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Molecular and Genetic Substrates Linking Stress and Addiction

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Abstract

Drug addiction is one of the top three health concerns in the United States in terms of economic and health care costs. Despite this, there are very few effective treatment options available. Therefore, understanding the causes and molecular mechanisms underlying the transition from casual drug use to compulsive drug addiction could aid in the development of treatment options. Studies in humans and animal models indicate that stress can lead to both vulnerability to develop addiction, as well as increase drug taking and relapse in addicted individuals. Exposure to stress or drugs of abuse results in long-term adaptations in the brain that are likely to involve persistent alterations in gene expression or activation of transcription factors, such as the cAMP Response Element Binding protein, CREB. The signaling pathways controlled by CREB have been strongly implicated in drug addiction and stress. Many potential CREB target genes have been identified based on the presence of a CRE element in promoter DNA sequences. These include, but are not limited to CRF, BDNF, and dynorphin. These genes have been associated with initiation or reinstatement of drug reward and are altered in one direction or the other following stress. While many reviews have examined the interactions between stress and addiction, the goal of this review is to focus on specific molecules that play key roles in both stress and addiction and are therefore posed to mediate the interaction between the two. Focus on these molecules could provide us with new targets for pharmacological treatments for addiction.

Keywords

Stress; Addiction; CREB; BDNF; CRF; Dynorphin

Introduction

Drug addiction is a major public health concern in the U.S. costing taxpayers billions of dollars annually. While some addictions have moderately effective treatments available, relapse rates remain high. Cocaine addiction is particularly troubling as there are currently no effective pharmacological treatments available for the 2.3 million cocaine users in the United States (Sofuoglu and Kosten, 2006). Clinical research indicates that life stress is not only a risk factor in the development of addiction, but also a trigger for relapse to drug use (Brown et al., 1990; Brown et al., 1995; Dewart et al., 2006; McFall et al., 1992; Ouimette et al., 2007) suggesting treatment aimed at reducing stress may be therapeutically effective for drug addiction. Therefore, elucidating the molecular mechanisms underlying the interactions between stress and drug abuse will be critical to promote the identification of such therapies.

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This review focuses on the role of CREB within the fields of stress and addiction and demonstrates how CREB is uniquely posed to mediate the interaction between the two. Furthermore, we discuss a number of CREB target genes and how they mediate response to stress in drug addiction

Stress and Addiction

Clinical research has demonstrated that individuals exposed to chronic stress exhibit a higher propensity to become drug addicts or alcoholics. For example, abuse rates in combat veterans suffering from PTSD are significantly higher than those veterans without the disorder and stress-induced relapse is higher in these individuals following abstinence (Donovan et al., 2001; McFall et al., 1992; Ouimette et al., 2007; Penk et al., 1988; Zaslav, 1994). Additionally, sexual abuse, as well as other childhood trauma, has been shown to increase vulnerability to addiction (DeWit et al., 1999; Teusch, 2001; Triffleman et al., 1995; Walker et al., 1998). Along with these types of chronic stressors, severe acute trauma has also been shown to increase addiction vulnerability as well as relapse rates (Dewart et al., 2006). Comorbidity analyses indicate that there is a higher prevalence of addiction in patients diagnosed with anxiety disorders and depression (Ford et al., 2009; Herrero et al., 2008; Shaffer and Eber, 2002) suggesting that stressful life events may predispose individuals to become addicts and perpetuate the cycle of addiction.

To determine whether stress is a casual factor in the development of addiction, animal models have been used to evaluate the interaction between stress and drug addiction. Repeated stress exposure leads to sensitized responses to acute drug challenge. More specifically, behavioral responses to cocaine, amphetamine and morphine, such as locomotor activity and stereotypy, are augmented following stress (Antelman et al., 1980; Hahn et al., 1986; Herman et al., 1984; Leyton and Stewart, 1990; MacLennan and Maier, 1983). Additionally, stress leads to a potentiation in cocaine-induced extracellular dopamine levels as well as amphetamine-induced striatal dopamine release (Pacchioni et al., 2002; Sorg and Kalivas, 1993). Along with leading to a sensitized behavioral and neurochemical response to drug administration, repeated stress exposure has been shown to facilitate acquisition of drug self-administration (Haney et al., 1995; Kabbaj et al., 2001; Piazza et al., 1989; Piazza et al., 1990; Tidey and Miczek, 1997). Stress has also been shown to potentiate both cocaine and morphine conditioned place preference (Der-Avakian et al., 2007; McLaughlin et al., 2006a; McLaughlin et al., 2006b; Rozeske et al., 2009). Conversely, both repeated and acute drug administration can lead to sensitized behavioral and neurochemical responses to stress. Behavioral stress responsivity, such as freezing behavior in response to shock and anorexia in response to mild tail pinch, is increased in drug-experienced animals (Antelman et al., 1980; Hamamura and Fibiger, 1993). Furthermore, chronic drug exposure leads to enhanced dopamine metabolism in the prefrontal cortex and nucleus accumbens in response to footshock stress as well an enhanced dopamine release in the medial prefrontal cortex (Hamamura and Fibiger, 1993; Kalivas and Duffy, 1989).

