The CRF System as a Therapeutic Target for Neuropsychiatric Disorders

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Abstract

The major neuropsychiatric disorders are devastating illnesses that are only modestly responsive to treatment. Improving the treatment of these conditions will require innovative new strategies that depart from previously focused upon pharmacological mechanisms. Considerable preclinical and clinical data point to Corticotropin-Releasing Factor (CRF) signaling as a target for new psychotropic drug development. Here we review alterations in the CRF system reported in several psychiatric conditions. We also examine the preclinical work that has dissected the distinctive roles for CRF receptors in specific circuits relevant to these disorders. We further describe the clinical trials of CRF1 receptor antagonists that have been conducted. Although these clinical trials have thus far met with limited therapeutic success, the unfolding complexity of the CRF system promises many future directions for studying its role in the etiology and treatment of neuropsychiatric conditions.

Keywords

CRF; Stress; Psychopathology; Treatment; Polymorphisms; Preclinical

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Several neuropsychiatric disorders are severe and chronic conditions that are challenging to treat [1]. Most of the medications used to treat these conditions act on monoamine systems, a paradigm of drug action that has not changed in half a century. The less than optimal efficacy for these medications points to the need for innovative new approaches that depart from these conventional drug development approaches [2]. Advances in basic neurobiology point to corticotropin-releasing factor (CRF) signaling as a target for psychotropic development [3, 4]. CRF is a 41 amino acid neuropeptide that is implicated in the pathophysiology of many psychiatric disorders, including depression, post-traumatic stress disorder (PTSD) and substance/alcohol abuse [3, 5, 6]. In recent years, state-of-the-art research has advanced the understanding of CRF's role in regulating behavioral, endocrine,

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immune and autonomic responses to stress [4, 7-11]. These studies, added to decades of prior research [5, 12], suggest that targeting CRF receptors might open new avenues for treating psychopathology. In this review we summarize the CRF system and the body of evidence that alterations in these circuits play a seminal role in many of these psychiatric conditions. We further examine the preclinical research that has informed on the role of specific brain circuits containing CRF relevant to these disorders. We also describe all of the clinical trials thus far conducted of CRF receptor antagonists and potential future directions.

The Corticotropin Releasing Factor (CRF) System

In 1981 Wylie Vale and colleagues at the Salk Institute in La Jolla, CA first reported the biochemical characterization of CRF [13]. Subsequent studies found CRF mRNA and CRF to be broadly distributed in the central nervous system (CNS), enriched in the paraventricular nucleus of the hypothalamus (PVN), brain stem, amygdala, hippocampus and neocortex [4]. Upon being released from neurons, CRF binds mainly to two, seven transmembrane, G protein coupled receptors with high sequence homology (~70% amino acid identity) designated as CRF1 and CRF2 [4] (Figure 1).

CRF binds with high affinity to the CRF1 receptor [4]. This receptor has an overlapping distribution with CRF in many brain areas and is found in the anterior pituitary, hippocampus, cortex and amygdala. Within the anterior pituitary, CRF1 plays a pivotal role in regulating the activation of the hypothalamic-pituitary-adrenal (HPA) axis both at baseline and after exposure to stress [4]. Anterior pituitary CRF1 stimulation results in adrenocorticotropin (ACTH) release from the hypothalamus and subsequent cortisol release from the adrenal cortex. Cortisol, in turn, activates glucocorticoid receptors (GR) and mineralcorticoid receptors (MR) to initiate intracellular signaling cascades mediating the intracellular response to stress [4].

In humans, multiple splice variants of CRF1 (CRF1 α, β, c-h and i) have been described [14, 15]. CRF1α is considered to be the only endogenously expressed CRF1 receptor that is functionally active. [14]. CRF1β is impaired in its signal transduction and is also predisposed to premature de-sensitization [16]. CRF1 c-h, harbor mutations that interfere with signaling [14]. Although functions for splice variants remain to be clarified, they may play key roles [17]. CRF1d interferes with the cell surface expression of functional CRF1 receptors acting as a dominate-negative regulator of CRF signaling [18].

