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Corticotropin Releasing Factor (CRF) and Addictive Behaviors

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Abstract

Drug addiction is a complex disorder that is characterized by compulsivity to seek and take the drug, loss of control in limiting intake of the drug, and emergence of a withdrawal syndrome in the absence of the drug. The transition from casual drug use to dependence is mediated by changes in reward and brain stress functions and has been linked to a shift from positive reinforcement to negative reinforcement. The recruitment of brain stress systems mediates the negative emotional state produced by dependence that drives drug seeking through negative reinforcement mechanisms, defined as the “dark side” of addiction. In this chapter we focus on behavioral and cellular neuropharmacological studies that have implicated brain stress systems (i.e., corticotropin-releasing factor [CRF]) in the transition to addiction and the predominant brain regions involved. We also discuss the implication of CRF recruitment in compulsive eating disorders.

Keywords

Extended Amygdala; GABA; CRF; alcohol dependence

Introduction

Addiction is a complex, chronic relapsing disorder characterized by compulsive seeking and taking of a substance of abuse, loss of control in limiting intake, and the emergence of a withdrawal syndrome with negative emotional components upon cessation of use (Association, 1994; Organization, 1992). Clinically, the occasional and limited use of an abused substance is distinct from the escalated, uncontrolled use and compulsive seeking that defines addiction (G. F. Koob & Volkow, 2010). Each year, about half of all American adults suffer from an addictive disorder (Sussman, Lisha, & Griffiths, 2011). Addiction imposes a major public health burden with devastating medical and socioeconomic consequences (Kessler et al., 2005). Alcohol misuse alone has an annual prevalence of 10% in the United States (Sussman et al., 2011) and accounts for 10% of total disability in developed countries (Rehm et al., 2009). In 2015, 20.5 million Americans age 12 or older had a substance use disorder; of these, 2 million involved prescription pain relievers and 591,000 involved heroin (Quality, 2016). Furthermore, drug overdose is the leading cause of accidental death in the United States, with 52,404 lethal drug overdoses in 2015, more than 60% involving opioids (Rudd, Seth, David, & Scholl, 2016).

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Addiction has been conceptualized as a cycle with three stages — *binge/intoxication*, *withdrawal/negative affect*, and *preoccupation/anticipation* — that worsen over time and use and culminate in a severe neurobiological disorder. Much ongoing research seeks to identify the molecular and cellular neuroadaptive changes that result from exposure to substances of abuse and which promote the transition from casual use to addiction. Chronic substance use, even if begun for its rewarding effects, progressively leads to anxiety, irritability, and depressed mood during abstinence, resulting in negatively reinforced use in order to “self-medicate” the negative emotional state. An extension of the “opponent process theory of affective regulation” (Solomon & Corbit, 1974), this hypothesis of addiction proposes that substances with abuse potential initially activate brain structures that subserve positive emotional states (e.g., pleasure, contentment, well-being), such as dopaminergic inputs to the nucleus accumbens (NAc) from the ventral tegmental area (VTA) and opioid inputs to the extended amygdala from the arcuate nucleus of the hypothalamus. To restore emotional homeostasis, however, a counter-regulatory opponent process then decreases mood and increases vigilance/tension via downregulation of brain reward systems (e.g., nucleus accumbens) and upregulation of brain stress systems (Breese, Sinha, & Heilig, 2011; George et al., 2012; Heilig, Goldman, Berrettini, & O’Brien, 2011; Heilig & Koob, 2007; Heilig, Thorsell, et al., 2010; Koob & Volkow, 2010; Logrip, Koob, & Zorrilla, 2011). With continued cycles of intoxication/withdrawal, the neuroadaptive opponent process predominates over the primary rewarding process. Then, more of the substance of abuse is needed just to re-attain euthymia. If drug use stops, negative emotional symptoms emerge during acute withdrawal. As a result, associated environmental cues and stress can trigger the development of preoccupation with obtaining the substance in anticipation of its alleviating effects. With enough drug use history, symptoms of dysphoria may episodically reappear even weeks or months after detoxification as components of the protracted withdrawal syndrome. Exaggerated reactivity to otherwise mild stressors also can occur. Accordingly, fMRI activation responses to negative affective pictures are sensitized in detoxified alcoholics (Gilman & Hommer, 2008). Under this conceptual framework, substance use escalates and becomes compulsive because it mitigates the counter-regulatory, long-term emotional disturbances that persist despite abstinence (Heilig & Koob, 2007; G. F. Koob & Volkow, 2010; Zorrilla, Heilig, de Wit, & Shaham, 2013). As will be reviewed, corticotropin-releasing factor (CRF) stress systems are hypothesized to play a key role in all three stages of the addiction cycle but particularly in the *withdrawal/negative affect* stage.

Corticotropin–releasing factor stress systems

Since the successive discovery by Wylie Vale and his colleagues of the 41-residue stress-related peptide corticotropin-releasing factor (CRF; also known as corticotropin-releasing hormone or CRH) (Vale, Spiess, Rivier, & Rivier, 1981), the structurally-related urocortins (Ucn 1, Ucn 2, Ucn 3), and their cognate receptors (CRF₁, CRF₂) (Bale & Vale, 2004; Fekete & Zorrilla, 2007), CRF systems have received attention as therapeutic targets for substance abuse. CRF₁ and CRF₂ receptors are class B1 (“secretin-like”) G-protein coupled receptors with ~70% sequence identity for one another. Though most functional significance is attributed to the CRF_{1(a)} subtype, there are multiple CRF₁ receptor isoforms (e.g., CRF_{1a}-CRF_{1h}). In humans, the CRF₂ receptor has three known membrane-associated functional

subtypes -- CRF_{2(a)}, CRF_{2(b)}, and CRF_{2(c)}. CRF is a preferential agonist for CRF₁ over CRF₂ receptors. Ucn 1 is a high-affinity agonist at both receptor subtypes, and the type 2 urocortins (Ucn 2 and Ucn 3) are selective CRF₂ receptor agonists. A CRF-binding protein (CRF-BP) binds CRF and Ucn 1 with equal or greater affinity than do CRF receptors, and Ucn 2 with somewhat lesser affinity, and has been suggested to act to sequester peptide (inhibiting activity) or alternatively to chaperone/complex with peptide to provide a different signaling method. Most CRF receptor antagonists do not bind to the CRF-BP, confirming the different structural requirements for binding to CRF receptors vs. the CRF-BP (Fekete & Zorrilla, 2007; Zorrilla & Koob, 2004). Pharmacological and transgenic studies indicate that brain and pituitary CRF₁ receptors mediate endocrine, behavioral, and autonomic responses to stress (Heinrichs & Koob, 2004; Koob & Heinrichs, 1999; Zorrilla et al., 2013; Zorrilla & Koob, 2010), and CRF₂ receptor activation has been associated with decreased feeding (Fekete & Zorrilla, 2007; Pellemounter et al., 2000; M. Spina et al., 1996).

CRF, the HPA Axis, and Addiction

CRF was first identified as the central initiator of the classic hypothalamic-pituitary-adrenal (HPA)-axis stress neuroendocrine response. Stressors elicit CRF synthesis in the paraventricular nucleus of the hypothalamus and its release, via the median eminence, into the portal blood. Then, CRF activates CRF₁ receptors on anterior pituitary corticotrophs, stimulating ACTH synthesis and release into circulation, which culminates in the production and secretion of the glucocorticoid cortisol (structurally-similar to corticosterone in rodents) by the adrenal cortex.

Most drugs with abuse potential, including opioids (Buckingham, 1982), amphetamine (Swerdlow, Koob, Cador, Lorang, & Hauger, 1993), cocaine (Calogero, Gallucci, Kling, Chrousos, & Gold, 1989), nicotine (Buckingham & Hodges, 1979), marijuana (⁹-tetrahydrocannabinol; (Weidenfeld, Feldman, & Mechoulam, 1994)), and alcohol (J. Rivier, Rivier, & Vale, 1984), acutely activate the HPA axis via hypothalamic CRF (C. L. Rivier, Grigoriadis, & Rivier, 2003; Sarnyai, Biro, Penke, & Telegdy, 1992). This HPA-axis activation, via glucocorticoids, has been hypothesized to facilitate activity in brain motivational circuits, drug reward, and the acquisition of drug-seeking behavior (Fahlke, Hard, & Hansen, 1996; Goeders, 1997; Piazza et al., 1993; Piazza & Le Moal, 1997). For example, acute HPA activation is involved in the development of drug-induced locomotor sensitization (Cole et al., 1990), and inhibition of CRF₁ receptors blocks drug-induced behavioral sensitization (Fee, Sparta, Picker, & Thiele, 2007; Przegalinski, Filip, Frankowska, Zaniowska, & Papla, 2005). Genetic deletion of CRF₁, but not CRF₂ receptors, similarly reduces the development of ethanol-induced behavioral sensitization (Pastor et al., 2008). Supporting a role for glucocorticoids in this effect, adrenalectomy or corticosteroid synthesis inhibitors reduce not only cocaine-induced locomotor activation, but also the acquisition of cocaine self-administration behavior (Goeders & Guerin, 1996). Importantly, withdrawal from all drugs of abuse studied to date also activates the HPA-axis and glucocorticoid release. Thereby, both exposure- and withdrawal-induced CRF-induced glucocorticoid release may promote the development of self-administration of substances of abuse.

