Most of the somatosensory and viscerosensory information is directly mediated by catecholaminergic pathways (Liposits et al 1986, Liposits et al 1987, Swanson & Sawchenko 1983), while cortical and limbic inputs are processed through gamma-aminobutyric acid (GABA) and/or glutamatergic local circuits (Herman et al 2002, Herman et al 2005, Roland & Sawchenko 1993). These stress-related inputs activate various signal transduction pathways in the parvocellular

neurosecretory neurons that converge upon the regulatory region of the CRH gene to initiate CRH transcription. Stress-induced increase of CRH mRNA depends on the integrity of ascending catecholaminergic (noradrenergic) pathways originating in the brain stem (Pacak et al 1996). Stress-induced activation of parvocellular neurons and CRH synthesis can be reproduced by norepinephrine (NE) injection into the PVH that selectively increases CRH heteronuclear (hn)RNA in the parvocellular neurosecretory neurons (Cole & Sawchenko 2002, Itoi et al 1999). Increased NE signals at alpha1 and beta adrenergic receptors on CRH neurons and increases cAMP (and DAG) second messengers (Day et al 1999). cAMP activates protein kinase A (PKA) to phosphorylate cAMP response element binding protein CREB (Montminy et al 1990). CRH promoter contains cis-acting elements among those the cAMP-response element (CRE) is of the highest significance in stress-initiated CRH transcription (Kovacs & Sawchenko 1996b, Seasholtz et al 1991, Seasholtz et al 1988) . This site integrates cAMP-PKA (Majzoub et al 1993), MAPK -ERK 1/2 (Khan et al 2011, Khan et al 2007), PKC (Majzoub et al 1993) and intracellular Ca^{2+} signaling via phosphorylation of CREB (Khan et al 2011, Kovacs & Sawchenko 1996a). This relatively simple scenario of CRH regulation is complicated by several factors. (1) Activation of CRH transcription requires recruitment of specific coactivators such as Transducer of Regulated CREB activity (TORC) (Martin et al 2012, Wang et al 2008) especially TORC2, which is co-localized in CRH neurons (Liu et al 2010, Watts et al 2011). (2) Ongoing CRH transcription also depends on interaction with several trans-acting factors among those Inducible cAMP Early Repressor (ICER) has been proposed to terminate stress-induced activation of CRH gene expression in the PVH (Shepard et al 2005).

It is noteworthy that glutamatergic excitatory input does not reliably increase CRH expression in the parvocellular neurosecretory neurons (Cole & Sawchenko 2002). In contrast,

pharmacological (by GABA A receptor antagonist) or genetical (GABBA A1b KO in CRH neurons) interference with inhibitory GABAergic input to the parvocellular neurons, increased CRH expression in PVN (Bali & Kovacs 2003, Cole & Sawchenko 2002, Gafford et al 2012). The cellular and molecular mechanisms that mediate CRH transcription after suspension of GABAergic inhibition remains to be elucidated.

Timing of the CRH neuroendocrine stress cascade

Acute stressors depolarize hypohyseotropic neurons that promptly release CRH into the portal circulation. This is followed by ACTH release from the pituitary corticotropes peaking 5-15 min after acute challenge. The maximal corticosterone (CORT) response by the adrenals is seen between 15-30 min following the onset of acute stress. Meanwhile CREB is phosphorylated in the CRH neurons within 15 min after stress and CRH hnRNA became clearly detectable in the cell nuclei of parvocellular neurons at 5-30 min post stress (Kovacs & Sawchenko 1996b). CRH mRNA levels usually peak after 2 hours post stress and decline thereafter. ICER mRNA and protein appears between 1-3 hours post-stress that coincides with decline of CRH mRNA level and corticosterone secretion (Shepard et al 2005).

Glucocorticoid Negative Feedback on CRH in the PVH

One important factor that constrains basal and stress-induced activity of hypophyseotropic CRH expression is the glucocorticoid negative feedback. Glucocorticoid hormones have direct and indirect effects on CRH neurons. A critical amount of evidence suggests that CRH neurons in the

medial dorsal parvocellular subdivision of the PVH are directly sensitive to glucocorticoids (Bali et al 2008, Kovacs et al 1986, Kovacs et al 2000). Glucocorticoid receptor (GR) immunoreactivity is co-localized in CRH neurons (Uht et al 1988) and glucocorticoid implants in the PVH effectively decreased CRH mRNA levels and immunoreactivity in adrenalectomized (ADX) rats (Kovacs & Mezey 1987, Sawchenko 1987b). Furthermore, CRH transcription is reduced by glucocorticoid hormones in organotypic cultures of the PVH that lack extrahypothalamic connections (Bali et al 2008). Experiments on GR knockout mice revealed that neurosecretory CRH synthesis is tonically repressed by glucocorticoids even under basal (no stress) conditions (Kretz et al 1999). To further support the direct inhibitory effect on CRH gene, it has been recently shown that targeted disruption of GR signaling within the PVH results in upregulation of CRH mRNA levels (Jeanneteau et al 2012).

Within the neurosecretory neurons GRs may repress CRH transcription by a putative negative glucocorticoid response element (nGRE). Despite the significant inhibitory effect of various glucocorticoid receptor agonists on CRH mRNA levels, the regulatory region of the CRH gene itself does not seem to contain classical consensus GRE. However, Guardiola-Diaz *et al*. demonstrated several regions of high-affinity GR binding using rat GR DNA-binding domain in a DNase I protection assay (Guardiola-Diaz et al 1996). Indeed, other studies also confirmed a cis-acting regulatory element, located between −278 and −249 bp upstream of the transcription start site, which is important in glucocorticoid-mediated repression and to which GR binds with high affinity and specificity, indicating that GR directly inhibits CRH gene transcription. However, this region of the CRH promoter is a so called GR/AP-1 “composite site/ element” that may confer both stimulatory and inhibitory actions in a context dependent manner. This site is

required for corticosteroid inhibition of cAMP-induced CRH transcription (Malkoski & Dorin 1999, Malkoski et al 1997).

Furthermore, ligand-activated glucocorticoid receptor may interact with other transcription factors and modify their interaction with DNA. Such protein-protein interaction has been revealed between GR and AP-1, NGFI-B, CREB and NFkB transcription factors. This "cross-talk" does not require functional DNA binding domain of GR further suggesting indirect action of glucocorticoids. Corticosteroid suppression of CRH transcription in the parvocellular neurosecretory neurons might also be brought about by competition for transcriptional transactivators.

Additional inhibitory actions of corticosteroids might also be mediated indirectly through modification of intracellular signal transduction pathways via inhibition of MAP-kinases or c-Jun-N terminal kinase (JNK) (Lasa et al 2002, Yao & Denver 2007).

Finally, glucocorticoids affect the half life of CRH transcripts. For instance, adrenalectomy (ADX) decreases the rate of CRH mRNA degradation and corticosterone replacement decreases the half life of CRH mRNA in the rat paraventricular nucleus (Ma et al 2001).

One emerging transcription factor regulating CRH gene transcription in the parvocellular neurons is the NRSF, Neuron-Restrictive Silencing Transcription Factor, also known as RE1-Silencing Transcription factor (REST). REST is involved in the repression of neural genes in non-neuronal cells (Seth & Majzoub 2001). The intron of the CRH gene contains NRSE, and in vitro NRSF may confer repression as well as enhancement of CRH expression (Seth & Majzoub 2001). Recent findings revealed the role of NRSF in long-term repression of CRH gene in response to augmented maternal care (Korosi et al 2010).

One other important aspect of the negative feedback on HPA axis is the effect of glucocorticoids on limbic areas, which is mediated by local GABAergic inputs to the CRH neurons (Bali & Kovacs 2003, Cole & Sawchenko 2002, Cullinan et al 2008, Miklos & Kovacs 2002).

It should be noted, however, that CRH expression might be differentially regulated by glucocorticoids in the functionally distinct (ie. hypophyseotropic vs. autonomic projection) neurons of hypothalamic paraventricular nucleus. While ADX results in an increase of CRH mRNA and protein in all CRH expressing neurons, cells in the dorsal and ventral medial subdivisions seem to be more resistant to glucocorticoicd negative feedback than those, which project to the median eminence (Kovacs et al 1986) .

2. Regulation and Function of Central (Extrahypophyseotropic) CRH

Central CRH is upregulated during stress in most of the limbic and brainstem areas including those in the central amygdala, BNST and Barrington's nucleus. Studies on molecular mechanisms through which CRH is stimulated in these areas lag behind compared to that of PVH. It has been shown that psychosocial stress increases CRH mRNA levels in the CeA (Hsu et al 1998, Kalin et al 1994) and laterodorsal (oval) subnucleus of BNST (Makino et al 1999) and in the Barrington's nucleus (Wood et al 2009). Although CRH mRNA is elevated in both of CeA and BNST to most of physical and emotional challenges, interoceptive stressors such as opiate withdrawal results in a unique increase of CRH in the amygdala without affecting that of in the BNST (McNally & Akil 2002). In spite that several studies report on stress-induced elevation of CRH mRNA in brain CRH system, there are no reports on CRH hnRNA increases at these very same neuron population. Whether it is due to extreme low level of ongoing

transcription and/or to differences in mRNA stability needs further investigation. There is only one single study by now, which found increased CRH hnRNA in the extended amygdala following intracerebral kainate induced seizures (Foradori et al 2007).

