HHS Public Access

Author manuscript

Neurosci Biobehav Rev. Author manuscript; available in PMC 2016 April 11.

Published in final edited form as:

Neurosci Biobehav Rev. 2015 November ; 58: 63–78. doi:10.1016/j.neubiorev.2015.07.011.

Evidence for the role of corticotropin-releasing factor in major depressive disorder

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Abstract

Major depressive disorder (MDD) is a devastating disease affecting over 300 million people worldwide, and costing an estimated 380 billion Euros in lost productivity and health care in the European Union alone. Although a wealth of research has been directed toward understanding and treating MDD, still no therapy has proved to be consistently and reliably effective in interrupting the symptoms of this disease. Recent clinical and preclinical studies, using genetic screening and transgenic rodents, respectively, suggest a major role of the CRF_1 gene, and the central expression of CRF_1 receptor protein in determining an individual's risk of developing MDD. This gene is widely expressed in brain tissue, and regulates an organism's immediate and long-term responses to social and environmental stressors, which are primary contributors to MDD. This review presents the current state of knowledge on CRF physiology, and how it may influence the occurrence of symptoms associated with MDD. Additionally, this review presents findings from multiple laboratories that were presented as part of a symposium on this topic at the annual 2014 meeting of the International Behavioral Neuroscience Society (IBNS). The ideas and data presented in this review demonstrate the great progress that has been made over the past few decades in our understanding of MDD, and provide a pathway forward toward developing novel treatments and detection methods for this disorder.

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Conflict of interest

Parts of the presented findings in Section 9 have been supported by Neurocrine Biosciences Inc., San Diego, CA, USA, the Janssen Research Foundation, Beerse, Belgium, and by NeuroNova gGmbH, Munich, Germany. Otherwise, no conflicts exist.

Keywords

Depression; CRF; CRF_1; Stress

1. Major depression

Major depressive disorder (MDD) is a devastating, multifactorial psychiatric disorder, characterized by successive episodic changes in affect, cognition, and neurovegetative function. MDD patients possess overwhelming feelings of sadness, “emptiness” or irritable mood, accompanied by somatic and cognitive changes, which significantly affect an individual’s productivity, and general capacity to function (American Psychiatric Association, 2013). Suicide is also a critical concern in patients diagnosed with MDD, with suicidal thoughts, ideation, and attempts contributing a significant proportion of the reduced productivity, and in some cases premature deaths, that are associated with MDD (Krishnan and Nestler, 2008).

MDD is highly prevalent worldwide, appearing at similar frequencies across cultural, regional, and economic borders. A comprehensive study to determine the global burden of MDD in disability-adjusted life years (DALY), which estimates the future years of disability-free life that an individual loses to a disease, found that MDD contributes an estimated average of 65.6 years of lost productivity to those afflicted worldwide, the highest global burden for any disease. While this is observed in both sexes, the study also confirmed the higher occurrence of depression in women (100% higher than men), and this is reflected in the higher burden of the disease that is observed in women (Kessler, 2003; Kessler et al., 1993; Collins et al., 2011; Marcus et al., 2014).

The growing concern over the burden of MDD is apparent in an increase in the number of studies published on the topic of depression over the past decades (PubMed: keyword search [depression] AND [mood] since 1970) (Fig. 1). These studies have advanced our understanding of the etiology of MDD, and have improved our ability to understand and recognize the behavioral and physiological symptoms of this disease. Despite these advances, no universally applicable mechanism has been identified that specifically detects and addresses the physiological and behavioral dysfunctions associated with MDD.

One emerging candidate for this purpose is corticotropin-releasing factor (CRF), the hypothalamic secretogogue, identified three decades ago by Wylie Vale (Vale et al., 1981, and reviewed within). Initially discovered as an initiator of the hypothalamic–pituitary–adrenal (HPA) axis, this peptide also exhibits high levels of expression across multiple brain areas, and modulates the activity of multiple neurotransmitter systems (Bale and Vale, 2004; Hauger et al., 2009; Sahuque et al., 2006, and many others cited within this article). This article reviews the current state of research on CRF physiology and the role that it plays in the etiology of MDD. This report also presents data from a panel of scientists who are actively investigating this neuropeptide as a source, a therapeutic pathway, and a biomarker for MDD.

2. Corticotropin releasing factor peptide and receptors (Table 1 *for summary*)

2.1. CRF family ligands

The 41 amino acid peptide referred to as corticotropin releasing factor (CRF), hormone (CRH), or corticoliberin (Vale et al., 1981) is the eponymous member of a family of peptides, which also includes three urocortins: Urocortin 1 [sharing roughly 45% homology with CRF in humans (Donaldson et al., 1996)], Urocortin 2 or stresscopin-related peptide, and Urocortin 3 or stresscopin, three urotensins (urotensin 1, urotensin 2, and urotensins 3), and sauvagine. The CRF family of peptides transduces neural and endocrine signals by binding to two major CRF receptor types, CRF_1 and CRF_2, the actions of which can be modified for all peptides in the family by CRF binding protein (CRF_{BP}; Hauger et al., 2003).

2.2. CRF receptors

The CRF_1 and CRF_2 receptors are similar in composition, constructed of seven transmembrane α-helical proteins (class II or B receptor super-family) with binding in the interior of the helical protein cone stimulating signal transduction via G proteins (Hillhouse and Grammatopoulos, 2006; Perrin and Vale, 1999). Distinct genes encode for CRF_1 (human chromosome 17q21.31, mouse 11E1) and CRF_2 receptors (human chromosome 7p4.3; mouse 6B3), retaining a 70% peptide sequence homology. The CRF_1 receptor protein and its variants are constructed from 415–446 amino acids. The protein variants of the CRF_2 receptors have from 397–438 amino acids.

2.3. CRF receptors variants

Receptor variability is increased by alternative splicing, resulting in isoforms that are archetypal ($CRF_{1(a)}$, $CRF_{2(a)}$), N-terminal variants ($CRF_{1(c)}$, $CRF_{1(e)}$, $CRF_{1(h)}$, $CRF_{2(b)}$, $CRF_{2(c)}$), and have altered intracellular ($CRF_{1(b)}$, $CRF_{1(f)}$) or transmembrane ($CRF_{1(d)}$, $CRF_{1(g)}$) domains (Lovenberg et al., 1995; Zmijewski and Slominski, 2010). CRF binds with high affinity to the CRF_1 receptor, and exhibits a much lower (15 times) affinity for the CRF_2 receptor (Hauger et al., 2003; Perrin and Vale, 1999). Urocortins, urotensins, and sauvagine also bind CRF receptors, although the three urotensins and sauvagine have not been identified in mammals, and will not be discussed further. Among the urocortins, Urocortin 1 binds CRF_1 receptors with similar affinity to CRF, and binds CRF_1 and CRF_2 with similar affinities. In contrast, Urocortin 2 and Urocortin 3 bind with much greater affinity to the CRF_2 receptor, with little or no effect on CRF_1 receptor. Urocortin 1, Urocortin 2, and Urocortin 3 also bind the CRF_2 receptor isoforms with approximately 100 times greater affinity than does CRF (Hauger et al., 2003). Therefore CRF and Urocortin 1 can be considered the endogenous ligands for the CRF_1 receptor, and while the entire family of CRF peptides generally binds CRF_2 receptors, Urocortin 2 and Urocortin 3 are CRF_2 specific (Hauger et al., 2003). The CRF binding protein (CRF_{BP}) is a 37KDa, 322 amino acid glycoprotein that binds CRF and urocortins (except Urocortin 3) with a high affinity, which is similar to or greater than that of CRF receptors (Behan et al., 1995a; Boorse and Denver, 2006; Huising and Flik, 2005; Potter et al., 1991; Seasholtz et al., 2002).

2.4. CRF binding proteins

While CRF_{BP} in plasma reduces bioavailability of CRF-like peptides by binding CRF and dimerizing, perhaps preventing CRF from binding to receptors (Behan et al., 1995a), more broadly the potential for the CRF_{BP} is for buffering, inhibiting, or enhancing the effects of the CRF family peptides binding to $CRF_{1\ or\ 2}$ receptors (Seasholtz et al., 2002). The type of effect produced by binding protein relies on localization and concentration, based on the Law of Mass Action; and in that way they are similar to receptors. The effect is almost assuredly different depending on the tissue (Seasholtz et al., 2002), and CRF_{BP} is highly expressed in brain, plasma, heart, lungs, intestines and placenta (Boorse and Denver, 2006; Potter et al., 1992; Vitoratos et al., 2006). Neurons and glia of all CRF related pathways in the brain express membranal CRF_{BP}, sometimes directly colocalized with CRF or CRF receptors (Behan et al., 1995b; Potter et al., 1992).

