Обзоры

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Brain corticotropin releasing hormone and stress reactivity

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Abstract. The hypothalamic-pituitary-adrenocortical axis is one of the main components of stress adaptation. Corticotropin-releasing hormone (CRH) coming from the nucleus paraventricularis hypothalami (PVN) is the canonical central regulator of the axis. This CRH acts on the CRH-R1 receptors of the pituitary, and, through adrenocorticotropin, stimulates glucocorticoid release from the adrenal cortex. However, it may be synthetized in other parts of the brain as well, and may act both on CRH-R1 and CRH-R2 receptors. These areas form the central CRH network. Many of them are also stress reactive and participate in physical and psychological stress response. The central nucleus of the amygdala and bed nucleus of stria terminalis are two areas best known for their role in emotions, while hippocampus is mostly involved in glucocorticoid feedback as well as memory formation, all heavily connected to stress adaptation. Among others, the brainstem raphe nuclei get dense CRHergic innervation that, through CRH-R1 receptors, may influence the serotoninergic tone of the brain. Both stress and serotonin are strongly implicated in depression, therefore, it is not surprising that CRH-R1 antagonists were developed as therapeutic tools that extensively act on the brain CRH system. Our review suggests a general role of brain CRH network in stress adaptation which is not restricted to PVN.

Keywords: corticotropin-releasing hormone (CRH), paraventricular nucleus of hypothalamus (PVN), bed nucleus of stria terminalis (BNST), amygdala, raphe nuclei, corticotropin-releasing hormone receptor of type 1 (CRH-R1).

Introduction

Stress, as a biological response of an organism to internal and external stimuli, has important physiological and psychological implications. Stress-induced changes are often temporary and reversible whenever the stressor is removed, however, the time and efficacy of the recovery vary (Charmandari et al. 2005). The main role of adaptation is to guarantee a quick and effective reaction to life-threatening situations. The sympathetic adrenomedullary system (SAS) as well as the hypothalamic-pituitary-adrenocortical axis (HPA) are responsible for the activation of biological mechanisms

of fighting or fleeing (Johnson et al. 1992). Feedback inhibition is an integral part of the optimal stress response (Backström, Winberg 2013).

Depending on chronicity, intensity, frequency and modality of stressors as well as on individual's inner state (determined by genes and early environment), the activation of stress adaptation processes may be manifested in many forms, being either adaptive or maladaptive (pathological) (Adler 2009). Chronic stress load may supersaturate the adaptive systems and lead to various pathological states, including psychiatric disorders (Chrousos 2009; Phillips et al. 2021). In fact, anxiety and depression are generally related to malfunctioning stress adaptation (Yehuda et al. 2015).

Here, we would like to focus on the HPA axis and on its hypothalamic component — the corticotropin-releasing hormone (CRH), and highlight its general role in stress adaptation, which seems to be general in the whole brain.

Stress regulation by CRH

How neurohormone systems respond to stress — the HPA axis

The HPA axis is a regulatory pathway of stress adaptation, ensuring homeostatic maintenance of the body, partly mediated by the bidirectional communication between the neuroendocrine and immune systems (Dunlavey 2018; Joseph, Whirledge 2017). This complex network is activated in response to physical or psychological stressors (Herman et al. 2016).

After a stressful event, initially noradrenaline and adrenaline are secreted as part of SAS. Reacting to the signal from A2 noradrenergic and C2 adrenergic brainstem neurones, parvocellular cells of the nucleus paraventricularis hypothalami (PVN) secret CRH into the hypophyseal portal blood. In the pituitary CRH binds to G-protein coupled receptors (corticotropin releasing hormone R1 receptors (CRH-R1)) and activates adenylate cyclase that results in the secretion of adrenocorticotropic hormone (ACTH). ACTH, reaching the adrenal gland, binds to melanocortin 2 receptors in the zona fasciculata of the adrenal cortex that leads to increased intracellular cAMP levels, which cause a rapid elevation in cholesterol biosynthesis. Cholesterol is the precursor for glucocorticoids (corticosterone in rodents, cortisol in primates). Glucocorticoids reach various peripheral organs and also provide feedback to the central nervous system. Indeed, bilateral adrenalectomy (ADX), removing the glucocorticoids, induced a robust increase of the CRH mRNA in the PVN measured by in situ hybridization (Makino et al. 1994a).

