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Role of Corticotropin-Releasing Factor in Drug Addiction: Potential for Pharmacological Intervention

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Abstract

Drug dependence is a chronically relapsing disorder that places an enormous strain on healthcare systems. For treatments to have long-term clinical value, they must address the causes of relapse. Corticotropin-releasing factor (CRF), a neuropeptide central to the stress response, may be one key to solving the relapse cycle. CRF is hypothesized to mediate the elevated anxiety and negative emotional states experienced during the development of dependence. This review summarizes existing data on changes in the CRF system produced by drugs of abuse and the function of CRF receptors in regulating behavioural responses to drugs of abuse, with an emphasis on drug dependence. Drug-induced changes in neuronal excitability throughout the limbic system, as well as the reversal of these neuroadaptations by CRF receptor antagonists, are also addressed. CRF receptor antagonists, by reducing the motivational effects of drug withdrawal and protracted abstinence, are proposed to be novel therapeutic targets for drug abuse and addiction.

1. Introduction

Drug addiction is a chronically relapsing disorder in which cycles of compulsive drug taking are followed by periods of abstinence, resulting in withdrawal, characterized by heightened anxiety, irritability and negative affect.[1] Although stress can impact all stages of drug addiction,[2,3] relapse to drug taking is particularly sensitive to stress exposure because of heightened anxiety in the post-dependent state.[4] Therefore, delineation of the neuroadaptations underlying elevated stress responsiveness during abstinence in drug-dependent individuals is essential for the development of therapies to treat drug addiction. One such neuroadaptation involves the neuropeptide corticotropin-releasing factor (CRF), a molecule central to both stress and drug withdrawal responses. Polymorphisms in the genes that encode CRF receptors have been associated in humans with exacerbated stress responses and the propensity to develop drug addiction,[5-9] and the CRF system has significant potential as a target for medication development.

This review provides a brief overview of the role of CRF in hypothalamic stress responses, then focuses on existing behavioural data supporting a role for CRF in drug withdrawal, addressing not only acute but also protracted withdrawal, a behavioural model that may more appropriately replicate the relationship between drug taking and drug relapse periods in humans. Additionally, this article reviews electrophysiological data that demonstrate that CRF modulation of neuronal activity is a possible mechanism underlying drug dependence.

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2. Corticotropin-Releasing Factor (CRF): The Central Component of the Stress Response

CRF is a 41-amino-acid peptide originally isolated from the hypothalamus[10] that acts via binding to two receptors: CRF_1 and CRF_2 .[11,12] The CRF receptors are 7-transmembrane G-protein-coupled receptors that principally function by interacting with the stimulatory G-protein (G_s), resulting in elevated adenylyl cyclase and cyclic adenosine monophosphate levels, although the receptors may also couple to other G-proteins.[13,14] Functional interactions between CRF and its receptors are antagonized by the CRF binding protein (CRF-BP), which sequesters CRF, thus reducing the quantity of CRF available for receptor binding.[15]

CRF was first characterized as the central activator of the endocrine stress response. Exposure to a stressor triggers the synthesis of CRF in the paraventricular nucleus of the hypothalamus. Subsequently, CRF is released via the median eminence into the portal blood to reach the pituitary gland. The peptide then activates CRF_1 receptors on pituitary corticotrophs, thereby stimulating adrenocorticotropic hormone synthesis and release into the circulatory system, which subsequently elevates the production and secretion of cortisol (corticosterone in rodents) by the adrenal gland.[16,17] In addition to its function as an effector of the stress response, cortisol also provides negative feedback on hypothalamic-pituitary-adrenal (HPA) axis activity via binding to glucocorticoid receptors in the brain and pituitary,[18] including inhibition of hypothalamic CRF production.[19] As a primary component of the HPA axis, CRF plays a central role in the initiation, maintenance and adaptation of stress responses.

Furthermore, CRF from extrahypothalamic sources has been demonstrated to be key to the expression of behavioural responses to stressors.[20] CRF-immunoreactive perikarya can be found in various brain regions, with particularly strong expression in the extended amygdala (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 nucleus accumbens [NAc]) and lateral septum,[21] all of which are activated by, and implicated in the expression of behavioural responses to, stressors.[22-24] CRF itself has been shown to be central to the involvement of these nuclei in behavioural stress responses, independent of HPA axis activation.[25] The distribution of the CRF-BP overlaps somewhat with that of CRF, with widespread expression in the cortex and high levels in the amygdala.[26] Interestingly, in the extended amygdala, terminals containing CRF-BP have been shown to colocalize with CRF-positive cell bodies,[26] suggesting that CRF-BP may directly regulate CRF function in these areas. CRF receptor distribution, determined by CRF binding assays, is even more widespread in the brain,[27] indicating a role for CRF and its receptors in regulating the development[28] and excitability[29-34] of many neuronal subpopulations.

