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Role of Corticotropin Releasing Factor in Anxiety Disorders: A Translational Research Perspective

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Abstract

Anxiety disorders are a group of mental disorders that include generalized anxiety disorder (GAD), panic disorder, phobic disorders (e.g., specific phobias, agoraphobia, social phobia) and posttraumatic stress disorder (PTSD). Anxiety disorders are among the most common of all mental disorders and, when coupled with an awareness of the disability and reduced quality of life they convey, they must be recognized as a serious public health problem. Over 20 years of preclinical studies point to a role for the CRF system in anxiety and stress responses. Clinical studies have supported a model of CRF dysfunction in depression and more recently a potential contribution to specific anxiety disorders (i.e., panic disorder and PTSD). Much work remains in both the clinical and preclinical fields to inform models of CRF function and its contribution to anxiety. First, we will review the current findings of CRF and HPA axis abnormalities in anxiety disorders. Second, we will discuss startle reflex measures as a tool for translational research to determine the role of the CRF system in development and maintenance of clinical anxiety.

Keywords

CRH; CRF; Posttraumatic stress disorder; Anxiety; Panic disorder; Startle

Overview of CRF neuroendocrine effects and its effects on G-protein-coupled receptors

Corticotropin releasing factor (CRF; also termed “CRH” for corticotropin releasing hormone) was first described in *Science* by Vale et al. (1981). They reported the discovery of a hypothesized hypothalamic factor, CRF, a 41 amino acid peptide which selectively and potently activated pituitary corticotropin (or adrenal corticotropin releasing hormone, ACTH) secretion. They predicted that this peptide could be “a key signal in mediating and integrating an organism’s endocrine, visceral and behavioral response to stress” (Vale et al., 1981 p. 1397). More than 20 years of subsequent animal research and clinical studies have confirmed this hypothesis, supporting a role for CRF, and its more recently discovered ligand family Urocortin 1, 2 and 3, in anxiety and stress responses (Lewis et al., 2001;Reyes et al., 2001;Spina et al., 1996). In this review, we will focus on the current state of knowledge of CRF system dysregulation in clinical anxiety and discuss future avenues of translational research on the role of CRF in startle phenotypes observed in some anxiety disorders.

CRF mediation of the neuroendocrine response to stress

In response to stress, CRF is released from the median eminence of the hypothalamus, where it subsequently binds to receptors at the anterior pituitary and increases ACTH release into the

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bloodstream. ACTH consequently acts at the adrenal cortex to facilitate release of glucocorticoids such as cortisol. This system, known as the hypothalamic-pituitary-adrenal axis (HPA), is an important component of the response to stress and has been shown to be dysregulated in both anxiety and depressive disorders (see below). CRF receptors are required for this stress response (Bale et al., 2002), which modifies peripheral physiological responses to support “fight or flight” reactions, such as mobilizing energy stores (Pecoraro et al., 2005).

CRF mediation of behavior stress responses

CRF containing neurons are not confined to hypothalamic regions; they are also found in a number of neural circuits that mediate information processing and behavior. In non-human primates, CRF immunoreactive fibers and/or perikarya are observed in the cortex (especially anterior cingulate), amygdalar complex and extended amygdala, hippocampus and hind brain regions such as the locus coeruleus and substantia nigra (Bassett and Foote, 1992;Bassett et al., 1992;Foote and Cha, 1988;Lewis et al., 1989). CRF has been shown to modulate diverse neurotransmitter systems, including glutamate, dopamine, serotonin and norepinephrine (Lavicky and Dunn, 1993;Price and Lucki, 2001;Valentino and Commons, 2005). Its modulation of serotonin and norepinephrine release specifically supports a role in emotional responding as these neurotransmitter systems are implicated in affective and anxiety responses (both normal and disordered) (Charney, 2004;Koob, 1999). Hence, CRF is well situated to modulate circuits involved in cognition, defensive behavior and emotion.