CRF binds with lower affinity to the CRF2 receptor [4]. In contrast to CRF1, CRF2 is localized to discrete brain areas such as the dorsal raphe nucleus (DRN), lateral septum (LS) and periaqueductal gray (PAG) [4]. Although the role of CRF2 is less studied than that of CRF1, it typically acts to counteract stress responses initiated by CRF1 stimulation [11]. Its divergent role from CRF1 is reflected in a differing localization within DRN neurons. Within these neurons CRF1 is primarily found on the cell membrane, while CRF2 is found in the cytoplasm. Stress reverses this distribution and causes CRF to excite rather than inhibit the DRN [19]. Similar to CRF1, CRF2 has multiple splice variants (CRF 2a-c). These splice variants result in minimal pharmacological variation and are thought to regulate expression [4].

CRF1 and CRF2 signal through multiple pathways [4]. Major pathways include $G\alpha_s$ signaling to stimulate cyclic AMP production and downstream activation of protein kinase A (PKA) [20]. Additional cascades involve the activation of $G\alpha_q$ and protein kinase C (PKC) [4, 21], and the extracellular signal-regulated kinase (ERK)-MAP kinase cascade [22]. CRF also signals through the Akt/protein kinase B, NOS-guanylyl cyclase and caspase pro-apoptotic pathways [4]. Added to this complexity, CRF1 may interchangeably signal through differing pathways. In the piriform cortex CRF1 normally signals through $G\alpha_q/11$. However, seizures change this linkage to $G\alpha_s$ [23].

CRF1 and CRF2 densities are regulated by chronic stress or agonist exposure [4, 24-26]. A downregulation of CRF1 and CRF2 to agonists occurs through homologous desensitization mechanisms that involve G protein-coupled receptor kinase (GRK) phosphorylation and β-Arrestin coupling [4, 27]. CRF1 cell surface trafficking is modulated by novel interactions with postsynaptic density 95 (PSD 95) and with cystic fibrosis transmembrane conductance regulator-associated ligand (CAL) [28, 29]. CRF binding protein (CRF-BP) acts to further regulate this system through sequestering CRF and through increasing CRF 2a cell surface levels [30].

In addition to CRF are three urocortin peptides (UCN1, UCN2 and UCN3). UCN1 is expressed in a hindbrain projection from the Edinger Westphal nucleus to the DRN. UCN2 is expressed in the locus coeruleus (LC), PVN and brain stem motor nuclei. UCN3 is expressed in neurons that project to the LS, bed nucleus of stria terminals (BNST) and hypothalamic nuclei. UCN1 binds with similar affinity to CRF1 and CRF 2.UCN2 and UCN3 are CRF2 specific [4].

CRF in Psychopathology; From Bench to Bedside

Abnormalities in the CRF system are implicated in a gamut of psychiatric disorders [5, 6, 31, 32]. Here we discuss data from patients affected by major categories of mental illness as classified in the Diagnostic and Statistical Manual of Mental Disorders, most recent Version; DSM-5 [33]. In parallel, we also examine preclinical studies seeking to dissect the significance of these CRF abnormalities to brain function. We further review the results of clinical trials that have tested CRF1 receptor antagonists in psychiatric disorders.

Affective (Mood) Disorders

Depressive disorders include several conditions that are characterized by an overly sad, empty or irritable mood [33]. Major depressive disorder (MDD) affects over 350 million people and is diagnosed in nearly two-thirds of individuals who commit suicide [1]. It is associated with alterations in sleep, appetite, concentration and psychomotor function. Despite this severe morbidity and mortality, pharmacological and psychotherapeutic treatments for MDD are ineffective for at least one-third of patients [2].

