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Review Article

Transcriptional regulation of corticotropin-releasing hormone gene in stress response

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ABSTRACT

As a central player of the hypothalamic-pituitary-adrenal (HPA) axis, the corticotropin -releasing hormone (CRH) neurons in the hypothalamic paraventricular nucleus (PVN) determine the state of HPA axis and play a key role in stress response. Evidence supports that during stress response the transcription and expression of CRH was finely tuned, which involved *cis*-element-transcriptional factor (TF) interactions and epigenetic mechanisms. Here we reviewed recent progress in CRH transcription regulation from DNA methylation to classic TFs regulation, in which a number of paired receptors were involved. The imbalance of multiple paired receptors in regulating the activity of CRH neurons indicates a possible molecular network mechanisms underlying depression etiology and directs novel therapeutic strategies of depression in the future.

Introduction

To cope with various stressors and maintain homeostasis it requires adaptive responses involving changes in the central nervous and neuroendocrine systems (Chrousos and Gold, 1992; De Kloet et al., 1998; McEwen and Stellar, 1993). Through different brain circuitries, physical or psychological stressors information are eventually conveyed to activate the neuroendocrine hypothalamic-pituitary-adrenal (HPA) axis, which has been most closely linked to the stress response in mammals. In this process, the neuropeptide corticotropin-releasing hormone (CRH), expressed and secreted from the parvocellular neurons of the paraventricular nucleus (PVN) in the hypothalamus, represents the final common path for the integration of the neuroendocrine stress response in the brain and has a well-established role in the regulation of the HPA axis (De Souza, 1995; Holsboer and Barden, 1996; Owens and Nemeroff, 1991; Vale et al., 1981).

The regulation of gene expression has been proposed as one molecular mechanism that could mediate stress response in the brain. It has been well documented that gene expression changes in specific brain regions either in animal models or in human brains, and have been related to altered behavior. Of these, CRH expression has been extensively investigated in limbic areas such like prefrontal cortex, amygdala and hypothalamus. Here we reviewed these findings, mainly focused on the regulation of CRH transcription from *cis*-element/transcription factors to epigenetic mechanisms.

Corticotropin-releasing hormone (CRH)

CRH gene is highly conservative throughout vertebrates, including fish, mouse, rat, cow, monkey and human. The CRH gene comprises two exons and one intron, and the entire coding region of CRH precursor protein locates in the second exon. After synthesis in the endoplasmic reticulum, CRH precursor protein is transferred to the Golgi apparatus for packaging, followed by transport, endoproteolysis and exocytotic release. It was believed that the majority of endoproteolysis occur in the so called large dense core vesicles or secretory granules, mainly at pairs of basic amino acid residues. A family of mammalian proteinases called proprotein convertases, which are stored in the secretory granules together with these precursor proteins, are responsible for the endoproteolytic cleavage process (Seidah and Chretien, 1997; Steiner, 1998).

As the central driving force of the HPA axis, CRH is mainly expressed by the parvocellular neurons of the hypothalamic paraventricular nucleus (PVN) and secreted into the hypophysial portal system; stimulating pituitary adrenocorticotropic hormone (ACTH) secretion and the latter inducing the biosynthesis and release of glucocorticoids from the adrenal cortex. In addition, CRH neurons send projections to other brain areas which are involved in mood regulation such as hippocampus and amygdala (Swaab et al., 2005). Integrating various stress-related inputs, regardless of whether or not the stressor is physical or psychological, CRH acts as a crucial neuromodulator, orchestrating the behavioral, endocrine, autonomic and immunological

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responses to stress (Lozovaya and Miller, 2003; Owens and Nemeroff, 1991). The homeostasis of CRH activity has great significance in affective disorders and over-expression of CRH has been confirmed to be causally linked to the onset of anxiety and other symptoms of depression (Keck and Holsboer, 2001). Chronic hyper-activation of the CRH system has been linked to stress-related emotional disorders such as anxiety, anorexia and depression. The regulation of CRH levels, especially CRH mRNA level, is a complicated and dynamic process, which involved the interaction of transcriptional factors and co-factors with *cis*-elements and epigenetic regulation such like DNA methylation and non-coding RNAs.

Epigenetic regulation

The epigenetic mechanisms, such like DNA methylation and histone modifications, alter gene activity by modulating DNA-protein interactions without changing the genetic code, which are strongly indicated in long-term and in rapid, dynamic gene expression regulation during stress. The gene sequence remains unchanged throughout life; however, environmental factors such as stress, diet or maternal care act through certain chemical reactions to influence the chromatin state, which can unravel the chromatin and cause a gene locus to be exposed for longer or shorter periods of time, essentially switching on or off the gene expression and allowing for changes in protein expression. Recent findings in epigenetics shed new light on the regulation of gene expression in the central nervous system (CNS) during or after exposure to stress (Jawahar et al., 2015; Stankiewicz et al., 2013) and established its role in synaptic plasticity, memory and cognitive processes as well as in shaping phenotypes and behavioral adaptations to stress.

Methylation of DNA at CpG dinucleotides may inhibit local gene transcription by interfering with transcription factor binding or by recruiting methylated-DNA binding proteins that alter transcription efficiency. Recent work has shown that early life stress in rodents and humans can change methylation patterns at specific loci of the genomic DNA, which in turn permanently alter gene expression in the brain and induce increases in anxiety behavior in the adult (Liu et al., 1997; McGowan et al., 2009; Murgatroyd et al., 2009; Weaver et al., 2004). The first line evidence of CRH promoter methylation reported by Ellilott et al. showed that methylation regulated the expression of the CRH gene and that chronic social stress in adult mice induced long-term hypomethylation of this genomic region (Elliott et al., 2010). It was found that high methylation level in the CRH promoter region compared with the intronic region and was involved in the inhibition of basal CRH mRNA expression. Social defeat stress induced decreased methylation of the CRH promoter at four specific CpGs in susceptible mice, accompanied with increased CRH mRNA expression in PVN and social avoidance behavior, in which DNA methyltransferase DNMT3b and histone deacetylase HDAC2 and the demethylation-promoting factor Gadd45 were involved. It was also found demethylation and social avoidance behavior were observed to be attenuated by an antidepressant, imipramine, or site-specific knockdown of CRH. Depression-like behavior and increase post-stress plasma corticosterone levels were evoked in adult male mice by prenatal chronic variable stress and were correlated with CRH promoter demethylation in both the hypothalamus and the centralnucleus of amygdala (Mueller and Bale, 2008). In rats maternal deprivation was associated with CRH promoter demethylation at two specific CpGs in PVN and enhances CRH transcriptional responses to stress in adulthood (Chen et al., 2012), whereas chronic variable mild stress (CVMS) induced site-specific changes in CRH gene methylation in a brain center-specific and sex-specific manner (Sterrenburg et al., 2011). Another work reported early life stress interacted with 5-HT transporter genotype to affect DNA methylation of the CRH gene promoter in the central nucleus of amygdala of adult male rats (van der Doelen et al., 2015). A latest work demonstrated CRH promoter methylation patterns predominantly controlled the epigenetic and functional diversity of the CRH gene in human trophoblasts (Pan et al., 2017). In a latest study comprising 88 suicide attempters, two CRH-associated CpG sites (cg19035496 and cg23409074) were significantly demethylated in the high-risk group of suicide attempters. In a subsequent adolescent cohort study, one of the above sites cg19035496 was hypermethylated in subjects with a high general psychiatric risk score (Jokinen et al., 2018).