Just as these studies help create a casual link between stress and the development of addiction, others have demonstrated that stress exposure can lead to relapse of drug seeking and conditioned reward in animals that have been chronically exposed to drug. Early studies examining the relationship between acute stress and drug mediated behaviors utilized footshock as a primary means of eliciting a stress response. Footshock leads to reinstatement of previously extinguished operant responding for cocaine (Ahmed and Koob, 1997; Erb et al., 1996), heroin (Shaham and Stewart, 1995; Shaham, 1996; Shaham et al., 1996), nicotine (Buczek et al., 1999) and alcohol (Le et al., 1998) self-administration. Footshock stress has also been shown to reactivate extinguished conditioned place preference (CPP) behavior for both cocaine and morphine conditioned reward (Lu et al., 2002; Wang et al., 2006; Wang et

al., 2001). In addition to footshock, stressors such as restraint, tail pinch, and forced swim stress have also been shown to reactivate drug CPP (Kreibich and Blendy, 2004; Leao et al., 2009; Sanchez et al., 2003). More recently an emphasis has been placed on ethologically relevant stressors in animal models as this may more closely recapitulate the human condition. For example, both chronic social stress and social defeat stress have been shown to augment conditioned place preference behavior (Mathews et al., 2008; Ribeiro Do Couto et al., 2006). Primate research has also demonstrated that cocaine is more reinforcing in subordinate animals within a social hierarchy compared with dominant animals and subordinate animals exhibit higher levels of cocaine self-administration (Czoty et al., 2005; Morgan et al., 2002).

The neural circuitry underlying responses to stress intersect with those that promote drug reward. Indeed, functional magnetic resonance imaging (fMRI) studies indicate that stress and drug exposure lead to activation of similar brain regions, including mesolimbic and mesocortical dopamine projection regions (Kufahl et al., 2005; Sinha and Li, 2007). Preclinical studes have demonstrated that both stress and drug exposure lead to an increase in mesolimbic dopamine transmission (Abercrombie et al., 1989; Di Chiara and Imperato, 1988; Kalivas and Duffy, 1989; Thierry et al., 1976). Additionally, acute drug administration and acute stress exposure elicit a similar enhancement in excitatory synaptic strength in the ventral tegmental area (VTA), strengthening the claim that these stimuli activate similar circuitry (Saal et al., 2003).

Within this circuitry a key projection from the central amygdala to the bed nucleus of the stria terminalis (BNST) is critically involved in the ability of stress modulate drug reward (Erb and Stewart, 1999; Erb et al., 2001). The BNST projects to the VTA and therefore can activate the mesolimbic and mesocortical dopamine pathways, supporting a mechanism whereby stress can activate drug-related circuitry (Geisler and Zahm, 2005). While certain components of neuronal circuits underlying stress and drug induced changes in behavior have been identified, less is known regarding the molecular mechanisms underlying this interaction. This review will therefore discuss the transcription factor, CREB, and a number of its target genes that appear to function at the intersection of both drug reward and stress response.

CREB

The transcription factor, cAMP response element-binding protein (CREB), is one candidate that is critical for both the response to stress (Barrot et al., 2002; Borsook et al., 1994) and drug exposure (Carlezon et al., 1998; Pandey et al., 2005a; Walters et al., 2005) as well as the ability of stress to reinstate conditioned drug reward (Kreibich and Blendy, 2004). Thus CREB may serve as a lynchpin at the intersection of stress and drug mediated behaviors. CREB regulates the transcription of over 10,000 target genes (Euskirchen et al., 2004), including those implicated in both stress and addiction, such as CRF, brain derived neurotrophic factor (BDNF), and dynorphin (Cole et al., 1995; Finkbeiner et al., 1997; Hyman et al., 1995; Itoi et al., 1996; Kim et al., 1993; Olson et al., 2005; Tao et al., 1998). CREB is widely expressed in the brain and is a member of the cAMP response element-binding protein family of transcription factors (Mayr and Montminy, 2001; Shaywitz and Greenberg, 1999). The activation of stimulatory G-protein coupled receptors activates adenylyl cyclase, which in turn leads to an accumulation of cAMP in the cytosol. Cyclic AMP then activates protein kinase A, which phosphorylates CREB at serine 133 (Gonzalez and Montminy, 1989; Gonzalez et al., 1991). While this seems to be the primary pathway regulating CREB phosphorylation, mitrogen-activated protein kinase (MAPK) activated ribosomal S6 kinases (RSKs) as well as calcium calmodulin kinase IV (CAMKIV) have also been shown to phosphorylate CREB at serine 133 (see Lonze and Ginty, 2002 for review; Xing et al., 1996). Although phosphorylation of CREB at serine 133 leads to activation and transcription of a variety of gene products, CREB is also phosphorylated at serine 142 by CaMKII, which leads to an inhibition of gene

transcription (Kornhauser et al., 2002; Matthews et al., 1994). Thus, CREB-mediated gene transcription is quite complex and both stress and drugs of abuse, acting on multiple intracellular pathways, may lead to upstream modifications that alter CREB function and therefore the transcription of downstream target genes.