Ipsilateral surgical section of ascending catecholaminergic pathways from the brainstem did not affect stress-induced CRH mRNA levels in the CeA, but significantly decreased CRH transcription in the PVH ipsilateral to the cut (Pacak et al 1996). These studies suggest that ascending brainstem pathways do not mediate stress-induced CRH increases in the amygdala.

A wealth of evidence documents the capacity of stress-induced corticosterone to stimulate CRH expression in several brain areas. Among these sites most prominent CORT effect was found in the central amygdala, CeA and the bed nucleus of the stria terminalis (BNST) (Makino et al 1994, Schulkin et al 1998, Watts & Sanchez-Watts 1995). It seems likely that excess glucocorticoids induce CRH gene expression in the CeA as well as in the dorsolateral (oval) nucleus of the BNST (Beyer et al 1988, Watts 2005). By contrast, CRH expression in the fusiform nucleus of BNST is not significantly dependent on corticosteroids (Watts 2005).

The mechanisms of the opposite corticosteroid action in the PVH vs. CeA on CRH transcription is not yet fully elucidated. Tissue specific differences in steroid receptor coactivators, such as SRC-1 might play a role in neuron-specific action of glucocortcoids on CRH transcription. SRC1a isoform is highly expressed in the PVH, while CeA is enriched with SRC1e that coincides with differential effect of corticosterone in these areas (Meijer et al 2000).

In contrast to the situation seen in neurosecretory neurons in the PVH, lack of corticosteroid hormones in the extended amygdala results in a decrease of CRH mRNA and immunoreactivity as revealed by experiments on adrenalectomized (ADX) animals. Most of the studies agree that

CRH mRNA and peptide levels in the CeA are decreased after ADX, however it seems likely that CRH expression in the BNST is less sensitive to the absence of glucocorticoid hormones (Kovacs et al 1986, Makino et al 1994, Santibanez et al 2005, Sawchenko 1987a, Watts 2005).

Previous work hypothesized the role of CeA in the regulation of HPA axis activity during stress. However, lesions of the CeA do not affect stress-induced CRH mRNA and c-Fos in the PVH and ACTH and CORT levels in stressed rats, rather, CeA is involved in long term modulation of basal HPA activity (Prewitt & Herman 1997). By contrast, lentiviral overexpression of CRH in the CeA amplified CRH and AVP expression in the PVH and impaired glucocortioid negative feedback on ACTH secretion (Keen-Rhinehart et al 2009).

CRH expression in the **neocortex** is also well established. CRH immunoreactive cell bodies are confined to layers II and III and show interneuronal morphology (Swanson et al 1983). These cells are abundant in limbic regions including prefrontal and cingulate areas. CRH neurons in the dentate gyrus and in the pyramidal cell layers CA1 and CA3, are parvalbumin positive GABAergic interneurons (Chen et al 2012, Yan et al 1998). In situ hybridization signals corresponding to CRH mRNA are increased in these areas by stressful stimuli and by local CRH administration (Givalois et al 2000). During stress, CRH is rapidly released in the synapses and facilitates hippocampus functions through postsynaptic type 1 corticotropin-releasing hormone receptor (CRH1R) (Chen et al 2004). CRH-induced acute activation of principal neurons contributes to synaptic plasticity and long-term potentiation (LTP), a cellular mechanism generally believed to underlie learning and memory. However, long lasting and repeated stressors reduce synaptic plasticity and impair memory together with overt morphological changes seen in dendritic morphology (Maras & Baram 2012). The corticosteroid dependence of

cortical CRH expression is much less studied. Scattered information is available suggesting that CORT does not affect CRH mRNA in the cortex (Frim et al 1990).

The pontine **Barrington's nucleus** harbors special population CRH positive neurons, which provide stress-related input to the lumbosacral parasympathetic neurons. Expression of CRH mRNA in these neurons is upregulated in response to stress (Wood et al 2009), but not to ADX (Imaki et al 1991). Increase of CRH in Barrington's nucleus by social stress has been linked to stress-induced bladder disfunction (Wood et al 2009, Wood et al 2013).

3. Life with excess CRH-41

Several transgenic mouse lines have been generated that help our understanding of the anatomy and physiology of the CRH system. For instance, CRH-gfp transgenic animals provide a tool for anatomical and electrophysiological studies on the CRH system (Alon et al 2009).

Vale's laboratory produced the first CRH overexpressing mice in which CRH gene was expressed under control of the metallothionein promoter. These animals display Cushing-like phenotype with increased ACTH and CORT secretion, hyperphagia, adult onset central obesity, increased adipose mass, thinned skin, osteoporosis and decreased muscle mass. (Stenzel-Poore et al 1992). Chronic CRH excess in these transgenic animals results in anxiety and hyperlocomotion (Coste et al 2001, Stenzel-Poore et al 1996).

Further on, CRH overexpressing mice were generated in which CRH gene is under the control of Thy-1 promoter and the transgene expression is limited to neural tissues (Dirks et al 2002). These animals do not have Cushing-like phenotype, however display chronic stress-like

neuroendocrine and autonomic changes, HPA axis abnormalities and their behavior is reminiscent to that of seen in depression (Groenink et al 2002).

In contrast, mice that express CRH transgene exclusively in the anterior and interior lobes of the pituitary have Cushing-like phenotype with elevated stress hormone levels, but do not display signs of emotional behavior (anxiety or depression) (Dedic et al 2012).

Conditional CNS restricted- (CRH-COE-Nes) and forebrain restricted (CRH-COE-CAM) overexpression of CRH have been achieved by Cre/Flox recombinase technology (Lu et al 2008). CRH overexpression in the entire central nervous system, but not when overexpressed in specific forebrain regions, resulted in stress-induced hypersecretion of stress hormones and active stress-coping behavior (reduced immobility in the forced swim test and tail suspension test)(Lu et al 2008) and increase in REM sleep (Kimura et al 2010).

Using a tetracycline-off system Muglia's laboratory produced mice with forebrain-restricted inducible expression of CRH. After transient elevation of central CRH during development only (from E0 to PN21), behavioral testing in adult mice revealed a persistent anxiogenic and despair-like phenotype (Kolber et al 2010).

To further specify central effects of CRH, unrestrained overproduction of the peptide by lentiviral constructs have been achieved in the central amygdala. These animals have increased CRH and AVP mRNA levels in the hypothalamic PVN and decreased glucocorticoid negative feedback similar to that seen in depression (Keen-Rhinehart et al 2009). Furthermore, they display increased acustic startle and passive stress coping behavior in forced swim test (Flandreau et al 2012, Keen-Rhinehart et al 2009).

4. Life without CRH – from paraventricular lesions to CRH-KO mice and lentiviral gene silencing

Surgical/electrical lesion of the hypothalamic paraventricular nucleus results in disappearance of CRH-ir material from the zona externa of the median eminence and attenuated hormonal response to wide range of stressors (Bruhn et al 1984, Makara & Kovacs 1997, Makara et al 1986). It is important to note that in spite of total lesion of the PVH, there is functional recovery of HPA axis and neuroendocrine stress response, 4-6 weeks after hypothalamic lesions (Makara et al 1986). These lesions affect all subdivisions of the PVH; lesioned animals are hyperphagic with increased uptake of carbohydrates (Shor-Posner et al 1985) have increased insulin levels (Sims & Lorden 1986) and develop central obesity. It has also been shown that large PVH lesions increase maternal aggressive behavior (Consiglio & Lucion 1996). Rats with more specific lesions placed to destroy only parvocellular neurons by ibotenic acid injections display less fear and an increase of exploratory behavior (Herman et al 1991).

CRH knockout mice have been generated in 1995 (Muglia et al 1995). CRH-KO pups born to homozygote mothers must have been supplemented by corticosterone from E12 until weaning to prevent pulmonary insufficiency. As expected, under basal conditions, CRH KO mice have blunted ACTH and CORT plasma levels. The requirement of CRH for ACTH release is further supported by the fact that plasma ACTH response to ADX is seen only if CRH is injected. In spite of low levels of circulating glucocorticoids, and elevated hypothalamic AVP levels, CRH KO mice have normal POMC expression in the corticotropes. CRH KO mice display stressor-specific heterogeneity of stress-induced pituitary-adrenocortical activation. Some stressors, such

as restraint and fasting require CRH secretion, while hypoglycemia and hemorrhage results in attenuated but significant ACTH and CORT responses in the absence of CRH (Jacobson et al 2000). In contrast, HPA responses to inflammatory and immune challenges do not require CRH drive (Muglia et al 2000).

To overcome developmental compensatory mechanisms and lack of spatial and temporal specificity in CRH KO animals, lentiviral vectors have been recently developed to silence CRH expression in site specific manner. Silencing of CRH gene exclusively in the central amygdala in adult mice attenuated stress-induced anxiety-like behaviors and increased basal CORT levels (Regev et al 2012).

5. The integrated stress response- view from CRH

CRH integrates many aspects of the stress response. Hypophyseotropic CRH initiates the neuroendocrine stress cascade, while central CRH triggers physiological and behavioral changes to prepare the organism for fight or flight meanwhile inhibits vegetative and reproductive functions and alters immunity.