2.5. CRF receptor intracellular signaling

Following CRF receptor binding, which results in G protein phosphorylation and dissociation of α subunits (from βγ) to stimulate 2nd messenger cascades (see below), G protein related kinases (GRKs) rapidly desensitize the receptor via phosphorylation of serines and threonines in the third intracellular loop or C-terminus (Dautzenberg et al., 2002; Kelly et al., 2008; Kohout and Lefkowitz, 2003; Krasel et al., 2005; Moore et al., 2007). Thus, the affinity of the receptor for β-arrestin is rapidly enhanced. Termination of receptor signaling for CRF_1 and CRF_2 can be accomplished by $\beta\text{-arrestin}_1$ and $\beta\text{-arrestin}_2$ which bind to clathrin and β-adaptin from vesicles which are internalized containing the complex of $CRF\text{-}CRF_{1\ or\ 2}$-arrestin (Markovic et al., 2008; Oakley et al., 2007). Internalized and desensitized receptors are dephosphorylated by specific phosphatases, and resensitized receptors are recycled to the plasma membrane.

Although amino acid sequences and affinities of CRF_1 and CRF_2 receptors are distinct, both stimulate the $G_{s\alpha} \rightarrow AC_{IC3}$ (3rd intracellular loop of adenylate cyclase) → cAMP → PKA second messenger cascade (Dautzenberg and Hauger, 2002; Hauger et al., 2003, 2006, 2009; Hillhouse and Grammatopoulos, 2006). The CRF_1 receptor interacts preferentially with $G_{s\alpha}$, but also binds with lower affinity to $G_{o\alpha}$, $G_{q/11\alpha}$, $G_{i\alpha}$ and $G_{z\alpha}$ (Grammatopoulos et al., 1999). Protein kinase A and inositol trisphosphate (IP_3) stimulated by CRF can trigger Ca^{2+} influx from cell membrane and intracellular ion channels, thereby activating calcium–calmodulin kinase II ($CamK_2$). Binding to CRF_1 or CRF_2 receptors, CRF and Urocortin 1 triggering PKA and $CamK_2$ stimulate the mitogen-activating protein kinases (MAPK) cascade through Rap_1 or Rap_2 → B-Raf → MEK_1 and MEK_2 → extracellular signal-regulated kinase (ERK) both ERK_1 and ERK_2. The CRF receptors can activate ERK, p38, or Jun N-terminal kinase (JNK) MAPK cascades. The CRF_1 enhanced production of cAMP also directly stimulates this cascade via guanine nucleotide exchange factor ($RAPGEF_3$ or Epac) stimulation of RAP GTPases. The CRF_1 mediated PKA cascade also upregulates serine-threonine protein kinase (SGK_1) (Sheng et al., 2008). Intracellular Ca^{2+} mobilization is enhanced by CRF_1 and CRF_2 receptors via AC → $Epac_2$, which stimulates the epsilon isoforms of phospholipase C (PLCε) and protein kinase C (PKC). The 2nd messenger cascades stimulated by CRF_1 and/or CRF_2 receptor binding may be influenced by the altered amino acid sequences in splice variant isoforms. In certain cells Urocortin 2 and

Urocortin 3, but not CRF, transduce ERK signaling via CRF_2 receptors. While it is unclear whether splice variation influences specific pathways of signal transduction, regional expression of CRF_1 and CRF_2 receptor isoforms is specifically correlated. Not every cell stimulated by CRF or Urocortin activates this full complement of 2nd messenger cascades; ERK systems may not be elicited.

2.6. CRF receptor variant modification of intracellular signaling

The functional expression of the CRF_1 signaling cascades may be modulated by expression or co-expression of CRF receptor isoforms (Zmijewski and Slominski, 2010). The classic $CRF_{1(a)}$ pathway stimulates 2nd messenger cascades, as does the $CRF_{1(b)}$ alternative pathway, and the intracellular $CRF_{1(h)}$ receptors. Classical signaling is inhibited by dimerization of $CRF_{1(a)}$ with $CRF_{1(d)}$, $CRF_{1(f)}$ or $CRF_{1(g)}$ receptors. This inhibition of classical signaling is extended by intracellular retention and degradation of $CRF_{1(a)}$ dimerized with $CRF_{1(d)}$, $CRF_{1(f)}$, or $CRF_{1(g)}$ receptors. Alternative signaling is limited in $CRF_{1(b)}$ receptors during their fast recycling. The $CRF_{1(c)}$ receptors exhibit impaired agonist binding, and $CRF_{1(d)}$ impaired G protein binding. Additional limitations on 2nd messenger cascade signaling may be due to mRNA decay caused by $CRF_{1(e, f, g, k)}$ receptors (due to premature stop codons introduced by alternative splicing) and secreted $CRF_{1(e)}$ and $CRF_{1(h)}$ receptors acting as decoy receptors (Zmijewski and Slominski, 2010). Translational science and clinical therapies must necessarily consider these receptor interactions to ensure positive therapeutic effects.

2.7. Functional anatomy of CRF expression

As CRF and the CRF family of peptides are likely to be the heart of a coordinated neural and endocrine stress response and coping system, the circuitry linking brain regions involved with behavioral, physiological and endocrine stress responses are critical. While it is likely that the CRF family of peptides produce a coordinated result, activating behavioral, neuroendocrine, and physiological stress response systems, the specific regional distribution of the peptides and receptors, along with different binding affinities, suggest more specific functions for each in the larger synchronized scheme. The peptide CRF has its highest expression in hypothalamus and median eminence, suggesting its potent hypothalamic–pituitary–adrenal (HPA) axis endocrine function, but it is also expressed in extrahypothalamic brain regions like amygdala, and in peripheral tissues like heart and blood vessels, skin, lung, spleen, pancreas, kidney, liver, adipose tissue, digestive tract, testes, ovaries and placenta (Boorse and Denver, 2006; Potter et al., 1994). Urocortins also appear to be widely distributed in brain, pituitary, heart and vasculature, skeletal muscle, kidney, adipose tissue, digestive tract and gonads (Boorse and Denver, 2006; Kageyama et al., 1999).

Regions of intensive CRF production exist in the extended amygdala, brainstem and several nuclei of the hypothalamus (Cummings et al., 1983; Olschowka et al., 1982; Swanson et al., 1983). The extended amygdala is implicated in the etiology of anxiety and depression, and contains CRF cells in central (CeA), basolateral (BLA), medial (MeA), lateral (LA), and posterior cortical amygdala, as well as the bed nucleus of the stria terminalis (BNST) and amygdalohippocampal area (Sakanaka et al., 1986). Of these, the greatest CRF fiber output

projects from dense pyramidal CRF neurons in the CeA to lateral hypothalamus, mesencephalic reticular formation, locus ceruleus (LC), raphé, ventral tegmental area (VTA), dorsal and ventral parabrachial nuclei, mesencephalic nucleus of the trigeminal nerve, core and shell ventromedial hypothalamus, ventral subiculum, corticomedial amygdala, and the lateral BNST (Cummings et al., 1983; Sakanaka et al., 1986). The MeA produces Urocortin 3 (Hsu and Hsueh, 2001; Lewis et al., 2001; Deussing et al., 2010), and a variety of amygdalar nuclei, including CeA and MeA have Urocortin 1 fibers (Weitemier et al., 2005; Wong et al., 1996). Neurons of the dorsomedial and fusiform subdivisions of the anterior BNST contain glutamate (Glu) and CRF (including expression of the CRF gene); (Ju and Swanson, 1989; Ju and Han, 1989; Moga et al., 1989; Choi et al., 2007). These regions of the BNST are also sites for CRF terminals, receiving Glu and CRF fibers from the CeA (Choi et al., 2007; Sakanaka et al., 1986, 1987). In addition, the posterior part of the BNST expresses Urocortin 3 (Hsu and Hsueh, 2001; Lewis et al., 2001; Deussing et al., 2010). While the BNST contains both CRF_1 and CRF_2 receptors, CRF_1 are more abundant (Chalmers et al., 1995; Rybnikova et al., 2003). The BNST also plays an important role in regulating endocrine output of CRF from the hypothalamus. In addition to inhibitory GABAergic control (Herman and Cullinan, 1997), the dorsomedial and fusiform regions of the BNST have excitatory CRF and Glu projections to the medial parvocellular PVN (Choi et al., 2007, 2008). The BNST therefore, both produces and receives CRF; together these sources of CRF influence endocrine physiology (Choi et al., 2008) and behavior (Sahuque et al., 2006).