As two major epigenetic modifications that are most intensively studied in the context of gene transcription, DNA methylation and histone acetylation are suggested by accumulating evidence to dynamically interplay in the epigenetic control of gene expression (Vaissiere et al., 2008). In the adult rats with postnatal maternal separation, impaired hippocampal synaptic dysfunction and memory defects were observed along with a significant increased hippocampal CRH expression. A significantly increased phosphorylation of Methyl CpG binding protein 2 (MeCP2) was observed in the hippocampal CA1 of the model rats and a consequent decreased occupancy of the MeCP2 and HDAC2 in the promoter region of *Crh* was also observed, in which transcriptional repressor HDAC2 was recruited to the promoter region by MeCP2. Consequently, histone H3 acetylation was also significantly increased in *Crh* promoter region. A latest work by Singh-Taylor et al. confirmed that MeCP2 binding to *Crh* promoter was enhanced in hypothalamic slices from immature augmented maternal care rats or exposed to glutamate receptor blockers CNQX/MK-801, followed by an increase of histone methylation at lysine residues H3K27 and H3K9 (Singh-Taylor et al., 2017). It was also revealed that enriched environment can reverse the epigenetic upregulation of hippocampal CRH induced by the postnatal maternal separation (Wang et al., 2014).

Non-coding RNAs (ncRNA) are functional RNA molecules that are transcribed from DNA but not translated into proteins, which are abundant in the mammalian brains and are involved in neuronal development (Mercer et al., 2010), plasticity (Bernard et al., 2010), and maintenance (reviewed in (Guennewig and Cooper, 2014)). A number of disease-associated genes were found regulating by miRNAs, and polymorphisms in their 3′UTR binding sites provide further possibilities for their dysregulation (Barry et al., 2014; Faghihi et al., 2008). However, it is still a large blank about the relationship between CRH expression and ncRNAs specifically involved in stress response and stress related disorders remains unknown. It is reasonable that there are some specific miRNA binding sites in 3′UTR of stress response associated genes and ncRNAs play a role in regulating their express much or less. Bioinformatics tools may predict a number of putative miRNA binding sites locates in the 3′UTR of CRH gene and its realistic role in regulating CRH expression need to be determined by *in vivo* and *in vitro* experiments. Much more elaborate work need to be done to identify and determine the role of other ncRNAs in stress response, specifically in modulating CRH transcription.

Regarding to other epigenetic mechanisms, we previously reported that combinational use of sodium butyrate (a histone deacetylase inhibitor) and estradiol benzoate resulted in a significant decrease in immobility behavior in forced swimming test (FST) in ovariectomized female rats. It was found that 5-HT_{1A} antagonist, WAY100635, significantly blocked this antidepressant-like effects induced by sodium butyrate plus estradiol benzoate, while no significant change of CRH mRNA levels were found in hypothalamus (Zhu et al., 2009). Another finding is sumoylation enhances estradiol's effect on CRH promoter activation through estrogen receptors. Specifically, we found CRH promoter activity was elevated to a much higher level in cells cotransfected ERα and SUMO1 than those with ER alone in the presence of estradiol, and the enhancement was blocked by the ER inhibitor. Endogenous CRH mRNA levels in BE2C cells were also significantly increased when transfected with ERα and SUMO1 in contrast to the transfection with ERα alone (Zhu and Zhou, 2008). These findings revealed the role of SUMO1 in the regulation of ER-mediated CRH promoter activation and indicates that post-translational modification of ER, especially sumoylation, is involved in the regulation of CRH transcription and HPA axis activity and may even participate in the stress

response and mood disorders.

Cis-elements and transcription factors

Transcription factors (TFs) are a cluster of nuclear regulatory proteins whose function is to activate (or to inhibit) DNA transcription by binding to specific DNA sequences, which are called *cis*-elements. Putative regulatory elements, such like the response elements for activator protein 1 (AP-1/Fos/Jun) and cAMP-response element binding protein (CREB), are present in the 5′-flanking DNA sequence of the *Crh* gene and it has been extensively reviewed by Masanori Yoshida (Yoshida, 2008). Next we will focus on a particular group of transcription factors and *cis*-elements, in which some TFs have opposite roles in regulating *Crh* gene transcription and contribute to a complicated fine-tuned regulating system, including mineralocorticoid receptor (MR) and glucocorticoid receptor (GR), estrogen receptor (ER) and androgen receptor (AR), and retinoic acid receptors.

MR and GR

Glucocorticoids (GCs, corticosterone in rat, cortisol in human) are considered to be key elements in the stress response and exert extensive effects in the center neural system as well as periphery system. Heterogeneous GC actions in response to stress were extensively categorized depending on the physiological endpoint (Sapolsky et al., 2000). Stress exposure activates the HPA-axis and results in the release of corticosteroids which bind to two closely related steroid hormone receptors in the brain (high-affinity MR and lower-affinity type-2 or glucocorticoid receptor GR) and trigger a signaling cascade of cellular and physiological changes *via* genomic transcriptional regulation. Both MR and GR mRNA signals have been detected in human hypothalamic PVN (Wang et al., 2008; Yu et al., 2002) and the distributions of GR and MR in rodent hypothalamus are also extensively characterized. A composite negatively regulated GRE (nGRE) has been identified in the human CRH gene promoter region and glucocorticoid dependent repression of CRH gene transcription predominantly occurred through this functionally defined nGRE on the CRH promoter (Malkoski et al., 1997). GR is capable of interacting directly with this functionally defined nGRE (Malkoski et al., 1997) and Bali et al. demonstrated that the direct inhibitory effect of corticosteroids on CRH transcription is probably mediated by GR since GR agonists directly inhibit basal and cyclic adenosine monophosphate (cAMP) -activated CRH mRNA expression in slice cultures of the rat hypothalamic PVN (Bali et al., 2008). Besides the trans-repression effect, GR is also capable to transactivate gene transcription. Using transcriptional regulation analysis we discovered a peculiar active glucocorticoid receptor response element (aGRE) site within the tree shrew CRH promoter and confirmed by chromatin immunoprecipitation assay (ChIP) (Fang et al., 2016), which continued to recruit co-activators including SRC-1 (steroid receptor coactivator-1) to promote CRH transcription under basal or forskolin and/or dexamethasone treatment conditions. It was found that basal CRH mRNA expression was increased when the aGRE was knocked into the CRH promoter in human HeLa cells using Cas9/CRISPR technology (Fang et al., 2016), which contributed to the higher CRH expression and susceptibility to stress in tree shrews.