CRF acts via at least 2 known G-protein-coupled receptors, CRF_1 and CRF_2 (Chang et al., 1993;Chen et al., 1993;Liaw et al., 1996;Lovenberg et al., 1995;Perrin et al., 1993; for a review, see Eckart et al., 2002 and Dautzenberg and Hauger, 2002). In rodents, both receptors are expressed in relatively discrete nuclei of the neocortex, amygdala and extended amygdala (bed nucleus stria terminalis), nucleus accumbens, hypothalamus, pituitary and sensory relay nuclei (Van Pett et al., 2000). In cortical and hindbrain regions, CRF_1 expression appears to predominate over CRF_2 expression (Van Pett et al., 2000). Strong CRF_2 receptor binding is observed in neocortex and pituitary in primates however, suggesting that CRF_2 receptor functions may be more varied in primates as compared to rodents (Sanchez et al., 1999). Expression of CRF_2 in human brain generally mirrors findings in monkeys, with robust expression in hippocampus, septum, amygdala and extended amygdala and weaker expression in frontal cortex, midbrain and hindbrain regions (Kostich et al., 1998). In non-human primates, CRF_1 receptors have been visualized in cortex, limbic regions and sensory relay nuclei in the brain stem (Kostich et al., 2004;Sanchez et al., 1999). This pattern of CRF receptor distribution has led to the hypothesis that CRF may play a role in (1) sensory processing and associations (e.g., via modulation of thalamus, pedunculopontine tegmentum, inferior colliculus); (2) defensive or anxious responses (via modulation of neurotransmission at the amygdala, hippocampus and hypothalamus); and (3) cognition. In human and non-human primates, CRF may be important for emotional cognition and interoception due to its strong cortical expression in primate anterior cingulate and insula and in human frontal cortex (Craig, 2002). Animal models indicate that the CRF system seems to play a predominant role in the stress response, shifting behavior towards defensive responding by increasing avoidance and fear-related behaviors with the concomitant suppression of appetitive behaviors such as feeding and reproduction.

The vast majority of evidence for the functional role of CRF_1 and CRF_2 receptors comes from animal literature (primarily in rodent) which is extensively reviewed elsewhere (Hauger et al., in press;Bakshi and Kalin, 2000;Koob and Heinrichs, 2004;Reul and Holsboer, 2002). The consistent findings that CRF_1 receptor blockade or gene deletion decreases defensive behaviors and attenuates physiological stress responses (e.g., autonomic and neuroendocrine activation)

offer compelling evidence for this receptor as a primary mediator of the stress response. In stressed, non-human primates, administration of the CRF_1 antagonist antalarmin reduced anxiety-like responses and shifted responding towards exploratory and sexual behaviors that are normally suppressed during stress (Habib et al., 2000). The anxiogenic-like effects of CRF_1 receptor activation support its potential as a target for pharmacotherapy for anxiety disorders (Dautzenberg and Hauger, 2002;Reul and Holsboer, 2002;Shekhar et al., 2005;Zorrilla and Koob, 2004). The role of CRF_2 receptors in anxiety is less clear. There is evidence for both anxiolytic- and anxiogenic-like functions after CRF_2 receptor activation or gene deletion (Bakshi et al., 2002;Bale et al., 2000;Coste et al., 2000;Hammack et al., 2003b;Kishimoto et al., 2000). A predominant hypothesis is that CRF_2 receptors facilitate recovery of stress responding and act to inhibit initial CRF_1-induced stress responses (Bale et al., 2000;Coste et al., 2006;Coste et al., 2001;Kishimoto et al., 2000;Koob and Heinrichs, 2004). An alternative hypothesis posits that, with chronic stress, CRF_2 receptors may play a role in facilitating behavioral shifts towards depressive-like behaviors over immediate defensive behaviors normally mediated by CRF_1 activation (Hammack et al., 2003a,b,2002; but see Bale and Vale, 2003).

Role of CRF in affective and anxiety disorders

Depression

In humans, most CRF system research has focused on its association with depression. Major depressive disorder is a serious public health problem, with up to 30% of women and 15% of men likely to experience depressive episode(s) during their lifetimes. The World Health Organization ranks major depression near the top of the list in terms of global disease (McKenna et al., 2005;Murray and Lopez, 1997). Major depressive episodes are characterized by at least 2 weeks (and often much longer, with average duration of depressive episodes being 4-6 months) of depressed mood and/or loss of interest, accompanied by cognitive symptoms (e.g., trouble concentrating) and somatic symptoms (e.g., appetite and sleep disturbance; low energy). One of the most serious complications of major depression is suicide, though there is growing evidence that depression itself may be a risk factor for multiple adverse health sequelae including cardiovascular disease and stroke (Ebmeier et al., 2006). Altered HPA axis function (e.g., hypercortisolemia, most often evidenced as abnormal 24-hour circadian secretion, in concert with resistance to suppression by exogenous glucocorticoids such as dexamethasone) has been frequently (albeit inconsistently) observed in studies of patients with major depression (Barden, 2004), but findings in anxiety disorders are even less consistent (see below).