However, stress itself activates CRH transcription (Imaki et al. 1995). Expression of the protooncogene c-Fos has been validated as a biomarker of neuronal activation. Rapid alterations in c-Fos mRNA expression were demonstrated in the PVN, followed by CRH mRNA accumulation in response to acute stressors (among others, restraint). The intensity of the c-Fos mRNA signal peaked at 30 min, then decreased and was undetectable 120 min after stress onset. In contrast, the concentration of CRH mRNA increased gradually and a significant elevation was first detected 60 min after the beginning of stress. ADX enhanced while administration of glucocorticoids inhibited c-Fos mRNA and CRH mRNA induction after stress.

Corticotropin-releasing hormone (CRH) and its receptors

CRH is a 41-amino-acid peptide that is present on many brain areas as well as at the periphery (adrenal gland, testis (Thompson et al. 1987), thymus, spleen (Keegan et al. 1994)). Its best known role is the regulation of the HPA axis and the physiological response to stress (Nezi et al. 2000). In this regard, CRH is primarily synthetized in the PVN located in the hypothalamus not only in rodents (Backström, Winberg 2013), but also in humans (Goncharuk et al. 2002). As a neuropeptide, its synthesis is secondary to the main, classical neurotransmitter — glutamate in hypophysiotropic cells of the PVN (as well as of the piriform cortex (Dedic et al. 2019)) characterised by vesicular glutamate transporter 2 (VGluT2) (Hrabovszky et al. 2005). In other areas, CRH colocalises with GABA (Dedic et al. 2019).

Anyhow, CRH is produced in many areas of the brain (Swanson et al. 1983). It is generally accepted that the area of synthesis (i. e., the cell body of the neurones) is where the mRNA of the peptide can be found as the peptide synthesis happens near the nucleus. By RNA blot analysis in rats (Thompson et al. 1987) as well as by in situ hybridization histochemistry in mice (Keegan et al. 1994), it was confirmed that the brainstem (medulla/pons) contained significant amount of CRH mRNA, but it was also detected in the hypothalamus, hippocampus, cerebral cortex and striatum, but not in the cerebellum. On the other hand, the peptide is transported rapidly to the axon terminals, thus, it can be detected mainly on the target areas. Therefore, at the peptide level, the area of synthesis can be detected only after administration of colchicine — an axonal transport inhibitor. All in all, based upon immunohistochemical distribution and functional considerations three major distinct CRH-producing networks were detected in rats

(Swanson et al. 1983) (Figure): (i) PVN forming the HPA axis; (ii) telencephalon, hypothalamus and brainstem regulating autonomous responses (central nucleus of the amygdala (CeA), bed nucleus of the stria terminalis (BNST), substantia innominata, medial and lateral preoptic areas, lateral hypothalamic area, central gray matter, laterodorsal tegmental nucleus, locus coeruleus (LC), parabrachial nucleus, dorsal vagal complex, and regions containing the A1 and A5 catecholamine cell groups); (iii) scattered CRH-cells can be found in interneurones of the cerebral cortex (prefrontal areas) and hippocampus as part of the limbic system regulating emotions. Similarly, after colchicine treatment in male golden hamsters CRH immunopositivity was detected in the hypothalamus, especially, in the PVN and preoptic area as well as in CeA, BNST and cortical areas (Delville et al. 1992). Interestingly, only the PVN was sensitive to glucocorticoid negative feedback modelled by ADX (Makino et al. 1994a).