The site of greatest expression for Urocortin 1 is the Edinger-Westphal nucleus (E-WN, or accessory oculomotor nucleus; Bittencourt et al., 1999; Ryabinin et al., 2005). In the rostral midbrain, its paired nuclei are posterior to the oculomotor nucleus and anterolateral to the aqueduct, sending innervation to and receiving CRF innervation from the dorsal raphé (Cummings et al., 1983). Early immunohistochemistry suggested PVN CRF cells projected to the midbrain adjacent to the aqueduct, in addition to the median eminence (Paull et al., 1982, 1984). The PVN also expresses Urocortin 2 in its magnocellular region (Hashimoto et al., 2004; Hsu and Hsueh, 2001; Reyes et al., 2001). Cells producing CRF are also found in the arcuate (ARC), dorsomedial (DMN), ventromedial (VMN), periventricular (PVa) and supraoptic (SON) of the hypothalamus and the mammillary bodies (Cummings et al., 1983; Krieger et al., 1977). Small SON and PVN rostral projections of CRF terminate in the SCN and septum (Paull et al., 1984). Lesions of the mammillothalamic tract induced CRF production in the mammillary body (Kovacs et al., 1985). In addition to CRF, the SON also expresses Urocortin 1 and Urocortin 2 (Bittencourt et al., 1999; Wong et al., 1996). The ARC produces both CRF and Urocortin 2 (Hashimoto et al., 2004; Hsu and Hsueh, 2001; Reyes et al., 2001), and the rostral perifornical area of the hypothalamus expresses Urocortin 3 (Hsu and Hsueh, 2001; Lewis et al., 2001).

In the cerebral cortex bipolar CRF interneurons are found, most commonly in limbic regions like prefrontal cortex and cingulate gyrus (Swanson et al., 1983). The hippocampus also has a small number of CRF producing cells that remain after a dramatic decline in hippocampal CRF from early postnatal life (Chen et al., 2001). Bipolar CRF cells are found in the dorsal and ventral regions of the LC (Cummings et al., 1983). The reticular nuclei also have a few multipolar CRF cells. A small group of serotonergic neurons in the dorsomedial portion of

the dorsal raphé nucleus also produces CRF (Commons et al., 2003). This colocalization suggests CRF and 5-HT are cotransmitters. Interestingly, the projection of these CRF/5-HT cells in the dorsomedial portion of the dorsal raphé is the CeA, describing a prominent reciprocal innervation. The extra-hypothalamic sites of Urocortin 1 expression outside of E-WN and amygdala include neocortex, hippocampus, lateral septum, nucleus of the solitary tract, and lateral superior olivary nucleus (Bittencourt et al., 1999; Wong et al., 1996). Extra-hypothalamic sites for Urocortin 2 include the LC and motor neurons of the brainstem and spinal cord (Hashimoto et al., 2004; Hsu and Hsueh, 2001; Reyes et al., 2001). The lateral septum expresses Urocortin 3 as well as Urocortin 1 and CRF (Hsu and Hsueh, 2001; Lewis et al., 2001).

Receptors for CRF and urocortins are widely distributed throughout the cerebral cortex (prefrontal, frontal, orbital, cingulate, insular, and temporal cortices; also cerebellum), limbic system (hippocampal dentate gyrus, amygdala, BNST, nucleus accumbens, mammillary bodies, olfactory tubercle, and dorsomedial thalamus) and other areas (striatum, superior and inferior colliculi, LC, raphé, VTA) as well as the pituitary in primates and rodents (Aguilera et al., 1987; Catt et al., 1987; Millan et al., 1986). In the central nervous system, both CRF_1 and CRF_2 receptor types are present, with some splice variants located in specific peripheral tissues (Chalmers et al., 1995; Hiroi et al., 2001; Potter et al., 1994). The CRF_1 receptor is the primary endocrine transduction pathway for CRF, and it is found at high densities in the anterior pituitary. In the brain CRF_1 receptors densely populate the cerebral cortex, hippocampus, amygdala, raphé nuclei and cerebellum. Peripheral CRF_1 receptors are located in adrenal gland, ovaries, testes, and skin. The CRF_2 receptors are located in brain as the $CRF_{2(a)}$ isoform (Lovenberg et al., 1995), in a variety of subcortical areas including amygdala, BNST, raphé nuclei, hypothalamus, and pituitary. The $CRF_{2(b)}$ isoform is found in retina, cerebellum, cerebral arterioles and choroid plexus as well as peripheral tissues (Lovenberg et al., 1995). Peripheral tissues including adrenal, ovaries, testes, skeletal muscle, GI tract, heart and lungs are populated by $CRF_{2(b)}$ receptors in rodents.

3. The role of stress in depression

Recent work has characterized chronic stress as one of the primary causal factors for the development and persistence of depressive behavioral phenotypes (Iniguez et al., 2014; Kleiman et al., 2014; Mahar et al., 2014; Monroe et al., 2014; Morris et al., 2014; Nederhof et al., 2014; Saravanan and Wilks, 2014; Shapero et al., 2014; Sickmann et al., 2014; Vinkers et al., 2014). In addition, exposure to stressful life events synergistically interacts with residual depressive symptoms (i.e., high depression scores following therapeutic interventions), to increase the risk of relapsing to a depressed state (Harkness et al., 2014). Major neural and endocrine sites of CRF production in the CeA, BNST, E-WN, and PVN tie the systemic and local delivery of CRF and CRF-like peptides, directly or indirectly, to all central and peripheral physiological systems associated with stress response (e.g., HPA axis, sympatho–adreno–medullary axis, central monoamine circuits; Ronan and Summers, 2011). Chronic exposure to stress is associated with dysfunctions in the negative feedback mechanisms that maintain homeostasis within these stress responsive systems, and this in turn, is associated with the increased expression and activation of neural and endocrine CRF,

CRF_1, and glucocorticoid systems, each of which is a hallmark of depressed patients (Binder and Nemeroff, 2010; Galard et al., 2002). Furthermore, increased central glucocorticoid levels lead to one of the more notable features in depression: reduced dendritic branching in hippocampal pyramidal cells (Sapolsky, 2000). Therefore, stress is linked with depression through its effects on structural and ultra-structural brain integrity as well as the modulation of neurotransmission, and evidence supports a role for CRF in each of these processes (Anacker, 2014; de Kloet et al., 2005; Duman, 2014; Mahar et al., 2014; McEwen, 2007). What is more, stressful events, both early and later in life, appear to be the causative link in gene-by-environment interactions that produce or exacerbate depression, through gene expression related to polymorphisms such as the $BDNF^{Val66/Met}$, and the serotonin transporter 5-HT_TLPR gene polymorphisms (Caspi et al., 2003; Hosang et al., 2014; Kruijt et al., 2014; Pezawas et al., 2008; Ressler et al., 2010). While the exact role of CRF in these gene by environment interactions is not conclusive, both human (Vigod and Stewart, 2009) and animal studies (Yu et al., 2012) demonstrate associations between these polymorphisms, depression (or depression-like behavior), and HPA axis reactivity (initiated by CRF).

Depression is fundamentally and etiologically a stress related disorder (Valdez, 2009) instigated and adjusted in patients by the neuroactive and hormonal modulators of stress responsiveness, including CRF (Goldstein and Klein, 2014; Ising et al., 2007); during clinical depression elevated CRF concentrations are measured in plasma (Galard et al., 2002) and cerebrospinal fluid (Banki et al., 1987; Hartline et al., 1996; Nemeroff et al., 1984). Furthermore, postmortem studies of humans afflicted with depression show evidence of a hyper-activation of CRF neurons in the PVN, cortical areas, pontine nuclei, and LC (Austin et al., 2003; Bissette et al., 2003; Merali et al., 2006; Raadsheer et al., 1994). Concomitant with this increased activation, CRF binding (also measured postmortem) in some regions of the brain, like the frontal cortex, is decreased (Nemeroff, 1998). This may be explained, in part, by the down-regulation of cortical CRF_1 (but not CRF_2) receptors that is observed in suicide victims (Merali et al., 2004). Noteworthy, a down-regulation of amygdala CRF_{BP} is also observed in patients with bipolar disorder (Herringa et al., 2006). It is clinically significant that elevated plasma CRF levels in depressed individuals are ameliorated with successful electroconvulsive shock therapy (Nemeroff et al., 1991) or antidepressant treatment (De Bellis et al., 1993; Heuser et al., 1998; Holsboer, 2000; Veith et al., 1993). The literature relating central CRF activity in depression to the genetic polymorphisms mentioned earlier is sparse, however their relationship to the role of CRF in the HPA axis is better established; both polymorphisms are associated with hyperactivity in this system (Hosang et al., 2014; Wust et al., 2009). A recent study indicates an interaction between the 5-HT_TLPR polymorphism and a polymorphism of the CRF_1 gene (rs878886), resulting in an increased response to stress in individuals possessing both genotypes (Heitland et al., 2013). The causative relationship between depression and CRF hyperactivity and receptor expression is not clear. However, improvement in the symptoms of depression, if coupled with persistently elevated CRF in the CSF, is associated with early relapse (Banki et al., 1992).