Studies show that CRF expression in the hypothalamus, raphe nucleus, locus coeruleus and frontal cortex is increased in depressed suicide victims (Austin et al., 2003;Merali et al., 2004;Raadsheer et al., 1994,1995). CRF receptor binding sites and expression are also reported to be lower in the cortex of depressed suicide victims, suggesting a down-regulation of receptor signaling in response to excessive CRF release (Bissette et al., 2003;Merali et al., 2004;Nemeroff et al., 1988), although these findings have not always been replicated (Hucks et al., 1997;Leake et al., 1990). Preliminary studies suggest that mutations in non-coding regions of the CRF binding protein (CRF-BP) gene are associated with depression (Claes et al., 2003). CRF-BP binds synaptic CRF and may be an endogenous mechanism to reduce CRF signaling (Behan et al., 1995), thus disruptions in CRF-BP expression could alter the ability of the brain to “fine tune” CRF signaling. Concentrations of CRF in cerebrospinal fluid (CSF) appear to be higher in depressed patients (Nemeroff, 1998;Nemeroff et al., 1984) and can be reduced with electroconvulsive shock treatment (Nemeroff et al., 1991). Antidepression medications may also reduce CSF CRF concentrations (Heuser et al., 1998). CSF CRF levels have been shown to be abnormally low in “atypical” depression patients however, and hence increased CSF CRF levels may not be seen in all forms of depression (Geracioti et al., 1997).

It is important to note that CSF CRF levels are also aberrant in disorders linked to basal ganglia dysfunction. CSF CRF levels have been reported to be increased in Tourette's syndrome and in some but not all studies in obsessive-compulsive disorder (Altemus et al., 1992;Chappell et al., 1996;Fossey et al., 1996), with no clear correlation to depression or anxiety symptom severity reported (Chappell et al., 1996). Conversely, CRF content is reduced in the brains of Parkinson's disease and Huntington's disease patients, with reciprocal increases in receptor expression (for a review, see De Souza, 1995). Hence, CRF dysfunction is not specific to emotional disorders but is also associated with other types of neuropathology.

Anxiety

In comparison to the findings in depression patients, relatively little is known of putative CRF system dysregulation in anxiety disorders. Anxiety disorders are among the most common of all mental disorders (Kessler et al., 2005), and, when coupled with an awareness of the disability and reduced quality of life they convey (Mendlowicz and Stein, 2000), they must be recognized as a serious threat to the health of the public. Anxiety disorders include generalized anxiety disorder (GAD; a chronic form of anxiety typified by excessive, uncontrollable worry), panic disorder (characterized by recurrent, unexpected paroxysms of anxiety, somatic and autonomic symptoms and fear), phobic disorders (e.g., specific phobias, agoraphobia, social phobia), posttraumatic stress disorder (PTSD; typified by unwanted, intrusive remembrances - as daytime thoughts and nighttime dreams and nightmares - and avoidance of activities and other cues associated with prior life-threatening trauma) and obsessive-compulsive disorder (OCD; characterized by recurrent obsessions and compulsions). OCD, although sharing some features with the other anxiety disorders, is thought (though this is controversial, Bartz and Hollander, 2006) to have a substantially different neurobiology (e.g., neural circuitry). For ease of presentation, we have decided not to further discuss OCD in this manuscript.

Initial investigations of CRF dysregulation, as measured by CSF concentrations, in anxiety disorders have been mostly negative, with GAD and panic disorder patients exhibiting no difference from controls (Banki et al., 1992;Fossey et al., 1996;Jolkkonen et al., 1993). The lack of differences in CRF concentrations in CSF does not negate the possibility of CRF aberrations contributing to these disorders, however (Arborelius et al., 1999). These negative findings are based on using a single lumbar puncture technique for CSF sampling, which, because it is stressful and increases CRF release in all subjects, may mask baseline differences in CRF concentrations between anxiety disorder and control populations (Geracioti et al., 1997;Geracioti et al., 1992). Thus, serial CSF sampling techniques, in which CSF is sampled over longer periods of time, may be a more sensitive method to detect baseline CRF abnormalities. There are no postmortem studies to our knowledge on CRF system markers in brain tissue of anxiety disorder patients, although there is a call for the development of a tissue data bank for anxiety disorders (Bracha et al., 2005;Osuch et al., 2004). Recently, single nucleotide polymorphisms (SNPs) in the CRF gene have been found to be associated with behavioral inhibition, a childhood risk factor for panic disorder and social phobia (Smoller et al., 2003,2005). Future studies will be required to determine what the functional effect of these and other SNPs are on CRF signaling and anxiety disorder outcomes.