MR-related research was accelerated by the finding that the MR rapidly enhances glutamatergic transmission in the hippocampus and the basolateral amygdala in the presence of corticosterone (Karst et al., 2010, 2005), which appears to be mediated by MRs located at the plasma membrane rather than genomic receptors (Groeneweg et al., 2012; Karst et al., 2010) and indicates a membrane-bound MR in the brain as a crucial stress modulator. It has been well summarized that a role of the MR in stress resilience and vulnerability for psychiatric disorders from preclinical and clinical studies (ter Heegde et al., 2015). The MR DNA binding domain (DBD) binds to specific DNA sequences, known as hormone response elements (HREs), to regulate transcription of target genes in a ligand-dependent manner. Although a number of putative HRE sites are predictively located in the promoter region of *Crh* gene, very little is known about the specific control of MR on CRH transcription in cooperation with transcriptional co-regulators, as well as rapid MR-mediated signaling effect at this aspect.

Although GR and MR preferentially bind as homodimers, there is a high degree of cooperativity of MR and GR in binding to a GRE. They can form heterodimeric complexes with different DNA-binding and transcription-regulating properties that are different from those of the respective homodimers (Trapp et al., 1994). We detected GR and MR were co-expressed in the human hypothalamus (Wang et al., 2008). In rat hypothalamic PVN, co-localization of GR and MR were found in the parvocellular region, where CRH neurons mainly reside, but not in the magnocellular region (Han et al., 2005). Recently a single cell RNA-sequencing analysis also confirmed that hypothalamic PVN CRH neurons contained GR (Nr3c1) mRNA (Romanov et al., 2015). Thus their relative levels (MR/GR ratio) and the concentration of their ligands will define the composition of corticosteroid receptor dimers and may have a decisive influence on hypothalamic CRH gene expression. Both GR and MR orchestrate the CRH regulation in the stress response and the balance between these two receptors may have more effect on the negative feedback of HPA axis. It is significant to note that adrenalectomized (ADX) rats given aldosterone alone, at a dose adequate to normalize sodium appetite, had significantly increased hypothalamic PVN-CRH mRNA levels compared with ADX animals with no steroid replacement (Watts and Sanchezwatts, 1995). These data show that in some stressful circumstances, MR occupation can be facilitatory to CRH gene expression, maintaining the ability of the CRH neuron to respond and secrete. Although the exact functional model of GR/MR in the modulation of CRH expression remains obscure, MR and GR may have differential regulating effects on the expression of CRH and operate synergistically in the feedback actions of GCs. Moreover, the proportion of hetero- and homo- dimers of the MR and GR receptors influences the efficacy of CRH gene transcription. The MR/GR ratio and the delicate balance in MR- and GR-mediated actions within the hypothalamus might be critical for CRH expression and HPA stress responsiveness. A disturbance change in the balance of MR and GR may contribute to the change of CRH transcription and be closely involved in the pathogenesis of depression.

It should also be pointed out that, glucocorticoids-mediated fast negative feedback in CNS is thought to possibly act through non-genomic mechanisms. Using whole-cell patch-clamp recordings in an acute hypothalamic slice preparation, Di et al. demonstrated a rapid suppression of excitatory glutamatergic synaptic inputs to hypothalamic parvocellular neurons including CRH neurons and TRH neurons by GCs without direct intracellular GCs perfusion (Di et al., 2003). The GCs effect was completely blocked the cannabinoid CB1 receptor antagonist AM-251. It was also confirmed in SD rats that local infusion of dexamethasone into the PVN rapidly inhibits restraint-induced ACTH and corticosterone release in a manner consistent with feedback actions, which was also blocked by AM-251, suggesting the involvement of local endocannabinoids (eCBs) (Evanson et al., 2010). Thus a fast feedback mechanism was proposed by Tasker et al. that nongenomic glucocorticoid inhibition *via* local eCB release in the hypothalamus. However, it is far more complicated since the rapid glucocorticoid effects on both excitatory and inhibitory synaptic transmission were lost with conditional deletion of GR in the PVN slices from a Sim1-cre-directed conditional GR knockout mouse (Nahar et al., 2015).

Impaired negative feedback inhibition of the HPA axis is closely associated with clinical depression and is proved to be present by endocrine challenge tests such as the dexamethasone suppression test (DST) and combined dexamethasone suppression/CRH (DEX/CRH) test in about 50% of the depressed patients (Holsboer, 2000; Sher, 2006). It is indirectly confirmed that in both bipolar and major depressive disorder patients (BD and MD), the expression of GRα (the functional subtype of GR) mRNA is significantly reduced, and as well in first-

degree relatives of BD patients (Belanoff et al., 2002). On the other hand, an increased functional activity of the MR system was found to be present in patients with MD by endocrine assays, despite the high basal cortisol levels (Young et al., 2003). These findings indicate an imbalance between these two receptors, which is critically linked with the dysregulated GCs negative feedback. Correction of the MR/GR imbalance is thought to facilitate the recovery processes of depression as appeared from clinical studies (de Kloet et al., 2007). The MR antagonist spironolactone showed beneficial effects on mood in premenstrual syndrome (Wang et al., 1995) and on residual symptoms in euthymic patients with BD (Juruena et al., 2009). However, spironolactone significantly decreased the negative feedback of HPA axis reflected by the DEX/CRH test in healthy people and can worsen the clinical outcome when administered in combination with an antidepressant for psychotic depression treatment (Holsboer, 2001; Young et al., 2003). Very interestingly, Otte et al. recently showed that in depressed patients treated with a standard antidepressant escitalopram, adding an MR agonist fludrocortisone significantly accelerated the treatment response by 6 days in the responders (Otte et al., 2010). These studies suggest that the exact functions of MR in the brain are much more complicated than traditionally expected and are still equivocal. There might be a shift in MR/GR balance towards predominant MR effects after GR antagonism is responsible for the beneficial effects of GR antagonists. However, there still lacks sufficient consistent data to link the effects of MR and GR ligands on mood with a hypothalamic MR.