The specific distribution of CRF_1 and CRF_2 receptors is minimally overlapping, with high-affinity CRF_1 receptors showing more widespread distribution throughout the cortex and cerebellum. High levels of CRF_1 receptors are found in the basolateral amygdala (BLA), MeA, medial septum and BNST, and moderate expression is found in the NAc and ventral tegmental area (VTA).[35,36] Interestingly, unlike other nuclei of the extended amygdala, very few CRF_1 receptors can be found in the CeA despite the high content of CRF.[35,36] In contrast, extrahypothalamic forebrain CRF_2 receptors are primarily confined to medial subdivisions of the extended amygdala (MeA and medial BNST), with the greatest expression in the lateral septum and ventromedial hypothalamus.[37] The high density of CRF and its receptors, as well as CRF-BP, in stress-responsive brain regions suggests the integral role of the peptide in the regulation of behavioural responses to stress. Not surprisingly, given the dissimilarity in receptor distribution, mice lacking either CRF_1 or

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CRF_2 receptors display differential alterations in stress responsiveness. CRF_1 receptor null mutants show a blunting of anxiety-like behaviour, regardless of whether the deletion is constitutive[38] or restricted to the postnatal forebrain.[39] In contrast, mice lacking CRF_2 receptors tend to exhibit elevated basal anxiety-like behaviour,[40,41] although this has not been observed in all CRF_2 receptor null mutant mice.[42] However, even in the absence of changes in basal anxiety-like behaviour, deletion of CRF_2 receptors resulted in impaired adaptation to prolonged stress exposure,[42,43] suggesting a deficient stress-coping system. This stress response system is both activated acutely by drugs of abuse and modulated by long-term drug exposure and withdrawal, suggesting a role for CRF systems in the development and maintenance of drug dependence and addiction.

3. Drugs of Abuse Acutely Upregulate CRF and Hypothalamic-Pituitary-Adrenal Axis Activity

Most drugs with abuse potential, including opiates,[44] amphetamine,[45] cocaine,[46] nicotine,[47] marijuana (Δ^9-tetrahydrocannabinol)[48] and alcohol (ethanol),[49] acutely activate the HPA axis via elevated hypothalamic production of CRF (figure 1a).[50,51] This acute HPA activation has been shown to participate in the development of drug-induced locomotor sensitization,[52] with antagonism of CRF_1 receptors blocking behavioural sensitization to multiple drugs of abuse.[53,54] Likewise, deletion of CRF_1, but not CRF_2, receptors inhibits the development of behavioural sensitization to ethanol and blunts the HPA axis response to acute ethanol treatment.[55] Interestingly, blocking the production of the final HPA axis effector, corticosterone, by either adrenalectomy or pharmacological inhibition of its synthesis inhibits not only locomotor activation by cocaine but also the acquisition of cocaine self-administration,[56] suggesting that CRF-induced HPA activation may be involved in the onset of drug self-administration.

4. Dysregulation of the CRF System during Withdrawal from Drugs of Abuse

While hypothalamic CRF may play a role in the acquisition of drug self-administration, the balance of data show that extrahypothalamic sources of CRF, particularly within the extended amygdala and other key limbic system structures, are integral to the development of negative reinforcement mechanisms associated with addiction.[57] That is, the primary involvement of CRF in the regulation of drug self-administration lies in the dysregulation of the CRF system following withdrawal of drug access in dependent individuals. Multiple lines of evidence have demonstrated that although acute drug exposure yields a transient elevation of CRF expression in multiple brain regions (figure 1a),[58,59] chronic exposure results in overactivation of the CRF system, which is central to the withdrawal and dependence phenotypes observed upon removal of drug access (figure 1b).[60-64] During the progression to dependence, drug exposure ceases to trigger elevated CRF expression,[58] resulting in a blunted HPA response.[65] However, when drug access is subsequently withdrawn, CRF release in the extended amygdala increases, accompanied by somatic and psychological withdrawal signs.[66-68] Particularly striking across multiple drugs of abuse is the elevation in CeA CRF at various withdrawal time points, which can be observed not only when assessing levels of messenger RNA (mRNA) expression[59,62,63] and protein content[60] but, importantly, also as an elevation of CRF released into the extracellular space.[64,66,69] Notably, a high level of CRF release at early withdrawal timepoints can yield paradoxically low CRF levels when protein content is determined at the intracellular level.[59,60,70,71] The synthesis of new CRF may lag behind the rate of release, thereby depleting the tissue content of CRF.