Multisynaptic tracing of autonomic circuits often label cells within the forebrain (BNST, dorsal and ventral medial subdivisions of the PVH, lateral hypothalamic area, central amygdala) which do contain CRH immunoreactive neurons (Buijs et al 2001, Denes et al 2005, Strack et al 1989). These pre-autonomic neurons have been implicated in providing relevant sympathetic/parasympathetic outflow during stress. Central administration of CRH mimics cardiovascular, metabolic and even behavioral responses that are seen during stress. It has also

been shown that in most of the cases, CRH effect on the sympathetic activity is mediated by CRH1Rs.

During stress, central CRH stimulates LC neurons and results in elevated noradrenaline levels thereby increases **arousal** (Berridge & Waterhouse 2003, Valentino et al 1991). This is supported by the demonstration of synaptic contacts between CRH immunoreactive terminals and TH positive cells (Van Bockstaele et al 1996). LC receive CRH positive afferent fibers from the brainstem, Barrington nucleus, central amygdala and from the PVH (Valentino et al 1992, Van Bockstaele et al 2001, Van Bockstaele et al 1996, Van Bockstaele et al 1998). Within the LC, CRH acts directly through CRH1R and increases firing of TH positive neurons (Jedema & Grace 2004) and results in norepinephrine release in LC target areas. To further support the involvement of CRH in activation LC sympathetic outflow it has been shown that CRH microinjections into the LC mimics certain sympathetic autonomical, behavioral and immune responses to stressors (Baldwin et al 1991, Kubota et al 2012, Monnikes et al 1996).

Central CRH delivery elevates heart rate and blood pressure while decreases heart rate variability (Arlt et al 2003), similar to that seen under stress or in CRH overexpressing mice (Dirks et al 2002). LC also plays a pivotal role in translation of stress challenges to bodily **cardiovascular responses**. However different stressors recruit different CRH pathways projecting to LC. For instance, during hypotensive stress CeA as a primary source of LC-activating CRH (Curtis et al 2002, Valentino et al 1991). Intra-BNST CRH system has also been implicated in coordination of stress-associated cardiovascular changes. CRH injected intracerebroventricular (icv). or directly into the BNST resulted in tachycardiac response, which was prevented either by β-adrenergic blockers or by CRH1R antagonists (Nijsen et al 2000). On the other hand, CRH,

released in the medial BNST during conditioned fear stress, contributes to cardiac stress responses, particularly by activating vagal outflow (Nijsen et al 2001).

Stress-induced endogenous-, or centrally injected CRH and related peptides affect several aspects of **food intake and energy metabolism** (Kuperman & Chen 2008). It is generally acknowledged that icv administration of CRH-41 significantly reduces food intake while its effect on metabolism is mediated through activation of sympathetic nervous system (SNS) outflow and increased thermogenesis (Rothwell 1990, Spina et al 1996). Based on studies using a non-selective CRH antagonist it has been suggested that appetite reducing effect of emotional stress is conferred by CRH1R (Hotta et al 1999). On contrary, CRH was able to decrease food intake in CRH1R knockout mice as much as in wild type littermates. Finally it is concluded that both CRH and urocortins attenuate food intake via CRH1R and type 2 corticotropin-releasing hormone receptor (CRH2R) however, with different time course (Sekino et al 2004).

CRH, released during stress, also affects **nutrient selection** (Heinrichs & Koob 1992). For instance, rodents prefer "comfort" food, rich in fat and carbohydrates when chronically stressed (Dallman et al 2003, Pecoraro et al 2004, Teegarden & Bale 2008). Ingestion of highly palatable food reduces the activity of the central stress response network, including CRH expression in the CeA, attenuates autonomic outflow and therefore represents a "self-treating" mechanism with which to reduce adverse effects of chronic stress (Dallman et al 2005). Further on, withdrawal from palatable food recruits anti-reward CRH –CRH1R in the extended amygdala that may be responsible for compulsive behavior and binge eating (Cottone et al 2009).

CRH is a mediator of leptin's anorectic effect via activation of sympathetic outflow (Costa et al 1997). Indeed, central infusion of the peptide has been repeatedly shown to increase sympathetic

activity, brown adipose tissue (BAT) UCP-1 expression and **thermogenesis**, lipolysis, which are independent from the hyperlocomotive behavioral response (Egawa et al 1990). Central CRH and increased sympathetic activity in BAT during stress is likely be involved in the stress-induced hyperthermia (Vinkers et al 2009). Stress-induced changes in body temperature are likely be mediated through central pathways including the preoptic area, the paraventricular and dorsomedial nuclei, rostral ventromedial medulla and target neurons in the intermediolateral cell column at the thoracic spinal cord (Morrison et al 2012).

Various external and internal stress challenges inhibit **reproduction** and reproductive behavior in both sexes, which is mediated partially by CRH and CRH-related peptides (Miwa et al 2011, Petraglia et al 1987, Rivier & Rivest 1991). Stress and stress-induced CRH delay puberty, while non-selective CRHR antagonist astressin B advances vaginal opening in females (Kinsey-Jones et al 2010). Although previous in vitro experiments suggested direct action of CRH through CRH2R on GnRH cell line GT1-7 (Kinsey-Jones et al 2006), more recent studies identified the GnRH pulse generator as the major potential target of stress-induced suppression of reproductive functions . To add the complexity, the inhibitory action of stress on the pulse generator is stressor dependent and mediated differentially through CRH1R and/or CRH2Rs (Li et al 2006). In fact, stress significantly attenuates expression kisspeptin and kisspeptin receptor Gpr54 in the hypothalamus, which are critical components of the GnRH pulse generator in the arcuate nucleus (Kinsey-Jones et al 2009, Li et al 2009). Recently, it has been shown that medial and central nuclei of the amygdala and the BNST as key mediators of the stress response are recruited in stressor-specific manner to inhibit LH pulses (Lin et al 2011). Specifically, the BNST CRH system activates hypothalamic GABAergic interneurons that may pose inhibition onto GnRH neurocircuit (Li et al 2011).

CRH acts as a neurotransmitter/neuromodulator in stress-associated limbic regions to propagate and integrate stress-induced **behaviors**. It has been shown shortly after it's discovery that intracerebroventricular infusion of CRH-41 reproduces many behaviors seen in during stress (Sutton et al 1982). Pharmacological studies, using CRH antagonists underscore the role of central CRH in mediating stress-related behaviors (Kalin et al 1988, Skelton et al 2007). Furthermore, CRH overexpressing mice also display a behavioral phenotype seen in stressed animals including increased anxiety (Kasahara et al 2007, Stenzel-Poore et al 1996). CRH increases locomotion in a familiar surroundings, decreases exploration in novel environment, induces grooming, burrowing, self-gnawing and decreases rearing and sleeping (Sherman & Kalin 1986), however does not affect analgesia. Some of these behaviors (grooming and exploration) can be initiated by CRH microinjections into the amygdala under resting conditions (Wiersma et al 1995). Interestingly, mice lacking the CRH gene exhibit normal stress-induced behavior that is specifically blocked by a CRH type 1 receptor antagonist, suggesting involvement of another endogenous CRH1R ligand such as urocortin (Weninger et al 1999).

The role of the extended amygdala in **fear and anxiety** is well established (Davis 1992, Davis et al 1994, Lee & Davis 1997, Merali et al 2003, Schulkin et al 1998). It has been shown that infusion of CRH into the BNST and amygdala provokes number of fear-related behavioral responses in a CRH1R receptor dependent manner (Lee & Davis 1997, Shepard et al 2000). Stress-induced CORT increases CRH in the amygdala and BNST and results in anxiety in rats (Shepard et al 2000, Shepard et al 2009). CeA projections to the periaqueductal gray are responsible for freezing (LeDoux 1995), while efferents to the nucleus reticularis pontis caudalis facilitate startle response to stress (Lee & Davis 1997, Rosen et al 1991). Chronic CORT

treatment elevates CRH mRNA in the CeA, increases fear, enhance learning and memory consolidation, however, does not potentiate innate fear responses (Rosen et al 2008).

CRH affects **stress coping strategy**. Mice displaying active coping in social interaction have significantly higher hypothalamic levels of CRH mRNA than passive mice (De Miguel et al 2011).

Acute and chronic stress exposure significantly modulates **immune defense** system. Although stress-released glucocorticoids are the best characterized players that mediate neuro-immune interaction, central CRH is also involved in brain-to-immune signaling via stimulation of the sympathetic outflow to the lymphoid organs (Elenkov et al 2000, Irwin et al 1992, Tsagarakis & Grossman 1994). Spleen, thymus and bone marrow receive extensive sympathetic/noradrenergic innervation (Denes et al 2005, Williams et al 1981) that is modulated by central CRH. Lymphoid tissues express relevant adrenoreceptors through which sympathetic nervous system affects lymphocyte traffic proliferation, and modulate Th1-proinflammatory/Th2 –anti-inflammatory cytokine balance (Elenkov & Chrousos 1999, Hauger et al 1993). Thus, the activation of SNS during an immune response might be aimed to localize the inflammatory response, through induction of neutrophil accumulation and stimulation of more specific humoral immune responses, although systemically it may suppress Th1 responses, and, thus protect the organism from the detrimental effects of proinflammatory cytokines and other products of activated macrophages (Elenkov & Chrousos 2002).