In these areas CRH executes the function of neurotransmitter and neuromodulator (Kovács 2013) and its expression is linked to a wide range of stress adaptive responses, including behavioural, autonomic, endocrine, reproductive, cardiovascular, metabolic and immunosuppressive (Kageyama et al. 2003; de Kloet et al. 2005; Slominski 2009; Takefuji, Murohara 2019). *In vitro* CRH proved to be neuroprotective against β-amyloid toxicity (Pedersen et al. 2001). Similarly, *in vivo* models of neuronal injury suggest that CRH may be protective. For instance, the levels of CRH mRNA rapidly and profoundly increased after focal cerebral ischemia in the cerebral cortex and amygdala of rats (Wong et al. 1995).

CRH effects are regulated by two distinct types of receptors, the CRH-R1 and CRH-R2. These G protein-coupled receptors are widespread in the brain (Wong et al. 1994), having high affinity to the neuropeptides urocortin, sauvagine and urotensin (Backström, Winberg 2013), and are responsible for mediating the stress response. CRH-R1 is involved in HPA axis regulation at the level of the pituitary, strongly connected to, e. g., anxiety. On the other hand, CRH-R2 appears to be linked to the regulation of other physiological responses to stress, also participating in the anxiety control

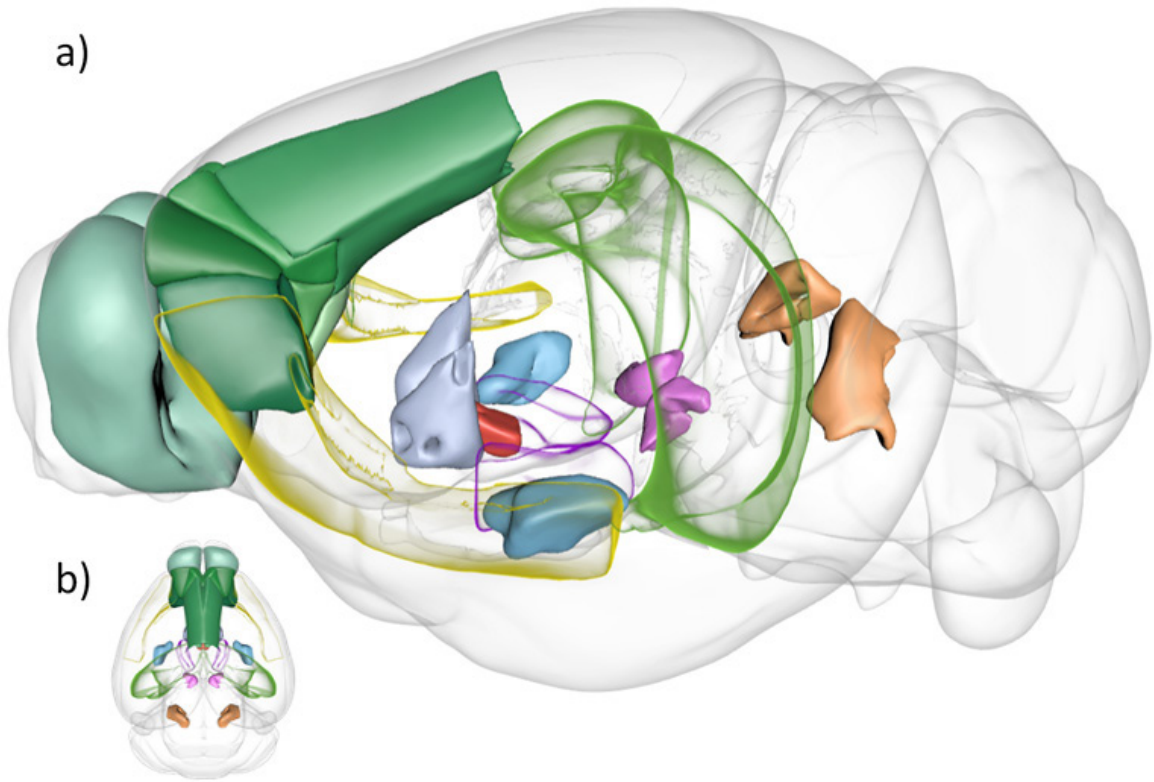

Fig. Brain corticotropin releasing hormone expression and stress reactivity (adapted from: Futch et al. 2017). 3D brain atlas: https://scalablebrainatlas.incf.org/composer/?template=ABA_v3. a) side view, b) top view; Abbreviations: PVN: paraventricular hypothalamic nucleus, LH: lateral hypothalamic area, VTA: ventral tegmental area, PB: parabrachial nucleus, CeA: central amygdalar nucleus, BNST: bed nuclei of the stria terminalis, HC: hippocampus, FrCx: frontal pole, cerebral cortex, CCx: cingular cortex, IA: insular area, OB: olfactory bulb

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(Grammatopoulos, Chrousos 2002). Interestingly, CRH-R2 can also be found in the pituitary (Klenerova et al. 2008), providing a link to the gonadal axis (Kageyama et al. 2003) and in amphibian participating in thyroid-stimulating hormone regulation (De Groef et al. 2003). In many studied brain areas (PVN, CeA, hippocampus) CRH co-localised with CRH-R1 and R2, suggesting a well-developed autoregulation (Fan et al. 2014). As a result, the two receptors are often involved in opposite responses, e. g., amygdala neurones are activated by CRH-R1 and inhibited by CRH-R2 (Ji, Neugebauer 2008).

We have to mention that CRH binding protein (CRH-BP) modulates CRH-R function (Ketchesin et al. 2017). Although not much is understood about this process, CRH-BP binds CRH with high affinity, reducing the availability of the free ligands. This suggests that CRH-BP functions as a negative regulator of CRH activity.