Perhaps more relevant to neuroadaptive aspects of addiction, progressive changes in the HPA axis occur during the transition from acute to chronic administration of drugs of abuse. Whereas acute administration of most drugs of abuse activates the HPA axis, repeated administration of cocaine, opioids, nicotine, and alcohol leads to blunted or dysregulated responses (Goeders, 2002; G. Koob & Kreek, 2007; Kreek & Koob, 1998; Rasmussen et al., 2000; Semba, Wakuta, Maeda, & Suhara, 2004; Sharp & Matta, 1993). Atypical HPA reactivity to stressors putatively contributes to the persistence and relapse to cycles of opioid dependence, a hypothesis that has been extended to other substances of abuse (Kreek & Koob, 1998).

High circulating levels of glucocorticoids exert negative feedback on the hypothalamus to shut-off the HPA-axis neuroendocrine stress response. However, relevant to drug-induced neuroadaptation, high levels of glucocorticoids appear to “sensitize” CRF systems in the CeA and BLA, which subserve behavioral stress responses (Imaki, Nahan, Rivier, Sawchenko, & Vale, 1991; Makino, Gold, & Schulkin, 1994; Schulkin, McEwen, & Gold, 1994; Shepard, Barron, & Myers, 2000; Swanson & Simmons, 1989). Perhaps accordingly, glucocorticoid receptor antagonists have been shown to reduce the development and expression of excessive alcohol self-administration that results from repeated, intermittent intoxication (Vendruscolo et al., 2012; Vendruscolo et al., 2015). A double blind, placebo-controlled human clinical study found that mifepristone (a glucocorticoid receptor and progesterone receptor antagonist) reduced alcohol-cued craving in the laboratory and naturalistic measures of alcohol consumption (Vendruscolo et al., 2015).

In sum, CRF-driven HPA axis activation may result from initial drug use and contribute to the *binge/intoxication* stage of addiction; continued activation may recruit extrahypothalamic brain stress systems that are involved in the *withdrawal/negative affect* stage (Koob & Kreek, 2007; Koob & Le Moal, 2005; Kreek & Koob, 1998).

Extrahypothalamic CRF systems

As noted, outside the hypothalamus, CRF-immunoreactive cell bodies also are found in many other brain regions, with particularly strong expression in the cortex, lateral septum, and a macrostructure known as the extended amygdala (which includes the central nucleus of the amygdala [CeA] and medial amygdala [MeA], bed nucleus of the stria terminalis [BNST], and a transition area in the medial [shell] part of the NAc) (Pilcher & Joseph, 1984), all of which are activated by stressors (Day, Nebel, Sasse, & Campeau, 2005; Hammack, Richey, Watkins, & Maier, 2004; Heinrichs, Menzaghi, Merlo Pich, Britton, & Koob, 1995; Melia, Sananes, & Davis, 1992). Accordingly, extrahypothalamic CRF is recognized to subserve behavioral stress responses (Heinrichs et al., 1995) independent of HPA axis activation (reviewed in G. F. Koob, 1999). Thus, central administration of CRF mimics the behavioral response to stress in rodents, and competitive CRF receptor antagonists generally have anti-stress-like effects in rodent models (Heinrichs et al., 1994; Spina et al., 2000); for reviews, see (Dunn & Berridge, 1990; Koob & Le Moal, 2001; Koob, Rassnick, Heinrichs, & Weiss, 1994; Logrip et al., 2011; Sarnyai, Shaham, & Heinrichs, 2001). The distribution of the CRF-binding protein (CRF-BP) overlaps partly with that of CRF, notably in the cortex and amygdala (Potter et al., 1992), where terminals containing

CRF-BP colocalize with CRF-positive cell bodies (Potter et al., 1992) consistent with the regulatory interaction posited for these molecules.

CRF receptors are distributed even more widely than the CRF-BP (De Souza & Battaglia, 1988), affirming a role for CRF family peptides in modulating the development (Swinny et al., 2003) and excitability (Fu & Neugebauer, 2008; Gallagher, Orozco-Cabal, Liu, & Shinnick-Gallagher, 2008; Miyata, Okada, Hashimoto, Kano, & Ito, 1999; Rannie et al., 2004; Schierloh, Deussing, Wurst, Zieglansberger, & Rammes, 2007; Schmolesky, De Ruiter, De Zeeuw, & Hansel, 2007) of many neuronal populations. CRF₁ receptors are highly expressed in stress-responsive forebrain regions, including the neocortex, BLA, BNST, medial septum, hippocampus, and thalamus, with moderate expression in the NAc and VTA as well as marked expression in autonomic midbrain and hindbrain nuclei (Grigoriadis et al., 1996; Primus, Yevich, Baltazar, & Gallager, 1997; Sanchez, Young, Plotsky, & Insel, 1999; Van Pett et al., 2000). The CRF₁ receptor distribution resembles that of its natural ligands CRF and Ucn 1 and accounts for the dissociable role of extrahypothalamic CRF₁ systems (i.e., outside the HPA-axis) to mediate behavioral and autonomic stress responses (Fekete & Zorrilla, 2007; Kozicz, Yanaihara, & Arimura, 1998; Swanson, Sawchenko, Rivier, & Vale, 1983; Zorrilla & Koob, 2004). In contrast, extrahypothalamic, forebrain CRF₂ receptors are primarily confined to the medial extended amygdala (MeA and medial BNST), lateral septum and ventromedial hypothalamus (Chalmers, Lovenberg, & De Souza, 1995).

Role for CRF-CRF₁ systems in animal models of addiction

Several preclinical lines of evidence support the hypothesis that central CRF systems contribute to the addiction cycle. For example, the anxiogenic-like response that results during withdrawal from repeated administration of cocaine, alcohol, nicotine, cannabinoids, and benzodiazepines can be reversed by CRF receptor antagonists, including after intracerebroventricular administration in rodent models of addiction (Baldwin, Rassnick, Rivier, Koob, & Britton, 1991; Basso, Spina, Rivier, Vale, & Koob, 1999; Knapp, Overstreet, Moy, & Breese, 2004; Overstreet, Knapp, & Breese, 2004; Rodriguez de Fonseca, Carrera, Navarro, Koob, & Weiss, 1997; Sarnyai et al., 1995; Tucci, Cheeta, Seth, & File, 2003). The increased ethanol (EtOH) self-administration that results from exposure to repeated cycles of chronic EtOH vapor (O'Dell, Roberts, Smith, & Koob, 2004; Rimondini, Arlinde, Sommer, & Heilig, 2002) likewise can be blocked by intracerebroventricular administration of a CRF₁/CRF₂ antagonist at doses that do not influence EtOH self-administration in nondependent animals (Valdez, Sabino, & Koob, 2004).

Many findings in animal models implicate CRF₁ receptors specifically in these “dark side” actions of CRF (or other endogenous CRF₁ agonists) to produce a negative emotional state. For example, the decreased brain reward function seen in animal models of withdrawal from nicotine, alcohol, or opioids, evident as increased current thresholds for intracranial self-stimulation behavior, can be blocked by CRF₁ antagonists (Bruijnzeel et al., 2012; Bruijnzeel, Prado, & Isaac, 2009; Bruijnzeel, Small, Pasek, & Yamada, 2010; Bruijnzeel, Zislis, Wilson, & Gold, 2007). A CRF₁ antagonist also prevented the development of a conditioned place aversion following precipitated withdrawal in opioid-dependent rats

(Stinus, Cador, Zorrilla, & Koob, 2005). Similarly, *Crhr1* knockout mice did not show opioid withdrawal-induced conditioned place aversion (Contarino & Papaleo, 2005; Garcia-Carmona, Almela, Baroja-Mazo, Milanes, & Laorden, 2012). Finally, systemic injections of brain-penetrant CRF₁ antagonists reduced the heightened anxiety-like behavior of dependent rodents acutely withdrawn from alcohol or other substances of abuse (Breese, Overstreet, & Knapp, 2005; Breese, Overstreet, Knapp, & Navarro, 2005; Gehlert et al., 2007; Knapp et al., 2004; Overstreet et al., 2004; Sommer et al., 2008).