CREB and Stress

Stress exposure leads to alterations in CREB activation in a variety of brain regions. Forced swim stress leads to an increase in phosphorylated CREB (pCREB) in the nucleus accumbens, amygdala, dentate gryus of the hippocampus, and the neortex (Bilang-Bleuel et al., 2002; Kreibich and Blendy, 2004; Shen et al., 2004). Similar to forced swim stress, footshock stress leads to an elevation in pCREB in the hippocampus and amygdala, and also within the parietal cortex and paraventricular nucleus of the hypothalamus (PVN, Bruijnzeel et al., 2001; Kudo et al., 2004; Stanciu et al., 2001). Restraint stress also leads to an increase in pCREB in the hippocampus, hypothalamus, and frontal cortex as well as the locus ceruleus (Hebert et al., 2005; Kwon et al., 2006; Miller et al., 2007; Sabban et al., 2004; Shimizu et al., 2004). Social stress has also been shown to increase pCREB in the periaquaductal grey and the hippocampus (Adamec et al., 2003; Boer et al., 2007).

Although there are many examples in the literature of acute or repeated stress activating CREB signaling, there is evidence that chronic stress may inhibit CREB function by reducing either total levels of CREB or its level of phosphorylation. Maternal deprivation stress been shown to decrease pCREB levels in the hippocampus (Huang et al., 2002) and chronic mild stress leads to a decrease in CREB mRNA in this same brain region (Song et al., 2006). Chronic unpredictable stress leads to decreases in pCREB in the hippocampus, striatum and frontal cortex (Laifenfeld et al., 2005; Trentani et al., 2002). Additionally, social isolation stress leads to a decrease in CREB activation within the nucleus accumbens shell (Barrot et al., 2005; Wallace et al., 2009). CREB is an activity dependent transcription factor and reductions of this activity may indicate a compensatory response to chronic stress.

Due to the lack of pharmacological tools to investigate the functional role of CREB, deletion or overexpression of CREB protein using genetic mouse models or viral vector technology has been utilized. Mice with a constitutive deletion of the α and Δ isoforms of CREB (CREBαΔ) exhibit altered behavioral responses to forced swim stress as well as learned helplessness paradigms. Specifically, CREBαΔ mice exhibit a decrease in immobility in the forced swim test as well as a decrease in escape failures in the LH paradigm (Conti et al., 2002; Conti, Picciotto & Blendy, unpublished data). However, these mice also exhibit an increase in anxiety-like behavior in the novelty suppressed feeding test, elevated plus maze, elevated zero maze and open field (Graves et al., 2002; Gur et al., 2007; Valverde et al., 2004). Interestingly, the CREBαΔ mice do not exhibit alterations in endocrine responses to acute stress, such as alterations in corticosterone (Conti et al., 2002; Hebda-Bauer et al., 2004).

This dissociation between anxiety and stress responsivity is also seen following viral manipulations of CREB in the nucleus accumbens shell. Eliminating CREB function by overexpression of a mutant form of CREB, mCREB, leads to an increase in anxiety-like behavior in the elevated plus maze while simultaneously leading to a decrease in immobility in the forced swim test as well as a decrease in shock-induced learned helplessness behavior. Conversely, overexpression of CREB within the NAc shell leads to a decrease in anxiety-like behavior in the elevated plus maze and an increase in immobility in the forced swim test and increased learned helplessness (Barrot et al., 2002; Barrot et al., 2005; Newton et al., 2002; Pliakas et al., 2001). While this may at first seem paradoxical, these findings parallel what is seen with pCREB induction following chronic or acute stress. As chronic stress leads to a decrease in CREB phosphorylation, decreasing CREB expression, either via genetic or viral manipulation may lead to this anxiety-like state that is seen following chronic stress exposure

(Ardayfio and Kim, 2006). However, as CREB phosphorylation is increased following acute stressors, blocking this activity may protect against the effects of discrete stress exposures.

A similar dissociation between anxiety and stress responsivity are seen when CREB levels are manipulated in the amygdala. Overexpression of CREB in the basolateral amygdala leads to a decrease in immobility in the forced swim test and a decrease in shock-induced learned helplessness behavior, while leading to an increase in anxiety behavior (Wallace et al., 2004). In contrast, overexpression of CREB in the hippocampus results in decreased immobility in the forced swim test and decreased learned helplessness behavior (Chen et al., 2001; Wallace et al., 2004). However, overexpression of CREB in the hippocampus does not alter anxiety behavior (Restivo et al., 2009).

Taken together, these results suggest a multi-faceted role of CREB in the nucleus accumbens, with increases in CREB activity mediating the effects of acute stressors, such as swim stress or shock, and decreases in CREB activity mediating the effects of chronic stressors and anxiety states. Within the amygdala, CREB plays an opposite role and within the hippocampus it may only mediate acute stress response.

CREB and Addiction

Just as stress exposure leads to alterations in CREB activation in a variety of brain regions, so do drugs of abuse. Both acute and chronic administration of amphetamine leads to an increase in pCREB in both ventral (nucleus accumbens) and dorsal (caudate putamen) striatum (Cole et al., 1995; Konradi et al., 1994; Turgeon et al., 1997). Chronic amphetamine has also been shown to increase pCREB within the olfactory bulb, hippocampus, and amygdala (Yin et al., 2006). Similarly, acute or chronic cocaine administration leads to an increase in the phosphorylation of CREB within the prefrontal cortex, nucleus accumbens, dorsal striatum, and amygdala (Edwards et al., 2007; Kano et al., 1995; Karasinska et al., 2005; Kreibich and Blendy, 2004; Lee et al., 2008; Mattson et al., 2005; Nazarian et al., 2009).