Conclusion

A wealth of knowledge has been accumulated since Wylie Vale's discovery of corticotropin-releasing hormone, CRH-41. CRH is widely distributed throughout the central nervous system and it is intriguing to note that most of CRH expressing sites are somehow related the central stress regulation. CRH, synthesized by the parvocellular neurosecretory neurons, acts as a neurohormone to initiate the neuroendocrine stress response, while CRH expressed in the extended amygdala, in the cortex and hippocampus is related to many vegetative and behavioral aspects of stress (Figure 1). Much is already known about stress-related neurotransmitters and intracellular signal transduction pathways that converge upon the regulatory regions of the CRH gene. However the network of transcription factors and coregulators that may mediate differential expression and corticosteroid regulation of CRH gene at different brain sites remains to be discovered.

Table 1. Site Specific Regulation of CRH Expression in the Brain

site	ADX	Stress	CORT	References
PVH mpd (hypophyseotropic)	↑	↑	↓	(Herman et al 1992, Kovacs & Mezey 1987, Kovacs & Sawchenko 1996b, Ma et al 1997, Swanson & Simmons 1989, Watts et al 2004)
PVH dp, mpv, lp (autonomic)	↑	↑	±↓/↑	(Swanson & Simmons 1989)
CeA	↓	↑	↑	(Hsu et al 1998, Kalin et al 1994, Makino et al 1994, Makino et al 1999, Shepard et al 2000, Watts & Sanchez-Watts 1995)
BNST oval	↓	↑	↑	(Makino et al 1994, Santibanez et al 2005, Watts 1996)
Barrington's nucl.	No change/↓	↑	No change	(Imaki et al 1991)
Cortex	↑	↑	↑(release)	(Merali et al 2008)
Olfactory bulb	?	↓	?	(Imaki et al 1991, Imaki et al 1989)

Acknowledgement:

I thank to Ágnes Polyák for graphical help and to Drs Szilamér Ferenczi and Éva Mikics for reading the proof.

References

Alon T, Zhou L, Perez CA, Garfield AS, Friedman JM, Heisler LK. 2009. Transgenic mice expressing green fluorescent protein under the control of the corticotropin-releasing hormone promoter. *Endocrinology* 150: 5626-32

Arlt J, Jahn H, Kellner M, Strohle A, Yassouridis A, Wiedemann K. 2003. Modulation of sympathetic activity by corticotropin-releasing hormone and atrial natriuretic peptide. *Neuropeptides* 37: 362-8

Baldwin HA, Rassnick S, Rivier J, Koob GF, Britton KT. 1991. CRF antagonist reverses the "anxiogenic" response to ethanol withdrawal in the rat. *Psychopharmacology* 103: 227-32

Bali B, Ferenczi S, Kovacs KJ. 2008. Direct inhibitory effect of glucocorticoids on corticotrophin-releasing hormone gene expression in neurones of the paraventricular nucleus in rat hypothalamic organotypic cultures. *J Neuroendocrinol* 20: 1045-51

Bali B, Kovacs KJ. 2003. GABAergic control of neuropeptide gene expression in parvocellular neurons of the hypothalamic paraventricular nucleus. *Eur J Neurosci*18: 1518-26

Berridge CW, Waterhouse BD. 2003. The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. *Brain Res Rev* 42: 33-84

Beyer HS, Matta SG, Sharp BM. 1988. Regulation of the messenger ribonucleic acid for corticotropin-releasing factor in the paraventricular nucleus and other brain sites of the rat. *Endocrinology* 123: 2117-23

Bruhn TO, Plotsky PM, Vale WW. 1984. Effect of paraventricular lesions on corticotropin-releasing factor (CRF)-like immunoreactivity in the stalk-median eminence: studies on the adrenocorticotropin response to ether stress and exogenous CRF. *Endocrinology* 114: 57-62

Buijs RM, Chun SJ, Niijima A, Romijn HJ, Nagai K. 2001. Parasympathetic and sympathetic control of the pancreas: a role for the suprachiasmatic nucleus and other hypothalamic centers that are involved in the regulation of food intake. *J Comp Neurol* 431: 405-23

Chen Y, Andres AL, Frotscher M, Baram TZ. 2012. Tuning synaptic transmission in the hippocampus by stress: the CRH system. *Front Cell Neurosci* 6: 13

Chen Y, Brunson KL, Adelmann G, Bender RA, Frotscher M, Baram TZ. 2004. Hippocampal corticotropin releasing hormone: pre- and postsynaptic location and release by stress. *Neuroscience* 126: 533-40

Cole RL, Sawchenko PE. 2002. Neurotransmitter regulation of cellular activation and neuropeptide gene expression in the paraventricular nucleus of the hypothalamus. *J Neurosci* 22: 959-69.

Consiglio AR, Lucion AB. 1996. Lesion of hypothalamic paraventricular nucleus and maternal aggressive behavior in female rats. *Physiol & Behavior* 59: 591-6

Costa A, Poma A, Martignoni E, Nappi G, Ur E, Grossman A. 1997. Stimulation of corticotrophin-releasing hormone release by the obese (ob) gene product, leptin, from hypothalamic explants. *Neuroreport* 8: 1131-4

Coste SC, Murray SE, Stenzel-Poore MP. 2001. Animal models of CRH excess and CRH receptor deficiency display altered adaptations to stress. *Peptides* 22: 733-41

Cottone P, Sabino V, Roberto M, Bajo M, Pockros L, et al. 2009. CRF system recruitment mediates dark side of compulsive eating. *Proc Nat Acad Sci USA* 106: 20016-20

Cullinan WE, Ziegler DR, Herman JP. 2008. Functional role of local GABAergic influences on the HPA axis. *Brain Struct Funct* 213: 63-72

Curtis AL, Bello NT, Connolly KR, Valentino RJ. 2002. Corticotropin-releasing factor neurones of the central nucleus of the amygdala mediate locus coeruleus activation by cardiovascular stress. *J Neuroendocrinol* 14: 667-82

Dallman MF, Pecoraro N, Akana SF, La Fleur SE, Gomez F, et al. 2003. Chronic stress and obesity: a new view of "comfort food". *Proc Nat Acad Sci USA* 100: 11696-701

Dallman MF, Pecoraro NC, la Fleur SE. 2005. Chronic stress and comfort foods: self-medication and abdominal obesity. *Brain Behav Immun*19: 275-80

Davis M. 1992. The role of the amygdala in fear and anxiety. *Annu Rev Neurosci* 15: 353-75

Davis M, Rainnie D, Cassell M. 1994. Neurotransmission in the rat amygdala related to fear and anxiety. *TINS* 17: 208-14

Day HE, Campeau S, Watson SJ, Jr., Akil H. 1999. Expression of alpha(1b) adrenoceptor mRNA in corticotropin-releasing hormone-containing cells of the rat hypothalamus and its regulation by corticosterone. *J Neurosci* 19: 10098-106.

De Miguel Z, Vegas O, Garmendia L, Arregi A, Beitia G, Azpiroz A. 2011. Behavioral coping strategies in response to social stress are associated with distinct neuroendocrine, monoaminergic and immune response profiles in mice. *Behav Brain Res* 225: 554-61

Dedic N, Touma C, Romanowski CP, Schieven M, Kuhne C, et al. 2012. Assessing behavioural effects of chronic HPA axis activation using conditional CRH-overexpressing mice. *Cell Mol Neurobiol* 32: 815-28

Denes A, Boldogkoi Z, Uhereczky G, Hornyak A, Rusvai M, et al. 2005. Central autonomic control of the bone marrow: multisynaptic tract tracing by recombinant pseudorabies virus. *Neuroscience* 134: 947-63

Dirks A, Groenink L, Bouwknecht JA, Hijzen TH, Van Der Gugten J, et al. 2002. Overexpression of corticotropin-releasing hormone in transgenic mice and chronic stress-like autonomic and physiological alterations. *Eur J Neurosci*16: 1751-60

Egawa M, Yoshimatsu H, Bray GA. 1990. Preoptic area injection of corticotropin-releasing hormone stimulates sympathetic activity. *Am J Physiol* 259: R799-806

Elenkov IJ, Chrousos GP. 1999. Stress Hormones, Th1/Th2 patterns, Pro/Anti-inflammatory Cytokines and Susceptibility to Disease. *TEM* 10: 359-68.

Elenkov IJ, Chrousos GP. 2002. Stress hormones, proinflammatory and antiinflammatory cytokines, and autoimmunity. *Ann NY Acad Sci* 966: 290-303.

Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. 2000. The sympathetic nerve--an integrative interface between two supersystems: the brain and the immune system. *Pharmacol Rev* 52: 595-638.