CRH producing brain areas reactive to stress

Amygdaloid complex

Central nucleus of amygdala (CeA)

Amygdala is known for its complex role in emotional behaviour, especially in fear responses (Janak, Tye 2015). The complex is made up of more than a dozen sub-nuclei, which have intricate inter- and intranuclear connectivity, as well as extensive afferent and efferent projections (see review: Duvarci, Pare 2014). According to the proposed functional model of the amygdala, different sensory information (e. g.: sound, light, pain) is directly relayed via sensory cortical areas and indirectly via the thalamus, and converge mostly, but not exclusively, on the basolateral nuclei (BLA). Additionally, other already processed information, such as memories and past experiences, are mediated by the hippocampus to the amygdala. This information is thoroughly processed via intranuclear connections and reciprocal projections. Most, but not all outputs arise from the CeA (LeDoux 2007). These efferents include projections to major behaviour and autonomic response regulating areas, such as the prefrontal cortex, the nuclei of the monoaminergic system, ventral tegmental area (VTA), striatum or the hypothalamus (PVN) (Sah et al. 2003), modulating stress induced behavioural and autonomic responses.

CRH is expressed in the CeA (Gray, Magnuson 1992), mainly in GABAergic neurones (Dedic et al. 2019). With in situ hybridization histochemistry, increased CRH mRNA was found in the CeA after corticosterone administration (Makino et al. 1994a). This increased signalling was accompanied by elevated viscerosomatic sensitivity (Myers, Greenwood-Van Meerveld 2010). In line with these findings, pharmacogenetic activation of CeA elicited anxiety-like behaviour, impaired short-term memory and object recognition (Paretkar, Dimitrov 2018). On the other hand, disruption of CRH signalling by RNA interference (Regev et al. 2012) or short hairpin RNA (Bolton et al. 2018) attenuated anxiety-like behaviour in response to restraint stress (Regev et al. 2012), or reversed early-life stress induced anhedonia (Bolton et al. 2018) without affecting depressive-like behaviour or fear learning. However, another study showed that activation of CRH positive amygdala neurones via pharmacogenetics had a positive effect on stress-induced depressive-like behaviour, a phenomenon at least partially mediated by dorsal raphe (DR) serotonergic neurones (Prakash et al. 2020). In connection with fear, deletion of CeA glucocorticoid receptors (GR) via LoxP-Cre system resulted in a decreased CRH mRNA expression and impaired fear behaviour (Kolber et al. 2008).