While both chronic and acute psychostimulants increase CREB phosphorylation, modulation of CREB by other drugs of abuse is a bit more complicated. While both acute and chronic ethanol exposure lead to an increase in pCREB in the striatum, chronic ethanol decreases CREB phosphorylation in the cerebellum (Yang et al., 1996; Yang et al., 1998). Furthermore, the ability of ethanol to increase pCREB in the central nucleus of the amygdala is correlated with voluntary oral consumption of ethanol (Pandey et al., 2005b). Acute nicotine leads to increased pCREB in the nucleus accubens, striatum, VTA and peduculopontine tegmental nucleus while after chronic administration nicotine only increases pCREB within the striatum and VTA (Brunzell et al., 2009; Walters et al., 2005).

In contrast to these drugs that lead to increases in CREB phosphorylation, opiate administration leads to a decreased in CREB phosphorylation. Acute and chronic morphine administration lead to decreases in pCREB within the locus coeruleus (Guitart et al., 1992). Additionally, decreases in pCREB have been seen in the nucleus accumbens and hippocampus following chronic morphine administration (Widnell et al., 1996; Yang and Pu, 2009). Although opiate administration leads to decreased CREB activation, withdrawal from opiate drugs has the opposite effect. There is in an increase in CREB phosphorylation during morphine withdrawal in the amygdala and the nucleus accumbens (Chartoff et al., 2003; Shaw-Lutchman et al., 2002). Similar increases in pCREB are seen in the dorsal striatum of animals withdrawal from heroin (Edwards et al., 2009).

Taken together, these studies suggest that psychostimulants, nicotine and ethanol primarily upregulate phosphorylation of CREB while opiates lead to downregulation. However, these studies do not tell us how CREB contributes to compulsive drug use. Studies utilizing genetic

mouse models and viral vectors have provided some insight into how manipulating CREB levels alters drug seeking and drug reward. CREBαΔ mice exhibit deficits in nicotine and morphine conditioned place preference behavior (Walters and Blendy, 2001; Walters et al., 2005). Additionally, CREBαΔ mice, as well as mice with a forebrain specific targeted deletion of CREB, exhibit a decrease in opiate withdrawal behaviors (Maldonado et al., 1996; Valverde et al., 2004). However, these mice exhibit an enhanced sensitivity to cocaine reward and increased voluntary alcohol intake (Pandey et al., 2004; Walters and Blendy, 2001).

Consistent with what is seen in CREBαΔ mice, expression of the mutant form of CREB (mCREB) in the nucleus accumbens leads to an increase in both morphine and cocaine reward, while overexpression of CREB leads to a decrease in reward behavior (Barrot et al., 2002; Carlezon et al., 1998; Pliakas et al., 2001). Furthermore, mCREB expression in the nucleus accumbens increases the ability of cocaine to lower reward thresholds in an intracranial self-stimulation procedure, supporting the theory that CREB in the nucleus accumbens works to dampen cocaine reward (Dinieri et al., 2009). Similarly, expression of mCREB abolishes nicotine conditioned place preference behavior (Brunzell et al., 2009), consistent with a lack of nicotine reward seen in CREBαΔ mice (Walters et al., 2005). Also consistent with CREB deficient mice, expression of mCREB in the rostral VTA blocks morphine CPP and overexpression has the opposite effect (Olson et al., 2005). These opposing effects on opiate reward versus psychostimulant reward are not entirely surprising in light of the CREB phosphorylation data however, the direction of the effects may be. As psychostimulant exposure leads to an increase in CREB phosphorylation, whereas deletion of CREB enhances psychostimulant reward, this suggests that CREB, at least within the NAc and rostral VTA, may be acting to compensate for drug-induced changes.

The role of CREB within morphine reward is a bit more complex than simply a compensatory one. In contrast to the rostral VTA, expression of mCREB in the caudal VTA or NAc shell leads to increases in morphine reward and CREB overexpression leads to decreases (Barrot et al., 2002; Olson et al., 2005). However, as mice deficicent in CREB within all brain regions exhibit a decrease in morphine reward, CREB activity within the rostral VTA, or additional brain regions not yet examined, may prevail over the activity within the NAc shell or caudal VTA.

CREB and the link between stress and addiction

While very little work has been done examining the role of CREB in mediating behaviors specific to stress and drug interactions, there is some evidence for its importance. Exposure to forced swim stress leads to an increase in CREB phosphorylation in the amygdala of cocaine-experienced mice and not drug naïve animals (Kreibich and Blendy, 2004). Additionally, CREBαΔ mice fail to exhibit stress-induced reactivation of cocaine conditioned place preference, while cocaine primed reinstatement is intact (Kreibich and Blendy, 2004). Furthermore, these mice do not exhibit stress-induced potentiation of cocaine reward (Kreibich et al., 2009). These studies suggest that CREB is necessary for stress-induced modulation of drug taking and drug relapse. However, it is not clear where in the brain CREB is acting to have these effects. Thus, the role of CREB in specific brain regions, such as the BNST, amygdala, NAc, and VTA is not known. This information would help identify downstream target genes that contribute to stress-induced potentiation of drug responses. Additionally, very little work has been done examining the role of CREB within the BNST, a brain region known to be necessary for stress-induced reinstatement (Erb and Stewart, 1999; Erb et al., 2001). Future studies are needed to determine the role of CREB within this brain region and how it may relate to interactions between stress and addiction.