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Similar to the CeA, increased CRF release has also been observed in the lateral BNST during drug withdrawal,[67] suggesting an elevated activation of CRF signalling throughout the extended amygdala. This heightened CRF activity may be further augmented during abstinence by long-lasting changes in receptor expression levels. Contrasting changes in CRF_1 and CRF_2 receptor levels have been observed 3 weeks after cessation of ethanol exposure.[63] Specifically, following extended abstinence, CRF_1 receptor levels in the BLA were elevated and CRF_2 receptor levels decreased, whereas CRF_1 receptor levels in the MeA were increased without changes in CRF_2 receptor mRNA.[63] The effects may be specific to a given abused drug or withdrawal timepoint, because precipitated morphine withdrawal acutely reduced CRF_1 receptor mRNA expression in the BLA and NAc.[72]

Data from CRF receptor knockout mice support a prominent role for CRF_1 receptors in symptoms of drug withdrawal and dependence-induced elevations in drug intake. Deletion of the CRF_1 receptor gene abolished dependence-induced elevations in the self-administration of ethanol[73] and opiate withdrawal-induced conditioned place aversion,[74] whereas deletion of the CRF_2 receptor gene had a marginal effect on ethanol intake in nondependent mice under limited-access conditions.[75] The Marchigian Sardinian ethanol-preferring (msP) rat line carries a polymorphism in the promoter region of the gene encoding the CRF_1 receptor, which is putatively responsible for the elevation in CRF_1 receptor expression observed in multiple regions of the msP brain, particularly within the extended amygdala and other key limbic system structures.[76] msP rats display high basal alcohol intake, which can be reduced by antagonizing the CRF_1 receptor.[76] These data suggest that altered expression of the CRF_1 receptor may regulate excessive self-administration of ethanol (and perhaps other drugs of abuse).

The balance of gene expression studies suggests a more prominent role for CRF_1 than CRF_2 receptors in the motivational aspects of drug withdrawal and dependence. Data from CRF receptor knockout mice suggest the involvement of both receptors in the somatic withdrawal syndrome associated with drugs of abuse. CRF_2 receptors may regulate the peripheral effects of opiate withdrawal, which were largely absent in CRF_2 receptor knockouts.[77] Deletion of CRF_1 receptors, which may cause a compensatory upregulation of CRF_2 receptors, yielded heightened signs of somatic withdrawal from opiates.[78] Altogether, these data suggest that CRF receptors present attractive targets for the modulation of drug self-administration and somatic withdrawal syndromes in dependent populations.

5. CRF Receptor Antagonists as Potential Treatments for Drug Addiction

As discussed in section 4, CRF receptor antagonists, particularly those targeting CRF_1 receptors, show promise for the development of treatments for drug abuse and addiction. Much effort has been placed on the development of high-affinity (low dissociation constant, K_i), blood-brain barrier-penetrating CRF_1 receptor-selective antagonists with drug-like properties,[79,80] including good oral bioavailability, volume of distribution (moderate) and clearance rates (half-life suitable for once daily dosing, ~12–36 hours) that may be useful as medications for human patients. A subset of these antagonists and their basic pharmacological properties can be found in table I; for a comprehensive review of existing CRF_1 receptor pharmacology, see Zorrilla and Koob.[93] Because of the upregulation of CRF and CRF_1 receptors during drug withdrawal, many studies have explored the ability of CRF receptor antagonists to reduce withdrawal-induced elevations in anxiety and drug self-administration. Table II summarizes CRF receptor antagonist modulation of the behavioural and neuroendocrine effects of abused drugs, including the efficacy of the antagonists in inhibiting relapse to drug seeking.

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5.1 CRF Receptor Subtype Nonspecific Antagonists

Prior to the discovery of the CRF receptor subtypes, several ligands that have affinity for both CRF receptor subtypes were developed as a means of competitively interfering with the function of endogenous CRF (table I). Among these (Met,[18] Lys,[23] Glu,[27,29,40] Ala,[32,41] Leu[33,36,38]) h/rCRF$_{9-41}$ (α-helical CRF$_{9-41}$),[130] a CRF receptor partial agonist,[93] and (D-Phe,[12] Nle,[21,38] C$^{\alpha}$MeLeu[37]) h/rCRF12-41 (D-Phe CRF$_{12-41}$),[131] a full antagonist of the CRF receptor,[93] have been the most widely used, with similar results. Both ligands inhibited footshock-induced reinstatement of cocaine self-administration in rats, whether injected systemically[98] or locally infused into the BNST[132] or VTA.[133] Similar results were observed with stress-induced reinstatement of ethanol-seeking[119] and heroin-seeking[106,134] behaviour. Interestingly, α-helical CRF$_{9-41}$ and D-Phe CRF$_{12-41}$ were unable to antagonize drug- or cue-primed reinstatement, unless the cue was presented in conjunction with stress pre-exposure.[119] Nonetheless, the peptide ligands showed great efficacy in reducing ethanol withdrawal-induced elevations in both self-administration[116,135] and anxiety-like behaviour.[116,117]

For ethanol, the actions of CRF receptor antagonists in reducing both self-administration and anxiety-like behaviour in dependent rats have been localized to the CeA.[71,136] Similar effects have been found for nicotine, with either central or CeA-specific infusion of D-Phe CRF$_{12-41}$ reducing withdrawal-associated elevations in brain reward stimulation thresholds,[124,137] an effect recently shown for ethanol withdrawal as well.[138] Likewise, CeA administration of α-helical CRF$_{9-41}$ blocked conditioned place aversion to an environment paired with precipitated morphine withdrawal.[104]

These data demonstrate that the subtype-nonspecific peptide CRF receptor antagonists α-helical CRF$_{9-41}$ and D-Phe CRF$_{12-41}$ reduce both the heightened anxiety-like behaviour and elevated self-administration observed in drug dependence. However, to improve receptor specificity and efficacy of systemic administration, several nonpeptide antagonists have been developed that have CRF$_1$ receptor specificity and show greater ability to penetrate the blood-brain barrier.