More than three decades of research implicate CRF in the MDD pathogenesis [5, 34, 35]. Seminal studies found elevated CRF concentrations in the cerebrospinal fluid (CSF) of drug-free MDD patients [5]. In postmortem studies, depressed patients exhibit elevated CRF mRNA expression in the PVN and LC [36]. Postmortem studies of suicide victims revealed

increased cortical CRF mRNA expression and reductions in CRF1 receptors, results consistent with excessive CRF production [37, 38]. Current studies have built upon this pioneering work, and study genetic variation in CRF1 receptors. Specific single nucleotide polymorphisms (SNPs, see Glossary) within the CRF1 gene are found to associate with MDD [35, 39-41]. More specifically, studies found that the SNP, rs110402, interacts with a history of child abuse to mediate MDD vulnerability in adulthood [35, 39-41]. A role for rs110402 in MDD may be related to its modulation of circuitry activated by emotional stimuli. Depending upon genetic variation at this SNP, MDD patients demonstrate abnormally high cingulate or low amygdala, hypothalamic and nucleus accumbens activation when presented with negative words [35].

While the downstream effects of CRF1 SNPs is a subject of ongoing study, preclinical models point to excessive CRF receptor activation in depression [10, 42-44]. For example, 'behavioral despair' refers to rodent immobility in the forced swim test that is regarded as a model of depressive symptoms. Behavioral despair is increased in mice by the forebrain-specific over-expression of CRF [43]. Further work has focused on the specific forebrain circuits where CRF may be acting. These studies find that behavioral despair is increased by site-specific overexpression of CRF in the BNST [44]. Other studies show that excessive CRF1 receptor activation, in particular, is important to behavioral despair because this behavior is decreased by a CRF1 antagonist [45].

Additional preclinical research implicates altered integration of CRF1 and CRF2 signaling in depressive symptoms. Thus, the co-activation of CRF1 and CRF2 increases dopamine release in the nucleus accumbens (NAc) [10]. However, in a mouse model of stress-induced depression, this phenomenon was abolished [10]. In a separate study, CRF2 deletion increased behavioral despair in association with increased CRF1 activation in the hippocampus. This behavioral despair was then rescued by the hippocampal-infusion of a CRF1 antagonist [42].

Taken together, these preclinical studies point to a role for excessive CRF1 receptor stimulation in depression. Based upon these findings, CRF1 receptor antagonists might be helpful for treating MDD. A pioneering study at the Max Planck Institute tested the CRF1 antagonist, NBI 30775/R121919 in patients with MDD. Depression symptoms were reduced as measured by the Hamilton Depression Rating Scale (HAMD) and sleep-EEG readings were improved in a randomly assessed subgroup of the treated patients [46, 47]. These promising findings for NBI 30775/R121919, though, were limited by hepatic toxicity [48].

Another trial studied the effects of the CRF1 antagonist, CP-316,311 in the treatment of MDD. This medication was well tolerated and did not demonstrate the hepatic toxicity associated with R121919. CP-316,311 treated patients, however, did not differ in their HAMD change scores compared to placebo treated controls [49] (Table 1).

Additional clinical trials of CRF1 antagonists have included GW 876008/Emicerfont, BMS 562086/Pexacerfont, ONO 2333MS, SSR125543 and GSK 561679/Verucerfont. Each of these clinical trials has failed to treat MDD (https://clinicaltrials.gov).

Trauma-and Stressor-Related Disorders

CRF's central role in stress physiology renders it a plausible candidate for a role in Trauma- and Stress or Related Disorders. These include PTSD, acute stress disorder and reactive attachment disorder [33]. These are disorders where exposure to trauma results in enduring psychological distress [33]. An important research goal is to clarify factors that differentiate vulnerable versus resilient individuals for developing these conditions. Although the majority of adults in the United States will experience a traumatic event in their lifetime, a minority, at the most 30%, will go on to develop PTSD [50].

Variations in the CRF system are a leading candidate for mediating the vulnerability to psychological symptoms after trauma. Elevated CRF concentrations are found in the CSF of patients with severe PTSD [12]. Additional studies find genetic variation in CRF1 and CRF2 receptors associated with PTSD. An epidemiological study of adults exposed to the 2004 Florida Hurricanes found that the CRF1 SNPs, rs12930831 and rs4792887, associate with PTSD symptoms [50]. The CRF2 SNPs, rs8192496 and rs2190242, are associated with PTSD symptoms in females [51]. CRF may also be playing a critical role in mediating childhood PTSD. In pediatric injury patients, the CRF1 SNP, rs 12944712, is associated with PTSD symptoms at 3 months and 1 year post-injury [52].