A number of genes are implicated in stress responses and still others are responsive to acute and/or chronic exposure to drugs of abuse. However, the subset of these genes that have been

associated with both the effects of stress and drugs of abuse are relatively few. BDNF, CRF, and dynorphin may represent a small fraction of the total number of CREB targets involved (McClung and Nestler, 2003; Renthal et al., 2009), however, these neuropeptides are directly involved in the interaction between stress and addiction. Future studies are necessary to examine additional CREB targets that might be involved and isolate where in the brain they are mediating the interaction between stress and drugs of abuse.

Brain-Derived Neurotrophic Factor (BDNF)

BDNF is the most prevalent neurotropin in the brain and is involved in activity-dependent synaptic plasticity, survival and differentiation of neurons (Ernfors et al., 1994; Huang and Reichardt, 2001; Jones et al., 1994). Specifically, BDNF has been implicated in the survival and functional of midbrain dopamine neurons (Hyman et al., 1991). CRE binding sites have been found on various BDNF promotors, identifying BDNF as a potential downstream target of CREB (Aid et al., 2007; Tao et al., 1998). Additionally, upregulation of BDNF transcription has been shown to be CREB dependent (Conti et al., 2002; Tao et al., 1998). Just as altering CREB can lead to changes in BDNF levels, manipulations of BDNF have been shown to alter CREB phosphorylation (Gooney et al., 2004; Pandey et al., 2006).

BDNF binds to the tyrosine receptor kinase B (TrkB) receptor, and activation of this receptor leads to autophosphorylation and increased interaction with docking proteins that regulate the mitrogen-activated protein kinase signaling cascade (Hashimoto et al., 2004). The TrkB receptor has three protein isoforms that are produced by alternative splicing of exons encoding the intracellular domain. Along with the full-length isoform, the TrkB-T1 isoform, which lacks the tyrosine kinase domain, and the TrkB-T-Shc isoform, which lacks the tyrosine kinase domain but contains the Shc binding site, are expressed in the brain (Stoilov et al., 2002). Both of the truncated isoforms can act to inhibit activity of the full-length isoform as well as mediate signal transduction independently of full-length TrkB receptors (Baxter et al., 1997; Eide et al., 1996; Haapasalo et al., 2001; Hartmann et al., 2004; Rose et al., 2003; Steinbeck and Methner, 2005; Tervonen et al., 2006). BDNF is expressed in several areas of the brain including the amygdala, the striatum, and the prefrontal cortex and its receptor is present on all mesencephalic dopamine neurons (Bland et al., 2005; Gordon et al., 2003; Numan and Seroogy, 1999; Rattiner et al., 2004; Yurek et al., 1996). This distribution puts BDNF in a position to impact both stress and drug circuitry as well as the interaction between the two.

BDNF and stress

Exposure to either acute or chronic stress alters BDNF mRNA and protein levels within the brain. Whether these are increases or decreases depend both upon the stressor and the brain region. Chronic or acute restraint stress leads to a decrease in both BDNF mRNA and protein levels in the hippocampus, however increases are seen in the paraventricular nucleus of the thalamus (Murakami et al., 2005; Nibuya et al., 1999; Smith et al., 1995a; Smith et al., 1995b; Xu et al., 2006). Acute forced swim stress as well as acute social defeat stress also lead to a decrease in BDNF in the hippocampus while maternal separation stress leads to an increase in this same region (Arunrut et al., 2009; Greisen et al., 2005; Pizarro et al., 2004). Furthermore, infusion of BDNF into the hippocampus protects against stress-induced impairments in learning and memory (Radecki et al., 2005). Constitutive deletion of BDNF leads to embryonic lethality (Erickson et al., 1996), however studies utilizing heterozygote knockout mice demonstrate that reductions in BDNF lead to an increase vulnerability to stress as well as an increase in anxiety behaviors suggesting that BDNF plays a protective role (Advani et al., 2009; Ren-Patterson et al., 2006). Additionally, female mice with conditional deletion of BDNF exhibit a decrease in anxiety in the elevated plus maze however they also show increased immobility in the forced swim test (Monteggia et al., 2007), a behavior associated with passive stress coping (Cryan and Mombereau, 2004; Cryan and Holmes, 2005; Thierry et al., 1984).

Taken together, these studies suggest that the role of BDNF is protective against stress however stress exposure leads to a decrease in BDNF levels. Following acute stress, CREB activation in the hippocampus may be working to compensate for these decreases in BDNF protein.

BDNF and addiction

Just as stress exposure alters BDNF levels in the brain, so does drug exposure. However, contrary to the decreases that are primarily seen following stress, exposure to drugs primarily lead to increases in BDNF expression. Acute cocaine administration leads to an increase in BDNF mRNA in the prefrontal cortex and repeated administration augments this increase (Fumagalli et al., 2007; Le Foll et al., 2005). An increase in nucleus accumbens BDNF mRNA and protein is also seen following a single cocaine injection (Graham et al., 2007). However, a decrease in BDNF is seen following acute nicotine administration, though with chronic administration the reverse effect is seen (Kenny et al., 2000). Unlike nicotine and cocaine, chronic alcohol leads to a decrease in BDNF, specifically in the hippocampus (Tapia-Arancibia et al., 2001). During withdrawal from chronic cocaine, increases in BDNF are seen in the hippocampus, ventral tegmental area and the nucleus accumbens and BDNF levels in the VTA and nucleus accumbens continue to increase over the course of withdrawal (Filip et al., 2006; Grimm et al., 2003). Augmentation of BDNF is seen in the periaquaductal grey of mice withdrawn from chronic morphine and the hippocampus of rats withdrawn from alcohol (Matsushita and Ueda, 2009; Tapia-Arancibia et al., 2001). While the effects of acute or chronic drug administration on BDNF expression are varied, the effects of withdrawal from stimulants, morphine, and alcohol all lead to an increase in BDNF.