Perhaps because they reduce the negative emotional state, CRF₁ receptor antagonists also reduce the seeking and taking of substances of abuse in dependence models. For example, systemic administration of CRF₁ antagonists reduced the escalated EtOH self-administration of dependent rats and mice acutely withdrawn from alcohol at doses that did not alter the intake of non-dependent animals (Chu, Koob, Cole, Zorrilla, & Roberts, 2007; Funk, Zorrilla, Lee, Rice, & Koob, 2007; Gehlert et al., 2007; Gilpin, Richardson, & Koob, 2008; Richardson et al., 2008; Sabino et al., 2006). Similarly, small-molecule CRF₁ antagonists differentially reduced the increase in drug self-administration associated with extended access to cocaine (Specio et al., 2008), nicotine (George et al., 2007), alcohol (Roberto et al., 2010), and heroin (Greenwell et al., 2009). Furthermore, both global (Chu et al., 2007) and conditional brain-specific *Crhr1* knockout mice (Molander et al., 2012) show reduced EtOH intake during withdrawal compared to their wildtype littermates. Consistent with a role for CRF systems in stress-induced substance use, the CRF₁ antagonist CP-154,526 reduced stress-induced potentiation of EtOH intake in non-dependent mice (Lowery, Sparrow, Breese, Knapp, & Thiele, 2008), and *Crhr1* knockout mice were resistant to the ability of repeated forced swim stress to increase deprivation-induced EtOH intake (Pastor et al., 2011).

These salutary actions of CRF₁ antagonists in animal models extend to the post-dependent phase, suggesting that CRF-CRF₁ activation can persist past detoxification into protracted withdrawal. For example, CRF₁ antagonists reduced potentiated stress-induced anxiogenic-like responses and EtOH intake during protracted withdrawal (Rimondini et al., 2002; Sommer et al., 2008; Valdez et al., 2002; Valdez, Zorrilla, Roberts, & Koob, 2003). CRF₁ antagonists also reduced the spontaneously greater levels of anxiety-like behavior (Breese, Overstreet, & Knapp, 2005; Breese, Overstreet, Knapp, et al., 2005; Sommer et al., 2008; Valdez et al., 2002; Zhao, Valdez, et al., 2007; Zhao, Weiss, & Zorrilla, 2007) and EtOH drinking that occur in post-dependent rats even in the absence of external stressors (Rimondini et al., 2002; Sommer et al., 2008; Valdez et al., 2002). Both actions may have implications for relapse prevention since negative emotional states predict relapse in alcohol use disorders (Mossberg, Liljeberg, & Borg, 1985; Pickens, Hatsukami, Spicer, & Svikis, 1985).

Though the CRF-BP had initially been regarded as exclusively serving an inhibitory role in the CRF system, it has increasingly been recognized to have other modulatory roles in the brain, some of which may be relevant to the neurobiology of excessive consumption (Westphal & Seasholtz, 2006). For example, CRF₂ can interact with the CRF-BP to produce actions independent from CRF₁ (Milan-Lobo et al., 2009; Slater, Cerda, Pereira, Andres, & Gysling, 2016; Ungless et al., 2003; B. Wang, You, Rice, & Wise, 2007). The CRF-BP has

recently received attention as a potential target for its role in alcohol use disorder (Haass-Koffler et al., 2016; Ketchesin, Stinnett, & Seasholtz, 2016), and its role in the escalation of alcohol drinking may involve its interaction with CRF₂ (Albrechet-Souza et al., 2015; Quadros, Macedo, Domingues, & Favoretto, 2016). Intriguingly, recent gene variant studies in humans have shown that the *CRHBP*rs1875999 locus was associated with risk for both cocaine and heroin addiction in African Americans in a study of heroin addicts ($n = 314$), cocaine addicts ($n = 281$), and healthy controls ($n = 208$) (Levrán, Peles, et al., 2014; Levrán, Randesi, et al., 2014). SNPs in the *CRHBP*(10kD) fragment, *rs10055255*, *rs10062367*, and *rs7728378* were each associated with increased risk of alcohol drinking and/or anxiety in patients with alcohol use disorder (Haass-Koffler et al., 2016).

Additional data that implicate CRF-CRF₁ activation in relapse behavior come from preclinical models of stress-induced reinstatement of substance seeking (Shaham, Shalev, Lu, De Wit, & Stewart, 2003; Stewart & de Wit, 1987). For example, systemic injections of the CRF₁ antagonist CP-154,526 attenuated footshock-induced reinstatement of EtOH-seeking in non-dependent rats (Le et al., 2000a), and the CRF₁ antagonist antalarmin attenuated reinstatement of EtOH seeking induced by yohimbine, an alpha-2 adrenergic antagonist with anxiogenic properties (Marinelli et al., 2007). Intracranial infusion of non-selective CRF antagonists or systemic administration of small-molecule CRF₁ antagonists also blocked stressor-induced reinstatement of cocaine-, opiate-, nicotine-, and methamphetamine-seeking behavior (Bruijnzeel et al., 2009; Le & Shaham, 2002; Lu, Shepard, Hall, & Shaham, 2003; Nawata, Kitaichi, & Yamamoto, 2012; Plaza-Zabala, Martin-Garcia, de Lecea, Maldonado, & Berrendero, 2010; Shaham, Erb, Leung, Buczek, & Stewart, 1998; Shaham et al., 2003). CP-154,526 also inhibited stress-induced reinstatement of conditioned place preference to morphine and cocaine (Lu, Ceng, & Huang, 2000; Lu, Liu, & Ceng, 2001; Lu, Liu, Ceng, & Ma, 2000). A CRF₁ antagonist also reduced social defeat stress-induced locomotor sensitization to cocaine and escalated “binge” operant self-administration of cocaine (Boyson, Miguel, Quadros, Debold, & Miczek, 2011) as well as stress-induced reinstatement of cocaine-seeking behavior in rats with a history of extended access to cocaine (Blacktop et al., 2011). Similarly, the CRF₁ antagonists antalarmin and MTIP were effective in attenuating footshock-induced reinstatement of EtOH seeking in alcohol-dependent rats or in genetically-selected, Marchigian Sardinian alcohol-preferring rats, which show innately upregulated CRF₁ mRNA expression in several brain areas (Gehlert et al., 2007; Hansson et al., 2006). Importantly, CRF₁ antagonists do not prevent cue-, substance-, or context-induced reinstatement. This specificity is consistent with the unique neuroanatomical and neuropharmacological bases for stress-induced reinstatement (Bossert, Marchant, Calu, & Shaham, 2013; Koob & Le Moal, 2008; Steketee & Kalivas, 2011) for reviews).

Similar to the reviewed anti-anxiety and anti-drug taking actions of CRF receptor antagonists, the ability of CRF₁ antagonists to reduce stress-induced reinstatement appears to involve non-neuroendocrine (i.e., extrahypothalamic) CRF. For example, intermittent footshock-induced reinstatement is not affected by adrenalectomy (Le et al., 2000b), and effective doses of antalarmin did not alter yohimbine-induced corticosterone levels (Marinelli et al., 2007). Accordingly, many findings affirm that stress-induced reinstatement of EtOH, cocaine, and heroin seeking are mediated by stress-induced activation of

extrahypothalamic CRF sites (Blacktop et al., 2011; Erb, Shaham, & Stewart, 1998; Le & Shaham, 2002; Le, Funk, Coen, Li, & Shaham, 2013; Le, Harding, Juzysch, Fletcher, & Shaham, 2002; Shaham et al., 1997; Wang et al., 2005; JWang, Fang, Liu, & Lu, 2006)

Central extended amygdala

Many of the long-term emotional disturbances associated with the withdrawal/negative affect stage of the addiction cycle have been attributed to activity within the central subdivision of the extended amygdala (Koob, 2008), which consists of the CeA, lateral BNST, and shell of the NAc (Heimer L, 1991). These regions share afferents from limbic cortices, the hippocampus, and basolateral amygdala (BLA), and have common effector targets, including the lateral hypothalamus and brainstem regions that produce behavioral and autonomic responses that have been associated with stress, fear and anxiety (Davis, Rainnie, & Cassell, 1994).