Clinical evidence for CRF system dysregulation in panic disorder, as reflected by the HPA axis abnormalities described in these patients, is mixed. In one study of 14 patients with panic disorder and 14 healthy control subjects who underwent a standard overnight metyrapone test and a combined metyrapone/low-dose dexamethasone test, no group differences in plasma ACTH or cortisol were detected (Kellner et al., 2004). In another study, patients with panic disorder demonstrated subtle evidence of overnight hypercortisolemia and increased activity in ultradian secretory episodes (Abelson and Curtis, 1996). Interestingly, it has been suggested

that anxiety disorder comorbidity might explain some of the differences in HPA axis activity among depressed patients (Young et al., 2004). This same group of researchers, in showing that the HPA response to a pharmacological agent in patients with panic disorder can be cognitively modulated, has suggested that HPA disturbances in panic disorder may be secondary to manipulable cognitive/emotional sensitivities (Abelson et al., 2005). Thus, the present consensus seems to be that the HPA axis abnormalities in panic disorder are subtle, reflecting altered responses to certain kinds of stress which, presumably, have as their origin differences in CRF secretion or altered CRF receptor signaling.

Posttraumatic stress disorder (PTSD) patients have been shown to exhibit excess CRF CSF concentrations (Baker et al., 1999;Bremner et al., 1997;Sautter et al., 2003). The two initial studies of CRF hypersecretion yielded mixed results in terms of any associations with depression or anxiety symptoms. Bremner et al. (1997), using a lumbar puncture technique, reported no significant associations between PTSD symptoms or depression. Baker et al. (1999), using the more sensitive serial CSF sampling technique, found a trend towards a positive correlation between depression and CRF levels, but no associations with PTSD symptoms. They did find a significant negative correlation, however, between 24-hour urinary-free cortisol excretion and PTSD symptoms. Sautter et al. (2003) reported that CRF elevations were specifically linked to psychotic symptoms in PTSD patients and suggested that excess CRF release may be unique to a more severely affected subclass of PTSD patients. Although it is generally presumed that the observed CRF hypersecretion in PTSD patients occurs only after trauma, this assumption has yet to be tested. It is also possible that excess CRF release is a predisposing factor for PTSD, similar to recent findings of reduced hippocampal volume in twin studies of PTSD (Gilbertson et al., 2002). Indeed, some animal studies (see below) indicate that CRF receptor activation enhances fear learning, hence individuals with high CRF tone might develop stronger trauma-related memories than those with lower CRF release. The literature on functioning of the HPA axis in PTSD is more controversial and conflicted. Some experts find reasonably consistent evidence of hypocortisolemia and enhanced HPA axis negative feedback (e.g., Yehuda, 2002), although these effects have not been consistently replicated in other studies which report either hypercortisolemia or even normal plasma cortisol in the presence of elevated CSF levels of cortisol (e.g., Baker et al., 2005).

Based on the evidence for CRF dysfunction in depression and anxiety patients, CRF_1 and CRF_2 receptors, as well as the CRF-BP, have been proposed as pharmacotherapeutic targets for depression and anxiety disorders (Arborelius et al., 1999;Grigoriadis, 2005;Valdez et al., 2005;Van Den Eede et al., 2005). Potent, orally active small molecule CRF_1 antagonists have now been developed and are ready for human investigation (Dyck et al., 2005). Trials with CRF_1 antagonists in humans for depression, buoyed by promising preliminary results from a small study (Zobel et al., 2000), are ongoing. It is unknown if similar trials targeting anxiety disorders, particularly PTSD, are also being planned.

CRF effects on the startle response: examples of modeling anxiety and CRF disruption “endophenotypes”

Above, we have discussed the evidence for a putative CRF disruption in anxiety disorders. As indicated above, CRF disruptions are not specific to anxiety or mood disorders, however, and do not always correlate with clinical symptoms. The fact that “typical” depression and PTSD patients exhibit similarly high CSF CRF concentrations yet different HPA axis sensitivity, a closely related biological marker of CRF function, highlights the notion that one measure of CRF dysfunction (e.g., CSF levels of CRF) tells us little about the underlying pathology for these disorders. For example, we do not know the source(s) (e.g., hypothalamus, amygdala, raphe nuclei) producing the increased CRF in CSF in either depression or PTSD patients, which

would likely make a large difference in resulting HPA axis and clinical symptomatology. Hence, it has been suggested that basic research on these disorders also focuses on the relationship between more simple "endophenotypes" found in these disorders as opposed to the relationship between a simple biological marker (i.e., CSF CRF) and a complex disorder such as anxiety. This approach may identify specific symptoms that can be linked to discrete pathology and inform current systems models of disease etiology (Braff et al., 2001;Hasler et al., 2004;Radant et al., 2001;Stein and Lang, 2004).