Thus, CRH synthesized in CeA seems to be highly stress sensitive and may orchestrate behavioural adaptation.

Bed nucleus of stria terminalis (BNST)

BNST plays a pivotal role in regulating trait anxiety, contextual fear memory and appetitive behaviour (Kalin et al. 2005), but it is also critical for mediating the neuroendocrine stress response (Vranjkovic et al. 2014). BNST is one of the most complex structures in the central nervous system (Larriva-Sahd 2006), which is densely connected with amygdala, hypothalamus, midbrain, and lower brainstem regions (Dong et al. 2001; Kalin et al. 2005).

CRH is highly expressed in BNST, especially in the oval nucleus of dorsolateral BNST (ovBNST) (Daniel, Rainnie 2016; Ju, Swanson 1989), colocalising with GABA (Dedic et al. 2019). The highest concentration of CRH neurones in the brain can be found in this area, however, high CRH fibres density has been also shown here (Daniel, Rainnie 2016; Morin et al. 1999).

A growing body of evidence suggests that stress activates the CRH system in the BNST and the dysfunction of CRH signalling here is associated with mood disorders, such as anxiety and depression (Walker et al. 2009). Chronic (2 weeks) high dose corticosterone administration increased CRH mRNA in BNST similarly to amygdala, with higher sensitivity of the dorsolateral than ventral parts (Makino et al. 1994b). However, ADX was ineffective (Pedersen et al. 2001), and the restrain stress-induced c-Fos expression was blocked by intracerebroventricular

(icv) administration of a competitive CRH-R antagonists (Arnold et al. 1992). Moreover, the ICV injection of CRH induced c-Fos expression in BNST (Arnold et al. 1992) and CRH microinjection into BNST increased heart rate (Nijsen et al. 2001). Based upon pharmacogenetic examinations CRH neurones of the BNST do not seem to participate in modulation of fear (Bruzsik et al. 2021).

All these changes suggest that CRH innervation, rather than locally produced CRH, is implicated in stress regulation. However, chronic variable stress, a model of depression, was able to enhance the cellular excitability of ovBNST CRH neurones in *ex vivo* slices, suggesting stress-related plasticity of this local system (Bock et al. 2005; Hu et al. 2020).

Brainstem

RNA blot analysis in rats suggested that rat brainstem (medulla/pons) contained the largest amount of CRH mRNA (Thompson et al. 1987). **VTA**, a well-known brain centre of reward consisting of dopaminergic neurones, also co-expresses CRH both in rodents and humans (Grieder et al. 2014). These dopamine-CRH cells were activated not only by nicotine administration, but by the highly stressful, adverse effect of nicotine withdrawal as well, providing a link between the stress system and drug abuse-induced brain changes. Of the brainstem nuclei, even **nucleus tractus solitarius** (NTS)/vagal complex plays an important role in the regulation of acute and chronic stress (Herman 2018). Indeed, NTS provides a link between the periphery, the SAS and the HPA by transmitting the vagal information to the PVN.

At the same time, CRH-Rs are also highly expressed in the brainstem (Fan et al. 2014), modulating serotonergic activity in the DR (Kirby et al. 2000), noradrenergic activity in the LC (Valentino et al. 1983) and dopaminergic activity in the VTA (Refojo et al. 2011). Several evidences indicated that CRHergic projections to these brain areas are deeply implicated in stress-induced behavioural alteration (e. g., DR in the depression model of learned helplessness (Hammack et al. 2003), amygdala-induced anxiety (McCall et al. 2015)). The CRH-R1 in the dorsal periaqueductal grey matter might also have an important role in anxiety disorders (Del-Ben, Graeff 2009).