The role for CRF in PTSD is paralleled by animal research highlighting it's involvement in stress vulnerability [26, 53, 54]. Fear levels in rats exposed to predator-cues correlate with BNST CRF1 upregulation and CRF2 downregulation [25]. An upregulation of CRF1 is also found in neonatal rats whose mothers were exposed to chronic stress [26]. These combined results suggest that PTSD treatments may be developed using CRF1 antagonists or CRF2 agonists. In support of this idea, treating traumatized mice with the CRF1 antagonist, SR125543, prevents sleep impairments [54]. In contrast, using a viral vector to overexpress CRF2 in the amygdala and BNST will decrease the behavioral impairments of rats exposed to predator-associated cues [25].

A recent study using the CRF1 antagonist, GSK56167, evaluated its efficacy in treating women diagnosed with PTSD [55]. Unfortunately the drug was no more efficacious than placebo (Dunlop, Nemeroff, et al., personal communication). Results of biomarkers that may predict treatment response, including variants of stress-related genes, gene expression profiles and indicators of HPA axis reactivity are pending (NCT01059227) (Table 1).

Substance-Related and Addictive Disorders

Substance-related and addictive disorders include substance use/abuse, intoxication and withdrawal disorders [33]. The CRF1 SNP, rs110402, interacts with a polymorphism in CRF-BP to alter the normal expression ratio of these molecules and to predict alcohol use disorder [56]. Variants in CRF1 also interact with a history of stressful and traumatic experiences to mediate substance abuse risk [57-59]. Indeed, a major role for CRF in these disorders may be to mediate interactions between stress and its tendency to facilitate drug seeking [60-64].

The involvement of CRF in stress-induced drug seeking has been explored in more detail in preclinical models [60-64]. These studies indicate that the ventral tegmental area (VTA) is a

critical site for CRF's actions in this behavior. Knocking down CRF1 in this region with short hairpin RNAs blocks acute food deprivation stress-induced reinstatement of cocaine seeking [60]. A combined role for CRF1 and CRF2 in the VTA depends upon the species and the experimental paradigm. Blocking CRF1 or CRF2 decreases cocaine sensitization to social defeat stress in rats [61]. However, blocking CRF1, while simultaneously stimulating CRF2, decreases binge-like ethanol intake in mice [63].

CRF may also be important to the anxiety associated with drug withdrawal [65]. Studies indicate that CRF1 activation may promote withdrawal symptoms, while CRF2 stimulation may prevent these symptoms [24, 66, 67]. In nicotine dependent animals, CRF1 are upregulated in the VTA [24]. The importance of this upregulation to withdrawal is illustrated by the ability of a VTA-specific CRF1 antagonist to decrease withdrawal symptoms [66]. A role for CRF2 in withdrawal symptoms is suggested by its upregulation in association with decreased withdrawal symptoms [66].

BMS 562086/Pexacerfont and GSK 561679/Verucerfont have been studied as treatments for stress-induced craving of alcohol [68, 69]. In these clinical studies neural responses to alcohol-related stimuli were also assessed with fMRI [68, 69]. BMS 562086/Pexacerfont was found to have no effect on alcohol craving or neural responses to the stimuli presented [68]. GSK 561679/Verucerfont also did not affect alcohol craving [69]. GSK 561679/Verucerfont decreased right amygdala responses to alcohol-related cues and there were increased neural responses to alcohol related stimuli in other brain regions [69] (Table 1).

Anxiety Disorders

Anxiety disorders include panic disorder, specific phobias and generalized anxiety disorder (GAD) [33]. Investigating CRF's role in these conditions has yielded mixed results. Early studies of GAD and panic disorder found CRF CSF concentrations that did not differ from normal controls [70]. However, the CRF1 SNP, rs87888, combined with the AVPR1B SNP, rs28632197, showed an association with panic disorder [71].