The startle response

Model systems have been used routinely to identify candidate biological pathways, neuroanatomical circuits and genes that may influence phenotypes in humans. One of the most widely studied phenotypes in model organisms of relevance to anxiety is the startle response. The startle response is a cross-species phenomenon, which consists of a series of involuntary reflexes elicited by a sudden, intense auditory or tactile stimulus and is considered to be a defensive behavior evolved to protect the body from impact during attack (Graham, 1975;Yeomans et al., 2002). It is a highly conserved behavior across mammalian species and is well suited for translational studies of pathology across animals and humans. Responses to tactile (e.g., an airpuff to the throat or face) or acoustic stimuli are recorded in animals as a whole body "flinch response" and in humans as the strength of the eye blink response (EMG electrodes at the orbicularis oculi muscles). Cortical and limbic brain regions, many of which are abnormally activated or exhibit altered volumes in anxiety disorders (as measured by fMRI or PET e.g., Gilbertson et al., 2002;Hull, 2002;Lorberbaum et al., 2004;Neumeister et al., 2004;Schneider et al., 1999), modulate startle responses (Davis, 1998;Funayama et al., 2001;Kumari et al., 2003;Swerdlow et al., 2001;Weike et al., 2005). The magnitude of the response is highly plastic: fear-inducing stimuli (termed fear-potentiated startle; FPS) or administration of anxiogenic compounds, such as CRF, increases startle (Brown et al., 1951;Davis et al., 1997;Swerdlow et al., 1986), while threat-reducing stimuli (Lang et al., 1990), anxiolytic and sedative drugs (Abduljawad et al., 2001) or sensory input in the case of prepulse inhibition (PPI) (Braff et al., 2001;Geyer et al., 2001;Graham, 1975;Swerdlow et al., 2001) reduces startle.

PPI of startle is an operational measure of sensorimotor gating and putative measure of pre-attentive information processing (Geyer and Braff, 1987). Across species, presentation of a neutral, non-startling acoustic "prepulse" 30-300 ms before a startling stimulus reduces startle magnitude, possibly by requiring the organism to allocate attentional resources to process the prepulse and hence filter or "gate" the subsequent startling stimulus (Graham, 1975;Hoffman and Ison, 1980;Norris and Blumenthal, 1996;Swerdlow et al., 1999). This phenomenon is an unconditioned inhibitory process, unlike fear extinction (Myers and Davis, 2002). Neuroanatomical substrates for modulation of PPI are numerous, including limbic regions such as the amygdala and nucleus accumbens, as well as cortical regions (Swerdlow et al., 2001). Importantly, these measures of baseline startle, exaggerated startle and PPI appear to be altered in some anxiety disorders and are also modulated by the CRF system.

Startle abnormalities in anxiety disorders

Abnormal startle responses, including reduced threshold for startle responding, reduced PPI, increased FPS and reduced habituation of startle, have been reported in subjects with anxiety disorders (Butler et al., 1990;Ludewig et al., 2005;Ludewig et al., 2002;Metzger et al., 1999;Morgan et al., 1995;Morgan et al., 1996;Orr et al., 1995). The startle symptoms of PTSD and other anxiety disorders are very thoughtfully and thoroughly discussed in a recent review (Grillon and Baas, 2003). In brief, startle abnormalities are generally observed in PTSD patients, although exaggerated startle may not be consistently found at longer periods posttrauma. Startle reactivity changes may also depend on the type of trauma and age at which

the trauma was experienced. Exaggerated startle may also be reported as increased baseline startle, increased startle during threat (i.e., FPS) or increased startle in contexts that evoke memories of past trauma (Butler et al., 1990;Grillon and Morgan, 1999;Grillon et al., 1998b;Grillon et al., 1996;Morgan et al., 1995;Morgan et al., 1996;Orr et al., 1995;Wessa et al., 2005). In a longitudinal study of subjects recently exposed to trauma, startle responding was similar in all subjects initially, however, those that did not develop PTSD became less reactive over time, while those that went on to develop PTSD continued to be reactive over these repeated sessions (Shalev et al., 2000). These studies touch on the question if exaggerated startle is a risk factor for PTSD development or whether it occurs only after trauma. A small prospective study of firefighters exposed to trauma found a modest positive correlation between pretrauma startle magnitude and posttrauma PTSD-like symptoms, however, a clear PTSD diagnosis was not found in any of the subjects tested (Guthrie and Bryant, 2005). Hence, more studies are required to test if startle is a vulnerability factor for development of PTSD (i.e., exaggerated startle is present pretrauma) or a state-dependent symptom of PTSD.