4. Neurotransmitter systems that influence depression

While this review focuses on the effects and relation of central CRF systems to MDD, numerous other transmitter and modulatory systems clearly influence depression (reviewed in Hamon and Blier, 2013; Hirschfeld, 2012; Krishnan and Nestler, 2008; Mulinari, 2012). The depressive effects of these additional systems are often modulated through, or otherwise involve CRF actions in the brain, demonstrating the prominent and multi-faceted role of CRF in MDD (Hauger et al., 2009). Here, we briefly summarize the evidence of two prevailing neurophysiological theories of MDD, highlighting a role for CRF in these systems.

Extensive evidence suggests that monoamine neurotransmitter systems contribute (Hirschfeld, 2012) to the etiology of MDD. In fact, all approved pharmacological treatments for depression target these neurotransmitter systems (Nestler et al., 2002). Four ligands comprise the major monoamine neurotransmitters, the indoleamine (5-HT), and three catecholamines dopamine (DA), norepinephrine (NE), and epinephrine (Epi) (Hamon and Blier, 2013). The major cell bodies for all of these neurotransmitters (NE in the LC, 5-HT in the dorsal raphé, and DA in the VTA) exhibit high levels of CRF_1 and CRF_2 receptor expression, and the total expression levels of these receptors, as well as the ratio of their expression, influences an individual's stress coping ability and risk of developing MDD (Bangasser and Valentino, 2012, 2014; Polter and Kauer, 2014; Wood et al., 2010, 2013b). Thus, the stress induced changes that are observed in these brain systems seem to be involved, or mediated by, CRF activity in either the cell body, or terminal regions, suggesting a pivotal role for this peptide in the established relationship of monoamine neurotransmitters and MDD.

Further studies suggest a close association between volume and synaptic connectivity in the hippocampus and prefrontal cortex with depression (Jha et al., 2011; Miller and Hen, 2014); parameters that are highly dependent on the presence and activity of neurotrophic factors, specifically brain derived neurotrophic factor (BDNF). Through multiple circuits (e.g., extended amygdala –hippocampus, periaqueductal gray, and VTA), CRF influences the production, release, and activity of BDNF, as well as many other neurotrophins (Bennett and Lagopoulos, 2014). A recent study elegantly demonstrates the importance of CRF in BDNF signaling. The authors demonstrate distinct stress mediated changes in BDNF signaling in the dopaminergic reward system (VTA/nucleus accumbens pathway). They go on to show that these changes in BDNF, that result in depression-like behavior, are directly 'gated' by CRF activity in the accumbens (Walsh et al., 2014).

Multiple theories describe central neurotransmitter systems that contribute to MDD, highlighting the heterogeneous nature of this disease. As outlined above, and in later sections of this review, the effects of stress on these systems are often mediated through stress related changes in CRF signaling. These observations support the idea that CRF may provide a common pathway for stress related diseases, such as MDD, and could serve as a more comprehensive therapeutic target for this disease.

5. CRF physiology and depression

Animal models have been successfully used to demonstrate the strong link between CRF and behavior associated with stress-mediated pathology, such as MDD. For example, i.c.v. injection of CRF induces these characteristic behaviors, including anxiety, anhedonia, decreased appetite, reduced libido, reduced slow wave sleep, and psychomotor alterations (Binder and Nemeroff, 2010; Keck, 2006). Conversely, CRF_1 receptor knockout mice exhibit diminished responses to stressful stimuli (Contarino et al., 1999; Smith et al., 1998; Timpl et al., 1998). Together, these observations suggest that the CRF system plays an important role in depression, and other stress-related psychiatric disorders. In animal models of depression, such as social defeat, learned helplessness, tail suspension, and forced swim, CRF_1 receptor antagonists, such as antalarmin, CP-154, CRA1000, 526, DMP696, DMP904, LWH234, R121919/NBI-30775, R278995/CRA0450, and SSR125543A reverse or inhibit the development of depressive-like behavioral traits (Valdez, 2009). Significant antidepressant effects, such as the reversal of shock escape deficit (by CP-154,526, CRA1000, and R278995/CRA0450), tail suspension immobility (by R121919 and DMP696), and forced swim immobility (by LWH234, antalarmin, and SSR125543A) have been demonstrated in these models, however not all of the drugs are equally or universally effective (for the shock escape deficit: DMP696 and DMP904; tail suspension: antalarmin, DMP904, CP154,526 and R278995/CRA0450; forced swim immobility: antalarmin, CP-154,526, R121919, R278995/CRA0450, DMP696, and DMP904 were all ineffective) (Chaki et al., 2004; Griebel et al., 2002; Jutkiewicz et al., 2005; Nielsen et al., 2004; Webster et al., 1996; Yamano et al., 2000). In rodents predisposed to higher baseline levels of forced swim immobility, this behavior is effectively ameliorated with SSR125543A and CP-154,526 (Overstreet et al., 2005).

CRF_2 receptor knockout mice increased immobility in the forced swim test, suggesting that the CRF_2 receptor may also be an influential factor in the relationship between CRF systems and depression, and may exert effects that oppose those of the CRF_1 receptor (Bale and Vale, 2003). This is supported by the observation that CRF_2-selective ligands (Urocortin 2 and Urocortin 3) reduce forced swim immobility (Tanaka and Telegdy, 2008). Surprisingly, female Urocortin 2 knockout mice exhibit less forced swim and tail suspension immobility, although males did not (Chen et al., 2006) – suggesting sex differences in the relationship between the CRF system and depression. In the learned helplessness model, Urocortin 2 injected directly into the dorsal raphé potentiates escape deficits (Hammack et al., 2003). Thus, it seems likely that CRF_1 and CRF_2 receptor effects on depression are site specific, and it will be important to consider the dynamics of these receptors in opposing brain regions as well as the impact of their relative densities.

Not surprisingly, the activation or inhibition of *CRF* gene expression can be induced by social stress in adult animals, and thereby invoke symptoms and behavior associated with depression (Elliott et al., 2010). Subjecting rodents to chronic social stress produces defeat, social avoidance, and susceptibility to depression-like behaviors in some subjects, but not others (Arendt et al., 2014; de Kloet et al., 2005; Krishnan et al., 2007; Krishnan and Nestler, 2010, 2011). The mesolimbic DA reward pathway is implicated in depressive behaviors (Krishnan et al., 2007), and pro-depressive effects generated through BDNF in

this pathway are modulated by CRF (Walsh et al., 2014). In stress susceptible mice, chronic social stress induces long-term demethylation of the *CRF* gene, increasing its expression, and resulting in depression-like behavior (Elliott et al., 2010). In the same study, stress resilient mice did not exhibit this effect of social stress on *CRF* gene induction, nor did they exhibit depressive-like behavior. The causative role for *CRF* gene expression in depression-like behavior was demonstrated through a site-specific knockdown of the *CRF* gene in the PVN, which attenuated this depression-like response. Increased *CRF* gene expression in the PVN also leads to increased HPA axis activation, suggesting that susceptible individuals are also potentially more stress reactive (Shapero et al., 2014; Wood et al., 2010), or perhaps differently stress reactive (Morris et al., 2014), than stress resilient individuals. In effect, stress-induced epigenetic modification and expression of genes for CRF and its CRF_1 receptor may be the critical factors for engendering susceptibility or resilience to the potential for depression and depression-like behavior (Elliott et al., 2010; Ressler et al., 2010).

The gene loci for CRF-family ligands and receptors are found in disparate sites in humans, with the *CRF* gene on chromosome 8q13.1, (containing 2 exons, spanning 2 kb of genomic DNA), and *Urocortin 1* (chromosome 2p23.3, 2 exons, 1 kb), *Urocortin 2* (chromosome 3p21.3, 2 exons, 2 kb), *Urocortin 3* (chromosome 10p15.1, 2 exons, 9 kb), *CRF_1* (chromosome 17q21.31, 13–14 exons, 20–51 kb) and *CRF_2* receptors (chromosome 7p15.1, 12–15 exons, 29 kb; 3 different promoter sites/3 different first exons to encode the $CRF_{2(a)}$ $CRF_{2(b)}$ and $CRF_{2(c)}$ isoforms) and *CRF binding protein* (*CRF_{BP}*, chromosome 5q13.3, 7exons, 17 kb) distinctively separated (Binder and Nemeroff, 2010). Linkage studies have suggested an association between the 8q region in or distal to the *CRF* gene and the 3p region containing *Urocortin 2* gene with bipolar disorder as well as combined anxiety with the early onset of major depressive symptoms (Camp et al., 2005; Kelsoe et al., 2001; Liu et al., 2003; Marcheco-Teruel et al., 2006; McQueen et al., 2005; Segurado et al., 2003). A rare SNP (rs503875) for the *CRF* gene appears to interact significantly with a functional SNP (ThtIII1) in the *glucocorticoid receptor (GR)* gene (Rosmond et al., 2001). Behavioral inhibition in children of parents with anxiety disorders is associated with a repeat polymorphism and three SNPs near the *CRF* gene (Gu et al., 1993; Smoller et al., 2003, 2005). In addition, SNPs for CRF_1 and vasopressinergic V_{1B} receptors were associated with panic disorder (Keck et al., 2008). Three *CRF_1* SNPs (rs1876828, rs242939 and rs242941) are over-represented in patients with major depression (Liu et al., 2006) or have been associated (rs4792887) with stress, depression, and attempted suicide (Wasserman et al., 2008). Associations between response to antidepressant treatment (fluoxetine, desipramine, or citalopram) and three SNPs, a promoter SNP, or an intronic SNP (rs110402) within the *CRF_1* gene have been reported (Licinio et al., 2004; Liu et al., 2006; Papiol et al., 2007). Additionally, *CRF_1* SNPs interacting with the *serotonin transporter* (*$5\text{-}HT_T$*) SNPs and child abuse, also predict adult depression (Ressler et al., 2010). Finally, treatment of affective disorders with citalopram was positively associated with *CRF_2* intronic SNP (Papiol et al., 2007).

