Hormones and Behavior 76 (2015) 125–135

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

Cognitive disruptions in stress-related psychiatric disorders: A role for corticotropin releasing factor (CRF)

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ARTICLE INFO

Available online 14 April 2015

Keywords:
Corticotropin releasing hormone
Stress
Fear conditioning
Declarative memory
Executive function
Attention
Working memory
Post-traumatic stress disorder (PTSD)
Major depression
Sex difference

ABSTRACT

This article is part of a Special Issue "SBN 2014".

Stress is a potential etiology contributor to both post-traumatic stress disorders (PTSD) and major depression. One stress-related neuropeptide that is hypersecreted in these disorders is corticotropin releasing factor (CRF). Dysregulation of CRF has long been linked to the emotion and mood symptoms that characterize PTSD and depression. However, the idea that CRF also mediates the cognitive disruptions observed in patients with these disorders has received less attention. Here we review literature indicating that CRF can alter cognitive functions. Detailed are anatomical studies revealing that CRF is poised to modulate regions required for learning and memory. We also describe preclinical behavioral studies that demonstrate CRF's ability to alter fear conditioning, impair memory consolidation, and alter a number of executive functions, including attention and cognitive flexibility. The implications of these findings for the etiology and treatment of the cognitive impairments observed in stress-related psychiatric disorders are described.

Introduction

Some of the most common psychiatric disorders are post-traumatic stress disorder (PTSD) and major depression, which have a lifetime prevalence of 5.7% and 14.4%, respectively (Kessler et al., 2012). The defining symptoms of these disorders are different, such that PTSD is characterized by the re-experiencing of a traumatic event, avoidance, and hyperarousal, while depression is characterized by a persistent low mood often accompanied by feelings of hopelessness, helplessness, and anhedonia (American Psychiatric Association, 2013). Despite differences in their diagnostic criteria, PTSD and depression share several features. For example, patients with these disorders suffer from cognitive deficits, reporting impairments in learning, memory, and attention (for review see, Aupperle et al., 2012; Marazziti et al., 2010; Milad et al., 2006; Samuelson, 2011). These deficits impact daily function, thereby compounding the disruptions in affect caused by these disorders. Another shared feature is stress, and, in fact, PTSD and depression are sometimes referred to as stress-related disorders. PTSD, by definition, is precipitated by a traumatic event (Breslau, 2009; Shabsigh and Rowland, 2007). Stress also is associated with the onset and severity of depression (Kendler et al., 1995; Melchior et al., 2007; Newman and Bland, 1994). Moreover, patients with these disorders have alterations in stress circuitry (Hamilton et al., 2008; Karl et al., 2006; Kitayama et al., 2005), as well as dysregulated stress hormones and stress-related neuropeptides (Deuschle et al., 1997; Elzinga et al., 2003; Holsboer, 2001; Nemeroff et al., 1984; Yehuda et al., 2005). Given the common features of PTSD and depression, it is likely that these disorders share some etiological factors.

One stress-related neuropeptide that is linked to both PTSD and major depression is corticotropin releasing factor (CRF; e.g., Gold and Chrousos, 2002; Kasckow et al., 2001; Nemeroff and Vale, 2005). CRF acts at the level of the pituitary to initiate the hypothalamic pituitary adrenal (HPA) axis response, as well as centrally to modulate brain regions that regulate behavioral responses to stress (Bale and Vale, 2004; Owens and Nemeroff, 1991; Vale et al., 1981). Although typically CRF release facilitates appropriate stress coping, its hypersecretion is thought to be maladaptive (Holsboer and Ising, 2008; Kasckow et al., 2001; Nemeroff, 1996). In fact, some patients with PTSD and depression have elevated levels of CRF in their cerebrospinal fluid, which positively correlates with symptom severity (Baker et al., 1999, 2005; Banki et al., 1992; Bremner et al., 1997; Nemeroff et al., 1984; Sautter et al., 2003). Moreover, in postmortem tissue of depressed patients, high levels of CRF and altered CRF receptor expression indicative of protracted CRF dysregulated are observed (Austin et al., 2003; Bissette et al., 2003; Raadsheer et al., 1994; Wang et al., 2008). Single nucleotide polymorphisms (SNPs) in the CRF_1 receptor gene also have been reported in patients with PTSD and depression (Amstadter et al., 2011; Liu et al., 2006; Polanczyk et al., 2009; Wasserman et al., 2008). Collectively, these studies suggest that alterations in the CRF system could contribute to the symptoms of these stress-related disorders.