There is some evidence that heightened startle reactivity is linked with “risk” for anxiety disorder development. Children of patients with anxiety and depressive disorders exhibit exaggerated startle (either baseline or only during threat) compared to children with no family history for these disorders, suggesting that startle responsiveness could be a marker of vulnerability for development of clinical anxiety (Grillon et al., 1997;Merikangas et al., 1999;Grillon et al., 1998a) and depression (Grillon et al., 2005b). This latter finding is somewhat surprising as baseline startle appears to be normal, or even reduced, in adults with depression (Kaviani et al., 2004;Perry et al., 2004;Quednow et al., 2006). One interpretation of this result is that startle reactivity may change with the onset and progression of depression, although this speculation has yet to be tested. Interestingly, children classified as “fearless” have been reported to exhibit significantly reduced startle responses (Goozen et al., 2004). These findings support the potential utility of startle as a potential “trait” marker for mapping of genes involved with anxiety phenotypes (Baker et al., 2006). Links between behavioral inhibition and startle reactivity have been mixed (e.g., Fullana et al., 2005;Hawk and Kowmas, 2003;Nitschke et al., 2002), although the sample populations (e.g., infants vs. older children and adults), methodologies (e.g., affective modulation of startle using images or painful stimuli) and measures used (e.g., assessment scales) are very diverse, making comparisons across studies difficult.

Trait anxiety effects on startle have also been shown to be gender-dependent, with the type of startle effect (baseline vs. fear induced) and sometimes direction (increase vs. decrease) of the startle effect differing between males and females. In a study of startle reactivity in children at risk for developing anxiety disorders (“at risk” was defined as having a 1st degree relative with a clinical anxiety disorder), at risk females exhibited greater baseline startle compared to controls (Grillon et al., 1998a). Conversely, at risk males exhibited normal baseline startle compared to controls, but greater startle reactivity during conditions when a mild shock was expected (Grillon et al., 1998a). Other reports indicate that the direction of anxiety effects on startle can also depend on sex. Compared to controls, children with a history of physical and mental abuse have sex-dependent startle abnormalities, with boys exhibiting reduced startle reactivity and girls exhibiting increased startle reactivity (Klorman et al., 2003). Similarly, women with PTSD have been reported to exhibit reduced startle compared to controls, in contrast with most reports of exaggerated startle in males with PTSD (Medina et al., 2001). Some of these discrepancies must be viewed with caution as they may reflect the different types and duration of trauma experienced by the subjects as opposed to sex differences *per se* (e.g., domestic violence vs. combat related trauma). However, they may also reflect the effects of different hormones on emotional modulation of startle reactivity, as described by Toufexis et al. (this volume).

Interestingly, panic disorder and PTSD patients exhibit mild but significant disruptions in PPI (Grillon et al., 1998b,1996;Ludewig et al., 2005,2002;Ornitz and Pynoos, 1989). PTSD patients also exhibit deficient P1 suppression, another measure of inhibitory or gating processes (Gillette et al., 1997;Skinner et al., 1999). One study found negative correlations between PPI and PTSD symptoms, however, this was not replicated in a subsequent study (Grillon et al., 1998a,b,1996). Studies have also shown that PPI performance is negatively correlated with trait anxiety in panic disorder patients (Ludewig et al., 2005,2002). Panic disorder patients also exhibit reduced startle habituation, a simple form of inhibition (Davis and Wagner, 1969;Ludewig et al., 2002) as well as increased baseline startle (Ludewig et al., 2005). PPI performance and baseline startle appeared to be the most disrupted in panic disorder patients that were not undergoing treatment during the study, while patients receiving treatment appeared to have relatively milder PPI impairments and normalized startle (Ludewig et al., 2005,2002). These preliminary results suggest that startle abnormalities in this population may be sensitive to certain types of anti-anxiety pharmacotherapy. Interestingly, unipolar depression patients do not exhibit startle and PPI abnormalities, hence startle measures may be a useful behavioral probe for pathology specifically linked to anxiety over depression (Ludewig and Ludewig, 2003;Perry et al., 2004;Quednow et al., 2006).