Taken together, there is substantial evidence to suggest that neural and endocrine CRF-related gene expression and signaling influence the potential risks and outcomes of major depression and comorbid psychological disorders.

6. The role of CRF in mediating an individual's risk to social stress-induced psychopathology (*chapter contributed by S.K. Wood, PhD*)

As noted earlier, stressors of a social nature are the most common type of stress in people that precipitate psychopathologies such as depression and anxiety (Bjorkqvist, 2001). An animal model of social stress useful for studying stress-induced psychopathology is the resident-intruder paradigm. This model is characterized by threats and attacks by a large aggressive male rat (resident) toward a smaller male rat (intruder) (Miczek, 1979). Exposure to this stressor induces a robust neuroendocrine and cardiovascular activation as well as hyperthermia (Bhatnagar et al., 2006; Buwalda et al., 1999; Sgoifo et al., 1999; Tornatzky and Miczek, 1993; Wood et al., 2010). Subsequently, intruder rats exhibit increased behavioral despair, anhedonia, decreased social interactions, and long lasting changes in HPA axis function (Becker et al., 2008; Bhatnagar et al., 2006; Buwalda et al., 1999; Rygula et al., 2005; Sgoifo et al., 2002). As such, social stress exposure produces a depressive-like phenotype in rats that corresponds well with clinical manifestations of affective disorders (American Psychiatric Association, 2013).

Rodents exposed to social stress also vary greatly in their behavioral response, exhibiting either passive behaviors (supine postures) or proactive behaviors characterized by greater territorial control, upright postures and counter attacks (Meerlo et al., 1999; Walker et al., 2009; Wood et al., 2010). These diverse coping strategies are related to divergent physiological responses to stress, as passive behaviors are characterized by higher HPA axis reactivity and active behaviors are associated with enhanced sympathetic activity (Koolhaas et al., 1999). Importantly, rats demonstrating passive behavioral strategies also exhibit heightened vulnerability to stress-related consequences, similar to that observed in humans (Billings and Moos, 1984; Folkman and Lazarus, 1980). For example, passive responses during social stress are related to greater impairment of diurnal rhythms, HPA dysfunction, and behavioral despair while active coping confers resistance to developing many stress-related consequences (Meerlo et al., 1999; Wood et al., 2010). In fact, a study evaluating the effect of repeated intermittent exposures to social stress revealed evidence of sustained HPA activation in passive coping rats, but not in those demonstrating active responses. Furthermore, behavioral despair and anhedonia were evident only in the passive coping rats following social stress (Wood et al., 2010, 2015). These studies mimic findings in melancholic depressed patients indicating that HPA dysregulation co-occurs with depressive behaviors (Swaab et al., 2005).

A growing body of evidence suggests that the stress-sensitive neuropeptide CRF is a critical factor mediating one's risk of developing stress-induced psychopathology. Initially recognized as the neurohormone that initiates the HPA axis (Vale et al., 1981), CRF in extrahypothalamic regions contributes to anxiety and depressive-like behaviors in animal models (Dunn and Swiergiel, 2008). Overproduction of CRF as evidenced by increased CRF expression in PVN neurons, increased CRF-immunoreactivity in the noradrenergic nucleus locus ceruleus and the 5-HT containing dorsal raphé nucleus (DR) as well as increased CRF levels in cerebrospinal fluid has also linked CRF with depressive disorders in humans (Austin et al., 2003; Bissette et al., 2003; Merali et al., 2004, 2006). The intersection

between CRF and monoamines provides a mechanism by which CRF can have a major impact on one's risk of depression. One monoaminergic target of CRF implicated in depressive disorders is the DR-5-HT system (Valentino and Commons, 2005). Within the DR, CRF has opposing effects on 5-HT neuronal activity dependent upon its actions at CRF_1 or CRF_2. CRF_1 activation in the DR enhances gamma-aminobutyric acid (GABA)ergic inhibition of DR-5-HT neurons and CRF_2 activation excites DR-5-HT neurons thereby increasing extracellular 5-HT in DR targets (Kirby et al., 2000, 2008; Price et al., 1998; Roche et al., 2003). In naïve rats, CRF_1 is localized predominantly on the plasma membrane, while CRF_2 is located within the cytoplasm (Waselus et al., 2009). Repeated intermittent exposure to social stress in the more stress resistant, active coping rats results in a redistribution of these receptors such that CRF_2 is recruited to the plasma membrane and CRF_1 is internalized. This effect is absent in rats displaying a passive response to social stress (Wood et al., 2013b). Although differences in protein expression of B-arrestin2 or splice variants of the CRF_2 receptor could account for differential CRF receptor trafficking, significant differences in protein expression of these molecules within the DR were not evident 24 h after social defeat (Wood et al., 2013b). Consistent with the findings of internalized CRF_1 receptors in the active coping phenotype, daily administration of a CRF_1 antagonist shifts the behavioral response to a proactive strategy and prevents the development of behavioral despair in the forced swim test and adrenal hypertrophy (Wood et al., 2012). In addition to the convincing role that CRF plays in depressive symptomatology, CRF is also poised to contribute to the pathogenesis of stress-related medical disorders that are comorbid with affective disorders, including urinary disorders and cardiovascular disease. Social stress-induced overexpression of CRF within Barrington's nucleus, the pontine micturition center of the brain, has been linked to urodynamic dysfunction (Valentino et al., 2011). These physiological manifestations of stress were blocked by either CRF_1 antagonism or shRNA knockdown of CRF in Barrington's nucleus (Wood et al., 2013a). In addition, social stress has been linked to cardiovascular dysfunction such as cardiac hypertrophy and reduced heart rate variability. Importantly, CRF_1 antagonist treatment during social stress mitigates both the effects of social stress on depressive-like behaviors and the cardiovascular system (Wood et al., 2012). Taken together results of these studies underscore a critical CRF-related mechanism that is capable of mediating the individual differences in vulnerability to social stress.

7. Sex differences in corticotropin releasing factor receptors (*chapter contributed by D.A. Bangasser, PhD*)

Women are twice as likely to suffer from depression as men (Kessler, 2003; Kessler et al., 1993). Given the link between CRF and depression, it is possible that sex differences in CRF sensitivity could contribute to this sex bias in depression rates. Specifically, there is mounting preclinical evidence for sex differences in CRF receptors. For example, sex differences in CRF receptor binding have been identified in nearly every brain region examined (Weathington et al., 2014). CRF_1 receptor binding is greater in adult female than male rats in regions implicated in depression, including the cingulate cortex, accumbens, and amygdala (Weathington et al., 2014). In contrast, males have greater CRF_2 receptor binding than females in many regions, such as the BNST (Lim et al., 2005; Weathington et al.,

2014). The functional relevance of these sex differences remains unknown. However, as noted, stress sensitivity is thought to be increased via CRF_1 receptor activation, but decreased via CRF_2 receptor activation (Bale and Vale, 2004). While this statement is likely an oversimplification of CRF receptor effects on behavior universally, if it holds true for the aforementioned brain regions (cingulate cortex, accumbens, amygdala), then higher CRF_1 but lower CRF_2 receptor binding observed in these regions in females could render them more sensitive to stress.

Sex differences in CRF_1 receptor coupling and signaling also have been identified. As stated earlier in this review, the CRF_1 receptor is a G protein-coupled receptor that preferentially binds the Gs protein to activate the cAMP-PKA signaling cascade (Grammatopoulos et al., 2001; Hillhouse and Grammatopoulos, 2006). Female rats have greater cortical CRF_1 receptor coupling to the Gs protein than males (Bangasser et al., 2010). This suggests that when activated, female CRF_1 receptors would initiate greater cAMP-PKA signaling than male CRF_1 receptors. In fact LC neurons of female rats are more sensitive to CRF than those of males, and this increased sensitivity is linked to greater activation of the cAMP-PKA signaling cascade in females (Bangasser et al., 2010; Curtis et al., 2006). Thus, sex differences at the level of receptor signaling can translate into sex differences in stress physiology. In turn, these physiological sex differences could result in sex differences in stress-induced arousal, which is mediated by the effects of CRF in the LC. Typically, activation of the LC during a stressful event is thought to be adaptive, as it promotes appropriate cognitive and behavioral coping responses (Snyder et al., 2012; Valentino and Van Bockstaele, 2005). However, inappropriate activation of this system by benign stimuli could be disruptive. Because sex differences in the CRF_1 receptor render female LC neurons more sensitive to CRF, females are more likely to have these inappropriate arousal responses than males.