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http://dx.doi.org/10.1016/j.yhbeh.2015.04.003
0018-506X/

To more directly link CRF hypersecretion to disordered behavior, researchers have turned to non-human animal models where causality can more easily be tested. The focus of much of this work has been to identify how CRF and the activation of CRF receptors alter anxiety and endocrine responses to stress. These preclinical studies have shown, for example, that CRF overexpression leads to an anxious phenotype (Stenzel-Poore et al., 1994; van Gaalen et al., 2002). Studies on the two CRF receptors, CRF_1 and CRF_2, have revealed that they can differentially modulate stress-related behavior. Specifically, CRF_1 receptor activation initiates the HPA axis response and leads to anxiogenic behavior (Bale and Vale, 2004; Contarino et al., 1999; Heinrichs et al., 1997; Smith et al., 1998; Takahashi, 2001; Timpl et al., 1998). In contrast, activation of CRF_2 receptors attenuates the HPA axis, and, in some cases, decreases anxiety (Bale et al., 2000; Bale and Vale, 2004; Coste et al., 2000, 2001). The underlying mechanisms of the sometimes opposing actions of CRF_1 and CRF_2 receptors are unclear. However, in the dorsal raphe, differences in the density of CRF_1 and CRF_2 receptors on serotonergic versus GABAergic neurons are thought to underlie different functions (Commons and Valentino, 2002). Additionally, distinct trafficking of CRF_1 and CRF_2 receptors within dorsal raphe neurons has been linked to alterations in stress-coping strategies (Waselus et al., 2009). However, more research is needed to understand the molecular basis for the sometimes opposing effects of CRF_1 and CRF_2 receptors in other brain regions.

In addition to the effects of CRF on the regulation of anxiety and endocrine responses to stress, an underexplored but intriguing possibility is that CRF also mediates the changes in cognition observed in patients with PTSD and depression. This idea is based on the fact that CRF and its receptors are found in regions critical for learning and memory (Justice et al., 2008; Merchenthaler, 1984; Primus et al., 1997; Van Pett et al., 2000). Moreover, emerging preclinical research suggests that mnemonic processes can be mediated by CRF. Here we review these studies and provide evidence that the cognitive disruptions that impair function in patients with PTSD and depression could result from high levels of CRF.

CRF and fear learning

Fear is an emotional response to a threat or perceived threat. In addition to expressing fear, animals can learn about cues that predict threatening situations and remember those cues to promote future survival. A growing body of literature suggests a critical role for CRF in *learning* about fearful situations, and these findings may be clinically relevant. Although learning about threating situations is adaptive, it becomes maladaptive when traumatic memories are activated inappropriately or persistently, and such responses are linked to the etiology of stress-related psychiatric disorders. PTSD in particular is thought to be caused, at least in part, by dysregulated fear learning (e.g., Blechert et al., 2007; Mahan and Ressler, 2012; Milad et al., 2006; Orr et al., 2000; Pitman, 1989; VanElzakker et al., 2014; Wessa and Flor, 2007). Learning disruptions can occur at the time of the traumatic event when associations between the trauma and various environmental cues become so strong that they later trigger intrusive recollections (Orr et al., 2000; Pitman, 1989). Additionally, patients with PTSD can have difficulty extinguishing responses to cues associated with the trauma (Blechert et al., 2007; Wessa and Flor, 2007). Although abnormal fear learning is most associated with PTSD, depressed patients and even the children of depressed and anxious mothers have disrupted fear learning (Nissen et al., 2010; Waters et al., 2014). Thus, alterations in the mnemonic aspects of fear processing may be a premorbid risk factor for several stress-related psychiatric disorders.