Alterations in BDNF are associated with increases in cocaine craving suggesting a causal relationship between BDNF and drug mediated responses (Lu et al., 2004b). In support of this, infusions of BDNF into the ventral tegmental area during withdrawal lead to a potentiation of cocaine seeking (Lu et al., 2004a) and infusions of BDNF into the nucleus accumbens during cocaine self-administration training increase drug intake (Graham et al., 2007). Infusions of BDNF into the either the nucleus accumbens or the VTA enhance both the stimulant and conditioned rewarding effects of cocaine (Horger et al., 1999). Furthermore, overexpression of either BDNF or TrkB in the nucleus accumbens leads to an increase in cocaine conditioned reward, a decrease in extinction of CPP, and an increase in cocaine-primed reinstatement (Bahi et al., 2008). However, infusions of BDNF into the prefrontal cortex blocks cocaine seeking as well as the effects of cocaine on glutamatergic function in the nucleus accumbens, alterations in which are thought to be critically involved in addiction (Berglind et al., 2007; Berglind et al., 2009). In support of a role for BDNF in facilitating addictive behavior, BDNF-deficient mice exhibit a decrease in both the locomotor stimulating and the rewarding properties of cocaine (Hall et al., 2003). These studies suggest that similar to the role of BDNF in stress, its role in addiction is complex and dependent upon the brain region and drug of abuse examined.

BDNF and the link between stress and addiction

Along with changes in BDNF seen following either stress or cocaine, interactions between stress and cocaine may also be linked to BDNF expression. Exposure to swim stress leads to an increase in BDNF mRNA in the nucleus accumbens in animals withdrawn from cocaine that is not seen in naïve mice (Cleck et al., 2008). In contrast, repeated stress exposure blocks the ability of acute cocaine to increase BDNF in the prefrontal cortex (Fumagalli et al., 2009). Thus, it is clear that BDNF, a CREB target gene involved in neuronal plasticity, not only mediates the effects of stress and drugs of abuse individually but may also play a role in the interaction between the two. However, additional studies comparing the effects of both stress and drugs are needed to clarify a functional interaction.

Corticotropin-Releasing Factor

CRF is a neuropeptide that mediates autonomic, neuroendocrine and behavioral responses to stress (Berridge and Dunn, 1986; Dunn and Berridge, 1987; Dunn and Berridge, 1990; Vale et al., 1981). While CRF is distributed in a number of different forebrain regions, the highest density is found within the paraventricular nucleus of the hypothalamus (Sawchenko and Swanson, 1985). The CRF promotor contains CRE elements that allow for transcriptional regulation by CREB (Guardiola-Diaz et al., 1994; Itoi et al., 1996).

CRF binds to two types of seven transmembrane, stimulatory G-protein coupled receptors, CRF receptor type 1 (CRFR1) and CRF receptor type 2 (CRFR2) (Blank et al., 2003; Grammatopoulos et al., 2001). These receptors increase cyclic AMP through adenylate cylase and lead to phosphorylation of CREB (Rossant et al., 1999). CRFR1 is widely expressed throughout the brain most prominently within the cerebral cortex, sensory relay nuclei and the cerebellum (Van Pett et al., 2000). Distribution of CRFR2 receptors in the brain is more restricted than CRFR1, with the highest density in the olfactory bulb, lateral septum, BNST, ventral hippocampus, and the amygdala (Van Pett et al., 2000). Along with binding to CRFR1 and CRFR2 receptors, CRF also binds to CRF-binding protein (CRF-BP), which sequesters CRF and prevents it from binding to receptors and thus activating downstream signaling cascades (Petraglia et al., 1996).

CRF and stress

Both chronic and acute stress lead to increased CRF both in the periphery and the brain (Chappell et al., 1986; Hashimoto et al., 1989; Herman et al., 1992). CRF administration enhances stress related behaviors such as acoustic startle, conditioned fear and stress-induced freezing behavior (Cole and Koob, 1988; Swerdlow et al., 1986). Administration of CRF receptor antagonists have been shown to blunt the behavioral and neurobiological effects of stress exposure (Berridge and Dunn, 1989; Cole et al., 1990; Price et al., 2002). Furthermore, site-specific injections of CRF antagonists have identified brain regions critical in mediating stress-induced behaviors. CRF receptors in the locus ceruleus mediate shock-induced freezing behavior as well as stress-induced modulation of norepinephrine signaling (Kawahara et al., 2000; Melia and Duman, 1991; Swiergiel et al., 1992). However, it has also been shown that antagonism of CRF action in the lateral septum as well as the amygdala also blocks shock-induced freezing suggesting that CRF activity in multiple brain regions in necessary for stress-induced behaviors (Bakshi et al., 2002).