CRF effects on startle

Preclinical studies have indicated an important modulatory role for CRF on startle reactivity and PPI. Various stressors (e.g., 24 h social isolation, repeated tail pinch, bright light, acute and repeated restraint, footshock) increase startle magnitude and/or reduce PPI in rats (Brake et al., 2000;de Jongh et al., 2003;Faraday, 2002;Sipos et al., 2000). CRF receptor activation is necessary for the effects of many of these stressors (e.g., light, shock, restraint) on other behaviors such as locomotion, avoidance and freezing (Bakshi and Kalin, 2000;Bakshi et al., 2002;Gutman et al., 2003;Heinrichs et al., 2002;Ho et al., 2001;Le et al., 2002) and on startle in the case of light stress (de Jongh et al., 2003) and perhaps FPS (de Jongh et al., 2003;Schulz et al., 1996;Swerdlow et al., 1989;Walker and Davis, 2002a;Risbrough and Geyer, 2005). The extended amygdala (specifically the bed nucleus stria terminalis) is required for both CRF- and stress-induced increases in startle (de Jongh et al., 2003;Gewirtz et al., 1998;Lee and Davis, 1997;Toufexis et al., this volume). Rats bred for differing levels of emotionality have been shown to differ in both CRF peptide levels in the amygdala and fear-potentiated startle performance, suggesting that these two markers may be linked (Yilmazer-Hanke et al., 2002). Indeed, CRF receptor activation in the amygdala appears to enhance consolidation of learned fear (Roozendaal et al., 2002), hence increased CRF tone in the amygdala may facilitate acquisition and/or extinction of FPS.

In rodents, exogenous CRF administration also disrupts inhibition of startle as measured by PPI (Conti, 2005;Conti et al., 2002). We have recently shown that CRF_1 receptor activation is required for CRF-induced increases in startle and CRF_2 receptor activation appears to have an additive effect with CRF_1, increasing startle (Risbrough et al., 2003b,2004). The two receptors have opposing function on PPI, however, as CRF_1 activation decreases PPI while CRF_2 activation increases PPI (Risbrough et al., 2004). Hence, excess signaling of CRF_1 or reduced signaling of CRF_2 could theoretically disrupt startle and sensorimotor gating functions during stress. In rats, CRF_1 receptor expression in limbic regions has been shown to be positively correlated with increased startle reactivity (Nair et al., 2005). Mice with constitutive CRF over-expression also exhibit reduced PPI with an inconsistent reduction in startle reactivity (Dirks et al., 2002,2003). Future studies will determine if region-specific alterations of CRF expression (e.g., whole central nervous system vs. hypothalamic or forebrain CRF over-expression, Deussing and Wurst, 2005) will result in startle phenotypes that better mimic those reported in PTSD and panic disorder (e.g., reduced startle habituation, increased startle

threshold and reduced PPI). Nevertheless, these preliminary animal studies suggest that excess CRF release and CRF_1 receptor signaling could contribute to startle and PPI abnormalities reported in PTSD and panic disorder. Future studies are required in clinical populations to determine if there is a link between abnormal CRF system markers (e.g., CRF peptide release or HPA axis sensitivity) and abnormal startle behaviors. Such studies, although difficult, would be invaluable aids to model building for PTSD and panic disorder pathology. It is important to note here that *exogenous* CRF effects on startle are not dependent upon glucocorticoid release, supporting the idea that central CRF modulation of startle is independent of the HPA axis (Lee et al., 1994). This finding does not preclude the ability of glucocorticoids to have additional effects on startle reactivity however.

In humans, there are some links between HPA axis function and startle responding. Serum cortisol levels have been shown to be positively associated with startle reactivity during threat or after anxiogenic drug administration (Grillon et al., 2005a). In primates, adverse rearing conditions increase both basal cortisol levels as well as startle reactivity (Sanchez et al., 2005). Thus, there is some indication that HPA system response predicts startle reactivity. There is also some evidence for a direct effect of glucocorticoids on startle responding. In healthy human subjects, exogenous cortisol administration increases startle at low doses and reduces it at high doses (Buchanan et al., 2001). In rats, low doses of corticosterone enhance CRF-induced increases in startle (Lee et al., 1994). These glucocorticoid-induced increases in startle may be mediated by limbic CRF release in response to glucocorticoid receptor activation, as corticosterone administration is reported to increase CRF expression in the amygdala (Lee et al., 1994;Makino et al., 1994a,1994b;Shepard et al., 2003).