CRF_1 receptors are also differentially affected by stressor exposure or excessive CRF release in males compared to females. In vitro, CRF_1 receptors become desensitized and internalized (i.e., trafficked from the membrane to the cytosol) in response to saturating concentrations of CRF (Hauger et al., 2000; Teli et al., 2005). This internalization is considered a cellular adaptation to high levels of CRF release because the internalized receptors cannot be activated. CRF_1 receptor internalization also occurs in vivo in males. Both local CRF administration and forced swim stress result in the internalization of CRF_1 receptors in LC dendrites in male rats (Bangasser et al., 2010; Reyes et al., 2006, 2008). Additionally, CRF_1 receptor internalization in LC dendrites is observed in male CRF overexpressing mice (Bangasser et al., 2013). In contrast, CRF_1 receptor internalization fails to occur in stressed female rats and female mice that overexpress CRF (Bangasser et al., 2010, 2013). Rather, these females have more CRF_1 receptors in the plasma membrane than their unstressed or wild type same sex counterparts. This suggests that females lack the compensatory response of internalization, which could make their LC neurons more sensitive to conditions of CRF hypersecretion. In support of this, LC neurons of female CRF overexpressing mice fire roughly 3× faster than neurons of wild type mice (Bangasser et al., 2013). However, LC neurons of male CRF overexpressing mice maintain their firing rate at wild-type levels, despite excessive CRF release in their LC (Bangasser et al., 2013). The

CRF_1 receptor internalization observed in male, but not female CRF overexpressing mice can explain these physiological sex differences.

Sex differences in CRF_1 receptor internalization can be attributed to sex differences in binding of β-arrestin, the protein that initiates CRF_1 receptor internalization (Hauger et al., 2009; Holmes et al., 2006; Oakley et al., 2007). In cortical tissue, stressor exposure induced β-arrestin binding to the CRF_1 receptor in male but not female rats, an effect that may explain why CRF_1 receptors of females do not internalize following excessive CRF release (Bangasser et al., 2010). In addition to its role in initiating internalization, β-arrestin also activates its own suite of signaling cascades that are often distinct from signaling pathways activated by G proteins (DeWire et al., 2007; Lefkowitz and Shenoy, 2005). This has led to the proposal that the signaling of the CRF_1 receptor is sex biased, such that it signals more through β-arrestin mediated pathways in males and Gs-mediated pathways in females (Bangasser and Valentino, 2012; Valentino et al., 2013a,b). Sex biased CRF_1 receptor signaling may be an important, yet underexplored, mechanism by which sex differences in CRF responses are established.

Overactivation of the LC-NE system can lead to symptoms of hyperarousal, including agitation, restlessness, and sleep disturbances (Gold and Chrousos, 1999, 2002). Sex differences in CRF_1 receptors render LC neurons of females more sensitive to CRF and less adaptable to conditions of CRF hypersecretion, effects that could translate into increased hyperarousal in females during stressful conditions. If these sex differences occur in humans, they may explain the sex bias in the rates of depression, as well as the prevalence of certain hyperarousal symptoms in depressed women (Nolen-Hoeksema et al., 1999; Plante et al., 2012). Additionally, sex differences in CRF receptor function may affect the treatment of depression. CRF_1 receptor antagonists that are being designed to treat depression may work differently in males and females due to sex differences in CRF_1 receptors. Indeed, administration to the dorsal raphé of a small molecule CRF_1 receptor antagonist reduced stress-related behavior in male but not female mice (Howerton et al., 2014). Importantly though, by comparing CRF receptors in males and females, novel therapeutic targets can be identified (Bangasser, 2013). For example, a drug that biases the CRF_1 receptor toward β-arrestin binding, thereby promoting internalization, may be an effective treatment for depression, especially in women. Together these studies underscore the need to consider sex differences when trying to understand the etiology of depression and develop effective treatments for the disorder.

8. Dissecting CRH-controlled neurocircuitries of stress and anxiety – (*chapter contributed by J.M. Deussing, PhD*)

While the role of CRF as an indispensable initiator of the neuroendocrine cascade of the HPA axis is well defined, we are just starting to comprehend the role of extrahypophysiotropic CRF with regards to emotionality and behavioral responses to stress. This is somewhat surprising considering that already soon after its discovery (Vale et al., 1981), numerous groups demonstrated that intracerebroventricular (i.c.v.) application of CRF in rodents can elicit a broad spectrum of physiological and behavioral reactions sharing typical characteristics with stress (reviewed in: Dunn and Berridge, 1990a). Independent of

its effect on the HPA axis, exogenous CRF acts within the central nervous system to increase sympathoadrenal outflow, which in turn activates cardiovascular function, increases plasma glucose levels and oxygen consumption – typical signs of the fight-or-flight response (Brown et al., 1982; Dunn and Berridge, 1987; Fisher et al., 1982). In agreement with the established positive relationships of CRF with multiple modes of stress related behavior (Berridge and Dunn, 1986; Swerdlow et al., 1986; Britton et al., 1982, 1986a; Koob et al., 1993; Sutton et al., 1982), CRF antagonists are capable of attenuating or reversing the effects of various stressors, strongly suggesting that CRF itself is a mediator of these responses (Berridge and Dunn, 1987; Britton et al., 1986b; Dunn and Berridge, 1990a). Taken together, these findings indicate that the extrahypophysiotropic CRF system on its own may be both necessary and sufficient to execute stress responses (Dunn and Berridge, 1990b; Heinrichs et al., 1995).

In the previous two decades, the CRF system has extensively been studied using gain- and loss-of-function mouse models. Numerous models of CRF overexpression have been developed to further refine previous experiments of i.c.v. CRF application and to mimic CRF hyperactivity observed in depressed patients (Nemeroff et al., 1984). These mouse lines have proven extremely valuable given their ability to reflect different degrees of the activating, arousing and anxiogenic-like properties of CRF (Dedic et al., 2012; Dirks et al., 2002; Kolber et al., 2010; Lu et al., 2008; Refojo et al., 2011; Stenzel-Poore et al., 1994; Vicentini et al., 2009). However, a direct comparison of different CRF overexpressing mouse models reveals substantial discrepancies and inconsistencies, which are largely related to differences in the design of these animal models, including the expression level and the spatio-temporal properties of the utilized promoters driving CRF overexpression (reviewed in: Laryea et al., 2012). Another confounding factor appearing in several CRF overexpressing mouse lines is the hypercorticosteronism accompanied by a Cushing-like phenotype. In recent years, approaches applying viral expression systems (lenti- and adeno-associated viruses) have been used that provide means to overexpress CRF in a spatially more restricted manner allowing for more refined analyses of CRF actions in different brain nuclei (Flandreau et al., 2012; McFadden et al., 2012; Qi et al., 2014; Regev et al., 2011, 2012). Nevertheless, all approaches of CRF excess published until now are confounded by a substantial amount of ectopic expression. Although it can be assumed that even ectopic CRF mediates its biological effects only via its cognate receptors, it remains unclear which receptor is involved, and where the overexpressed CRF is released, i.e. locally or in a far distance to the site of overexpression.

In contrast, targeted inactivation of the CRF gene in the mouse enabled the direct assessment of in vivo functions of CRF with respect to HPA axis activity, emotionality and behavioral stress responses. As expected, constitutive CRF knockout mice display a blunted HPA axis (Muglia et al., 1995). Surprisingly, these animals do not show any alterations in anxiety-related behavior under basal conditions or in response to stress. Moreover, different selective CRF_1 antagonists are still capable of attenuating stress-induced behaviors in constitutive CRF knockout mice, suggesting that stress-induced behaviors require CRF_1 but not CRF (Weninger et al., 1999).