One of the most common biological changes reported in depressed patients is HPA axis hyperactivity with enhanced CRH synthesis (Pariante, Lightman 2008), which might also be detected in extra-hypothalamic brain regions, including brainstem (Austin et al. 2003). Indeed, 30% higher CRH immunoreactivity was detected in the LC, 39% in the median raphe, and 45% in the caudal DR. However, this radioimmunocytochemistry study concluded on the role of CRH innervation (i. e. CRH in axon terminals) rather than locally produced CRH.

Cortical areas

Prefrontal (PFC), cingulate, and insular cortical areas contain CRH producing cells, which might also contribute to psychological and behavioural consequences of stress (Pedersen et al. 2001). Indeed, depressed patients who committed suicide showed enhanced CRH mRNA level in their PFC in comparison to age-matched controls (Zhao et al. 2015). However, during the fearful stimulus of fear conditioning there was no measurable increase in extracellular CRH concentration of the PFC (Mountney et al. 2011). Moreover, CRH-Rs are also present here, which might bind CRH coming from other areas (e. g. amygdala) and contribute to habituation (Jaferi, Bhatnagar 2007).

CRH is also expressed in the **olfactory bulb** (Delville et al. 1992). A specific area of the olfactory cortex of mice may transmit volatile predator odour-induced fearful olfactory signal directly to the PVN, thereby promoting CRH release (Kondoh et al. 2016). However, the role of locally synthesized CRH in stress adaptation is not clear yet.

In chicken, CRH neurones in the nucleus of the **hippocampal** commissure initiate, while PVN CRH neurones sustain the early response of the HPA axis to stress (Kadhim et al. 2019). In rodents and humans, through mineralocorticoid receptors, hippocampus is highly involved in negative feedback regulation of the HPA axis (Reul et al. 1990). Moreover, hippocampus is well known for its role in memory formation. CRH expressing interneurones of the hippocampus form local regulatory circuitry (Gunn et al. 2019). Not only in rodents but also in humans this hippocampal CRH/CRH-R system regulates neurogenesis, affecting spatial memory (Koutmani et al. 2019). Indeed, local administration of a CRH-R1 antagonist prevented acute stress-induced cognitive impairment (Chen et al. 2010).

CRH-R antagonists and depression

In the past years, a lot of attention has been given to CRH-R1 antagonists by the pharmaceutical industry. However, despite all the interest, no phase III study has revealed a definitive advantage of these compounds over different types of placebo (active and inactive). In fact, many studies were discontinued due to the strong adverse effects (Contoreggi 2015). Nonetheless, there are still growing evidences that these antagonists have the potential to become a new standard for the pharmacological treatment of stress-related diseases, including depression, as

 https://www.doi.org/10.33910/2687-1270-2021-2-1-6-14

CRH-R1 antagonist compounds NBI-30775/RS121919 and NBI-34041 have shown promising results in reducing the secretion of the stress hormone and having antidepressive effects without serious side effects (Kunzel et al. 2003; Spierling, Zorrilla 2017).

Conclusion

CRH is widely expressed in the brain, and the whole network seems to be stress sensitive, forming an ancient, unified stress regulatory system. However, in some brain areas CRH innervation (i.e., CRH-Rs) rather than the locally synthesized neuropeptide seems to be more important (see BNST, raphe). We cannot disregard the local autoregulation of CRH biosynthesis either (Aguilera, Liu 2012). Moreover, different stress stimuli may induce CRH synthesis in cells normally lacking this neuropeptide, e. g., hypertonic load in oxytocin producing magnocellular PVN cells (Kovács, Sawchenko 1993), which should be take into consideration as well.

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