5.2 Specific CRF$_1$ Receptor Antagonism

A significant advance in CRF$_1$ receptor pharmacology occurred with the discovery of blood-brain barrier-penetrating CRF$_1$ receptor antagonists, including CP-154,526[139] and antalarmin.[82] These compounds were the first major CRF$_1$ receptor antagonists with therapeutic potential for CNS disorders, such as drug addiction. Importantly, antalarmin was shown to be capable of inhibiting anxiety-like behaviour, resulting from intracerebroventricular CRF treatment, in the elevated plus maze,[140] indicating not only brain penetrance, but also efficacy following systemic delivery in blocking the central effects of CRF. Like the subtype nonselective peptide antagonists, the small-molecule antalarmin reduced withdrawal-associated elevations in ethanol self-administration in both rats[109] and mice,[73] as well as ethanol intake in ethanol-preferring msP rats.[76]

Similarly, the ability of antalarmin to reduce cocaine self-administration was evident selectively in rats given extended (6-hour) daily access to cocaine (‘long access’ [LgA]), a schedule with which self-administration escalates across days, but not in rats given brief (1-hour) daily access (‘short access’ [ShA]), in which intake does not escalate.[94] In addition to reducing elevated drug self-administration in dependent animals, antalarmin also inhibited stress-primed reinstatement of ethanol self-administration[110] as well as stress-induced elevations in ethanol self-administration[110] and palatable food intake.[129] These effects may be due to the ability of antalarmin to reduce the negative emotional state of withdrawal, as the compound reduced the development of conditioned avoidance of a location previously

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paired with acute morphine withdrawal.[105] These data demonstrate that antalarmin specifically reduces drug withdrawal effects and self-administration in dependent, but not nondependent, individuals.

Similar to antalarmin, CP-154,526 effectively antagonized stress-induced reinstatement of drug seeking for cocaine,[99] heroin[99] and ethanol,[120] as well as cue- and drug-primed methamphetamine reinstatement.[141] It also inhibited stress-induced reinstatement of conditioned place preference to morphine[142,143] and cocaine.[144] Interestingly, the compound may have efficacy in reducing maintenance self-administration responding,[95,111-113] although many experiments that showed effects on maintenance responding were performed at some point post-stress, such as following a history of forced swim testing or extinction training. CP-154,526 also inhibited the reduction in social interaction observed after restraint stress in rats with a history of multiple cycles of ethanol withdrawal.[145] Important for efficacy in human drug treatment, this anxiolytic-like effect was observed whether the CRF_1 receptor antagonist was administered prior to the restraint stress or during each of the withdrawal periods, suggesting that the use of the antagonist to alleviate the stress of withdrawal may have a lasting ability to blunt the heightened stress sensitivity in post-dependent individuals.

Wills and colleagues[146] suggested that stress pre-exposure may be integral to the ability of CP-154,526 to reduce self-administration in non-dependent rats. However, recent data have shown that CP-154,526 reduced ethanol intake in the absence of stress in nondependent mice under-going a limited-access two-bottle choice paradigm.[111,113] CP-154,526 has also been used to inhibit locomotor sensitization to multiple drugs of abuse, demonstrating the involvement of CRF activation of CRF_1 receptors in the expression,[54] or acquisition and expression,[53] of sensitization to cocaine and ethanol, respectively. Importantly, following systemic administration, this antagonist blocked the central generation of anxiety-like responses without altering peripheral HPA axis activity,[147] a key feature for efficacy in human treatment because blunting of all stress responses would be disadvantageous.

The search for optimal, drug-like CRF_1 receptor antagonists has spurred the development and testing of many additional antagonists in recent years. Similar to CP-154,526, CRA-1000 reduced ethanol withdrawal-induced anxiety.[148,149] R121919 (also known as NBI30775),[150] at doses that do not alter normal HPA function, has been shown to reduce anxiety-like behaviour in rats with high basal anxiety, but not in rats without high basal anxiety.[151] Low doses of R121919 have similarly been demonstrated to reduce anxiety-like behaviour in mice[152] and depression in humans[153,154] without significantly modulating basal HPA activity. Similar to antalarmin, R121919 also reduced LgA but not ShA cocaine self-administration,[94] as well as LgA, but not ShA, heroin self-administration.[102] The antagonist also reduced both binge eating of palatable food and the anxiety-like behaviour precipitated by the removal of access to that food.[128]