The effects observed in CRF knockout mice are even more surprising in the light of CRF_1 mutant mice, which show distinct behavioral phenotypes. Constitutive CRF_1 knockout mice fully phenocopy the HPA axis phenotype of CRF knockout mice, including a chronic corticosterone deficit and a blunted stress response. In addition, the two independently generated CRF_1-deficient mouse lines show a clear decrease in anxiety-related behaviors in various test paradigms compared to wild-type littermates (Smith et al., 1998; Timpl et al., 1998). CRF_1 is a prime example of the power of mouse genetic tools, which enable the dissection of gene function in a very refined manner. In the first instance, conditional mutagenesis was used to specifically delete CRF_1 in the forebrain, including limbic structures. Thereby, it could be demonstrated that CRF_1 modulates anxiety-related behavior in a completely HPA axis independent manner (Muller et al., 2003). These mutants further demonstrate that the absence of CRF_1 can protect from aversive effects of chronic stress during early life or adulthood (Wang et al., 2011a,b, 2012). The fact that CRF_1 is expressed throughout the brain in different types of neurons suggested that the receptor might have specific functions depending on the cellular context (Refojo et al., 2011). Consequently, the function of CRF_1 was probed in different neurotransmitter circuits using respective Cre driver lines that provided selectivity for glutamatergic, GABAergic, dopaminergic and serotonergic neurons. This approach revealed a previously unknown bidirectional control of anxiety-related behavior via CRF_1, suggesting that an imbalance of CRF_1-controlled anxiogenic glutamatergic and anxiolytic dopaminergic circuits might be involved in the manifestation of stress-related disorders (Refojo et al., 2011). Along these lines, Lemos and colleagues could demonstrate that stress can switch the action of CRF from appetitive to aversive, involving dopamine release within the nucleus accumbens (Lemos et al., 2012).

These recent findings indicate a previously unexpected complexity of the CRF system, which is further complicated by the existence of a second receptor, a binding protein and soluble variants of CRF_2 that are regulating the bioavailability of CRF. The discrepancy between CRF and CRF_1 mouse mutants with respect to behavioral outcomes might originate from different causes: (1) The early deletion of CRF might trigger compensatory processes; (2) the corticosterone deficiency might mask potential phenotypes; (3) Urocortin 1 as the single other ligand activating CRF_1 might compensate for the loss of CRF; (4) CRF might exert its action primarily under conditions of chronic or severe stress; (5) the CRF_1 receptor might comprise ligand-independent activity, e.g. due to constitutive activity or heteromerization with other receptors.

To better understand the role of CRF in emotionality and stress responses it will be of major importance to gain insights at the neurocircuit level. It will be crucial to understand under which circumstances CRF is released and where it will be active. Earliest hints came from i.c.v. application studies (Bittencourt and Sawchenko, 2000) but again, these have not shed light on the endogenous CRF system, which might involve local as well as distant release. CRF is a neuropeptide and thus stored within dense core vesicles but it is fully unclear which physiological stimuli trigger the release within the extrahypophysiotropic CRF system in vivo and whether CRF is synaptically released or rather in a mode of volume transmission (van den Pol, 2012). Moreover, it will be of major importance to unravel the identity of CRF expressing neurons in stress-involved brain structures in greater detail. In this regard, it will be mandatory to develop better tools, such as conditional CRF mice as well as Cre drivers

that provide genetic access to subpopulations of CRF and Urocortin 1 neurons (Taniguchi et al., 2011).

9. Clinical biomarkers for central CRF overexpression –identifying the right patient for CRF_1 antagonistic treatment (*chapter contributed by M. Ising, PhD and F. Holsboer, MD, PhD*)

Depression is a typical example of a stress-related disorder of the brain. Severe early life stress increases the risk of adult depression, certain stressors trigger the incidence of a depressive episode, and features of acute depression resemble symptoms of chronic stress (Hammen, 2005; Paykel, 2003). A large number of clinical findings including post-mortem studies in suicide victims and results from cerebrospinal fluid studies in acutely depressed patients point to a pathological overactivity of CRF in major depression. Neuroendocrine challenge tests like the combined dexamethasone (dex)/CRF test conducted in acute depression indicate a profound dysregulation of the stress response in the majority of patients (Holsboer and Ising, 2010). These disturbances typically disappear under successful antidepressant medication (Ising et al., 2005). Animal studies of anxiety and chronic stress also point to a prominent role of CRF, which mainly exerts its stress effects mainly via CRF_1 receptors. For instance, CRF overexpressing mice show features of hyperarousal and anxiety, while specific deletion of forebrain CRF_1 led to a marked reduction of anxiety-like behavior (Muller et al., 2003).

A number of small-molecule non-peptide antagonists with high affinity for CRF_1 have been developed for the treatment of depression and anxiety disorders. While these compounds displayed substantial anxiolytic effects in diverse animal models of CRF overactivity and chronic stress, controlled clinical trials in patients with major depression or anxiety disorders were mostly negative. As a result, no CRF_1 antagonist has yet been approved for clinical use in depression or anxiety disorders (Griebel and Holsboer, 2012).

However, it is important to note that not all acutely depressed patients show symptoms of pathological CRF overactivity in terms of an impaired stress response regulation. Accordingly, specific CRF_1 antagonistic treatments are likely to be effective in only those patients characterized by such a CRF-related pathology. Nevertheless, all clinical trials with CRF_1 antagonists have so far been conducted in unselected patient samples, which might explain the disappointing results (Griebel and Holsboer, 2012). Validated biomarkers for identifying patients with central CRF-related depression pathology are currently not available; however, there are promising approaches for the development of such biomarkers.

Overexpression of hypothalamic neuropeptides including CRF seems to be a major factor contributing to an impaired stress response regulation in many patients suffering from depression, and sensitive laboratory tests to identify these impairments like the combined dex/CRF test are readily available. However, in addition to CRF, other neuropeptides like arginine-vasopressin and an altered sensitivity of corticosteroid receptors contribute to a disturbed stress response regulation (Holsboer and Ising, 2010), which limits the CRF specificity of such laboratory tests.

Another core feature of depression physiology is disinhibited rapid eye movement (REM) sleep (Fig. 2), which specifically associates with central CRF activity (Steiger, 2003). Accordingly, elevated REM sleep should indicate increased central CRF activity (concomitant with decreased levels of the slow sleep wave-promoting hormone, growth hormone releasing hormone [GHRH]), and thus characterize patients with CRF-related depression pathology.

In fact, conditional mice mutants with forebrain CRF overexpression display increased REM sleep, which reverts to normal sleep under CRF_1 antagonistic (DMP696) treatment (Kimura et al., 2010). These REM suppressive effects of CRF_1 antagonists could be replicated in further animal models (Ahnaou et al., 2012), and with diverse CRF_1 antagonists (Kimura and Romanowski, personal communication).

One single clinical trial evaluating safety and tolerability of the CRF_1 antagonist R121919 included recordings of sleep EEG before and after 28 days of treatment (Held et al., 2004). A recent re-analysis of the EEG data revealed that baseline REM density indicating impaired REM sleep predicted treatment outcome with the CRF_1 antagonist (Holsboer and Ising, 2010). The majority of patients with substantial REM sleep abnormality (Fig. 3, shaded area) showed between 50 and 90% improvement of depression symptoms, while improvement in patients without REM sleep abnormality was consistently below 50%.

Neuropeptide receptor ligands like CRF_1 antagonists are highly selective treatments that require the availability of appropriate biomarkers to identify the right patients who would optimally benefit from such specific intervention. This benefit of targeting subpopulations of individuals that suffer from MDD has been previously demonstrated (Mehta et al., 2013). The summarized findings suggest that besides laboratory tests of stress response regulation, REM sleep disinhibition is a promising candidate for such a biomarker to reflect central CRF overexpression, and thus, to identify the appropriate target population for successful CRF_1 antagonistic treatment in depression and anxiety disorders.

10. An integrated view of CRF and depression

Depression is a stress-induced psychopathology and disorder of the brain. It is especially well realized by social stressors, the most common type of stress in humans, and the most intensely stressful (Koolhaas et al., 1997). Women are twice as likely to suffer from depression as men, and animal models of depression reveal similar sex-related physiological and behavioral differences. Social stress in animal models corresponds well with clinical manifestations of affective disorders. As in humans, animal models describe significant variability of stress responsiveness in populations, which include more passive and proactive individual proclivities. Passive coping is associated with increased susceptibility to the consequences of stress and depression in animals and in humans. Clinically, major depression is characterized by a pathological over activity of CRF systems. In addition to CRF, altered arginine vasopressin and glucocorticoid receptor sensitivity contribute to disturbed stress responses in depressed individuals. Neuroendocrine challenges (dexamethasone/CRF) indicate a profound dysregulation of stress responsiveness in the majority of depressed patients (Holsboer and Ising, 2010; Ising et al., 2005). Typically, this

lack of negative feedback sensitivity to challenge or stress-induced elevated hormonal concentrations disappears under successful antidepressant treatment.

Therefore, dysregulation of HPA function co-occurs with depression, and with this extrahypothalamic CRF appears to drive anxiety and depressive behavior. What is more, CRF_1 receptors modulate anxious behaviors independently of the HPA axis. Specific deletion of CRF_1 receptors results in a marked reduction of anxious behavior. Absence of CRF_1 receptors protects individuals form aversive effects of chronic stress during early life or adulthood. It is important to note that CRF_1 receptors have specific functions depending on cellular context. Recent work has suggested bidirectional control of anxious behavior via CRF_1 receptor activities.