Flandreau EI, Ressler KJ, Owens MJ, Nemeroff CB. 2012. Chronic overexpression of corticotropin-releasing factor from the central amygdala produces HPA axis hyperactivity and behavioral anxiety associated with gene-expression changes in the hippocampus and paraventricular nucleus of the hypothalamus. *Psychoneuroendocrinol* 37: 27-38

Foradori CD, Lund TD, Nagahara AH, Koenig JI, Handa RJ. 2007. Corticotropin-releasing hormone heterogeneous nuclear RNA (hnRNA) and immunoreactivity are induced in extrahypothalamic brain sites by kainic-acid-induced seizures and are modulated by estrogen. *Brain Res* 1164: 44-54

Frim DM, Robinson BG, Pasieka KB, Majzoub JA. 1990. Differential regulation of corticotropin-releasing hormone mRNA in rat brain. *Am J Physiol*258: E686-92

Gafford GM, Guo JD, Flandreau EI, Hazra R, Rainnie DG, Ressler KJ. 2012. Cell-type specific deletion of GABA(A)alpha1 in corticotropin-releasing factor-containing neurons enhances anxiety and disrupts fear extinction. *Proc Nat Acad Sci USA* 109: 16330-5

Gibbs DM, Vale W. 1982. Presence of corticotropin releasing factor-like immunoreactivity in hypophysial portal blood. *Endocrinology* 111: 1418-20

Givalois L, Arancibia S, Tapia-Arancibia L. 2000. Concomitant changes in CRH mRNA levels in rat hippocampus and hypothalamus following immobilization stress. *Brain Res. Mol Brain Res* 75: 166-71

Groenink L, Dirks A, Verdouw PM, Schipholt M, Veening JG, et al. 2002. HPA axis dysregulation in mice overexpressing corticotropin releasing hormone. *Biol Psychiatry* 51: 875-81

Guardiola-Diaz HM, Kolinske JS, Gates LH, Seasholtz AF. 1996. Negative glucorticoid regulation of cyclic adenosine 3', 5'-monophosphate-stimulated corticotropin-releasing hormone-reporter expression in AtT-20 cells. *Mol Endocrinol* 10: 317-29

Hauger RL, Irwin MR, Lorang M, Aguilera G, Brown MR. 1993. High intracerebral levels of CRH result in CRH receptor downregulation in the amygdala and neuroimmune desensitization. *Brain Res* 616: 283-92

Heinrichs SC, Koob GF. 1992. Corticotropin-releasing factor modulates dietary preference in nutritionally and physically stressed rats. *Psychopharmacology* 109: 177-84

Herman JP, Cullinan WE, Ziegler DR, Tasker JG. 2002. Role of the paraventricular nucleus microenvironment in stress integration. *Eur J Neurosci* 16: 381-5.

Herman JP, Ostrander MM, Mueller NK, Figueiredo H. 2005. Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. *Prog Neuro-Psychopharmacol Biol Psychiat* 29: 1201-13

Herman JP, Schafer MK, Thompson RC, Watson SJ. 1992. Rapid regulation of corticotropin-releasing hormone gene transcription in vivo. *Mol Endocrinol* 6: 1061-9.

Herman JP, Thomas GJ, Wiegand SJ, Gash DM. 1991. Lesions of parvocellular subdivisions of the hypothalamic paraventricular nucleus alter open field behavior and acquisition of sensory and spatial discrimination. *Brain Res* 550: 291-7

Hotta M, Shibasaki T, Arai K, Demura H. 1999. Corticotropin-releasing factor receptor type 1 mediates emotional stress-induced inhibition of food intake and behavioral changes in rats. *Brain Res* 823: 221-5

Hsu DT, Chen FL, Takahashi LK, Kalin NH. 1998. Rapid stress-induced elevations in corticotropin-releasing hormone mRNA in rat central amygdala nucleus and hypothalamic paraventricular nucleus: an in situ hybridization analysis. *Brain Res* 788: 305-10

Imaki T, Nahan JL, Rivier C, Sawchenko PE, Vale W. 1991. Differential regulation of corticotropin-releasing factor mRNA in rat brain regions by glucocorticoids and stress. *J Neurosci* 11: 585-99.

Imaki T, Nahon JL, Sawchenko PE, Vale W. 1989. Widespread expression of corticotropin-releasing factor messenger RNA and immunoreactivity in the rat olfactory bulb. *Brain Res* 496: 35-44.

Imaki T, Xiao-Quan W, Shibasaki T, Yamada K, Harada S, et al. 1995. Stress-induced activation of neuronal activity and corticotropin- releasing factor gene expression in the paraventricular nucleus is modulated by glucocorticoids in rats. *J Clin Invest* 96: 231-8.

Irwin M, Hauger R, Brown M. 1992. Central corticotropin-releasing hormone activates the sympathetic nervous system and reduces immune function: increased responsivity of the aged rat. *Endocrinology* 131: 1047-53

Itoi K, Helmreich DL, Lopez-Figueroa MO, Watson SJ. 1999. Differential regulation of corticotropin-releasing hormone and vasopressin gene transcription in the hypothalamus by norepinephrine. *J Neurosci* 19: 5464-72.

Jacobson L, Muglia LJ, Weninger SC, Pacak K, Majzoub JA. 2000. CRH deficiency impairs but does not block pituitary-adrenal responses to diverse stressors. *Neuroendocrinology* 71: 79-87

Jeanneteau FD, Lambert WM, Ismaili N, Bath KG, Lee FS, et al. 2012. BDNF and glucocorticoids regulate corticotrophin-releasing hormone (CRH) homeostasis in the hypothalamus. *Proc Nat Acad Sci USA* 109: 1305-10

Jedema HP, Grace AA. 2004. Corticotropin-releasing hormone directly activates noradrenergic neurons of the locus ceruleus recorded in vitro. *J Neurosci* 24: 9703-13

Kalin NH, Sherman JE, Takahashi LK. 1988. Antagonism of endogenous CRH systems attenuates stress-induced freezing behavior in rats. *Brain Res* 457: 130-5

Kalin NH, Takahashi LK, Chen FL. 1994. Restraint stress increases corticotropin-releasing hormone mRNA content in the amygdala and paraventricular nucleus. *Brain Res* 656: 182-6.

Kasahara M, Groenink L, Breuer M, Olivier B, Sarnyai Z. 2007. Altered behavioural adaptation in mice with neural corticotrophin-releasing factor overexpression. *Genes, brain, and behavior* 6: 598-607

Keen-Rhinehart E, Michopoulos V, Toufexis DJ, Martin EI, Nair H, et al. 2009. Continuous expression of corticotropin-releasing factor in the central nucleus of the amygdala emulates the dysregulation of the stress and reproductive axes. *Mol Psychiatry* 14: 37-50

Khan AM, Kaminski KL, Sanchez-Watts G, Ponzio TA, Kuzmiski JB, et al. 2011. MAP kinases couple hindbrain-derived catecholamine signals to hypothalamic adrenocortical control mechanisms during glycemia-related challenges. *J Neurosci* 31: 18479-91

Khan AM, Ponzio TA, Sanchez-Watts G, Stanley BG, Hatton GI, Watts AG. 2007. Catecholaminergic control of mitogen-activated protein kinase signaling in paraventricular neuroendocrine neurons in vivo and in vitro: a proposed role during glycemic challenges. *J Neurosci* 27: 7344-60

Kimura M, Muller-Preuss P, Lu A, Wiesner E, Flachskamm C, et al. 2010. Conditional corticotropin-releasing hormone overexpression in the mouse forebrain enhances rapid eye movement sleep. *Mol Psychiatry* 15: 154-65

Kinsey-Jones JS, Li XF, Bowe JE, Lightman SL, O'Byrne KT. 2006. Corticotrophin-releasing factor type 2 receptor-mediated suppression of gonadotrophin-releasing hormone mRNA expression in GT1-7 cells. *Stress* 9: 215-22

Kinsey-Jones JS, Li XF, Knox AM, Lin YS, Milligan SR, et al. 2010. Corticotrophin-releasing factor alters the timing of puberty in the female rat. *J Neuroendocrinol* 22: 102-9

Kinsey-Jones JS, Li XF, Knox AM, Wilkinson ES, Zhu XL, et al. 2009. Down-regulation of hypothalamic kisspeptin and its receptor, Kiss1r, mRNA expression is associated with stress-induced suppression of luteinising hormone secretion in the female rat. *J Neuroendocrinol* 21: 20-9

Kolber BJ, Boyle MP, Wieczorek L, Kelley CL, Onwuzurike CC, et al. 2010. Transient early-life forebrain corticotropin-releasing hormone elevation causes long-lasting anxiogenic and despair-like changes in mice. *J Neurosci* 30: 2571-81

Korosi A, Shanabrough M, McClelland S, Liu ZW, Borok E, et al. 2010. Early-life experience reduces excitation to stress-responsive hypothalamic neurons and reprograms the expression of corticotropin-releasing hormone. *J Neurosci* 30: 703-13

Kovacs K, Kiss JZ, Makara GB. 1986. Glucocorticoid implants around the hypothalamic paraventricular nucleus prevent the increase of corticotropin-releasing factor and arginine vasopressin immunostaining induced by adrenalectomy. *Neuroendocrinology* 44: 229-34

Kovacs KJ, Foldes A, Sawchenko PE. 2000. Glucocorticoid negative feedback selectively targets vasopressin transcription in parvocellular neurosecretory neurons. *J Neurosci* 20: 3843-52.

Kovacs KJ, Mezey E. 1987. Dexamethasone inhibits corticotropin-releasing factor gene expression in the rat paraventricular nucleus. *Neuroendocrinology* 46: 365-8.