Data continue to highlight interactions between CRF and other neuromodulatory systems in anxiety disorders. For example, data show that interactions between the CRF and endocannabinoid system are involved in these conditions [8, 72]. Normally, anxiety is decreased by cannabinoid type 1 receptor (CB1) stimulation by anandamide (AEA) in the basolateral amygdala (BLA). CRF promotes anxiety by inducing fatty acid amide hydrolase (FAAH), an enzyme that degrades AEA [8]. In anxiety disorders there is an interaction between the CRF1 SNP (rs110402) and FAAH SNP (rs324420). This interaction is associated with altered BLA function and an increased risk for these disorders [72].

Other studies have attempted to determine the specific involvement of CRF1 versus CRF2 in rodent models of anxiety. Stimulating CRF1 is anxiogenic in mice [20]. Conversely, CRF2 are typically considered to be anxiolytic [11, 42]. Current data, though, points to an anxiogenic effect for CRF2 depending upon the brain region [7, 9]. Optogenetic activation of CRF2 expressing neurons in the LS promotes anxiety [7]. Simulating CRF2 in the BNST increases anxiety, impairing normal maternal behaviors [9].

To test the effects of CRF1 antagonist treatment in GAD, a clinical trial tested BMS 562086/ Pexacerfont [73]. BMS 562086/Pexacerfont-treated patients did not differ from placebo treated controls on the Hamilton Anxiety Scale (HAMA), and responded less well than those treated with the SSRI escitalopram [73]. There was no relationship between treatment outcomes and polymorphisms in CRF1, GR, CRF-BP [73] (Table 1).

Feeding and Eating Disorders

Feeding and Eating Disorders are defined by a persistent disturbance in eating behavior and include anorexia nervosa, bulimia nervosa and binge eating disorder [33]. High CSF CRF concentrations have been reported in anorexia nervosa [74]. In a rat model of binge eating, CRF1 antagonists infused into the BNST reduce stress-induced binge eating behavior [32]. Clinical trials on CRF1 antagonists in Feeding and Eating Disorders have not been pursued.

Neurocognitive Disorders

Neurocognitive Disorders include Alzheimer's Disease (AD), Parkinson's and vascular dementia [33]. A risk for AD is increased in Veteran's who have PTSD and this may be through a CRF1-dependent mechanism [75]. This is suggested by studies showing that CRF1 antagonists prevent stress-induced β amyloid- deposition in mouse models of AD [31, 76]. Postmortem studies have revealed marked reductions in CRF concentrations in multiple cerebrocortical areas in AD [77]. CRF1 antagonists also prevent stress- induced tau phosphorylation in the hippocampus [78]. Clinical trials on CRF1 antagonists in Neurocognitive Disorders have not been pursued.

Concluding Remarks and Future Perspectives

In conclusion, these data strongly support the hypothesis of altered CRF signaling in the etiology of Mood Disorders, Trauma and Stressor-Related Disorders and Substance-Related and Addictive Disorders [34, 51, 52, 57]. These data reveal a more complex association between CRF and Anxiety Disorders, where interactions with other neuromodulatory systems likely mediate its role in these pathologies [71, 72].

In agreement with early clinical studies [5, 12], preclinical research suggests that excessive CRF receptor activation contributes to symptoms in several of these conditions. In particular, excessive CRF1 stimulation in specific brain circuits within the hippocampus, NAc, LS, BNST, VTA and amygdala may be involved [10, 25, 44, 60-62]. Furthermore, although CRF2 generally acts in a manner that counteracts the effects of CRF1 [25, 42, 63, 67], there are distinctions in CRF2's function according to both the preclinical model and the brain region where it is stimulated [7, 9, 61] (Table 2).

Given the large body of research that points to excessive CRF1 signaling in psychopathology, the limited therapeutic success of CRF1 antagonists is surprising [47, 49, 68, 69, 73]. Faced with these modest outcomes there are factors related to patient selection, CRF1 antagonists and animal models to be considered. Although early studies of CRF in MDD and PTSD found higher CSF levels on average, many patients exhibited normal levels [5, 6]. Those specific patients with high CRF levels may be subject to excessive CRF1 receptor stimulation, resulting in the harmful psychological effects associated with over-

activation of this receptor. Therefore, it may be that patients need to be stratified according to CSF CRF concentrations with the true hypersecretors benefitting the most from CRF1 antagonist treatment.

