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Review

Corticotropin releasing factor: A key role in the neurobiology of addiction

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ABSTRACT

Drug addiction is a chronically relapsing disorder characterized by loss of control over intake and dysregulation of stress-related brain emotional systems. Since the discovery by Wylie Vale and his colleagues of corticotropin-releasing factor (CRF) and the structurally-related urocortins, CRF systems have emerged as mediators of the body's response to stress. Relatedly, CRF systems have a prominent role in driving addiction via actions in the central extended amygdala, producing anxiety-like behavior, reward deficits, excessive, compulsive-like drug self-administration and stress-induced reinstatement of drug seeking. CRF neuron activation in the medial prefrontal cortex may also contribute to the loss of control. Polymorphisms in CRF system molecules are associated with drug use phenotypes in humans, often in interaction with stress history. Drug discovery efforts have yielded brain-penetrant CRF_1 antagonists with activity in preclinical models of addiction. The results support the hypothesis that brain CRF–CRF_1 systems contribute to the etiology and maintenance of addiction.

1. Introduction

According to a 2012 report by the Substance Abuse and Mental Health Services Administration, within the past 12 months, approximately 15% of the population aged 12 and older experienced substance use disorders on alcohol, cigarettes, or an illegal drug. Alcohol use disorders alone have an annual prevalence of approximately 10% and account for 4.6% of all disability-adjusted life-years in developed countries (Rehm et al., 2009). Available pharmacotherapies for substance use disorders have only modest long-term efficacy and are underutilized (Heilig et al., 2011). Since the successive discovery by Wylie Vale and his colleagues of corticotropin-releasing factor (CRF) (Vale et al., 1981), the structurally-related urocortins (Ucn 1, Ucn 2, Ucn 3), and their cognate receptors (CRF_1, CRF_2) (Bale and Vale, 2004; Fekete and Zorrilla, 2007), CRF systems have emerged as therapeutic targets for substance abuse.

CRF binds with high and moderate potency to CRF_1 and CRF_2 receptors, respectively. Ucn 1 is a high-affinity agonist at both of these G-protein coupled receptors, whereas the type 2 urocortins (Ucn 2 and Ucn 3) are selective CRF_2 receptor agonists (Bale and Vale, 2004; Zorrilla and Koob, 2004; Fekete and Zorrilla, 2007). Vale and colleagues first demonstrated that CRF initiates the hypothalamic–pituitary–adrenal (HPA) axis neuroendocrine stress response by binding CRF_1 receptors in the anterior pituitary after release into portal blood. In addition, however, CRF_1 receptors are widely distributed in stress-responsive brain regions, including the neocortex, central extended amygdala, medial septum, hippocampus, thalamus, cerebellum, and autonomic midbrain and hindbrain nuclei (Grigoriadis et al., 1996; Primus et al., 1997; Sanchez et al., 1999; Van Pett et al., 2000). The brain CRF_1 receptor distribution resembles the distribution of its natural ligands CRF (Fig. 1) and Ucn 1 and accounts for the dissociable, non-endocrine role of extrahypothalamic CRF_1 systems (i.e., outside the HPA axis) to mediate behavioral and autonomic stress responses (Swanson et al., 1983; Kozicz et al., 1998; Bale and Vale, 2004; Zorrilla and Koob, 2004; Fekete and Zorrilla, 2007).

Extensive preclinical data suggest that extrahypothalamic CRF_1 systems subserve negative emotional states. Accordingly, small-molecule CRF_1 antagonists are being developed as potential

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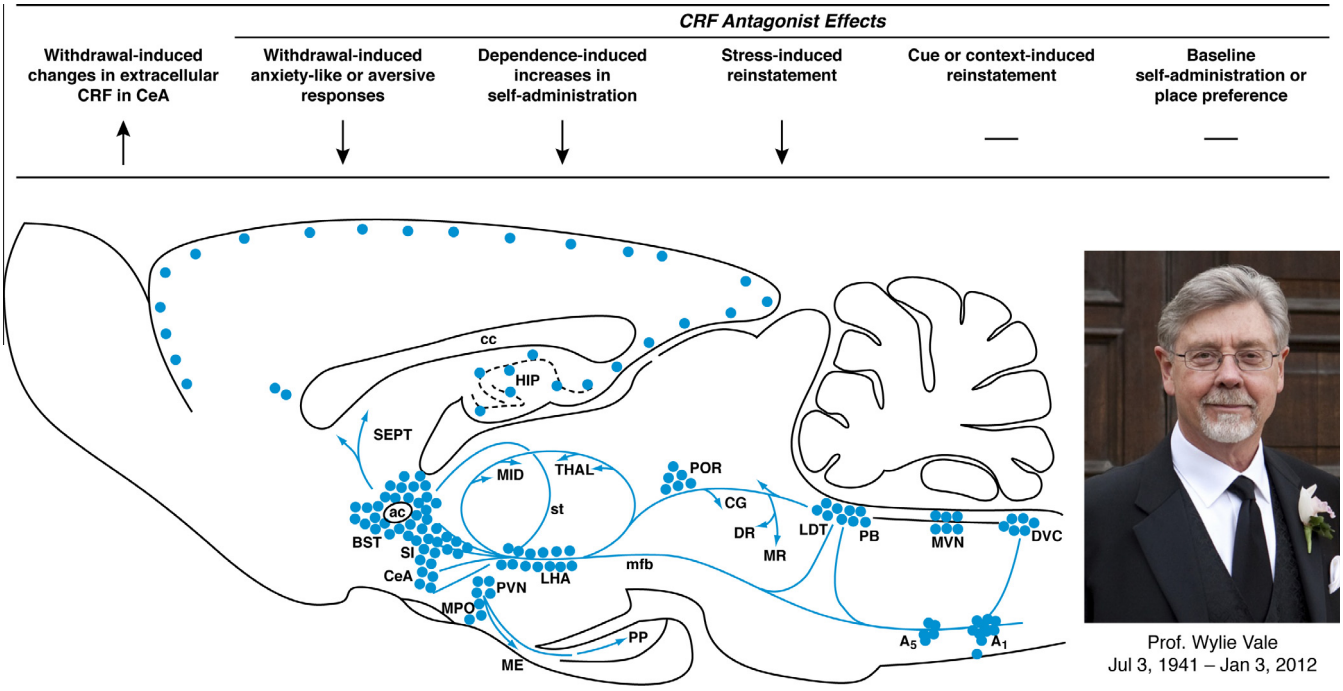