Kovacs KJ, Sawchenko PE. 1996a. Regulation of stress-induced transcriptional changes in the hypothalamic neurosecretory neurons. *J Mol Neurosci* 7: 125-33.

Kovacs KJ, Sawchenko PE. 1996b. Sequence of stress-induced alterations in indices of synaptic and transcriptional activation in parvocellular neurosecretory neurons. *J Neurosci* 16: 262-73.

Kretz O, Reichardt HM, Schutz G, Bock R. 1999. Corticotropin-releasing hormone expression is the major target for glucocorticoid feedback-control at the hypothalamic level. *Brain Res* 818: 488-91

Kubota N, Amemiya S, Motoki C, Otsuka T, Nishijima T, Kita I. 2012. Corticotropin-releasing factor antagonist reduces activation of noradrenalin and serotonin neurons in the locus coeruleus and dorsal raphe in the arousal response accompanied by yawning behavior in rats. *Neurosci Res* 72: 316-23

Kuperman Y, Chen A. 2008. Urocortins: emerging metabolic and energy homeostasis perspectives. *TEM* 19: 122-9

Lasa M, Abraham SM, Boucheron C, Saklatvala J, Clark AR. 2002. Dexamethasone causes sustained expression of mitogen-activated protein kinase (MAPK) phosphatase 1 and phosphatase-mediated inhibition of MAPK p38. *Mol Cellular Biol* 22: 7802-11

Lee Y, Davis M. 1997. Role of the hippocampus, the bed nucleus of the stria terminalis, and the amygdala in the excitatory effect of corticotropin-releasing hormone on the acoustic startle reflex. *J Neurosci* 17: 6434-46

Lennard DE, Eckert WA, Merchenthaler I. 1993. Corticotropin-releasing hormone neurons in the paraventricular nucleus project to the external zone of the median eminence: a study combining retrograde labeling with immunocytochemistry. *J Neuroendocrinol* 5: 175-81.

Li XF, Bowe JE, Kinsey-Jones JS, Brain SD, Lightman SL, O'Byrne KT. 2006. Differential role of corticotrophin-releasing factor receptor types 1 and 2 in stress-induced suppression of pulsatile luteinising hormone secretion in the female rat. *J Neuroendocrinol* 18: 602-10

Li XF, Kinsey-Jones JS, Cheng Y, Knox AM, Lin Y, et al. 2009. Kisspeptin signalling in the hypothalamic arcuate nucleus regulates GnRH pulse generator frequency in the rat. *PloS one* 4: e8334

Li XF, Lin YS, Kinsey-Jones JS, Milligan SR, Lightman SL, O'Byrne KT. 2011. The role of the bed nucleus of the stria terminalis in stress-induced inhibition of pulsatile luteinising hormone secretion in the female rat. *J Neuroendocrinol* 23: 3-11

Lightman SL, Young WS, 3rd. 1988. Corticotrophin-releasing factor, vasopressin and pro-opiomelanocortin mRNA responses to stress and opiates in the rat. *J Physiology* 403: 511-23.

Lin Y, Li X, Lupi M, Kinsey-Jones JS, Shao B, et al. 2011. The role of the medial and central amygdala in stress-induced suppression of pulsatile LH secretion in female rats. *Endocrinology* 152: 545-55

Liposits Z, Phelix C, Paull WK. 1986. Electron microscopic analysis of tyrosine hydroxylase, dopamine-beta-hydroxylase and phenylethanolamine-N-methyltransferase immunoreactive innervation of the hypothalamic paraventricular nucleus in the rat. *Histochemistry* 84: 105-20

Liposits Z, Phelix C, Paull WK. 1987. Synaptic interaction of serotonergic axons and corticotropin releasing factor (CRF) synthesizing neurons in the hypothalamic paraventricular nucleus of the rat. A light and electron microscopic immunocytochemical study. *Histochemistry* 86: 541-9

Liu Y, Coello AG, Grinevich V, Aguilera G. 2010. Involvement of transducer of regulated cAMP response element-binding protein activity on corticotropin releasing hormone transcription. *Endocrinology* 151: 1109-18

Lu A, Steiner MA, Whittle N, Vogl AM, Walser SM, et al. 2008. Conditional mouse mutants highlight mechanisms of corticotropin-releasing hormone effects on stress-coping behavior. *Mol Psychiatry* 13: 1028-42

Ma XM, Camacho C, Aguilera G. 2001. Regulation of corticotropin-releasing hormone (CRH) transcription and CRH mRNA stability by glucocorticoids. *Cell Mol Neurobiol* 21: 465-75

Ma XM, Levy A, Lightman SL. 1997. Rapid changes in heteronuclear RNA for corticotrophin-releasing hormone and arginine vasopressin in response to acute stress. *J Endocrinology* 152: 81-9.

Majzoub JA, Emanuel R, Adler G, Martinez C, Robinson B, Wittert G. 1993. Second messenger regulation of mRNA for corticotropin-releasing factor. *Ciba Found Symp* 172: 30-43

Makara GB, Kovacs KJ. 1997. Lesioning of the hypothalamic paraventricular nucleus inhibits ether-induced ACTH but not prolactin release. *Neurobiology* 5: 403-11

Makara GB, Stark E, Kapocs G, Antoni FA. 1986. Long-term effects of hypothalamic paraventricular lesion on CRF content and stimulated ACTH secretion. *Am J Physiol* 250: E319-24

Makino S, Gold PW, Schulkin J. 1994. Effects of corticosterone on CRH mRNA and content in the bed nucleus of the stria terminalis; comparison with the effects in the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus. *Brain Res* 657: 141-9

Makino S, Shibasaki T, Yamauchi N, Nishioka T, Mimoto T, et al. 1999. Psychological stress increased corticotropin-releasing hormone mRNA and content in the central nucleus of the amygdala but not in the hypothalamic paraventricular nucleus in the rat. *Brain Res* 850: 136-43

Makino S, Smith MA, Gold PW. 1995. Increased expression of corticotropin-releasing hormone and vasopressin messenger ribonucleic acid (mRNA) in the hypothalamic paraventricular nucleus during repeated stress: association with reduction in glucocorticoid receptor mRNA levels. *Endocrinology* 136: 3299-309.

Malkoski SP, Dorin RI. 1999. Composite glucocorticoid regulation at a functionally defined negative glucocorticoid response element of the human corticotropin-releasing hormone gene. *Mol Endocrinology* 13: 1629-44

Malkoski SP, Handanos CM, Dorin RI. 1997. Localization of a negative glucocorticoid response element of the human corticotropin releasing hormone gene. *Mol Cell Endocrinol* 127: 189-99

Maras PM, Baram TZ. 2012. Sculpting the hippocampus from within: stress, spines, and CRH. *TINS* 35: 315-24

Martin F, Nunez C, Marin MT, Laorden ML, Kovacs KJ, Milanes MV. 2012. Involvement of noradrenergic transmission in the PVN on CREB activation, TORC1 levels, and pituitary-adrenal axis activity during morphine withdrawal. *PloS one* 7: e31119

McNally GP, Akil H. 2002. Role of corticotropin-releasing hormone in the amygdala and bed nucleus of the stria terminalis in the behavioral, pain modulatory, and endocrine consequences of opiate withdrawal. *Neuroscience* 112: 605-17

Meijer OC, Steenbergen PJ, De Kloet ER. 2000. Differential expression and regional distribution of steroid receptor coactivators SRC-1 and SRC-2 in brain and pituitary. *Endocrinology* 141: 2192-9

Merali Z, Anisman H, James JS, Kent P, Schulkin J. 2008. Effects of corticosterone on corticotrophin-releasing hormone and gastrin-releasing peptide release in response to an aversive stimulus in two regions of the forebrain (central nucleus of the amygdala and prefrontal cortex). *Eur J Neurosci* 28: 165-72

Merali Z, Michaud D, McIntosh J, Kent P, Anisman H. 2003. Differential involvement of amygdaloid CRH system(s) in the salience and valence of the stimuli. *Prog Neuro-Psychopharmacol Biol Psychiatry* 27: 1201-12

Merchenthaler I. 1984. Corticotropin releasing factor (CRF)-like immunoreactivity in the rat central nervous system. Extrahypothalamic distribution. *Peptides* 5 Suppl 1: 53-69

Merchenthaler I, Hynes MA, Vigh S, Schally AV, Petrusz P. 1984. Corticotropin releasing factor (CRF): origin and course of afferent pathways to the median eminence (ME) of the rat hypothalamus. *Neuroendocrinology* 39: 296-306.