In particular, the CeA is a brain region uniquely situated to function as an interface between stress- and addiction-related processes. The CeA is not only critical in aversive (e.g., fear) conditioning, but also in the negative emotional states that define drug dependence and withdrawal. The CeA is composed mostly of inhibitory γ -aminobutyric acid (GABA) projection neurons and interneurons (McDonald & Augustine, 1993; Pare & Smith, 1993; Sun & Cassell, 1993; Veinante & Freund-Mercier, 1998), and modulation of local intra-CeA inhibitory gating is involved in the control of fear and anxiety-like behavior (Davis, Walker, Miles, & Grillon, 2010; Ehrlich et al., 2009; Pape & Pare, 2010).

The CeA is the major output region of the amygdaloid complex; as such, it receives complex inputs from other amygdaloid nuclei, as well as from other brain regions that integrate sensory information from the external environment (e.g., cortex, thalamus). The CeA is functionally and anatomically divided into lateral (CeL) and medial (CeM) subdivisions that themselves are interconnected and mainly populated by both inhibitory interneurons and GABAergic projection neurons. Additionally, both the CeL and CeM subdivisions project to the lateral division of the BNST (Davis et al., 2010; Dong, Petrovich, & Swanson, 2001; Petrovich, Risold, & Swanson, 1996; Sun, Roberts, & Cassell, 1991), another extended amygdala structure dominated by inhibitory neurotransmission (Sun & Cassell, 1993; Veinante & Freund-Mercier, 1998). Importantly, there are also reciprocal connections between the CeA and BNST, and the CeA is a major source of corticotropin-releasing factor (CRF) in the BNST (Sakanaka, Shibasaki, & Lederis, 1986). As the CeM subdivision projects to regions that produce behavioral and physiological responses to emotionally relevant events (Le Gal LaSalle, Paxinos, & Ben-Ari, 1978; Pitkänen, 2000), it likely plays a major role in the behavioral changes associated with extrahypothalamic CRF signaling. However, more recent data suggest that the CeL also sends GABAergic projections to behavioral and physiological effector regions (Penzo, Robert, & Li, 2014).

Substantial preclinical data implicate extended amygdala CRF-CRF₁ systems in excessive or addiction-like consumption. While acute drug exposure only yields a transient elevation of CRF expression (Maj, Turchan, Smialowska, & Przewlocka, 2003; Zhou et al., 1996), chronic exposure leads to more sustained overactivation following cessation of drug use

(Caberlotto, Rimondini, Hansson, Eriksson, & Heilig, 2004; George et al., 2007; Sommer et al., 2008; Zhou, Spangler, Ho, & Kreek, 2003; Zorrilla, Valdez, & Weiss, 2001). For example, *in vivo* microdialysis showed that acute withdrawal from chronic administration or self-administration of drugs of abuse increases extracellular CRF in the extended amygdala, a stress-like response (Merlo Pich et al., 1995; Richter, Zorrilla, Basso, Koob, & Weiss, 2000). Extracellular levels of CRF increase in the CeA and BNST of dependent rats withdrawn from EtOH (Merlo Pich et al., 1995; Olive, Koenig, Nannini, & Hodge, 2002). Similarly, extracellular CRF levels increased in the CeA during precipitated withdrawal from chronic nicotine (George et al., 2007), opioids (Weiss et al., 2001) or cannabinoids (Rodriguez de Fonseca et al., 1997) as well as during withdrawal from binge cocaine self-administration (Richter & Weiss, 1999). Increased CeA CRF mRNA also has been seen at various withdrawal time-points (Caberlotto et al., 2004; Maj et al., 2003; Roberto et al., 2010; Sommer et al., 2008). The high levels of CRF release at early withdrawal time-points can paradoxically yield low tissue content of CRF peptide (Funk, O'Dell, Crawford, & Koob, 2006; Maj et al., 2003; Sarnyai et al., 1995; Zorrilla et al., 2001) because CRF synthesis may lag behind release, resulting in transient depletion of CRF levels.

Consistent with a functional role for central extended amygdala CRF receptor activation in the negative affect/withdrawal stage, site-specific injections of CRF receptor antagonists into the CeA reduce anxiety-like behavior, motivational deficits for other reinforcers, and excessive self-administration of addictive substances during acute withdrawal in animal models (Funk et al., 2006; Funk et al., 2007; Heilig, Egli, Crabbe, & Becker, 2010; Heilig & Koob, 2007; G. F. Koob & Zorrilla, 2010; Logrip et al., 2011; Parylak, Koob, & Zorrilla, 2011; Rassnick, Heinrichs, Britton, & Koob, 1993). Furthermore, intra-CeA infusion of D-Phe CRF₁₂₋₄₁, a CRF receptor antagonist, reduced the elevations in brain reward stimulation thresholds that result from withdrawal from nicotine (Marcinkiewicz et al., 2009; Bruijnzeel, 2007 #96) or EtOH (Bruijnzeel et al., 2010). Intra-CeA administration of α -helical CRF₉₋₄₁ also blocked the formation of a conditioned place aversion to precipitated morphine withdrawal (Heinrichs et al., 1995). Finally, administration of CRF receptor antagonists into the BNST, where CRF mRNA levels increase following stress and which also receives CRFergic projections from the CeA, reduces stress-induced reinstatement of drug-seeking as well as stress-induced reinstatement of conditioned place preference for substances of abuse (Erb, Salmaso, Rodaros, & Stewart, 2001; Erb, Shaham, & Stewart, 2001; Erb & Stewart, 1999; McReynolds et al., 2014; Shalev, Morales, Hope, Yap, & Shaham, 2001; J. Wang et al., 2006).

Altered expression in amygdala CRF-CRF₁ systems has been seen at both the peptide and receptor level several weeks after detoxification from repeated EtOH intoxication/withdrawal in animal models (Sommer et al., 2008; Zorrilla, Valdez & Weiss, 2001). With respect to receptors, contrasting changes in CRF₁ vs. CRF₂ were reported 3-weeks post-cessation of alcohol exposure (Sommer et al., 2008). Within the BLA and MeA, CRF₁ levels were reportedly elevated, whereas BLA CRF₂ levels decreased. The generality of these changes across substances of abuse and withdrawal time points is unclear, however. For example, precipitated morphine withdrawal acutely reduced CRF₁ mRNA expression in the BLA and NAc (Iredale et al., 2000). With respect to CRF peptide levels, both EtOH- and cocaine-withdrawn animals initially exhibited a reduction of CRF-like tissue content in the

amygdala, followed by a progressive increase that culminated in elevated levels by 6-weeks post-withdrawal (Funk et al., 2006; Maj et al., 2003; Sarnyai et al., 1995; Zorrilla, Valdez & Weiss, 2001). Thus, dysregulation of extended amygdala CRF systems continues into protracted abstinence and is thereby also hypothesized to contribute to the *preoccupation/anticipation* stage of the addiction cycle.

Cellular mechanisms of CRF:

Much of the research into the cellular actions of CRF in addictive disorders has focused on interactions with alcohol in extrahypothalamic stress systems. Therefore, although we will briefly discuss cellular CRF interactions with other drugs of abuse later, we will focus mainly on CRF produced in the CeA and the effects of acute and chronic alcohol on neurotransmission and plasticity in CeA and the role of these effects in the mediation of alcohol-related behaviors.

The CeA is particularly enriched with neuropeptides that regulate anxiety- and alcohol-related behaviors (Koob, 2008). These neuropeptides can be conceptually divided into pro-stress and anti-stress peptides, which respectively promote and rescue negative affective disturbances during drug abstinence following heavy drug use. Pro-stress peptides include CRF, dynorphin, and orexin; anti-stress peptides include neuropeptide Y (NPY), oxytocin, and nociception/orphanin FQ (N/OFQ). Notably these peptides interact in a complex way in the extended amygdala to modulate inhibitory GABAergic and excitatory glutamatergic transmission. Acute and chronic alcohol dysregulate these peptidergic systems and their modulatory role on neurotransmitter systems.