At the genomic level,CRF1 polymorphisms might help to guide CRF1 antagonist treatment towards likely responders. The ability of CRF1 SNPs to predict CRF1 antagonist response in MDD and PTSD, where abnormal CRF signaling is strongly implicated, has not been studied. Clinical trials that include an analysis of SNPs in the CRF system might yield more promising results [55].

Patient selection might also be better informed by other aspects of the psychosocial history. Psychiatric disorders and over-activity of the CRF system are both common outcomes of patients with childhood trauma histories [12, 79]. Moreover, a history of developmental trauma is found to interact with CRF1 variants to increase the risk for adult psychopathology [39-41, 57-59]. Therefore, patients with trauma histories might be more likely to respond CRF1 antagonist treatment.

Beyond patient selection the pharmacological characteristics and dosage of the CRF1 antagonist needed to obtain sufficient receptor occupancy remains unclear. Accurately determining the dose would require a specific CRF1 ligand that is suitable for positron emission tomography (PET) imaging. Radioligands with PET imaging potential have been developed, but are still being characterized [80]. Furthermore, since greater time occupying the receptor is associated with increased antagonist efficacy, the dissociation kinetics of antagonists may be important for clinical efficacy. [3].

The inherent limitations of animal models is another factor that may contribute to the poor translation of preclinical CRF data [1]. In particular, many adult patients with MDD and anxiety disorders suffer from these conditions for years, with the first presentation in adolescence. The CRF system targeted in these chronic human states may differ from the system targeted in animals.

Because CRF2 counteracts the effects of CRF1 in many preclinical paradigms [25, 42, 63, 67], the future development of CRF2 agonists may be another approach to develop effective novel therapeutics. Added to these potential directions, is the possibility of testing CRF1 antagonists in eating and neurocognitive disorders, where new data suggests that CRF may be playing a role in these diseases [31, 32].

In conclusion, CRF has been studied as a putative therapeutic target for neuropsyical disorders for nearly 40 years. Although positive therapeutic results from clinical trials of CRF1 antagonists have been limited, the unfolding complexity of this system promises many future directions for studying its role in the etiology and treatment of neuropsychiatric disorders.

Acknowledgments

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Glossary

Antagonist

A compound that blocks a drug from binding to a receptor

Basolateral Amygdala (BLA)

A division of the amygdala that is commonly involved in the expression of fear and anxiety

Bed Nucleus of Stria Terminalis (BNST)

A brain structure that is involved in anxiety and reward. It is commonly involved in drug seeking behavior in rodents

Behavioral Despair

Immobile responses that animals make when they are forced to swim in a container from which they cannot escape

Post-Traumatic Stress Disorder

A psychological illness that follows from a traumatic event and that consists of re-experiencing the trauma, avoiding trauma-related stimuli, hyperarousal and negative alterations in cognition and mood

Preclinical Model

Rodent models that resemble, etiologic, anatomical, behavioral and biochemical features of a human disease. The model responds to treatments that predicts the effects of those treatments in humans

Seven transmembrane G protein coupled receptor

Receptors that couple with G proteins to signal intracellularly when activated by a ligand. Their structure passes through the cell membrane seven times

Single Nucleotide Polymorphism (SNP)

Variation in a single nucleotide that occurs at a precise genomic position

Ventral Tegmental Area (VTA)

A specific group of neurons in the brain that produce dopamine and that project to many brain regions. It is commonly involved in drug seeking behavior in rodents

Outstanding Questions

- Will CRF1 antagonist treatment efficacy be improved if patients are stratified according to baseline CSF CRF concentrations?

- Do CRF1 SNPs modulate the effects of CRF1 antagonist treatment?

- Are there aspects of patients' psychosocial histories, such as childhood abuse or neglect, which modify response to CRF1 antagonists?

- What dose of CRF1 antagonist is needed to obtain sufficient receptor occupancy?

- What pharmacological properties, such as rapid versus slow dissociating occupancy of the receptor, predict clinical efficacy?