By examine the post mortem samples of human brain, our group found that the transcript level of MR in the hypothalamic PVN is markedly increased in depressed patients although there are no significant changes of GR expression observed (Wang et al., 2008). These findings were also confirmed in the prefrontal cortex of patients with mood disorders, a suprahypothalamic structure inhibiting PVN-CRH. Just exactly opposite to what was found in the hypothalamus, Xing et al. found the MR mRNA expression was significantly decreased in all laminae (I–VI) of the post-mortem prefrontal cortex of patients with BD (Xing et al., 2004). More recently, our group detected a significant decreased transcript level of the MR in the superior gyrus of the PFC (SPFC) and anterior cingulate cortex (ACC) in depressed patients. Moreover, the GR/MR mRNA ratio in the two areas was markedly upregulated (our unpublished data). To our surprise, the changes in the expression of MR are much more dramatically than those of GR both in the hypothalamus and cortex in depression patients, indicating that the MR may take a more important part in the modulation of HPA axis than the GR in the depressed patients who had long period duration of the disease. Webster et al. examined the GR expression by *in situ* hybridization in post-mortem brains from patients suffering from mood disorders (depression and BD) and showed that in depression group GR mRNA levels were significantly decreased in frontal cortex and inferior temporal cortex, while in BD group GR expression were reduced in inferior temporal cortex, entorhinal cortex and subiculum (Webster et al., 2002). The PVN-GR expression changes involved in depression were mainly demonstrated in animal models. In neonatal rats following 24 h maternal deprivation the PVN-GR mRNA levels were significantly reduced immediately (Avishai-Eliner et al., 1999). The rats subjected to early maternal separation during the first 3 weeks of life, showed a decrease in the expression of GR in the PVN when exposed to variable chronic stress in adulthood (Renard et al., 2010). Long-term antidepressants treatment or electroconvulsive therapy has been found upregulating the GR mRNA and protein expression in the PVN in animal models of depression (de Kloet et al., 2007).

Taken together, the functional model of MR and GR for the regulation of HPA axis was traditionally thought to be that hippocampal and hypothalamic MR exert a tonic inhibitory influence of GCs on HPA activity while hypothalamic GR mediates the negative feedback to stress-induced elevations in HPA activity (de Kloet et al., 2007; Holsboer, 2000). It should be noted that during chronic stress, the setpoint of the HPA axis goes up to a higher value while the tone of MR's activity also climbs to a higher level. The MRs exert their control of PVN-CRH expression also on a continuous high tonic platform in depression, which is evidently different from that during the physiological state. The long periods of stress (in depression this can be decades) certainly influences the functional model of MR and GR. However, in the pathogenesis of depression MR may indeed play a more pivotal role in the regulation of HPA axis than ever believed. The exact function of MR during chronic stress and the possible changes of MR and GR action are long underestimated and little investigated in depression. GCs may also influence CRH gene transcription in the PVN using two mechanisms: first, inhibition, which probably uses GR-dependent mechanisms and contributes to classic negative feedback; and second, facilitation, which possibly uses MR mechanisms.

ER and AR

Gender differences in the stress response have been studied for more than 100 years since Walter Cannon first proposed the famous "fight or flight" hypothesis. It is generally believed that the involvement of sex hormones in HPA axis development and regulation may be the neuroendocriological bases for the sex difference in stress response (Roca et al., 2005; Uhart et al., 2006). Indeed, estrogen replacement increases basal levels of ACTH in postmenopausal women (Fonseca et al., 2001). Moreover, women in the midluteal phase with relatively high progesterone and estrogen levels show enhanced ACTH levels in response to a stressor (Altemus et al., 2001). In rats, ovariectomy reduces basal and stress-induced levels of corticosteroids which are restored to normal by administration of estrogens (Ramaley, 1976).

Estrogen receptor (ER) and androgen receptor (AR) are two major sex hormone receptors that have been detected in the brain of many species including human, non- human primates and rodents. In the human brain, ER (ERα and ERβ) protein as well as mRNA was found in the cerebral cortex, hippocampus and hypothalamus (Gonzalez et al., 2007; Hu et al., 2003; Kruijver et al., 2002, 2003; Lu et al., 2003). The brain mapping of ER mRNA and protein in the rodents shows in general similar pattern with that in human (Laflamme et al., 1998; Perez et al., 2003; Simerly et al., 1990). ERα mRNA expression in human brain is most abundant in the hypothalamus and amygdala while in rodents ER β but not α is the most abundant receptor subtype in the hypothalamus (Isgor et al., 2003). The co-localization of CRH neurons with ERα in the human PVN (Bao et al., 2005) and with ERβ in the rat PVN (Miller et al., 2004) has been reported. Both ER subtypes (ERα and ERβ) are suggested involved in the regulation of CRH expression as well as the HPA axis state. The presence of AR-immunoreactivity (AR-ir) was found in the human cortex in paraffin-embedded sections and frozen material (Puy et al., 1995). In human hypothalamus, a medium-to-weak AR-ir was detected in most of the PVN cells (Fernandez-Guasti et al., 2000) and our group also identified the colocalization of CRH with nuclear/cytoplasmic AR in PVN (Bao et al., 2006). AR mRNA is widely distributed in the rat brain including the hypothalamus (Simerly et al., 1990). However, the colocalization of AR-ir with CRH neurons has not been reported in all areas examined of rats (Bingaman et al., 1994). A recent study in goats showed that AR is expressed strongly in the ventromedial hypothalamic nucleus and co-localizes with CRH (Maejima et al., 2009).

Our recent study investigated the systemic and intrahypothalamic estradiol response to physical restraint stress in female rats (Liu et al., 2011). We used jugular catheterization and intrahypothalamic microdialysis to simultaneously measure plasma estradiol and local estradiol concentrations in the PVN of the hypothalamus. The mRNA expression of CRH and ER (ERα and ERβ) in the PVN were also assessed by quantitative PCR immediately after the acute stress period. As expected, PVN-CRH mRNA and plasma corticosterone were significantly increased after acute stress. Interestingly, the local estradiol concentration in the PVN also increased during the 1-h stress period in proestrus and ovariectomized (OVX) animals. PVN ERβ, but not ERα mRNA

expression was significantly elevated in proestrus animals. Plasma estradiol levels increased 10 min after stress, both during proestrus and estrus, but not in OVX animals. These data reflected an intra-hypothalamic estradiol action to restraint stress. The rising hypothalamic estradiol concentration together with increased ERβ gene expression indicates a positive feedback of hypothalamic estradiol signaling during acute stress in rats (Liu et al., 2011).