At the cellular level, acute alcohol and CRF increase presynaptic GABA release in both rat (Roberto et al., 2010; Roberto, Madamba, Moore, Tallent, & Siggins, 2003) and mouse (Nie et al., 2004) CeA neurons via activation of CRF₁ (Nie et al., 2009; Roberto et al., 2010). Many studies on chronic alcohol effects on CeA neurotransmission now utilize a chronic intermittent ethanol (CIE) vapor inhalation model to induce alcohol dependence in rodents (Gilpin, Richardson, Cole, & Koob, 2008). Of note for electrophysiological studies, alcohol-dependent rats are maintained in the EtOH vapor chamber until the preparation of CeA slices under EtOH-free conditions. Thus, recordings of CeA neurons are performed at 2–8 hrs of EtOH withdrawal for these neurons. In the CeA of alcohol-dependent rats, baseline frequency of miniature (mIPSCs) and spontaneous inhibitory postsynaptic currents (sIPSCs), as well as baseline evoked inhibitory postsynaptic currents (eIPSCs), are significantly higher. Additionally, baseline paired pulse facilitation (PPF) ratios of eIPSCs are significantly lower, suggesting that basal CeA GABA release is augmented by chronic EtOH exposure (Roberto et al., 2010; Roberto et al., 2003; Roberto, Madamba, Stouffer, Parsons, & Siggins, 2004; Varodayan, de Guglielmo, Logrip, George, & Roberto, 2017). Interestingly, acute EtOH application significantly increases eIPSCs and s/mIPSC frequencies in slices from dependent rats to an extent equivalent to that in slices from non-dependent rats, suggesting a lack of tolerance for these acute EtOH effects (Roberto, Madamba, Stouffer, Parsons, & Siggins, 2004; Varodayan, de Guglielmo, Logrip, George, & Roberto, 2017). Consistent with *in vitro* electrophysiological results at the same time points (2–8 hours of withdrawal), *in vivo* EtOH administration directly into the CeA via a

microdialysis probe reveals a significant elevation in basal dialysate GABA levels in the CeA of alcohol-dependent rats compared with alcohol-naïve rats, further suggesting increased GABAergic tone during alcohol dependence (Roberto et al., 2004). A lack of tolerance to the alcohol-induced increases in dialysate GABA content in alcohol-dependent rats is also observed *in vivo* (Roberto et al., 2010).

CRF increases GABA release in the CeA of alcohol-dependent rats beyond levels already significantly enhanced during withdrawal, along with concomitant increases in CRF and CRF₁ mRNA levels, and increases in CRF release (Merlo Pich et al., 1995; Roberto et al., 2010). This supports the electrophysiological data indicating upregulation of the CRF-CRF₁ system with alcohol dependence. Importantly, the application of CRF₁ antagonists alone decreases GABA release, suggesting tonic facilitation of GABA release by endogenous CRF (or other CRF-like molecules) via these receptors in the CeA (Nie et al., 2004; Roberto et al., 2010). CRF₁ antagonists also block the acute alcohol-induced increase in GABAergic transmission in the CeA. Additionally, *in vivo* intra-CeA administration of a CRF₁ antagonist via retro-microdialysis reverses dependence-related elevations in extracellular GABA dialysates and blocks alcohol-induced increases in GABA in CeA of both dependent and nondependent rats (Roberto et al., 2010). Ongoing electrophysiological studies reveal that the increased sensitivity of CeA GABAergic synapses to exogenous application of CRF persist after 2 weeks of withdrawal from alcohol vapor exposure (unpublished observations from the Roberto lab), suggesting that the neuroadaptive changes associated with chronic alcohol are long-lasting. Given the prominent action of acute CRF₁ receptor antagonist administration in reducing alcohol self-administration in dependent rats, dependent rats chronically treated with a CRF₁ receptor antagonist prevents the development of dependence-induced increases in alcohol drinking (Roberto et al., 2010). These results strongly point to the critical role of CeA CRF system not only in the expression, but also the development, of alcohol dependence in animal models.

Similarly, binge-like alcohol drinking increases CRF₁ signaling in the CeA of C57BL/6J mice (Chu et al., 2007), and CRF₁ antagonists reduce binge-like alcohol drinking in non-dependent rodents without affecting non-binge-like alcohol intake (Funk et al., 2006; Funk et al., 2007; Lowery-Gionta et al., 2012). However, the ability of CRF to increase GABAergic transmission in CeA is blunted in mice with a history of binge-like alcohol drinking (Chu et al., 2007), in contrast to the upregulated CRF/CRF₁ signaling observed in CeA of alcohol-dependent rats (Roberto et al., 2010). Lowery-Gionta et al. (2012) suggest that binge alcohol drinking may abolish CRF effects on GABAergic transmission in CeA via functional down-regulation or desensitization of CRF₁ (Lowery-Gionta et al., 2012), as seen in the dorsal raphe following stress (Cippitelli et al., 2012; Waselus, Nazzaro, Valentino, & Van Bockstaele, 2009).

Although the precise mechanisms by which alcohol and CRF enhance GABA release have yet to be completely identified, previous studies have examined the role of intracellular signaling pathways, such as adenylyl cyclase and protein kinase C (PKC), in the facilitatory effect of acute alcohol on GABAergic transmission. The ability of acute alcohol and CRF to augment GABAergic transmission in the CeA is contingent on the integrity of PKC ϵ intracellular signaling pathways (Bajo, Cruz, Siggins, Messing, & Roberto, 2008). The

alcohol- and CRF-induced increase in GABA release is abolished in the CeA of mice that lacked PKC ϵ (Bajo et al., 2008), suggesting that PKC ϵ facilitates vesicular GABA release. Protein kinase A (PKA) activity is initiated following CRF $_1$ activation, via G $_s$ and G $_q$ protein cascades. Interestingly, type 7 adenylate cyclase plays a role in the modulation of presynaptic GABA release in the mouse CeA by alcohol and CRF (Cruz et al., 2011), and a PKA antagonist blocked CRF from regulating spontaneous GABA release in rat CeA (Cruz, Herman, Kallupi, & Roberto, 2012; Varodayan et al., 2017), suggesting that the presynaptic PKA pathway plays an essential role in CRF-induced GABA release.

More recently, L-type voltage-gated calcium channels (LTCCs) have been implicated in the EtOH-induced increases in CeA action-potential dependent activity (neuronal firing rates and GABA release) in naïve rats, and alcohol dependence reduces CeA LTCC membrane abundance (Varodayan et al., 2017). Nifedipine, an LTCC antagonist, prevents alcohol's potentiation of sIPSC frequencies and firing in naïve rats, but not in alcohol-dependent rats where a CRF $_1$ antagonist (R121919) did. This switch from an LTCC- to a CRF $_1$ -based mechanism with alcohol dependence is accompanied by a shift from a role for inositol triphosphate receptor (IP $_3$ R) mediated calcium-induced calcium release to the involvement of ryanodine receptors (RyRs) (Varodayan et al., 2017). Notably, intra-CeA LTCC blockade reduces alcohol intake in non-dependent rats, and R121919 blocks the escalated alcohol intake of alcohol-dependent rats. Collectively, these data indicate that alcohol dependence functionally alters the molecular mechanisms underlying the CeA's response to alcohol (from LTCC- to CRF $_1$ -driven). This mechanistic switch contributes to and reflects the prominent role of the CeA in the negative emotional state that drives excessive drinking. Critically, P/Q-type voltage-gated calcium channels mediate alcohol-induced CeA vesicular GABA release in a PKA and PKC dependent manner in both naïve and EtOH dependent rats (unpublished data from the Roberto lab).

Given the importance of CRF $_1$ signaling, transgenic mice expressing green fluorescent protein (GFP) in CRF $_1$ expressing neurons (CRF $_1$ +) have been used to examine the effects of chronic EtOH exposure on inhibitory signaling in CRF $_1$ + CeA neurons, and, more recently on the excitability and acute EtOH sensitivity of CeA projection neurons that output to downstream targets in the extended amygdala (Herman, Contet, Justice, Vale, & Roberto, 2013; Herman, Contet, & Roberto, 2016). CeA neurons display two types of inhibition: phasic, which involves IPSCs that reflect "point to point" transmission; and tonic, which involves persistent inhibitory currents resulting from ambient GABA acting at highly-sensitized GABA $_A$ receptors (Belelli et al., 2009; Glykys & Mody, 2007). Tonic inhibition regulates neural network activity (Semyanov, Walker, Kullmann, & Silver, 2004) and is modulated by both acute and chronic alcohol (Jia, Chandra, Homanics, & Harrison, 2008; Liang et al., 2008; Mody, Glykys, & Wei, 2007). As described above, acute alcohol reversibly increases phasic GABA release in a dose-dependent fashion in the CeA (Roberto et al., 2003; Roberto et al., 2004), independent of GABA $_B$ R blockade (Roberto et al., 2008). Acute alcohol also increases phasic and tonic inhibition in a population of CeA neurons that synapse onto CeA output neurons, resulting in disinhibition of CeA output to BNST (Herman et al., 2013).