Both R121919 and MJL-1-109-2 dose-dependently decreased ethanol self-administration during withdrawal, with no effect in nondependent rats,[109] as did LWH-63 when administered to dependent Sardinian alcohol-preferring rats.[114] None of these three CRF_1 receptor antagonists reduced homecage drinking when ethanol was available continuously, although they paradoxically slightly increased ethanol intake under limited homecage access conditions in nondependent rats.[114]

The newer heterocyclic CRF_1 receptor antagonists MPZP[92] and MTIP[91] also reduced dependence-induced ethanol self-administration. Surprisingly, MTIP also reduced excessive drinking in nondependent msP rats. This reduction in nondependent ethanol intake was likely attributable to genetic differences between msP rats and other strains, rather than via a

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novel action of MTIP compared with other CRF_1 receptor antagonists, as the msP line shows a high incidence of a CRF_1 receptor promoter polymorphism that yields elevated CRF_1 receptor expression.[91] The striking similarity in the ability of the various CRF_1 receptor-selective antagonists to inhibit withdrawal-associated elevated anxiety-like responses and drug self-administration confirms the integral role of CRF activity at the CRF_1 receptor in regulating the negative effects of drug withdrawal.

5.3 Targeting the CRF_2 Receptor

Unlike CRF_1 receptors, fewer pharmacological tools have been developed to specifically modulate the CRF_2 receptor, perhaps because of the perception that CRF_1 receptors regulate the majority of central CRF effects. Indeed, several studies have shown an inability of CRF_2 receptor antagonists to modulate withdrawal-induced behavioural adaptations.[142,148] However, the functionality of the CRF_2 receptor in modulating drug self-administration and reinstatement has begun to emerge. Activation of the CRF_2 receptor in the CeA by urocortin 3 (Ucn3) reduced ethanol self-administration in dependent rats while increasing self-administration in nondependent rats.[155] The effects of Ucn3 on dependent ethanol self-administration may stem from the ability of Ucn3 to inhibit anxiety-like behaviour during acute ethanol withdrawal.[156] Under a two-bottle choice limited-access paradigm, central infusions of Ucn3 reduced ethanol intake similarly to CRF_1 receptor antagonists,[113,157] suggesting that either inhibition of CRF_1 receptors or activation of CRF_2 receptors can decrease the propensity to consume ethanol even in non-dependent individuals.

Unlike ethanol self-administration, footshock-induced reinstatement of cocaine seeking can be reduced by blockade, rather than activation, of the CRF_2 receptor. Using the preferential CRF_2 receptor antagonist antisauvagine-30 in rats, reinstatement of self-administration of cocaine following footshock stress was blocked.[158] The involvement of CRF_2 receptors in the modulation of stress-induced relapse likely operates through a different circuitry than for CRF_1 receptor regulation of drug self-administration. Whereas CRF_1 receptor antagonists may exert their greatest effects in the extended amygdala, CRF_2 receptor antagonists inhibited stress-induced reinstatement in rats via activity in the VTA[158] and reduced withdrawal-induced anxiety-like behaviour in rats via the dorsal raphe nucleus.[159] Together, these data demonstrate that developing pharmacological tools for more selective targeting of CRF_2 receptors warrants increased attention. The currently available compounds lack utility as treatment options for drug abuse because they must be centrally administered and display much lower CRF receptor subtype specificity than CRF_1 receptor antagonists (e.g. antisauvagine-30, although roughly 100-fold more selective for CRF_2 than CRF_1 receptors, is not CRF_2 receptor specific[160]).

6. Role of CRF in Drug Relapse Following Extended Periods of Abstinence

To date, much of the preclinical research into the role of CRF in regulating drug dependence has focused heavily on acute withdrawal paradigms. These studies are very pertinent to human drug addiction in the early stages of ceasing drug taking (i.e. the ability to gain sobriety), but it is uncertain how they translate to the more common human situation, in which relapse to drug taking occurs following extended periods of abstinence. In contrast to the acute withdrawal window, which is characterized by both somatic withdrawal symptoms and negative affect, the protracted abstinence period is distinguished by heightened anxiety-like behaviour and drug craving.[161-163] For example, in rats, withdrawal of chronic ethanol access via either liquid diet[164] or ethanol vapour[165] yielded elevated anxiety-like behaviour and brain reward thresholds within the first 24 hours,[164,165] followed by a return to normal baseline but heightened stress-induced anxiety-like behaviour at 2 weeks post-withdrawal[164,165] and a resurgence of increased baseline anxiety-like behaviour after 6

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weeks of abstinence.[165] These data demonstrate that abstinence is not a static condition but rather one in which neuroadaptations continue over a prolonged period of time.