CRF and addiction

Drugs of abuse both mediate CRF activity and changes in CRF mediate drug taking and reward. Initial studies examining the effects of cocaine on the HPA axis demonstrated that acute cocaine or morphine lead to alterations in the HPA axis that are dependent upon CRF (Buckingham, 1982; Buckingham and Cooper, 1986; Rivier and Vale, 1987; Sarnyai et al., 1992a; Sarnyai et al., 1992b). More specifically, acute cocaine administration leads to an increase in CRF immunoreactivity in the amygdala as well as a decrease in the frontal cortex, basal forebrain, hypothalamus, and hippocampus (Gardi et al., 1997; Sarnyai et al., 1993). CRF mRNA levels increase in the central nucleus of the amygdala following acute and chronic cocaine or morphine (Maj et al., 2003). Additionally, nicotine has also been demonstrated to activate the HPA axis via hypothalamic CRF activity (Matta et al., 1987). Both acute cannabinoid and alcohol administration have been shown to increase ACTH and corticosterone however whether this is due to direct hypothalamic activity or extrahypothalmic mechanisms is debated (Puder et al., 1982; Rivier et al., 1984; Rodriguez de Fonseca et al., 1996). Interestingly, while acute experimenter administered cocaine leads to an increase in CRF release in the

hypothalamus this is not seen in animals undergoing i.v. self-administration procedures (Richter et al., 1995; Richter and Weiss, 1999).

While transient increases in CRF are seen following acute drug administration, chronic drug administration leads to sustained increases. Chronic cocaine leads to a sustained increase in extracellular CRF (Richter et al., 1995), and in the case of chronic opiate administration this leads to the development of tolerance to the HPA activating effects of the drug (el Daly, 1996). Along with these modifications following drug administration, there is a large body of work looking at CRF alterations during drug withdrawal (Heilig and Koob, 2007; Koob, 1999; Koob and Le Moal, 2008). While CRF immunoreactivity is decreased in the amygdala, frontal cortex, and hippocampus during withdrawal from cocaine or alcohol, this decrease seems to be indicative of an increase in CRF release rather than a global decrease in CRF (Richter and Weiss, 1999; Sarnyai et al., 1995; Zorrilla et al., 2001). In support of this, microdialysis studies indicate that withdrawal from ethanol, cannabinoids, cocaine and nicotine leads to an increase in CRF release (George et al., 2007; Merlo Pich et al., 1995; Richter and Weiss, 1999; Rodriguez de Fonseca et al., 1997).

CRF and the link between stress and addiction

Exposure to a variety of drugs of abuse can alter CRF levels, and this response is behaviorally relevant as modulating CRF can alter drug taking and reward as well as the interaction between stress and addiction. CRF antagonists decrease both cocaine and heroin self-administration behavior in rats on an extended access schedule (Greenwell et al., 2009; Specio et al., 2008). Intracerebroventricular injections of CRF lead to reinstatement of cocaine, nicotine, heroin, and alcohol seeking (Bruijnzeel et al., 2009; Erb et al., 2006; Le et al., 2002; Shaham et al., 1997). Within the BNST both corticotropin-releasing factor (CRF) and norepinephrine (NE) release are required for stress-induced reinstatement of drug seeking (Erb et al., 2001; Leri et al., 2002). Moreover, studies utilizing CRF antagonists have determined that the CRF projection from the amygdala to the BNST, stimulating CRFR1 receptors in the BNST, is necessary for reinstatement of both self-administration and conditioned place preference by stress (Erb et al., 1998; Erb and Stewart, 1999; Erb et al., 2001; Wang et al., 2006). Additionally, blocking CRFR2 receptors in the VTA also prevents stress-induced reinstatement of drug seeking (Wang et al., 2007). Thus, CRF influences drug-taking and drug reward and its effects may be intimately connected to mechanisms associated with CREB activity..

Dynorphin

Dynorphin, an opiate peptide arising from the precursor prodynorphin, is the endogenous ligand for the kappa opioid receptor and is widely distributed throughout the brain (Chavkin et al., 1982). Activation of cAMP second messenger pathway leads to induction of dynorphin mRNA in the striatum through a CREB-dependent pathway and the prodynorphin gene contains multiple CRE elements (Douglass et al., 1994; Simpson and McGinty, 1995). Futhermore, CREB has been shown to regulate dynorphin expression (Cole et al., 1995). Accordingly, overexpression of CREB leads to increased dynorphin mRNA and expression of mCREB has the opposite effect (Carlezon et al., 1998).

Kappa opioid receptors (KOPr) are coupled to Gi/Go proteins, which have an overall inhibitory effect in the cell. In addition KOPr signaling has been linked to potassium and N-type calcium ion channels as well as activation of mitrogen-activated protein kinase cascades (Belcheva et al., 2005; Bohn et al., 2000; Henry et al., 1995; Tallent et al., 1994). These studies suggest multiple pathways exist through which this receptor could modulate CREB phosphorylation.

Although there is pharmacological evidence suggesting that multiple subtypes of the kappa receptor exist (Heyliger et al., 1999; Horan et al., 1993), there is some debate on whether this

is actually the case. Recent work suggests that the putative agonists for these subtypes may in fact bind to other opioid receptors to have their effect (Bhushan et al., 2004; Jordan and Devi, 1999; Olianas et al., 2006). Activation of kappa opioid receptors is aversive; kappa agonists serve as negative reinforcers and produce dysphoria in humans and aversion in experimental animals (Mucha and Herz, 1985; Pfeiffer et al., 1986). Furthermore, in contrast to addictive substances, kappa opioid receptor agonists decrease mesolimbic dopamine transmission (Di Chiara and Imperato, 1988).