It is logical to propose that the functional sexual dimorphism of the HPA axis in a stress response originates from the interaction between sex hormones and the CRH neurons in the PVN. By examining the CRH concentration, one postmortem brain investigation performed in brains from 14 schizophrenic patients and 21 controls reported that female have a higher mean of CRH content in the hypothalamus relative to male (Frederiksen et al., 1991). Bao et al. analyzed the total number of CRH-immunoreactive neurons by means of immunocytochemistry and image analysis in the postmortem hypothalamic PVN of 22 control adults (11 males and 11 females). However, the data showed that men have a significantly larger number of CRH neurons than women ($p = 0.004$) (Bao and Swaab, 2007). In the avenue of searching molecular mechanism of the estrogen effect on the CRH, Vamvakopoulos et al. provided first evidence that the human CRH gene contains five perfect half-palindromic estrogen responsive elements (EREs) within its 5′ flanking region (Vamvakopoulos and Chrousos, 1993). They and Torpy et al. (Torpy et al., 1997) both proposed that the sexual dimorphism of human stress response may be causally related to the direct ER-mediated stimulation of CRH synthesis and subsequent secretion. Our group demonstrated that ERα is co-localized with CRH in ~40% of total CRH neurons in the human PVN, suggesting that estrogens can influence CRH neurons directly *in vivo* (Bao et al., 2005). We further investigated the effect of ER on CRH mRNA expression and the underlying mechanism (Chen et al., 2008). Although in PC12 cells estrogen receptors α and β were reported to differentially regulate the transcriptional activity of urocortin (UCN, another member of CRH family) *via* a half ERE and a CRE site, respectively (Haeger et al., 2006), we found in the BE2C cell line (a human neuroblastoma cell line which express endogenous CRH), both ERα and ERβ can significantly stimulate the CRH gene expression. ChIP assays further showed that both of the ER subtypes can be recruited by the CRH promoter in the presence of estradiol. Using transient co-transfection, site-directed mutagenesis and reporter gene assays in the CHO cell line (Chinese hamster ovary cell line which does not express endogenous ER), we clarified that ER's stimulation of CRH gene transcription requires both ERE half sites and cAMP regulatory element (CRE), and among them the ERE at the site -316 may be the most effective one (Chen et al., 2008). Another group also investigated 17β-estradiol (E2) effects on CRH expression as well as the molecular mechanisms in the AR-5 amygdaloid cell line (Lalmansingh and Uht, 2008). They found that CRH mRNA levels were increased by 1 min of E2 treatment, peaking at 3 min, returned to basal levels and then increased by 60 min. The temporal pattern of the mRNA response was mimicked by recruitment of ER α and β, phospho-CRE-binding protein, co-activators steroid receptor coactivator-1 and CRE-binding protein-binding protein (CBP), and an increase in histone 3 and 4 acetylation. With respect of the involvement of AR in the regulation of expression of human CRH, our group demonstrated that about one-third of the CRH neurons were colocalized with AR in the hypothalamic PVN in human brain. Furthermore, a specific androgen-responsive element (ARE) were identified present in the human CRH promoter region. Co-transfection experiment confirmed that AR in the presence of testosterone can repress CRH promoter activity through this ARE site between −2205 and −2145 (Bao et al., 2006). These observations provide evidence that androgens are capable of inhibiting human CRH production directly through AR. Up to now most of the ER/AR functional work comes from heterologous cell lines. With the advancement of biological technology, it is possible to address promoter occupancy *in vivo* by gel shift or ChIP assay, which might give us more substantial insights in near future.

In animal models, there is a sharp increase in CRH mRNA in the ventral PVN which is time related to the estrous cycle in intact female rats. Moreover, high levels of estrogen replacement increase basal levels of CRH mRNA in the PVN of ovariectomized rats (Ochedalski et al., 2007). In addition to confirming the co-localization of ERβ with CRH in the rat hypothalamic PVN, Miller et al. also demonstrated that CRH promoter activity could be stimulated by ERβ *in vitro*, further suggesting that the expression of PVN-CRH in rats, just like that in humans, could be up regulated by ER directly (Miller et al., 2004). In contrast, studies examining the effects of androgen on the regulation of CRH mRNA expression following gonadectomy (GDX) have shown that GDX increased hypothalamic CRH content, while DHT hormone replacement decreased the number of CRH-immunoreactive cells in the PVN of GDX male rats (Lund et al., 2004).

All in all, the CRH neurons in the PVN seem to be a direct target not only for estrogens but also for androgens. So far it seems clear that estrogen can increase the expression of CRH *via* the ERE while androgen may decrease the expression of CRH mediated by the ARE on the promoter of CRH. These findings fit nicely with the sex difference in the stress response. However, the interaction between the sex hormones and CRH neurons is much more complex *in vivo* that could not be explained by this simple direct effect. There is a close relationship and overlapping function between testosterone and estradiol. Besides directly binding to AR, circulating testosterone can be converted to estradiol through the aromatase pathway. The highest levels of brain aromatase activity have been found in various limbic regions, such as the preoptic and other hypothalamic regions, which overlap extensively with brain regions containing ER. Brain aromatase activity (AA), and transcription are markedly increased by genomic actions of sex steroids. In the meantime, AA is also regulated by post-translational modifications such like phosphorylation process after exposure to stress or agents affecting intracellular calcium or glutamate concentrations. In the ventromedial and tuberal hypothalamus of Japanese quail, acute restraint stress induced a quick and sustained decrease in AA in females, but in males, only a slight increase (ventromedial) or no change (tuberal) in aromatase activity was observed (Dickens et al., 2011). We also found in female rats aromatase mRNA expression in the PVN was increased markedly in prooestrus but only modestly in oestrus after restraint stress (Liu et al., 2011). In addition, testosterone can also be converted to DHT, a more potent androgen, through the 5-α reductase pathway, with potent activity at the AR. Nonetheless, the activity of DHT may not occur solely through its activation of ARs. 3β-diol, a metabolite of DHT, has been reported to preferentially bind ERβ (Kuiper et al., 1998), and it is considered to act as an endogenous estrogen in the prostate (Weihua et al., 2002, 2001). Also, 3β-diol facilitated ER-mediated transcription through classical ER binding to an ERE signaling pathway in a neuronal cell type, while its stereoisomer 3α-diol had no effect (Pak et al., 2005). Our recent work provides experimental evidence that 3β-diol could directly stimulate CRH promoter activity *via* ERα and ERβ receptors *in vitro* and chronic 3β-diol administration enhanced CRH mRNA expression in the hypothalamus of rats subjected to the forced swim test (Huang et al., 2008). The above results indicate there is a complicated interacting-network among sex hormones and their receptors. The balance between ER and AR is not just a simple "seesaw" but may be a part of more complex functional interactions.