Miklos IH, Kovacs KJ. 2002. GABAergic innervation of corticotropin-releasing hormone (CRH)-secreting parvocellular neurons and its plasticity as demonstrated by quantitative immunoelectron microscopy. *Neuroscience* 113: 581-92

Miwa Y, Nagase K, Oyama N, Akino H, Yokoyama O. 2011. Effect of corticotropin-releasing factor receptor antagonist on psychologically suppressed masculine sexual behavior in rats. *J Sex Med* 8: 688-95

Monnikes H, Tebbe J, Bauer C, Lauer G, Arnold R. 1996. Microinfusion of corticotropin-releasing factor into the locus coeruleus/subcoeruleus nuclei inhibits gastric acid secretion via spinal pathways in the rat. *Brain Res* 728: 157-65

Montminy MR, Gonzalez GA, Yamamoto KK. 1990. Regulation of cAMP-inducible genes by CREB. *TINS* 13: 184-8

Morrison SF, Madden CJ, Tupone D. 2012. Central control of brown adipose tissue thermogenesis. *Fronti Endocrinology* 3

Muglia L, Jacobson L, Dikkes P, Majzoub JA. 1995. Corticotropin-releasing hormone deficiency reveals major fetal but not adult glucocorticoid need. *Nature* 373: 427-32

Muglia LJ, Bethin KE, Jacobson L, Vogt SK, Majzoub JA. 2000. Pituitary-adrenal axis regulation in CRH-deficient mice. *Endocr Res* 26: 1057-66

Nijsen MJ, Croiset G, Diamant M, De Wied D, Wiegant VM. 2001. CRH signalling in the bed nucleus of the stria terminalis is involved in stress-induced cardiac vagal activation in conscious rats. *Neuropsychopharmacol* 24: 1-10

Nijsen MJ, Croiset G, Stam R, Bruijnzeel A, Diamant M, et al. 2000. The role of the CRH type 1 receptor in autonomic responses to corticotropin- releasing hormone in the rat. *Neuropsychopharmacol* 22: 388-99

Pacak K, Palkovits M, Makino S, Kopin IJ, Goldstein DS. 1996. Brainstem hemisection decreases corticotropin-releasing hormone mRNA in the paraventricular nucleus but not in the central amygdaloid nucleus. *J Neuroendocrinol* 8: 543-51

Palkovits M, Brownstein MJ, Vale W. 1985. Distribution of corticotropin-releasing factor in rat brain. *Fed Proc* 44: 215-9

Pecoraro N, Reyes F, Gomez F, Bhargava A, Dallman MF. 2004. Chronic stress promotes palatable feeding, which reduces signs of stress: feedforward and feedback effects of chronic stress. *Endocrinology* 145: 3754-62

Petraglia F, Sutton S, Vale W, Plotsky P. 1987. Corticotropin-releasing factor decreases plasma luteinizing hormone levels in female rats by inhibiting gonadotropin-releasing hormone release into hypophysial-portal circulation. *Endocrinology* 120: 1083-8

Plotsky PM. 1985. Hypophyseotropic regulation of adenohypophyseal adrenocorticotropin secretion. *Fed Proc* 44: 207-13

Plotsky PM, Bruhn TO, Vale W. 1985. Hypophysiotropic regulation of adrenocorticotropin secretion in response to insulin-induced hypoglycemia. *Endocrinology* 117: 323-9.

Prewitt CM, Herman JP. 1997. Hypothalamo-Pituitary-Adrenocortical Regulation Following Lesions of the Central Nucleus of the Amygdala. *Stress* 1: 263-80.

Regev L, Tsoory M, Gil S, Chen A. 2012. Site-specific genetic manipulation of amygdala corticotropin-releasing factor reveals its imperative role in mediating behavioral response to challenge. *Biol Psychiatry* 71: 317-26

Rivier C, Rivest S. 1991. Effect of stress on the activity of the hypothalamic-pituitary-gonadal axis: peripheral and central mechanisms. *Biol Reprod* 45: 523-32

Roland BL, Sawchenko PE. 1993. Local origins of some GABAergic projections to the paraventricular and supraoptic nuclei of the hypothalamus in the rat. *J Comp Neurol* 332: 123-43.

Rosen JB, Hitchcock JM, Sananes CB, Miserendino MJ, Davis M. 1991. A direct projection from the central nucleus of the amygdala to the acoustic startle pathway: anterograde and retrograde tracing studies. *Behav Neurosci* 105: 817-25

Rosen JB, Pagani JH, Rolla KL, Davis C. 2008. Analysis of behavioral constraints and the neuroanatomy of fear to the predator odor trimethylthiazoline: a model for animal phobias. *Neurosci Biobehav Rev* 32: 1267-76

Rothwell NJ. 1990. Central effects of CRF on metabolism and energy balance. *Neurosci Biobehav Rev* 14: 263-71

Santibanez M, Gysling K, Forray MI. 2005. Adrenalectomy decreases corticotropin-releasing hormone gene expression and increases noradrenaline and dopamine extracellular levels in the rat lateral bed nucleus of the stria terminalis. *J Neurosci Res* 81: 140-52

Sawchenko PE. 1987a. Adrenalectomy-induced enhancement of CRF and vasopressin immunoreactivity in parvocellular neurosecretory neurons: anatomic, peptide, and steroid specificity. *J Neurosci* 7: 1093-106.

Sawchenko PE. 1987b. Evidence for a local site of action for glucocorticoids in inhibiting CRF and vasopressin expression in the paraventricular nucleus. *Brain Res* 403: 213-23.

Sawchenko PE, Swanson LW, Vale WW. 1984. Corticotropin-releasing factor: co-expression within distinct subsets of oxytocin-, vasopressin-, and neurotensin-immunoreactive neurons in the hypothalamus of the male rat. *J Neurosci* 4: 1118-29.

Schulkin J, Gold PW, McEwen BS. 1998. Induction of corticotropin-releasing hormone gene expression by glucocorticoids: implication for understanding the states of fear and anxiety and allostatic load. *Psychoneuroendocrinology* 23: 219-43

Seasholtz AF, Bourbonais FJ, Harnden CE, Camper SA. 1991. Nucleotide sequence and expression of the mouse corticotropin-releasing hormone gene. *Mol Cell neurosci* 2: 266-73

Seasholtz AF, Thompson RC, Douglass JO. 1988. Identification of a cyclic adenosine monophosphate-responsive element in the rat corticotropin-releasing hormone gene. *MolEndocrinol* 2: 1311-9

Sekino A, Ohata H, Mano-Otagiri A, Arai K, Shibasaki T. 2004. Both corticotropin-releasing factor receptor type 1 and type 2 are involved in stress-induced inhibition of food intake in rats. *Psychopharmacology* 176: 30-8

Seth KA, Majzoub JA. 2001. Repressor element silencing transcription factor/neuron-restrictive silencing factor (REST/NRSF) can act as an enhancer as well as a repressor of corticotropin-releasing hormone gene transcription. *J Biol Chem* 276: 13917-23

Shepard JD, Barron KW, Myers DA. 2000. Corticosterone delivery to the amygdala increases corticotropin-releasing factor mRNA in the central amygdaloid nucleus and anxiety-like behavior. *Brain Res* 861: 288-95

Shepard JD, Chambers CO, Busch C, Mount A, Schulkin J. 2009. Chronically elevated corticosterone in the dorsolateral bed nuclei of stria terminalis increases anxiety-like behavior. *Behav Brain Res* 203: 146-9

Shepard JD, Liu Y, Sassone-Corsi P, Aguilera G. 2005. Role of glucocorticoids and cAMP-mediated repression in limiting corticotropin-releasing hormone transcription during stress. *J Neurosci* 25: 4073-81

Sherman JE, Kalin NH. 1986. ICV-CRH potently affects behavior without altering antinociceptive responding. *Life Sci* 39: 433-41

Shor-Posner G, Azar AP, Insinga S, Leibowitz SF. 1985. Deficits in the control of food intake after hypothalamic paraventricular nucleus lesions. *Physiol Behav* 35: 883-90

Sims JS, Lorden JF. 1986. Effect of paraventricular nucleus lesions on body weight, food intake and insulin levels. *Behav Brain Res* 22: 265-81

Skelton KH, Gutman DA, Thrivikraman KV, Nemeroff CB, Owens MJ. 2007. The CRF1 receptor antagonist R121919 attenuates the neuroendocrine and behavioral effects of precipitated lorazepam withdrawal. *Psychopharmacology* 192: 385-96

Spiess J, Rivier J, Rivier C, Vale W. 1981. Primary structure of corticotropin-releasing factor from ovine hypothalamus. *Proc Nat Acad Sci USA* 78: 6517-21

Spina M, Merlo-Pich E, Chan RK, Basso AM, Rivier J, et al. 1996. Appetite-suppressing effects of urocortin, a CRF-related neuropeptide. *Science* 273: 1561-4

Stenzel-Poore MP, Cameron VA, Vaughan J, Sawchenko PE, Vale W. 1992. Development of Cushing's syndrome in corticotropin-releasing factor transgenic mice. *Endocrinology* 130: 3378-86.

Stenzel-Poore MP, Duncan JE, Rittenberg MB, Bakke AC, Heinrichs SC. 1996. CRH overproduction in transgenic mice: behavioral and immune system modulation. *Ann N Y Acad Sci* 780: 36-48

Strack AM, Sawyer WB, Hughes JH, Platt KB, Loewy AD. 1989. A general pattern of CNS innervation of the sympathetic outflow demonstrated by transneuronal pseudorabies viral infections. *Brain Res* 491: 156-62

Sutton RE, Koob GF, Le Moal M, Rivier J, Vale W. 1982. Corticotropin releasing factor produces behavioural activation in rats. *Nature* 297: 331-3

Swanson LW, Sawchenko PE. 1983. Hypothalamic integration: organization of the paraventricular and supraoptic nuclei. *Annu Rev Neurosci* 6: 269-324

Swanson LW, Sawchenko PE, Rivier J, Vale WW. 1983. Organization of ovine corticotropin-releasing factor immunoreactive cells and fibers in the rat brain: an immunohistochemical study. *Neuroendocrinology* 36: 165-86

Swanson LW, Simmons DM. 1989. Differential steroid hormone and neural influences on peptide mRNA levels in CRH cells of the paraventricular nucleus: a hybridization histochemical study in the rat. *J Comp Neurol*285: 413-35.