CRF₁+ neurons make up a distinct component of CeA circuitry that are not directly activated by acute EtOH but instead are engaged via a local microcircuit involving increased inhibition at local CRF₁- interneurons that synapse onto CRF₁+ neurons (Herman et al., 2013; Herman et al., 2016), thus CRF₁+ neurons are normally under tonic inhibitory control. This inhibitory control is lost with chronic EtOH exposure. In particular, the loss of tonic inhibition in CRF₁+ neurons that project into the dorsal lateral BNST occurs in parallel with an increase in phasic and tonic signaling in a subpopulation of late-spiking (LS) CRF₁- neurons. This loss of tonic inhibition is also accompanied by an increase in baseline firing and loss of sensitivity to acute EtOH. Together, these data suggest that chronic EtOH exposure produces a functional switch in tonic signaling in the CeA, such that the balance of inhibitory control shifts from CRF₁+ projection neurons to LS CRF₁- interneurons. This switch results in increased output of the CeA CRF₁ system via disinhibition of projection neurons, and includes a loss of sensitivity to acute EtOH (Herman et al., 2013; Herman et al., 2016). Interestingly, many of these changes persist into EtOH withdrawal (5–7 days). Thus, they may represent long-term neuroadaptations that play a role in alcohol-dependent behaviors, like escalated alcohol intake and the susceptibility to relapse.

As previously mentioned, CRF has been shown to augment GABA transmission in the CeA via actions at CRF₁ (Nie et al., 2004; Roberto et al., 2010) and CeA CRF neurons employ GABA as a co-transmitter as well as displaying increased activity after chronic stress (Partridge et al., 2016). It is important to note that the CRF₁ mouse model just discussed only reflects neurons that express CRF₁ (Justice, Yuan, Sawchenko, & Vale, 2008), and provides no information on CRF peptide actions or circuitry. It is not currently known if the CRF₁+ CeA neurons in the CRF₁:GFP mouse display any overlap with CRF neurons in the CeA. Although progress has been made with other reporter mice (Silberman, Matthews, & Winder, 2013), more sophisticated animal models and/or technological approaches are required to more directly pinpoint the intersection of the CRF and CRF₁ systems in the CeA. Recently, the development of a transgenic *Crh*-Cre rat has permitted genetic access to CRF neurons, thereby allowing direct investigation of their anatomy and roles in physiology and behavior (Pomrenze et al., 2015). The CRF-expressing CeA neurons identified in this transgenic rat project to several brain regions including the basal ganglia, extended amygdala, brainstem, and hypothalamus. In addition, these CRF-expressing neurons are mainly localized in the CeL subdivision of the CeA, where they act as local interneurons to provide both inhibitory (GABA) and excitatory (CRF) signals within the CeL and CeM (Pomrenze et al., 2015).

Although the CeA is a nucleus containing a heterogeneous mix of neuronal types, recent studies have begun to characterize distinct cell populations and their role in circuits governing specific behaviors and CRF effects. For example, circuitry-specific changes in CeA processing have been implicated in conditioned fear (Haubensak et al., 2010) and in anxiety (Botta et al., 2015). A common theme of these studies is the importance of local inhibitory signaling in the flow of information through distinct circuits. Specific inhibitory microcircuits in the CeA govern different aspects of fear learning (Ciocchi et al., 2010) and extrasynaptic inhibition regulates the changes in excitability underlying the encoding of generalized fear or anxiety (Botta et al., 2015). Disinhibition of CeA projection neurons is implicated in critical circuitry changes related to learning and memory in various brain

regions and neurotransmitter/neuromodulator systems (Letzkus, Wolff, & Luthi, 2015). If the development of alcohol dependence can be conceptualized as a pathological expression of learning, then it is compelling that both processes would employ a similar mechanism of disinhibition for the engagement of specific components of brain circuitry. This view agrees with the current focus on the role of disease-specific alterations in distinct amygdala circuits as major contributing factors in the development of addiction (Koob & Volkow, 2016; Koob & Zorrilla, 2010) and the commonalities between addiction and pathological anxiety (Luthi & Luscher, 2014).

In other extended amygdala regions, such as the vBNST, chronic intermittent, but not continuous, ethanol vapor exposure increases the temporal summation of NMDAR-mediated synaptic transmission. This effect is not dependent on changes in glutamate release, but rather on an increase in the levels of NR2B-containing NMDARs. Furthermore, acute ethanol modulation of NMDARs in the vBNST is altered after intermittent alcohol exposure (Kash, Baucum, Conrad, Colbran, & Winder, 2009), supporting the concept of homeostatic regulation of the NR2B subunit in both acute ethanol inhibition of NMDARs and chronic alcohol withdrawal-induced effects on glutamatergic synaptic function in the BNST (Kash et al., 2009; Wills, Kash, & Winder, 2013; Wills et al., 2012). Specifically, chronic intermittent ethanol enhances long-term potentiation (LTP) within the BNST, an effect that is dependent upon GluN2B (Wills et al., 2013; Wills et al., 2012), and GluN2B is upregulated within the BNST following chronic intermittent ethanol (Kash et al., 2009). Interestingly, electrophysiological studies report that CRF exerts multiple actions in the BNST, including enhancement of glutamatergic signaling by increasing both the frequency of sEPSC (Kash, Nobis, Matthews, & Winder, 2008) and cell firing. Glutamate release is similarly enhanced by CRF₁-mediated signaling in mice exposed to chronic intermittent ethanol vapor (Silberman et al., 2013; Silberman & Winder, 2013).

Several studies, both functional (Meloni, Gerety, Knoll, Cohen, & Carlezon, 2006) and anatomical (Day, Curran, Watson, & Akil, 1999; Phelix, Liposits, & Paull, 1994; Rodaros, Caruana, Amir, & Stewart, 2007), have reported an interaction between DA and CRF in the BNST. DA increases excitatory glutamatergic transmission through activation of endogenous CRF/CRF₁ signaling in the BNST (Kash et al., 2008). Subsequent studies have reported that β -AR activation enhances excitatory transmission in the BNST, an effect that is dependent on intact CRF₁ signaling. Notably, this enhancement of excitatory transmission is disrupted by repeated cocaine administration, but not during withdrawal from this repeated cocaine administration. Furthermore, prior cocaine experience influences how CRF receptor signaling responds to subsequent cocaine challenges (Nobis, Kash, Silberman, & Winder, 2011).

Pharmacological experiments suggest that CRF and urocortin enhance GABAergic transmission through mainly postsynaptic responses to GABA via activation of the CRF₁ (Kash & Winder, 2006). Recent data suggests that CRF BNST neurons are exclusively GABAergic, and these GABAergic CRF neurons are highly interconnected with non CRF-expressing neurons within the BNST (Marcinkiewicz, Lowery-Gionta, & Kash, 2016; Mazzone et al., 2016; McElligott & Winder, 2009; Partridge et al., 2016; Vranjkovic, Pina, Kash, & Winder, 2017).

Francesconi et al. (Francesconi et al., 2009) reported a form of long-term potentiation of the intrinsic excitability (LTP-IE) of jcBNST neurons in response to high-frequency stimulation in the BNST. This LTP-IE is impaired during protracted withdrawal from self-administration of alcohol, cocaine, and heroin and was altered in a CRF-dependent manner.

Considering other drugs of abuse, Pollandt et al. (Pollandt et al., 2006) reported a long-lasting potentiation of glutamatergic transmission induced at lateral amygdala (LA)-to-CeA synapses by CRF in withdrawal from repeated intermittent cocaine administration. Bath application of CRF (12.5 nm) persistently increases amplitudes of fEPSPs in the LA–CeA pathway and this CRF-induced facilitation is greater after 2 weeks of withdrawal from chronic cocaine. CRF significantly decreases paired-pulse ratios at a 50-ms inter-stimulus interval, suggesting that presynaptic mechanisms play a role in CRF-induced LTP. In agreement with previous studies on the BLA-to-CeA synapse from the same lab (Liu et al., 2004), CRF-induced LTP in the LA–CeA pathway is mediated by pre- and postsynaptic mechanisms, primarily through activation of CRF₂. After 2 weeks of withdrawal from chronic cocaine, CRF-induced LTP depends on both CRF₁ and CRF₂ and the enhanced LTP in response to CRF is mediated by an up-regulation of CRF₁ receptor function. This switch was correlated to CRF₂ linked to PKC that became predominantly CRF₁ receptors linked to PKA during cocaine withdrawal. In addition, the increased response to CRF during withdrawal from chronic cocaine was accompanied by an increase in NMDA-mediated synaptic responses and Cav2.3 channels.