It has been known since ancient time that sex hormones may be closely involved in mood disorders. Epidemiological studies support that the lifetime prevalence of MD is twice as high in women as in men (Lehtinen and Joukamaa, 1994; Pearlstein et al., 1997). Not only the sex difference in the prevalence of depression, but also the level of sex hormone itself has an effect on the prevalence. The prevalence of MD increases during the reproductive years, especially during times of changes in gonadal hormone levels, *e.g.* the premenstrual and prepartum/postpartum periods and during the transition to the menopause (Lehtinen and Joukamaa, 1994; Paykel, 1991; Pearlstein et al., 1997;

Young and Korszun, 2002). There is also some evidence that hormone replacement therapy could improve and prevent postpartum depression (Gregoire et al., 1996; Sichel et al., 1995). Our group assessed the modulation in diurnal rhythmicity of estradiol over the menstrual cycle in salivary samples. We found that depressed females had significantly higher diurnal-free estradiol amplitudes and some higher, though not statistically significant 24-h mean levels of diurnal estradiol rhythms than age-matched controls, which is negatively correlated with the disease duration (Bao et al., 2004).With regard to male hormones, it was found that testosterone levels were lower in severely depressed man (Heuser, 2002) and that older men with lower bioavailable testosterone levels were more frequently depressed (Barrett-Connor et al., 1999). In controlled clinical studies, supraphysiological doses of androgens induce prominent mood changes in approximately 5% of eugonadal men, whereas in placebo-controlled clinical trials, physiological doses of testosterone produce antidepressant-like effects in hypogonadal men in some, but not all, studies (Pope et al., 2003, 2000; Seidman et al., 2001; Su et al., 1993).

The above mentioned data strongly imply a critical participation of sex hormones in the pathogenesis of depression, which may be causally associated with their central regulation of hypothalamic CRH through ER and AR, respectively. By analyzing autopsied brain samples of 13 subjects suffering from MD/major depressive disorder (8 cases) or BD (5 cases) and of 13 controls, matched for sex, age, brain weight, post-mortem delay, fixation time and season and clock time at death, our group demonstrated that the total population of CRH neurons (including the only CRH-containing and CRH-ERα double-staining neurons) was significantly larger in patients with mood disorders than found in the controls (Bao et al., 2005). Furthermore, the number of CRH-ERα double-staining neurons in the PVN was ~1.2 times higher than in controls, although a trend that did not reach significance. We also identified the co-locolization of AR and CRH in the PVN of human brain and a potential specific ARE was found present in the human CRH promoter region, suggesting the close involvement of AR in sex-specific pathogenesis of mood disorders (Bao et al., 2006).

As mentioned above, it seems that ER and AR mediate an opposite action on the transcription of CRH, while ER enhances, AR inhibits CRH expression. The ratio of ER/AR in the hypothalamus and the activity balance between the two sex hormone receptors may have an important influence on the expression of CRH and subsequent HPA axis state. Indeed an imbalance of ER and AR in the hypothalamus in human brain has been observed in depressed patients. In our recent work, we found a differential change in sex hormone receptors in the hypothalamic PVN in depression (Wang et al., 2008). We studied the brains of 7 patients clinically diagnosed with depression, either in the context of a MD or of a BD and of 7 controls, matched for sex, age, post-mortem delay, season and clock time of death, and brain weight. By laser microdissection and real-time PCR analysis, we found that the expression of ERα mRNA was up-regulated in the hypothalamus of depressed patients, whereas AR was down-regulated compared with the controls. Our data show that the basal levels of ER/AR ratio are obviously up-regulated in depressed individuals, and moreover, the balance between ER and AR is disrupted at the higher basal levels. Both changes go together with increased CRH expression.

Up to now, the majority of studies on sex hormone receptors in stress response seem to indicate that ERs play a dominating role in the modulation of CRH expression. Besides the direct stimulation of estrogens, ERs also receive the activating signal from aromatized androgens. It is very interesting that androgens could exert positive as well as negative regulation on CRH gene transcription through the two sex hormone receptor pathways, respectively. One remarkable question that has not been clarified yet is which pathway is the predominant one in the normal physiological state or in a pathophysiologic state such as depression. If androgen regulates the CRH expression mainly through the ER-mediated way, then, what role does the AR-mediated pathway play in the CRH-regulating functions of androgen? These queries deserve more delicate work in the future and may advance our understanding of the complex CRH expression modulation.

RAR and RXR

Emerging evidence now indicates that the retinoid signaling may also be required for adult brain functioning and it is intriguing to note that accumulating clinical case reports have described the development of depression and suicide in some acne patients treated with isotretinoin (13-cis-RA) (Hull and D'Arcy, 2005; Strahan and Raimer, 2006), although with some controversies. Retinoic acid (RA) has been used as a routine stimulus to induce gene expression and cell differentiation *in vitro* (Kasckow et al., 1995). Recently, we have demonstrated that retinoic acid receptor alpha (RARα) colocalized with CRH neurons in human hypothalamic PVN (Chen et al., 2009). In a chronic unpredictable mild stress (CUMS) rat model for depression, we found a dysregulated RA metabolism and signaling in the hypothalamus, including an increased expression of CRH and RARα. Moreover, chronic RA administration induces HPA axis hyperactivity and depression-like behavioral changes in young rats (Cai et al., 2010). Direct intracerebroventricular injection of RA induces potent HPA axis activation and typical depression-like behaviors in rats, but dexamethasone failed to suppress basal corticosterone secretion (Hu et al., 2013). This was paralleled by increased RAR-α and decreased GR protein expression in the hypothalamus. Additional *in vitro* studies confirmed that RA abolished GR-mediated glucocorticoid-induced suppression of CRH expression, indicating a negative cross-talk between RAR-α and GR signaling pathways. Finally, the above changes could be rapidly normalized by treatment with GR antagonist mifepristone. These results suggest RA-induced HPA axis hyperactivity involves impairments in glucocorticoid receptor (GR) negative feedback. Furthermore, abnormal endogenous retinoid signaling has also been found in the brains of depressed patients, including the hypothalamus, dorsolateral prefrontal cortex and anterior cingulate cortex (ACC) (Chen et al., 2009; Qi et al., 2015b). It was found that the density of RARα/CRH double-staining neurons and the ratio of double positive neurons to CRH positive neurons were both increased in the patients of affective disorders. In our study recruitment of RARα by the CRH promoter was observed in the rat hypothalamus and human neuroblastoma cell BE2C by ChIP assay and a retinoic acid response element (RARE) was identified in the CRH promoter region. A positive correlation between CRH and RARα expression level was demonstrated by overexpression or knocking down RARα expression in a cell model (Chen et al., 2009). In addition to the direct regulation on CRH expression, we also found brain-derived neurotrophic factor (BDNF), and its receptor TrkB were both affected by RA signaling (Qi et al., 2015b), which suggest that the RA signaling pathway may be involved in the pathophysiology of depression and provide an alternative novel target for BDNF-based antidepressant treatment.