In the laboratory, fear learning is studied utilizing the fear conditioning procedure. The rodent version of this task pairs an initially neutral stimulus, typically a tone, with an aversive unconditioned stimulus (US), typically a footshock. Because the tone proceeds and predicts the footshock, the rodent forms an association between these two stimuli, and the tone becomes a conditioned stimulus (CS). This association is tested 24 hours after the CS–US pairings when the tone is presented in a novel context and freezing (i.e., ceasing all motion as a defensive behavior) during the tone is measured. This freezing response is considered a conditioned response (CR), and the magnitude of freezing is thought to reflect the strength of the CS–US association. This simple procedure has been elegantly utilized to elucidate the circuitry critical for fear learning (e.g., Davis, 1992; Davis and Whalen, 2001; Fanselow and Poulos, 2004; Johansen et al., 2011; LeDoux, 2000; Maren, 2005; Medina et al., 2002; Quirk et al., 1995; Sah and Westbrook, 2008). This circuit consists of sensory regions that process stimuli, areas that regulate the mnemonic aspects of the task, and regions involved in generating the expression of fearful responses. Specifically, the CS and US are first processed by sensory regions, such as the auditory and somatosensory thalamus and cortices. This sensory information then converges on neurons in the lateral nucleus of the amygdala (LA). Through CS–US pairings, synaptic plasticity within the LA region enhances neuronal responses to the CS, indicating that the LA is critical for forming the association. The LA then projects both directly and indirectly (via the basal nucleus and intercalated masses) to the central nucleus of the amygdala (CE). The CE regulates the expression of fear via projections to brain regions involved in autonomic (lateral hypothalamus), endocrine (paraventricular nucleus of the hypothalamus), and defensive (periaqueductal gray) responses.

It is clear from this prior work that fear conditioning requires a network of brain regions. Interestingly, CRF is positioned to modulate many of these areas, including those involved in both non-mnemonic and mnemonic aspects of fear conditioning. For example, CRF receptors are found in thalamic and cortical regions involved in audition and somatosensation (Fig. 1; Primus et al., 1997; Van Pett et al., 2000). Therefore, CRF could directly modulate sensory processing of the CS and US, a possibility, which to our knowledge, has never been tested. CRF and its receptors are also present in regions critical for fear expression, including the lateral hypothalamus, paraventricular nucleus of the hypothalamus, and periaqueductal gray (Fig. 1; Merchenthaler, 1984; Potter et al., 1994; Van Pett et al., 2000). In fact, local infusions of CRF into the periaqueductal gray increase defensive behavior, such as freezing during fear conditioning (Carvalho-Netto et al., 2007; Stiedl et al., 2005). Anatomically, CRF is also positioned to affect amygdala regions involved in the mnemonic aspects of fear conditioning (Fig. 1). Both types of CRF receptors (CRF_1 and CRF_2) are found in the LA and CE regions, although CRF_1 receptors are expressed at higher levels than CRF_2 receptors (Chalmers et al., 1995; Justice et al., 2008; Van Pett et al., 2000; Weathington and Cooke, 2012). CRF immunoreactivity is found throughout the amygdala, but the CE in particular has a large number of CRF expressing cell bodies (Gray, 1993; Swanson et al., 1983). Interestingly, CRF projections from the CE terminate in fear expressing regions, including the lateral hypothalamus and periaqueductal gray (Gray, 1993; Gray and Magnuson, 1992), indicating that CRF may be a critical neuropeptide that links the amygdala with regions involved in fear expression.

There is evidence to suggest that moderate levels of CRF are actually required for appropriate fear learning. Exposure to footshock (the most common US) increases CRF expression in the amygdala of male rats (Yamano et al., 2004). This increase may be critical for fear conditioning because reducing the effects of CRF in both the basolateral amygdala (BLA; which includes the LA) and the CE disrupts the consolidation or stabilization of fear memories in male rats (Hubbard et al., 2007; Pitts and Takahashi, 2011; Pitts et al., 2009). Conversely, in the BLA of male rats, increasing free endogenous CRF concentrations by displacing CRF from its binding protein enhances memory consolidation of fearful events (Roozendaal et al., 2008).

The above studies suggest that CRF acts to enhance consolidation, however manipulations that cause very high CRF levels indicate that CRF can also have the opposite effect on the consolidation of fear memories (Isogawa et al., 2012). Specifically, in male rats, the addition of CRF into the LA by microinfusion immediately before or after training impairs fear conditioning, a time course consistent with CRF inducing