- Do CRF1 antagonists have a role in other clinical scenarios, such as in the treatment for neurocognitive disorders and feeding or eating disorders?

- Is there a future role for CRF2 agonist or antagonists to treat neuropsychiatric disorders?

- Are there abnormalities in other, less characterized aspects of CRF signaling that contribute to psychopathology? These might include polymorphisms that influence expression of CRF receptor splice variants, the regulation of the system by CRF-BP or that affect downstream signaling cascades.

Trends

Data support a role for altered CRF signaling in several neuropsychiatric disorders.

CRF1 variants interact with a history of trauma, particularly in childhood, to increase the risk for these conditions.

Clinical trials of CRF1 antagonists have had limited success in the treatment of Depressive Disorders, Substance Abuse, Anxiety Disorders and Trauma and Stress Related Disorders.

The modest success of clinical trials points to the need for continued research on CRF system function. Recent studies have unraveled distinctive roles for CRF1 and CRF2 receptors in balancing CRF's effects in stress and reward circuitry.
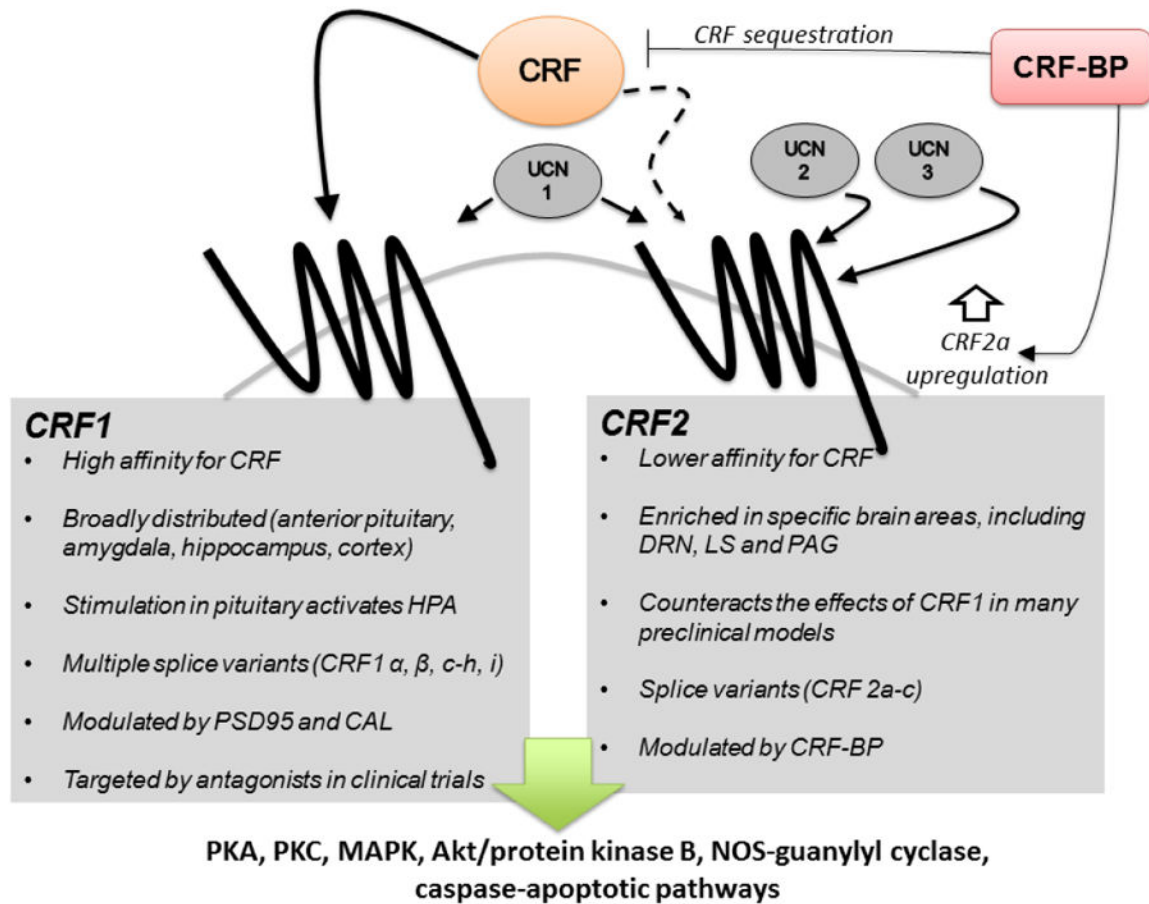
Figure 1. Diagram of CRF System