Although abscisic acid (ABA) and RA are direct derivatives of carotenoids and share a similar molecular structure (Bremner and McCaffery, 2008; Moise et al., 2009), recently we found a contrary role of ABA in regulating CRH expression compared with RA (Qi et al., 2015a). Under acute stress, ABA concentrations increased in the serum, but decreased in the hypothalamus and were accompanied by increased corticosterone in the serum and c-fos expression in the hypothalamus. Moreover, we also found ABA improved the symptom of chronic unpredictable mild stress in model rats, as indicated by increased sucrose intake, increased swimming in the forced swim test, and reduced mRNA expression of CRH and RARα in the rat hypothalamus. ABA treatment also induced a decreased expression of CRH mRNA across different types of neural cells. A negative correlation between ABA level and CRH level was also found in normal human serum. These results suggest that ABA may play a role in the pathogenesis of depression by down-regulating CRH mRNA expression shared with the RA signaling pathway, which highlights new functions for ABA in the central nervous

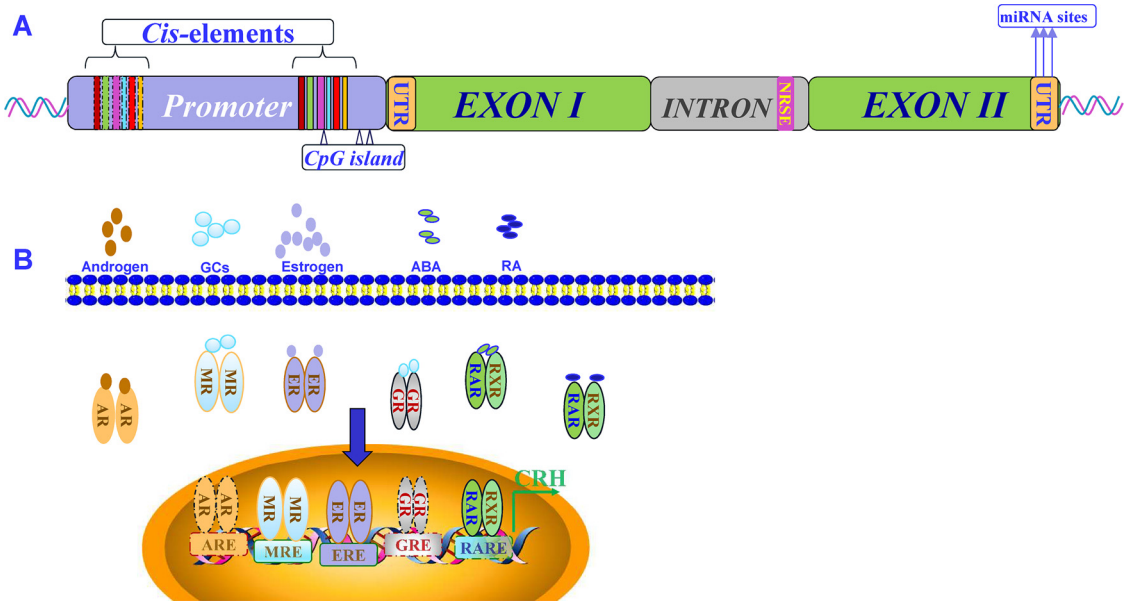

Fig. 1. Schematic diagram for CRH transcriptional regulation. A, CRH gene consists two exons and one intron. Most DNA methylation sites (CpG islands) and most *cis*-elements (positive, solid box; negative, dashed box) locate in the promoter region except NRSE, which is in the first intron. MicroRNA binding sites are predicted to locate in the 3′ untranslated region (UTR). B, Regarding to multiple paired receptors involved in the transcriptional regulation of CRH, after binding with the ligand, the receptors translocate to the nucleus and bind to the specific elements (positive, solid box; negative, dashed box) in the promoter region of CRH and regulate CRH mRNA expression. Abbreviations: AR, Androgen receptor; ER, Estrogen receptor; GR, Glucocorticoid receptor; MR, Mineralocorticoid receptor; RAR, Retinoic acid receptor; RXR, Retinoic X receptor; ARE, androgen response element; ERE, estrogen response element; GRE, glucocorticoid response element; MRE, mineralocorticoid response element; RARE, retinoic acid response element; NRSE, neuron-restrictive silencing element.

system and may propose novel therapeutic strategies for depression.

Another interesting thing is the RARE identified in the CRH promoter region displaying high similarity with ERE (Chen et al., 2009). It is worthwhile to mention that cross talk between RAR and ER has been recently been reported. Hua et al. (2009) showed that RARs exhibit extensive co-localization of their genomic binding regions with ERα, resulting in a widespread crosstalk of retinoic acid and estrogen signaling. ERα- and RAR- binding sites appear to be co-evolved on a large scale throughout the human genome, often inducing competitive binding activity at nearby or overlapping cis-regulatory elements (Hua et al., 2009). These findings indicate that RAR and ER are co-evolving to balance target gene expression and this balanced control of gene expression regulates fundamental cellular processes. The participation of a dysregulated RA signaling in the pathophysiology of affective disorders, along with the close involvement of ER in depression, further implies that the correlation between RAR and ER may modulate CRH gene expression. The vulnerable character of the critical proteins in RAR-ER interaction might be targets for novel therapeutic strategies for affective disorders. RAR heterodimerizes with retinoic X receptor (RXR) and binds to RARE. Recently, the study by Krzyzosiak et al. showed null mutation of RXRγ in mice led to increased despair behavior in the forced swim test and anhedonia, the key symptom of depression as measured in the sucrose preference paradigm (Krzyzosiak et al., 2010). In addition, Ishikawa et al. found that 13-cis-RA-induced morphologic changes of 5-HT neurons in cultured rat midbrain slices were could be completely blocked by RXR antagonist, whereas RAR antagonist only partially blocked the effects (Ishikawa et al., 2008). These data indicate RXR may also play a role in mood regulation. The expression of RXRγ protein has been found in the rodent hypothalamus (Krezel et al., 1999), however, whether or not RXR is involved in CRH modulation is still unclarified and needs further investigation. In addition, it should be noted that RXR is also a heterodimerization partner for many other nuclear receptors, such as thyroxine receptor and peroxisome proliferator-activated receptor, which makes more complicated.