Linking animal and human studies of CRF dysfunction and PTSD

One of the translational values of studying the startle response is that the neuroanatomical and neurochemical substrates mediating and modulating startle plasticity are relatively well defined, allowing greater hypothesis generation and interpretability before and after obtaining results (Braff et al., 2001;Davis et al., 1993;Geyer et al., 2001;Heldt et al., 2000;Lang, 1995;Mansbach and Geyer, 1988;Risbrough et al., 2003a,2004;Swerdlow et al., 2001;Walker and Davis, 2002b;Toufexis et al., this volume). A fairly recent example of the successful use of rodent startle is in the potential use of D-cycloserine as an adjunctive treatment with extinction or “exposure” therapies. A series of elegant studies by Davis and colleagues using FPS in rodents (Walker et al., 2002) found that administration of the glutamate partial agonist D-cycloserine into the amygdala enhanced extinction training. A subsequent clinical study found D-cycloserine to significantly enhance the efficacy of extinction therapy in phobic patients (Rattiner et al., 2004). These data provide compelling evidence for the predictive validity of the FPS extinction model. Recently, glucocorticoids have also been shown to enhance extinction in this model and indeed are reported to enhance extinction in human phobia patients as well (Soravia et al., 2006;Yang et al., 2006). In clinical studies of surgery-related PTSD, pre-operative hydrocortisone treatment had some protective effects against development of PTSD (Schelling et al., 2004). A similar result has recently been reported in rats, with corticosterone treatment before stress exposure (brief presentation of predator odor) reducing the percentage of rats that exhibit exaggerated anxiety-like behaviors post-stress (increased avoidance and startle reactivity, Cohen et al., 2006), providing initial support for the validity of this model for PTSD. This model may be particularly useful to determine if CRF system dysregulation is linked to emergence of exaggerated anxiety-like responses post-stress and to explore potential “preventive” treatments of PTSD-like symptoms.

There is some support for the speculation that PTSD patients may have deficits in their ability to extinguish learned fear (Orr et al., 2000;Peri et al., 2000;Rothbaum and Davis, 2003). Thus,

animal models of extinction may be well suited for translational studies of pathologies underlying abnormal fear learning and extinction, as proposed in PTSD (Milad and Quirk, 2002;Myers and Davis, 2002). For example, it is currently unknown if excess CRF release alters fear learning or extinction, although recent evidence indicates that glutamate transmission in the amygdala, which is required for fear learning and extinction, is modified with CRF_1 and CRF_2 receptor activation (Liu et al., 2004;Walker and Davis, 2002b). Preliminary evidence indicated that CRF receptors may be required for reinstatement of learned fear, although this study has not yet been published (Waddell and Falls, 2003). Hence, future animal studies of interest would be to determine the role of CRF receptors in extinction processes as well as explore further the mechanism of glucocorticoid effects on these processes (Schulkin et al., 2005). In animals, CRF has also been shown to enhance fear learning (Radulovic et al., 2000,1999;Sananbenesi et al., 2003;Roozendaal et al., 2002), and a recent meta-analysis suggests that increased fear conditioning may be an important feature of anxiety disorders (Lissek et al., 2005). Hence, future clinical studies of CRF system abnormalities in PTSD subjects may benefit from the addition of behavioral tests (such as startle) to determine what symptoms or "endophenotypes" (e.g., increased startle, increased fear conditioning and/or reduced extinction) may be most related to CRF dysfunction, in addition to psychiatric symptom measures. These studies would be invaluable for informing current models of CRF dysregulation effects in disorders of mood and anxiety.

Concluding remarks

Taken together, the current clinical findings of aberrant CRF system markers support continued efforts to test models of CRF mechanism contributions to anxiety disorders. At present, the rationale for studying CRF contributions to anxiety disorders is strongest for PTSD and panic disorder, but it is entirely possible that other, less well-studied anxiety disorders share similar CRF-related psychopathology; this possibility should be further explored. A future challenge for clinical studies will be to determine which anxiety-related phenotypes (e.g., increased startle reactivity, enhanced fear learning and/or reduced fear extinction) are linked to abnormal CRF signaling and which can be readily modeled preclinically. In parallel, future preclinical models of CRF dysregulation (e.g., CRF over-expression or selective breeding for trauma hyper-responsiveness) and aberrant fear learning/extinction will aid our understanding of how CRF modulates long-term responses to emotionally traumatic events. This translational research will help test the viability of CRF and glucocorticoid receptor ligands as treatments for PTSD and other anxiety disorders.

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