One study in rats suggested that this difference between acute and extended withdrawal may not diminish the clinical relevance of the preclinical findings. Administration of CRF receptor antagonists during multiple ethanol withdrawal periods had a long-lasting ability to decrease stress-induced anxiety-like behaviour during protracted abstinence periods.[145] Nevertheless, several additional studies have begun to address the role of the CRF system in long-term abstinence, all of which suggest continued CRF receptor antagonist efficacy throughout the abstinence period. Elevated anxiety-like behaviour and ethanol self-administration observed in dependent rats after 4 weeks of abstinence were reversed by D-Phe CRF_{12-41} antagonism of CRF receptors.[116] Similarly, following 6 weeks of abstinence, post-dependent rats showed increased sensitivity to the effects of restraint stress on anxiety-like behaviour, an effect that was blocked by D-Phe CRF_{12-41}.[166] These data suggest that the increased CRF-like immunoreactivity observed in the amygdala 6 weeks after withdrawal of chronic access to ethanol or cocaine[60] may regulate the heightened anxiety-like behaviour observed during protracted withdrawal. More recently, Heilig and colleagues[63] found elevated CRF_1 receptor mRNA expression in the BLA and MeA in post-dependent rats following 3 weeks of abstinence from ethanol vapour. These rats also showed elevated drinking following stress exposure compared with rats without a history of dependence, as well as elevated stress sensitivity that was ameliorated by the CRF_1 receptor antagonist MTIP.[63] Although similar data are lacking for other drugs of abuse, the sensitivity to CRF_1 receptor antagonist blockade of stress-induced drug reinstatement has been shown in multiple paradigms that involve prolonged extinction training,[99,142,158] suggesting persistent CRF system sensitivity over long periods of abstinence, regardless of the abused substance.

Altogether, these data indicate the potential for success in using CRF receptor antagonists to combat the proximal causes of relapse even following long periods of sobriety. This perseverance of CRF sensitivity throughout the abstinence period also suggests that common changes in neuroplasticity within the CRF systems of the extended amygdala and other limbic regions may underlie withdrawal-induced elevations in drug intake.

7. Elevated CRF Signalling Alters Plasticity Throughout the Extended Amygdala and Mesocorticolimbic System during Drug Withdrawal

The chronically relapsing nature of drug addiction suggests that long-lasting neuroadaptations govern the persistence of drug-seeking and drug-taking behaviour, for example, via changes in the strength of the synaptic connections within neurocircuits that subserve the response to drugs of abuse.[167] Because withdrawal from multiple drugs of abuse results in elevated levels of CRF and CRF_1 receptors in the extended amygdala, in particular within the amygdala[60,62,63,66,168] and BNST,[67] these nuclei present likely loci for drug-induced synaptic modifications that may underlie elevated anxiety-like behaviour and drug self-administration in dependent individuals. Acute ethanol treatment of brain slices increased inhibitory GABA signalling in the CeA via activation of CRF_1 receptors, and this effect could be blocked by deletion of the CRF_1 receptor gene or by D-Phe CRF_{12-41},[169] antalarmin, LWH-63 and R121919 treatment,[170] but not by the CRF_2 receptor antagonist astressin$_2$-B.[169] However, deletion of the CRF_2 receptor gene augmented ethanol-induced inhibitory postsynaptic currents (IPSCs).[169] Interestingly, the development of ethanol dependence *in vivo* did not preclude the ability of acute ethanol treatment to increase GABA IPSCs in brain slices of the CeA collected during early withdrawal.[170] However, unlike nondependent rats, in which CRF_1 receptor antagonists inhibited only the potentiation of CeA IPSCs by ethanol, co-application of antalarmin,

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LWH-63 or R121919 not only blocked ethanol-induced IPSCs but also reduced baseline inhibitory firing in the absence of ethanol.[170] Thus, CeA neurons maintain responsiveness to ethanol during withdrawal, and elevated extracellular CRF observed *in vivo* at this timepoint increases the baseline firing rate of CeA GABA-ergic neurons.

This dampening of baseline inhibitory tone by CRF_1 receptor antagonists may also occur, albeit at a much lesser level, in nondependent animals, providing a putative explanation for the reduction of ethanol intake by CRF_1 receptor antagonists in nondependent animals, similar to observations in several recent studies using limited access paradigms that aimed to replicate binge drinking.[111,113] These data suggest that the reduction in baseline IPSCs may, in fact, have functional consequences for the regulation of ethanol intake in nondependent individuals under certain access/intake conditions.

Whereas ethanol studies have focused on the effects of dependence on CRF modulation of inhibitory signalling in the CeA, cocaine withdrawal elevated excitatory synaptic firing, with effects appearing 2 weeks, but not 1 day, after withdrawal from drug treatment.[168,171,172] This potentiated response, observed at synapses from BLA projections to the CeA, involved not only greater activation in response to CRF treatment,[171] but also elevated long-term potentiation following high-frequency stimulation, an effect blocked by the CRF_1 receptor antagonist NBI27914[168,172] and reduced in magnitude by the CRF receptor antagonist astressin$_2$-B.[172] These data demonstrate that although multiple drugs of abuse alter plasticity within the CeA, the specific CRF synapses modified by drug withdrawal may not be uniform across different drugs.