Ventral tegmental area (VTA)

Unlike the reviewed, typically negative, findings with CRF₁ antagonists in non-dependent rats, some other behavioral data show that CRF₁ may contribute to excessive consumption in a manner that also suggests a role in the binge/intoxication phase of the addiction cycle. For example, *Crrh1* knockout mice drank less 20% v/v EtOH under basal conditions (Pastor et al., 2011), and *Crrh* knockout mice failed to develop a conditioned place preference to a moderate dose of alcohol (2g/kg) (Olive et al., 2003). Moreover, both *Crrh* and *Crrh1* knockout mice showed reduced EtOH intake and blood EtOH concentrations in a mouse model of scheduled, limited access to EtOH (“drinking-in-the-dark”) that can lead to binge-like intake (Kaur, Li, Stenzel-Poore, & Ryabinin, 2012). As mentioned earlier, systemic administration of small-molecule CRF₁ antagonists reduced binge-like, but not non-binge-like, EtOH intake in C57BL/6J mice and outbred rats (Cippitelli et al., 2012; Lowery et al., 2010; Simms, Nielsen, Li, & Bartlett, 2014; Sparta et al., 2008) (but see (Giardino & Ryabinin, 2013) data suggesting that the results may not be specific to substances of abuse). The neuroanatomical basis of these effects remain under investigation, but site-specific infusion of CRF₁ antagonists into the CeA or VTA likewise could reduce heightened EtOH intake in rodent models under intermittent access schedules (Hwa, Debold, & Miczek, 2012; Lowery-Gionta et al., 2012; Sparta et al., 2013).

Indeed, the involvement of CRF signaling in the VTA in the neurobiology of substance use disorders has received more attention within the past decade. Dopaminergic VTA neurons receive CRF inputs from fibers that originate in the BNST, the CeA and, to a lesser extent, the hypothalamic PVN (Rodaros et al., 2007), and VTA dopaminergic neurons also

synthesize CRF (Grieder et al., 2014). In the VTA, CRF increases dopamine neuron firing (Wanat, Hopf, Stuber, Phillips, & Bonci, 2008), and both stress (Wang et al., 2005) and drug withdrawal (Grieder et al., 2014; Zhao-Shea et al., 2015a, 2015b) have been associated with increased VTA CRF signaling. Given the known role of VTA dopaminergic efferents in stress-induced seeking and taking of substances of abuse (Holly & Miczek, 2016), it is unsurprising that stress-modulated VTA CRF systems have been implicated in reinstatement of drug seeking and excessive consumption. For example, social defeat stress phasically increased CRF levels in anterior vs. posterior compartments of the VTA, with repeated social defeat increasing levels in both subregions; furthermore, intra-VTA administration of CRF₁ or CRF₂ antagonists reduced cocaine-seeking behavior in previously defeated rats (Holly et al., 2016; Holly & Miczek, 2016). The recruitment of VTA CRF signaling, through a CRF₁ mechanism, also appears to play a key role in the aversive and anxiogenic-like effects of nicotine withdrawal and in the escalation of nicotine self-administration that occurs with intermittent, extended drug exposure (Grieder et al., 2014).

Whereas the bulk of reviewed data implicate CRF₁ signaling in the extended amygdala as contributing to addiction-related phenotypes, CRF₂ have been suggested also to play a role in the VTA (Wang et al., 2007), particularly in reinstatement of drug-seeking behavior, as observed in cocaine-experienced rats. For example, intra-VTA administration of the preferential CRF₂ antagonist antisauvagine-30, blocked reinstatement of both cocaine-conditioned place preference (Lu et al., 2001) and cocaine-seeking (Wang et al., 2007) following footshock stress. On the other hand, the CRF₂ mediation of antisauvagine-30's actions are now uncertain because anti-sauvagine-30 still has behavioral actions in *Crrhr2* knockout mice (Zorrilla et al., 2013). Furthermore, others who used the more selective CRF₂ antagonist astressin₂-B did not observe a reversal of stress-induced reinstatement of substance seeking (Brujinzeel et al., 2009), and very little CRF₂ mRNA is detected in the rodent VTA by *in situ* hybridization under basal conditions (Chalmers et al., 1995; Van Pett et al., 2000). Still, a role for VTA CRF₂ in addiction-related phenotypes, if confirmed, may also implicate possible roles for the urocortins, CRF peptide family members with higher affinity than CRF for CRF₂ (Gysling, 2012).

In a more general way, the role of CRF₂ in addiction-related phenotypes and excessive consumption remains unclear. Early studies indicated that i.c.v. infusion of Ucn 3, a selective CRF₂ agonist, reduced heightened anxiety-like behavior and increased EtOH self-administration in dependent rats during acute withdrawal (Valdez et al., 2004) as well as the alcohol intake of mice that receive limited, binge-like access to alcohol (Lowery et al., 2010; Sharpe & Phillips, 2009). Intra-CeA infusion of Ucn 3 likewise reduced EtOH self-administration in withdrawn, dependent rats (Funk & Koob, 2007), and infusion of Ucn 1 into the lateral septum, which abundantly expresses CRF₂, potentially reduced the acquisition and expression of alcohol intake in rats (Ryabinin, Yoneyama, Tanchuck, Mark, & Finn, 2008). On the other hand, CRF₂ antagonists did not influence withdrawal-associated behavioral changes in other studies (Lu, Liu, et al., 2000; Overstreet, Knapp, & Breese, 2004). Furthermore, several studies have implicated CRF₂ activation in opiate withdrawal. Genetic deletion of the CRF₂ receptor blocked somatic signs of opiate withdrawal (Papaleo et al., 2008) as well as dysphoria- or anhedonic-like behaviors (Ingallinesi, Rouibi, Le Moine, Papaleo, & Contarino, 2012). Perhaps the discrepant results reflect different roles of

CRF₂ with respect to different substances of abuse or, alternatively, that the actions of CRF₂ activation can depend on the particular CRF₂ ligand, concentration, or brain site (Fekete & Zorrilla, 2007; Ho et al., 2001; Takahashi, Ho, Livanov, Graciani, & Arneric, 2001; Zhao, Valdez, et al., 2007).

With regards to cellular physiology, CRF potentiates NMDA receptor currents on VTA dopamine (DA) neurons (Sparta et al., 2013; Ungless et al., 2003). Application of (100 nM) CRF induces a facilitation of NMDA currents in putative VTA DA neurons in brain slices of juvenile mice that consumed EtOH in the drinking in the dark (DID) procedure. This CRF-induced potentiation of NMDAR currents in EtOH-drinking mice is blocked by administration of the selective CRF₁ receptor antagonist CP-154,526. Furthermore, intra-VTA infusion of CP-154,526 significantly reduces binge EtOH consumption in adult mice. Notably, no alteration in VTA NMDAR number or function was observed but CRF₁-mediated signaling was increased suggesting that binge drinking may enhance VTA CRF₁ receptor mediated effects onto NMDARs (Sparta et al., 2013).

Another electrophysiological study reported a dose-dependent CRF-induced increase in VTA DA neuron firing, an effect that was prevented by antagonism of CRF₁, and was mimicked by CRF₁ agonists. This increase in DA firing was prevented by inhibition of the phospholipase C (PLC)-PKC signaling cascade, but not the cAMP-PKA pathway. In addition, PKC enhanced the I(h) current and increased the firing rate in VTA dopamine neurons (Wanat et al., 2008). Interestingly, the Brodie lab has reported that CRF and the CRF receptor agonist urocortin reversed inhibition produced by the D2 agonist quinpirole via increased glutamatergic signaling in the VTA (Nimitvilai et al., 2014).

In rat brain slices, CRF, in a concentration-dependent manner, facilitates (at low concentrations: 3–100 nM) and decreases (at higher concentrations: 300 nM) EPSCs in VTA neurons via presynaptic CRF₁ and CRF₂ receptors, respectively. A GABA_B receptor antagonist (CGP55843) blocks the CRF₂ attenuation (Williams, Buchta, & Riegel, 2014). Notably in the same study, CRF₂ activation-facilitates presynaptic release of GABA, suggesting that CRF₂ may regulate glutamate release via heterosynaptic facilitation of GABA synapses. Although, chronic cocaine self-administration does not alter the sensitivity of glutamate and GABA receptors, the ability of CRF₂ agonists to depress glutamate and potentiate GABA responses of VTA neurons is diminished. However, yohimbine plus cue reinstatement reverses the actions of CRF₂ on GABA and glutamate release. CRF₂ activation increases EPSCs as a result of a reduction in tonic GABA-dependent inhibition (Williams et al., 2014). These studies demonstrate that presynaptic CRF-R₁/R₂ tightly regulate glutamate transmission in the VTA in a concerted, heterosynaptic manner that is altered by stress-related pathologies, such as addiction.