Fig. 1. Brain CRF mediates the facilitation of compulsive-like drug use. As shown in the sagittal brain schematic, corticotropin-releasing factor (CRF), first isolated by Professor Wylie Vale (photo), is expressed in neuronal cell bodies (filled circles) and projections (blue arrows) that subserve behavioral, autonomic and neuroendocrine responses to stress. As summarized from left-to-right by the arrows, CRF systems play an integral role in regulating the intersection between drug self-administration and stress systems. For example, drug or alcohol withdrawal elevates CRF activity in the central extended amygdala, including the central nucleus of the amygdala (CeA), leading to a negative emotional state that motivates resumption of and maintenance of drug-taking. Pharmacological studies with CRF antagonists show that increased CRF–CRF_1 system activation underlies several withdrawal-induced behavioral phenotypes, including anxiety-like behavior, aversion, and elevated drug self-administration. CRF_1 antagonists also reduce the effect of acute stressors on drug-related behaviors, including stress-induced reinstatement. In contrast, CRF_1 antagonists do not alter non-stress mechanisms that reinstate drug-seeking, such as drug primes, cues or contexts, reflecting the distinct neuroanatomical substrates of relapse behavior. Blockade of CRF–CRF_1 systems does not have intrinsic rewarding (or aversive) properties in place conditioning models and has little effect on baseline intake in nondependent individuals.

treatments for affective-like disorders, including posttraumatic stress disorder, irritable bowel syndrome, anxiety disorders, and major depression (Zorrilla and Koob, 2004, 2010; Holsboer and Ising, 2008; Koob and Zorrilla, 2012; Zorrilla et al., 2013a). Indeed, Dr. Vale was a major force in the pharmaceutical development of drug-like small-molecule CRF_1 antagonists. He co-founded Neurocrine Biosciences, which successfully developed a wide range of such compounds, spanning multiple patents.

One proposed clinical indication for CRF_1 antagonists is drug addiction (Fig. 1), where the brain stress systems are hypothesized to impact key elements of the addiction cycle. Drug addiction is a chronically relapsing disorder characterized by loss of control over drug intake and emergence of a negative emotional state during abstinence. Drug addiction has been conceptualized as a cycle progressing through three stages—*binge/intoxication*, *withdrawal/negative affect*, and *preoccupation/anticipation*—that become worse over time and ultimately lead to a severe neurobiological disorder. CRF systems are hypothesized to play a key role in all three stages of the addiction cycle but particularly in the *withdrawal/negative affect* stage. Chronic use of a drug of abuse, even if initiated for its rewarding effects, increasingly leads to negative emotional symptoms and negatively reinforced substance use. An extension of the "opponent process theory of affective regulation" (Solomon and Corbit, 1974), this hypothesis of addiction proposes that drugs of abuse initially activate brain structures that subserve positive emotional states (e.g., pleasure, contentment). The positive reinforcing effects of drugs are regulated in part by the ventral striatum and extended amygdala reward system, as well as by dopaminergic and opioid inputs from the ventral tegmental area (VTA) and arcuate nucleus of the hypothalamus, respectively. To maintain emotional homeostasis, however, a counter-regulatory opponent process then decreases mood and increases vigilance/tension via downregulation of brain reward systems (e.g., ventral striatum) and upregulation of brain stress systems, including CRF and norepinephrine systems in the extended amygdala (Heilig and Koob, 2007; Heilig et al., 2010a,b, 2011; Koob and Zorrilla, 2010, 2012; Breese et al., 2011; Logrip et al., 2011). With continued cycles of intoxication/withdrawal, the opponent process allostatically predominates over the primary rewarding process (Fig. 2). As a result, more substance of abuse is needed simply to maintain euthymia. If drug use stops, negative emotional symptoms emerge (i.e., acute withdrawal: anxiety, dysphoria, irritability). With a sufficient drug use history, stress-like symptoms of dysphoria may episodically and spontaneously resurge even weeks or months after detoxification (i.e., protracted withdrawal). Furthermore, exaggerated responses to otherwise mild stressors may be seen despite continued abstinence. Under this conceptualization of addiction, substance abuse escalates because the drug of abuse mitigates the counter-regulatory negative emotional symptoms of acute and protracted withdrawal (Heilig and Koob, 2007; Koob and Zorrilla, 2010; Zorrilla et al., 2013a).

The reviewed opponent process putatively of otherwise silent brain CRF_1 receptor stress systems of the extended amygdala. For example, in dependent rat models, acute alcohol withdrawal activates CRF systems in the central nucleus of the amygdala (CeA) (Merlo Pich et al., 1995; Zorrilla et al., 2001; Funk et al., 2006; Roberto et al., 2010) and bed nucleus of the stria terminalis (Olive et al., 2002). Extracellular CRF in rats also increased in the CeA during precipitated withdrawal from chronic nicotine (George et al., 2007), withdrawal from binge cocaine self-administration (Richter and Weiss, 1999), and precipitated withdrawal from opioids (Weiss et al., 2001) and cannabinoids (Rodriguez de Fonseca