Teegarden SL, Bale TL. 2008. Effects of stress on dietary preference and intake are dependent on access and stress sensitivity. *Physiol Behav* 93: 713-23

Tsagarakis S, Grossman A. 1994. Corticotropin-releasing hormone: interactions with the immune system. *Neuroimmunomodulation* 1: 329-34

Uht RM, McKelvy JF, Harrison RW, Bohn MC. 1988. Demonstration of glucocorticoid receptor-like immunoreactivity in glucocorticoid-sensitive vasopressin and corticotropin-releasing factor neurons in the hypothalamic paraventricular nucleus. *J Neurosci Res* 19: 405-11, 68-9.

Vale W, Rivier C, Brown MR, Spiess J, Koob G, et al. 1983. Chemical and biological characterization of corticotropin releasing factor. *Recent Prog Horm Res* 39: 245-70

Vale W, Spiess J, Rivier C, Rivier J. 1981. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. *Science* 213: 1394-7

Valentino RJ, Page M, Van Bockstaele E, Aston-Jones G. 1992. Corticotropin-releasing factor innervation of the locus coeruleus region: distribution of fibers and sources of input. *Neuroscience* 48: 689-705

Valentino RJ, Page ME, Curtis AL. 1991. Activation of noradrenergic locus coeruleus neurons by hemodynamic stress is due to local release of corticotropin-releasing factor. *Brain Res* 555: 25-34

Van Bockstaele EJ, Bajic D, Proudfit H, Valentino RJ. 2001. Topographic architecture of stress-related pathways targeting the noradrenergic locus coeruleus. *Physiol Behav* 73: 273-83

Van Bockstaele EJ, Colago EE, Valentino RJ. 1996. Corticotropin-releasing factor-containing axon terminals synapse onto catecholamine dendrites and may presynaptically modulate other afferents in the rostral pole of the nucleus locus coeruleus in the rat brain. *J Comp Neurol*364: 523-34

Van Bockstaele EJ, Colago EE, Valentino RJ. 1998. Amygdaloid corticotropin-releasing factor targets locus coeruleus dendrites: substrate for the co-ordination of emotional and cognitive limbs of the stress response. *J Neuroendocrinol* 10: 743-57

Vinkers CH, de Jong NM, Kalkman CJ, Westphal KG, van Oorschot R, et al. 2009. Stress-induced hyperthermia is reduced by rapid-acting anxiolytic drugs independent of injection stress in rats. *Pharmacol Biochem Behav* 93: 413-8

Wang B, Goode J, Best J, Meltzer J, Schilman PE, et al. 2008. The insulin-regulated CREB coactivator TORC promotes stress resistance in Drosophila. *Cell Metab* 7: 434-44

Watts AG. 1996. The impact of physiological stimuli on the expression of corticotropin-releasing hormone (CRH) and other neuropeptide genes. *Front Neuroendocrinol* 17: 281-326

Watts AG. 2005. Glucocorticoid regulation of peptide genes in neuroendocrine CRH neurons: a complexity beyond negative feedback. *Front Neuroendocrinol* 26: 109-30

Watts AG, Sanchez-Watts G. 1995. Region-specific regulation of neuropeptide mRNAs in rat limbic forebrain neurones by aldosterone and corticosterone. *J Physiology* 484 (Pt 3): 721-36

Watts AG, Sanchez-Watts G, Liu Y, Aguilera G. 2011. The distribution of messenger RNAs encoding the three isoforms of the transducer of regulated cAMP responsive element binding protein activity in the rat forebrain. *J Neuroendocrinol* 23: 754-66

Watts AG, Tanimura S, Sanchez-Watts G. 2004. Corticotropin-releasing hormone and arginine vasopressin gene transcription in the hypothalamic paraventricular nucleus of unstressed rats: daily rhythms and their interactions with corticosterone. *Endocrinology* 145: 529-40

Weninger SC, Muglia LJ, Jacobson L, Majzoub JA. 1999. CRH-deficient mice have a normal anorectic response to chronic stress. *Regul Peptides* 84: 69-74

Wiersma A, Baauw AD, Bohus B, Koolhaas JM. 1995. Behavioural activation produced by CRH but not alpha-helical CRH (CRH-receptor antagonist) when microinfused into the central nucleus of the amygdala under stress-free conditions. *Psychoneuroendocrinology* 20: 423-32

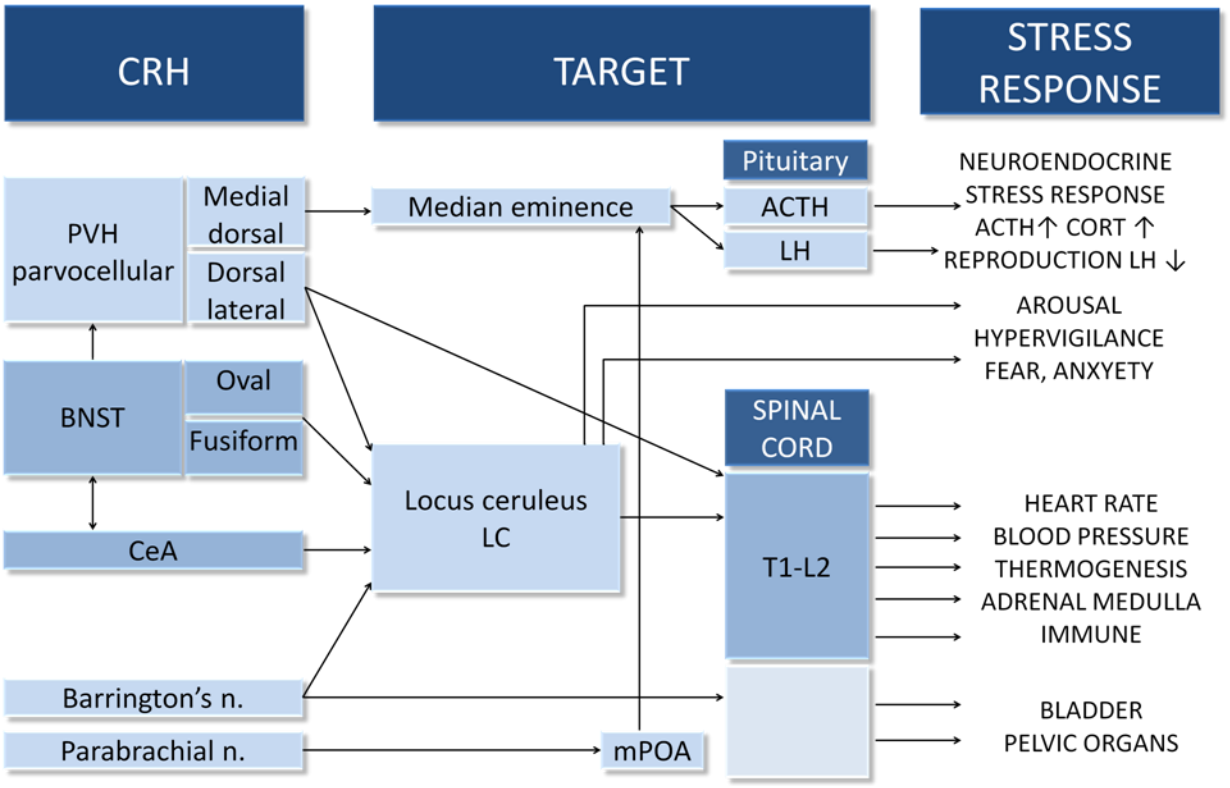
Williams JM, Peterson RG, Shea PA, Schmedtje JF, Bauer DC, Felten DL. 1981. Sympathetic innervation of murine thymus and spleen: evidence for a functional link between the nervous and immune systems. *Brain Res Bull* 6: 83-94

Wood SK, Baez MA, Bhatnagar S, Valentino RJ. 2009. Social stress-induced bladder dysfunction: potential role of corticotropin-releasing factor. *Am J Physiol Reg Integ Comp Physiol* 296: R1671-8

Wood SK, McFadden K, Griffin T, Wolfe JH, Zderic SA, Valentino RJ. 2013. A Corticotropin-releasing Factor Receptor Antagonist Improves Urodynamic Dysfunction Produced by Social Stress or Partial Bladder Outlet Obstruction in Rats. *Am J Physiol Reg Integ Comp Physiol*

Yan XX, Toth Z, Schultz L, Ribak CE, Baram TZ. 1998. Corticotropin-releasing hormone (CRH)-containing neurons in the immature rat hippocampal formation: light and electron microscopic features and colocalization with glutamate decarboxylase and parvalbumin. *Hippocampus* 8: 231-43

Yao M, Denver RJ. 2007. Regulation of vertebrate corticotropin-releasing factor genes. *GenCmp Endocrinol* 153: 200-16



Legend to the Figure

Figure 1. The major loci of corticotropin-releasing hormone (CRH) synthesis in the central nervous system: targets and roles in the integrated response to stress