A population of VTA DA neurons that synthesize CRF has been identified, and chronic nicotine exposure upregulates CRF mRNA in DA neurons of the posterior VTA, activates local CRF₁, and blocks nicotine-induced activation of transient GABAergic input to DA neurons (Grieder et al., 2014). Local downregulation of CRF mRNA and specific pharmacological blockade of CRF₁ in the VTA reverses the effect of nicotine on GABAergic input to DA neurons, prevents the aversive effects of nicotine withdrawal, and limits the

escalation of nicotine intake. These results link the brain reward and stress systems in the same brain region to signaling of the negative motivational effects of nicotine withdrawal (Grieder et al., 2014).

Prefrontal cortex

Emerging data also suggest that CRF systems in the medial prefrontal cortex (mPFC) may contribute to excessive substance use. Extended access to cocaine elicits escalated, compulsive-like self-administration as well as impaired working memory (George, Mandyam, Wee, & Koob, 2008). The degree of escalated cocaine intake correlates directly with impaired delayed non-matching to sample working memory performance under long delay conditions. Perhaps relatedly, rats receiving intermittent, extended access to 2-bottle choice EtOH intake, which leads to escalated drinking (Simms et al., 2008; Wise, 1973), show increased activation of CRF and GABAergic interneurons in the mPFC during abstinence. As with cocaine, working memory impairments in these rats correlated directly with greater alcohol intake following abstinence (George et al., 2012). Abstinence from escalated drinking was associated with functional disconnection of the mPFC and CeA, perhaps reflecting impaired inhibitory control over motivated behavior. CRF tissue content in the frontal cortex also is altered during acute or protracted withdrawal from EtOH or binge-like cocaine use, respectively (Zorrilla, Valdez & Weiss, 2001). The results have been proposed to indicate that CRF-mediated dysregulation of mPFC interneurons may contribute to disturbed executive control over self-administration of substances.

Compulsive Eating

A final domain of study suggests that addiction-like changes in CRF systems may be similarly implicated in the neurobiology of compulsive eating. So-called “food addiction” has been hypothesized to underlie many cases of obesity and eating disorders, which may collectively comprise the most prevalent and deadliest form of addictive behavior (Agh et al., 2016; Fichter & Quadflieg, 2016; Flegal, Kit, Orpana, & Graubard, 2013; Flegal, Kruszon-Moran, Carroll, Fryar, & Ogden, 2016; Hoang, Goldacre, & James, 2014; Kroes, Osei-Assibey, Baker-Searle, & Huang, 2016; Micali et al., 2017; Mitchell, 2016; Olguin et al., 2017; Perez, Ohrt, & Hoek, 2016; Smink, van Hoeken, & Hoek, 2013; Westmoreland, Krantz, & Mehler, 2016). In the United States, ~3 of 4 men and 2 of 3 women were overweight (25 < body mass index [BMI] < 30) or obese (BMI > 30) in 2013–2014, and ~33% of overweight/obese people (and ~54% of patients undergoing bariatric surgery for obesity) met diagnostic criteria of the Yale Food Addiction Scale (Flegal et al., 2016; Long, Blundell, & Finlayson, 2015; Pursey, Stanwell, Gearhardt, Collins, & Burrows, 2014). As with substances of abuse, CRF₁ antagonists reduce stress-induced reinstatement of palatable food seeking (Ghitza, Gray, Epstein, Rice, & Shaham, 2006). Furthermore, rats acutely withdrawn from intermittent access to a high-sucrose, chocolate-flavored diet (“diet cycling”) showed increased anxiety-like behavior (Cottone, Sabino, Steardo, & Zorrilla, 2009) in association with increased mRNA and peptide expression of CRF in the CeA; similar molecular changes were seen by Bale and colleagues in mice withdrawn from high-fat diet (Teegarden, Scott, & Bale, 2009). Systemic pretreatment with R121919, a selective CRF₁ antagonist blocked food withdrawal-associated anxiety at doses that did not alter the

behavior of chow-fed controls. Furthermore, the CRF₁ antagonist reduced the motivational deficits that emerged for otherwise acceptable reinforcers. Finally, CRF₁ antagonist pretreatment decreased the magnitude of overeating of the palatable sucrose-rich diet by diet-cycled animals at doses that did not alter the food intake of chow-fed controls or of animals fed the sucrose-rich diet, but without a history of diet cycling (Cottone, Sabino, Roberto, et al., 2009). When diet-cycled animals had access to the preferred, sucrose-rich diet, both anxiety-like behavior and CeA CRF levels normalized, supporting the hypothesis that activation of the amygdala CRF-CRF₁ system contributed to the withdrawal-like state. Subsequent studies identified an increased number of CRF-positive neurons in the CeA of diet-cycled rats irrespective of their current diet, and intra-CeA administration of CRF₁ antagonists normalized anxiety-like behavior and overeating of the palatable diet. Furthermore, intra-BLA administration of a CRF₁ antagonist reduced the rejection of otherwise acceptable, but less preferred, chow (Iemolo et al., 2013). The unique involvement of CRF systems may be greater with high-sucrose diets, because CRF₁ antagonists did not reduce binge-like intake of a comparably preferred diet that also contained fat (Parylak, Cottone, Sabino, Rice, & Zorrilla, 2012).

Interestingly, whereas initial clinical trials with CRF₁ antagonists for alcohol use disorders have yielded disappointingly negative results so far (see (Spierling & Zorrilla, 2017) for review), a recent double-blind, placebo-controlled trial in a small sample of healthy individuals with restrained eating yielded promising results for stress-related eating that appear to warrant further study. Because the study was stopped prematurely by the NIH IRB for reasons unrelated to adverse drug effects or efficacy (reinterpretation of the Common Rule for human subject protection under HHS, 45 CFR 46A), it was underpowered (30% power) to detect *a priori* effect sizes of interest. Nonetheless, the CRF₁ antagonist pexacerfont produced effect sizes more consistent with reduction of food craving and laboratory stress-induced eating than with a null result. The effect size for pexacerfont's reduction of laboratory stress-induced eating was $r = 0.30$ (counternull $r = 0.55$; (Rosenthal R, 1994)), and its reduction of craving for sweet foods (brownies and Swedish fish) ranged from $r = 0.28$ to 0.49 (counternull $r = 0.52 - 0.79$). Furthermore, in bogus taste tests that masked the true dependent measure of interest (intake), pexacerfont reduced palatable food intake independent of which imagery script was presented before food access (neutral, food cue, stress) with an effect size of $r = 0.34$ (counternull $r = 0.61$). Finally, nightly Yale Food Addiction Scores were lower in subjects that received pexacerfont (vs. placebo) beginning the evening after the first loading dose of pexacerfont with an effect size of $r = 0.39$ (counternull $r = 0.68$). Bayes factor analysis, a ratio that relates to the relative probability of an effect actually being present vs. the null effect (Goodman, 1999), and counternull analysis, which describes the effect size as likely to be true as the null, collectively indicated a strong positive potential of this CRF₁ antagonist to reduce palatable food craving and eating in restrained eaters (Epstein et al., 2016) and appear to justify a well-powered clinical trial in this domain. A caveat with these results is that the YFAS scores changed as soon as 24 hours post-treatment, when the degree of CNS exposure obtained is unclear, casting uncertainty on the CRF₁ antagonist mechanism of action.

At the cellular level, our labs have examined the effect of the CRF₁ antagonist (R121919) on GABAergic transmission in the CeA and found that withdrawal from palatable food, similar

to alcohol withdrawal, upregulates CRF/CRF₁ signaling in CeA (Cottone, Sabino, Roberto, et al., 2009). Although diet history did not alter baseline CeA GABAergic transmission, application of R121919 induced a greater reduction in evoked GABAergic responses in CeA neurons of diet-cycled rats versus chow-fed controls, supporting the hypothesis that a similar overactivation of the amygdala CRF-CRF₁ system during drug withdrawal is also seen during food withdrawal (Cottone, Sabino, Roberto, et al., 2009).

Conclusion

In this chapter we reviewed the importance of both hypothalamic and extrahypothalamic CRF systems and their roles in the development of dependence for all substances of abuse, as well as for compulsive eating. Notably, activation of brain stress systems contribute to the negative motivational state associated with acute withdrawal and could also contribute to vulnerability to stressors observed during protracted abstinence in humans. Thus, CRFergic circuits that normally subserve appropriate responses to acute stressors appear to pathologically contribute to the aversive emotional state that drives the negative reinforcement of addiction. In the development of drug dependence and withdrawal, the CRF system is recruited to produce stress-like, aversive states (Aston-Jones & Druhan, 1999; Koob & Le Moal, 2001). This state of compulsive substance seeking and use involves numerous neurobiological changes, including increased function of the CRF brain stress system in the extended amygdala (Koob, 2008; Roberto et al., 2010), as well as roles for CRF circuitry in the VTA and prefrontal cortex.

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