CRF=coritocotropin releasing factor, UCN=urocortin, CRF1 corticotropin release factor receptor type 1, CRF2=corticotropin releasing factor receptor type 2, DRN=dorsal raphe nucleus, LS=lateral septum, PAG=peri-aqueductal grey. CRF-BP=corticotropin releasing factor binding protein, PKA=protein kinase A, PKC=protein kinase C, MAPK=mitogen activated proteint kinase, CAL=cystic fibrosis transmembrane conductance regulator-associated ligand, PSD 95=postsynaptic density 95 [4, 11, 14, 27-30]

Table 1
Summary of CRF1 Antagonist Clinical Trials

Disorder	CRF1 Antagonist	Clinical Trial Design		Data	
Depressive Disorders	NBI30775/R121919	•	Open label, n=20 patients with MDD.	•	Decreased HAMD [47].
		•	Treated for 30 days	•	Improved EEG in a random subgroup of 10 patients [46].
				•	Liver toxicity
	CP316,311	•	Randomized, double-blind, placebo controlled study.	•	Unchanged HAMD for CP316,311 [49].
		•	Data reported from n=28 (CP316,311), n=31 (placebo), n=30 (Sertraline).	•	Sertraline HAMD decreased
		•	Treated for 6 weeks.		
Trauma and Stress-Related Disorders	GSK56167	•	Randomized, double blind, placebo controlled study of females with PTSD.	•	Results pending [55].
		•	Treated for 6 weeks.		
Substance Related and Addictive Disorders	BMS 562086/Pexacerfont	•	Randomized, double blind, placebo controlled study of alcohol dependence.	•	Unchanged alcohol craving [68]
		•	Data reported from n=29 (Pexacerefont), n=26 (placebo).	•	Unchanged neural responses to alcohol-related stimuli.
		•	Treated for 30 days.		
	GSK 561679/Verucerfont	•	Randomized, double blind, placebo controlled study of alcohol dependence.	•	Unchanged alcohol craving [69].
		•	Data reported from n=18 (Verucerfont), n=21 (placebo).	•	Right amygdale response to negative stimuli attenuated.
				•	Responses to alcohol-cues increased.

Disorder	CRF1 Antagonist	Clinical Trial Design		Data	
		•	Treated for 3 weeks.		
Anxiety Disorders	BMS 562086/Pexacerfont	•	Randomized, double blind, placebo controlled study of patients with Generalized Anxiety Disorder.	•	Unchanged HAMA [73].
				•	Escitalopram group HAM-A decreased.
		•	Data reported from n=76 (Pexacerfont) n=80 (placebo), n=43 (Escitalopram).	•	No relation to SNPs in CRF1.
		•	Treated for 8 weeks.		

Table 2

Summary of Roles for CRF1 and CRF2 in Preclinical Models of Neuropsychiatric Disorders

Disorder	Depressive Disorders	Trauma and Stress-Related Disorders	Substance Related & Addictive Disorders	Anxiety Disorders
Preclinical Models	*Forced swim test*	*Predator stress, Chronic unpredictable stress, Foot-shock stress*	*Stress-induced drug seeking. Binge-like ethanol intake. Withdrawal.*	*Elevated plus maze. Light-dark box, open field, novel object.*
CRF1	↑ [42, 45]	↑ [25, 26, 54]	↑ [24, 60, 63, 67]	↑ [20]
CRF2	↓ [42]	↓ [25]	↓ [63, 67] ↑ [61]	↓ [11] ↑ [7, 9]

↑ = Data indicate that receptor stimulation promotes symptoms.

↓ =Data indicate that receptor stimulation decreases symptoms.