Unlike the CeA, withdrawal-induced synaptic changes in the BNST appear to act via a common pathway, regardless of the abused substance. Similar to the CeA, CRF treatment increased GABAergic neuron firing via a CRF_1 receptor-dependent mechanism, as CRF modulation of inhibitory currents was blocked by NBI27914, but not by the CRF_2 receptor antagonist antisauvagine-30.[173] However, unlike the divergent mechanisms observed for ethanol and cocaine withdrawal in the CeA, withdrawal from chronic intermittent ethanol vapour, LgA cocaine self-administration and LgA heroin self-administration all reduced the fidelity of the intrinsic excitability of BNST juxtacapsular neurons, thus disrupting the long-term potentiation of these neurons.[174] This shift away from the excitation threshold occurred via a CRF_1 receptor-dependent mechanism, as R121919 treatment normalized the intrinsic excitability to levels comparable to nondependent controls.[174] These data demonstrate that withdrawal-induced upregulation of the CRF/CRF_1 receptor system in the CeA and BNST alters the excitability, and thus intrinsic responsiveness, of the extended amygdala to subsequent neural signals. The blockade of CRF_1 receptors returns these brain regions to activity levels similar to normal controls.

Unlike the extended amygdala, in which drug withdrawal alters synaptic efficacy mainly via a CRF_1 receptor-dependent mechanism, behavioural results suggest a prominent role for CRF_2 receptors in the VTA as mediators of drug seeking, as well as glutamate and dopamine release during stress-induced drug reinstatement.[158] At the synaptic level, application of CRF potentiated the response of VTA glutamate *N*-methyl-D-aspartate (NMDA) receptors to stimulation, an effect that was further heightened by chronic cocaine exposure.[175] This enhancement of CRF regulation of VTA excitability following chronic cocaine exposure was reduced by CRF_1 receptor antagonism but was completely blocked by CRF_2 receptor antagonism.[175] These results align with the existing data for stress-induced drug reinstatement, supporting a model of CRF regulation of VTA neuronal activity in which elevated CRF, caused by stress exposure, activates CRF_2 receptors to enhance dopamine and glutamate release, resulting in reinstatement of drug seeking. Within the same population of neurons, chronic cocaine exposure unmasked an additional ability of CRF to

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enhance excitatory responses via the glutamate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, which was insensitive to CRF in drug-naive animals.[175] Unlike the NMDA effect, however, potentiation of AMPA signalling by CRF in cocaine-experienced animals was insensitive to CRF_2 receptor antagonism and instead was blocked by inhibition of the CRF_1 receptor.[175] Thus, although CRF_2 receptors play a predominant role in CRF regulation of VTA neuronal activity, chronic drug exposure may produce an additional mechanism for elevated excitation via a CRF_1 receptor-dependent pathway. Together with the *in vivo* studies discussed previously, these data suggest that inhibition of CRF activity presents a useful pharmacological target for normalizing maladaptive changes in neuronal activity that may underlie the persistence of drug addiction.

8. Conclusion

As a chronically relapsing condition, drug abuse and addiction cannot be successfully treated without addressing the underlying cause of relapse. CRF is a key modulator of the anxiety observed in both acute and protracted abstinence from multiple drugs of abuse and thus presents an ideal target for medication development. The success of multiple CRF receptor antagonists in animal models of drug dependence and the variety of compounds now available provides hope that a clinically effective CRF receptor antagonist for the treatment of drug addiction may be on the horizon.

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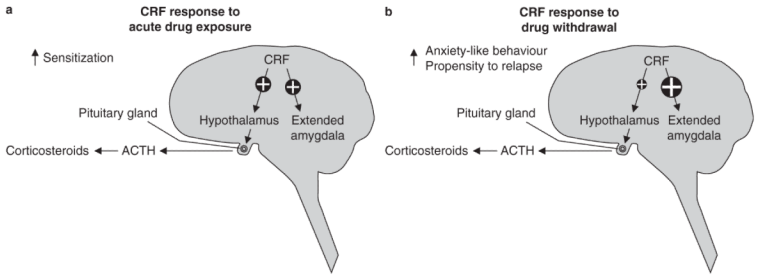

Fig. 1.

Time-dependent modulation of the corticotropin-releasing factor (CRF) response to exposure to drugs of abuse. (**a**) Acute exposure to drugs of abuse activates the hypothalamic-pituitary-adrenal (HPA) axis via increased hypothalamic synthesis and release of CRF, which is released into the portal blood from the median eminence. This triggers increased release of adrenocorticotropic hormone (ACTH) from the pituitary gland, which subsequently acts on the adrenal glands to elevate circulating corticosteroid levels. Acute drug exposure also increases CRF synthesis and release in the extended amygdala. (**b**) During drug withdrawal, activation of the HPA axis is attenuated compared with the drug-naive state, whereas CRF synthesis and release throughout the extended amygdala are greatly elevated. ↑ indicates increased.