NRSE and NRSF

Different from other *cis*-elements, a 21-bp sequence called neuron-restrictive silencing element (NRSE), also called repressor element-1 (RE-1), was found in the first intron of the CRH gene, which was previously shown to mediate transcriptional repression. The NRSE element has been identified in over 30 genes such like tubulin, BDNF, synaptophysin and proenkephalin, most of which are expressed in neurons (Bruce et al., 2004). The repressor element silencing transcription factor/neuron restrictive silencing factor (REST/NRSF) has been shown in a variety of genetic contexts to repress transcriptional activity *via* binding to this element. It has become clear that NRSF-NRSE function is far more complex than originally thought that the NRSF -NRSE system served as a molecular switch that helped distinguish neural from non-neural cell types, as the repression was thought to occur in non-neural cells, which contain NRSF. For example, multiple splice variants of NRSF have been identified, including at least one neural-specific form (19). Additionally, several groups have suggested that NRSF and/or the NRSE may serve a dual function, as either repressor or activator, depending on the spatial and temporal context of its expression.

Seth et al. evaluated the possible function of the NRSF-NRSE system in the transcriptional regulation of the CRH gene and showed that NRSF specific binds to the NRSE in the first intron of CRH gene (Korosi et al., 2010; Seth and Majzoub, 2001). It was also demonstrated that transcriptional repression of the CRH gene by NRSF requires an intact NRSE in a number types of cell lines including non-neuronal L6 myoblast cells, and the neuronal PC12 cells and NG108-15 neuroblastoma cells (Seth and Majzoub, 2001). Besides the TSA-sensitive transcriptional repression on CRH gene observed in L6 cells linked to HDAC activity, there was a novel finding that NRSF can function as a NRSE-independent enhancer of CRH transcription in NG108 cells (Seth and Majzoub, 2001). With regard to animal models, Korosi et al. firstly found in the rats subjected to augmented early-life experience, PVN NRSF levels were dramatically increased and induced a persistent repression of CRH expression (Korosi et al., 2010). Singh-Taylor et al. also demonstrated augmented maternal care reduced glutamatergic

synapses onto hypothalamic neurons and repressed CRH expression. In hypothalamus *in vitro*, reduced glutamatergic neurotransmission recapitulated the repressive effects of augmented maternal care on CRH, and NRSF binding to *Crh* promoter was enhanced, which induced an increased MeCP2 mediated DNA methylation. It was found in NRSF ChIP-seq analysis that, in addition to CRH, a group of genes involved in synaptic signaling and neuronal plasticity were identified, which contributed to behavior phenotypes (Singh-Taylor et al., 2017).

Summary

Gene transcription regulation is a subtle, balanced and dynamic process. As shown in Fig. 1A, there are many regulatory components at CRH gene loci, including positive /negative *cis*-elements, CpG sites, miRNA sites and a neuron-specific element. During stress response, hypothalamic CRH gene expression is in a refined control by multiple transcriptional regulation mechanisms. In short time, TFs and co-factors possess not only a positive, but also a negative transient effect on CRH expression to cope with stressors. However, it has been difficult to identify the molecular mechanisms that underlie such changes in gene expression; virtually all reported changes in transcription factors and other nuclear regulatory proteins in animal models may revert to normal within hours or days of perturbation. New RNA labeling and live imaging technology will make it feasible to detect gene expression change at a higher temporal-spatial resolution. In long time, epigenetic regulation mechanisms come into play in regulating CRH gene expression and it might be heritable. It has been determined genomic DNA modification at CRH loci like DNA methylation was changed in response to environmental factors stimulus and take a rather long effect on mRNA expression level. Non-coding RNAs especially microRNA and lincRNA should play a part in regulation of CRH expression, but it need more data to support.

The presence of multiple hormone response elements and transcription modulator elements in the promoter of CRH makes it to be a convergent avenue in the response to various stress stimulators (Fig. 1B). It is not surprising to find that the sequence of these elements in the CRH promoter is much conserved among different species since the adaptation to disparate stressor is the first selection in survival of organism. With this respect, it is intriguing to point out that so far the reported ERE or RARE in the promoter of CRH is the half-palindrome. It is logical to suppose that half-palindrome may deserve more plasticity in response to various stress factors and allow the steroid receptors share or interact with the same element.

In summary, the CRH gene expression in the brain is under the control of multiple paired receptors, and importantly, there are exists intra-imbalances of within these each paired receptors in depression. MR and GR are critical corticosteroid receptors mediating the feedback modulation of GCs at multi-levels of the HPA axis in which was intervened by eCB signaling; ER and AR underlie the sex dimorphisms in the stress response while their ligands are switchable through the aromatase pathway; RA and ABA share the same pathway in bidirectional regulating CRH expression. It should be noted that although evidences support the balanced bidirectional regulation of the multiple paired receptors, the inner essence of balance within these paired receptors is extremely complex and far from being fully understood. Moreover, among the multi-receptor systems there exist complicated interactions. A disrupted balance of multi-paired receptors in depression attests not only to the theory that multiple genes and molecules are together involved in depression but also to the therapeutic needs of combinational treatments to mood disorders. We hypothesize that during depression, various factors may lead to differential changes in gene expression within hypothalamus neurons, especially the hypothalamic PVN-CRH neurons, and jointly the interrupted balances of multi pairs of genes that regulate CRH expression result in over-production of CRH, and finally depression symptoms. How does the disruption of mood-controlling genetic network develop under stressful conditions? Are there any other seesaw gene pairs contributing to the pathogenesis of depression? Future analyses from a “paired” or “network” perspective on accumulating data may breathe fresh hopes for therapeutic strategies of depression.

Conflict of interest

The authors declare that they have no conflict of interest.

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