Repeated stress stimulates CRF activity, and modifies the functionality of the CRF system distinctively for males and females through unique CRF_1 and CRF_2 receptor cell physiology. Repeated stress results in CRF_1 receptor internalization, while CRF_2 receptors are recruited to the membrane. Internalization of CRF_1 receptors is absent in individuals coping with social stress by means of passive responses. This is particularly important for the demographics of depression, as CRF_1 receptor responses are sex biased; CRF_1 binding and coupling to G_s proteins is greater in females than males, in regions implicated in depression. In CRF-overexpressing mice, CRF_1 receptors in females fail to bind β-arrestin and become internalized. In contrast there is greater CRF_2 receptor binding in males in related brain regions such as the BNST. Daily CRF_1 antagonist treatment shifts behavioral responses to proactive coping and also prevents despair in animals. What is more, daily CRF_1 antagonism mitigates urinary and cardiovascular dysfunctions associated with depression.

The evidence suggests that CRF_1 controlled glutamatergic (anxiogenic), noradrenergic (anxiogenic) and dopaminergic (anxiolytic) circuits are involved in the manifestation of stress-related disorders such as depression. In this type of bi-directionally controlled system, stress can switch the action of CRF from appetitive to aversive involving DA in the nucleus accumbens. Similarly, individuals lacking the compensatory response of CRF_1-β-arrestin cellular internalization (as observed in females) exhibit more rapid firing of the LC. In this light it is important to remember that CRF_1 receptors have specific functions depending on cellular context, and that not all acutely depressed patients show symptoms of CRF over activity. Individual and sex related differences in overexpression of CRF, receptor binding, and cellular response may be reasons that in controlled clinical trials for small-molecule non-peptide CRF_1 antagonists were ineffective for some patients. It is reasonable to think that specific CRF_1 antagonists will only be effective in patients with a CRF over expression pathology. An essential feature of depression physiology in these patients is disinhibited REM sleep, which specifically interacts with CRF activity. The majority of patients with REM irregularities exhibit reduced symptoms of depression after CRF_1 antagonist treatment (Holsboer and Ising, 2010). As differences in CRF_1 function in women may lead to increased depressive symptoms, treatments for both women and men may also require customization to address sex responsiveness criteria.

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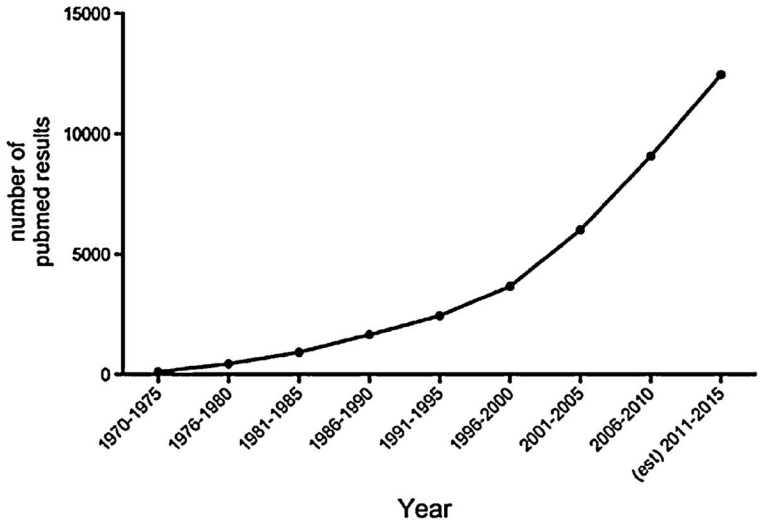

Fig. 1.

Graphical representation of the increase in number of publications returned using a PubMed search from (depression [title/abstract]AND(mood)AND(*year range*) 1970–2015. Future data (December 2014–December 2015) extrapolated from current numbers.

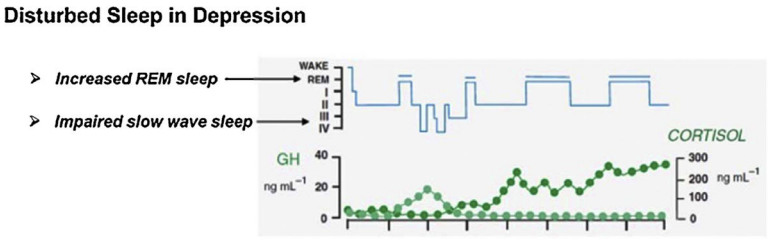

Fig. 2.

Disturbed sleep in depression is characterized by impaired slow-wave sleep and increased REM sleep resulting from an imbalance between GHRH and CRF (after Steiger, 2003).

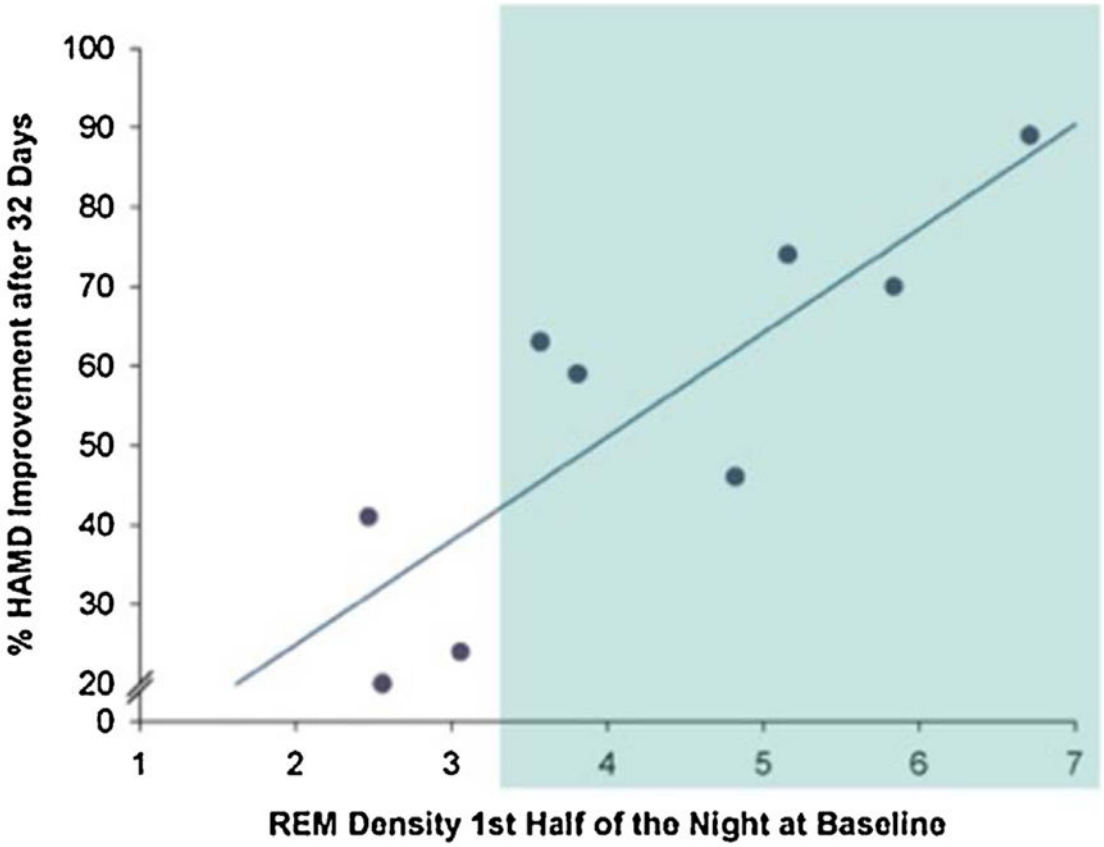

Fig. 3.

Elevated REM density (shaded area) indicating central CRF over-activity in depression potentially characterizes the appropriate target population for successful CRF_1 antagonistic treatment in depression and anxiety disorders. [HAMD: Hamilton rating scale for Depression] (after Holsboer and Ising, 2010).

Table 1

Summary list of CRF family peptides, splice variants of each receptor subtype, and the affinity of each ligand for receptors.

Receptor	Splice variant	Ligand affinity			
		CRF	**Urocortin 1**	**Urocortin 2**	**Urocortin 3**
CRF_1	CRF_{1A} (*archetype*)	High	Equal	Low	Low
	CRF_{1B} (*intracellular domain*)				
	CRF_{1C} (*N-terminus*)				
	CRF_{1D} (*transmembrane domain*)				
	CRF_{1E} (*N-terminus*)				
	CRF_{1F} (*intracellular domain*)				
	CRF_{1G} (*transmembrane domain*)				
	CRF_{1H} (*N-terminus*)				
CRF_2	CRF_{2A} (*archetype*)	Low	Equal	High	High
	CRF_{2B} (*N-terminus*)				
	CRF_{2C} (*N-terminus*)				