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Table I

Pharmacological properties of selected corticotropin-releasing factor ($CRF)_1$ receptor antagonists commonly used in animal models of drug addiction

Compound	CRF_1 receptor affinity (nmol/L)[a]	V_d (L/kg)[b]	$t_{½}$ (h)[b]	Comments[c]	References
α-Helical CRF_{9-41}	10.3	NA		Also binds to CRF_2 receptors and CRF binding protein; not blood-brain barrier penetrant	81
D-Phe CRF_{12-41}	15.5	NA		Also binds to CRF_2 receptors; not blood-brain barrier penetrant	81
Antalarmin	1.4				82
CP-154,526	2.7	105	51		83,84
R121919 (NBI30775)	3.5	16.7	1.7		85
NBI27914	2.3				86
MJL-1-109-2	1.9				87
CRA-1000	16–21			Also binds to serotonin 5-HT_{1A} and 5-HT_4 receptors, L-type Ca^{2+} channel, site 2 Na^{2+} channel, platelet-activating factor, and serotonin reuptake channels weakly	88,89
LWH-63 (NIH-3)	0.7				90
MTIP	0.22	1.7	3.9		91
MPZP	4.9				92

MPZP = *N*,*N*-bis(2-methoxyethyl)-3-(4-methoxy-2-methylphenyl)-2,5-dimethyl-pyrazolo[1,5-*a*] pyrimidin-7-amine; **MTIP** = 3-(4-chloro-2-morpholin-4-yl-thiazol-5-yl)-8-(1-ethylpropyl)-2,6-dimethyl-imidazo[1,2-*b*]pyridazine; **NA** = not applicable; **$t_{½}$** = compound half-life; **V_d** = volume of distribution of drug in plasma.

[a] CRF_1 receptor affinity defined as K_i, the dissociation constant of the antagonist to the CRF_1 receptor. K_i values determined at human or rat CRF_1, as detailed in cited reference.

[b] V_d and $t_{½}$ determined in rats *in vivo*.

[c] Unless otherwise noted, the antagonists are blood-brain barrier penetrant.

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Table II

Predicted therapeutic role of corticotropin-releasing factor (CRF) receptor antagonists in modulating processes related to drug addiction

Drug	Acute HPA activation	Behavioural sensitization	Self-administration		Withdrawal-induced place aversion	Anxiety during withdrawal/ abstinence	Relapse	
			maintenance	dependent/escalated drug taking			stress-induced reinstatement	drug- or cue-induced reinstatement
Cocaine	↓ [51][a]	↓ [54][b]	–/↓ [94-96][b,c]	↓ [94][b]		↓ [97][a]	↓ [98,99][b]	–/↓ [98][a]; [54,100][b]
Opiates	↓ [101][b]		_[102][b]	↓ [102,103][b]	↓ [104,105][b]		↓ [106][a]; [99,107][b]	–/↓ [106][a]; [107][b]
Ethanol	↓ [108][a]	↓ [53,55][b]	–/↓ [76,91,92,109-115][b,c]	↓ [116][a], [73,91,92,109,114-116][b]		↓ [116,117][a]; [91,92,118][b]	↓ [119][a]; [91,110,120][b,c]	–/↓ [119][a]; [121][b]
Nicotine	↓ [122][b]	↓ [123][a]	_[64][b]	↓ [64][b]		↓ [124][a][64][b]	↓ [125,126][b]	
Δ^9-tetrahydro-cannabinol	↓ [d]	↓ [127][a]				↓ [e]		
Palatable food				↓ [128][b]		↓ [128][b]	↓ [129][b]	_[129][b]

HPA = hypothalamic-pituitary-adrenal; ↓ indicates attenuation of HPA activation or behavioural measure following CRF receptor antagonist treatment; – indicates no effect of CRF receptor antagonist treatment on given behaviour.

[a] Studies used CRF receptor subtype nonspecific antagonists.

[b] Studies used CRF receptor-specific antagonists.

[c] References[110,112] involve studies of stress-induced elevation of maintenance drinking.

[d] Systemic CRF receptor antagonism not yet tested with cannabinoid agonist exposure, but decreases in HPA activation and sensitization are predicted based on the ability of CRF receptor antagonists to inhibit similar effects following exposure to other drugs of abuse in conjunction with activation of the HPA axis by the cannabinoid receptor agonist anandamide[48] (although intracerebroventricular administration of D-Phe CRF_{12-41} does not significantly alter corticosterone levels after acute cannabinoid agonist administration).[127]

[e] Systemic CRF receptor antagonism not yet tested with cannabinoid agonist exposure, but elevated anxiety-like behaviour and extracellular CRF observed in the extended amygdala during withdrawal from chronic cannabinoid agonist treatment.[69]

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