Dynorphin and stress

Acute or chronic immobilization stress leads to an increase in prodynorphin mRNA expression in the hippocampus (Chen et al., 2004). Acute immobilization stress and learned helplessness training have also been shown to increase dynorphin immunoreactivity in the hippocampus and nucleus accumbens (Shirayama et al., 2004). Similarly, food deprivation, tail pinch and insulin induced hypoglycemia increase dynorphin immunoreactivity in the cortex and hypothalamus and forced swim stress leads to increases in the hippocampus (Chavkin et al., 1983; Morley et al., 1982; Shirayama et al., 2004). Administration of a kappa opioid antagonist or genetic disruption of dynorphin gene expression blocks the behavioral responses (immobility, analgesia, potentiation of reward) to forced swim stress or social defeat stress (McLaughlin et al., 2003; McLaughlin et al., 2006b). Additionally, mice with genetic disruption of the prodynorphin gene do not exhibit stress-induced deficits in learning and memory that are seen in wildtype animals (Carey et al., 2009).

Dynorphin and addiction

Drugs of abuse can increase prodynorphin expression in both preclinical and clinical models. Postmortem studies of human cocaine addicts demonstrate an increase in both dynorphin mRNA and protein levels compared to controls (Frankel et al., 2008; Hurd and Herkenham, 1993). Furthermore, polymorphisms in the prodynorphin gene have been associated with opioid dependence, particularly in females (Clarke et al., 2009). Preclinical models have demonstrated that cocaine intake is causally responsible for increases in dynorphin mRNA (Daunais et al., 1993; Daunais et al., 1995). Increased striatal dynorphin expression is also seen following amphetamine, nicotine, morphine and ethanol administration (Brandon and Steiner, 2003; Mathieu-Kia and Besson, 1998; Turchan et al., 1998; Turchan et al., 2002; Wang et al., 1999). Additionally, animals with a genetic disruption of the prodynorphin gene as well as KOPr knockout mice exhibit decreased alcohol self-administration (Blednov et al., 2006; Kovacs et al., 2005). Similarly, KOPr knockout mice fail to exhibit behavioral sensitization following cocaine administration and exhibit a decreased dopaminergic response to acute cocaine (Chefer et al., 2005; Chefer and Shippenberg, 2006).

Dynorphin and the link between stress and addiction

Recent work indicates that dynorphin may also be involved in stress-induced changes in drug reward. Antagonism of kappa opioid receptors, dynorphin's target receptor, blocks the ability of stress to potentiate cocaine conditioned place preference (McLaughlin et al., 2003) Additionally, administration of kappa opioid receptor agonists leads to reinstatement of cocaine seeking and potentiation of cocaine conditioned place preference (McLaughlin et al., 2006a; Valdez et al., 2007). Furthermore, mice with a disruption in the prodynorphin gene fail to show stress-induced potentiation of cocaine conditioned place preference (McLaughlin et al., 2006b). Thus, dynorphin is another CREB target gene that may mediate stress-induced changes in addictive behavior through a CREB dependend mechanism.

Conclusions

It is clear that stress modulates the acquisition of drug taking, the transition to addiction as well as relapse to drug seeking. Behavioral, molecular and genetic approaches have helped identify molecules in stress and drug reward circuits, which appear to be important in both drug reward and reinstatement as well as in stress responsivity. Though the story is far from complete, CREB appears as a central player in establishing or maintaining drug and stress related behaviors. Many potential CREB target genes have been identified based on the presence of a CRE element in their promoter DNA sequences. We have described a subset of these targets; CRF, BDNF, and dynorphin. These peptides are not only well-characterized CREB target genes, their effector mechanisms either directly (CRF receptors, kappa receptors) or indirectly TrkB receptors) modulate CREB activity through regulation of phosphorylation

Although CREB is acting within a variety of brain regions to regulate a number of proteins, the data presented here provide us with some insight into how CREB might be mediating the interaction between stress and drugs of abuse. As blocking the action of dynorphin leads to a decrease in the ability of stress to potentiate drug seeking and relapse, similar to what is seen in CREBαΔ mice, CREB-mediated transcription of prodynorphin represents a possible intersection point in the drug and stress circuitry. As regional manipulations of prodynorphin have not been examined in stress-induced reinstatement models, currently it is not clear where in the brain this transcription may be occurring. CREB may also be acting within the amygdala to regulate CRF levels in response to acute stressors. If stress exposure is unable to activate CRF signaling, then it will not be able to activate drug reward circuitry (Erb et al., 1998; Erb et al., 2001; Kreibich et al., 2009). As CREB activity in the nucleus accumbens dampens reward and BDNF in this region increases drug seeking, it is unlikely that CREB is regulating BDNF levels following drug administration. However, CREB may be working within the hippocampus to decrease vulnerability to chronic stress by increasing levels of BDNF.

Taken together these studies demonstrate that the role of CREB in regulating stress responsivity, drug reward, and the interaction between the two is complex. CREB may be regulating a number of different peptides and other proteins in concert to facilitate stress-induced reinstatement. Insights into the molecular mechanisms underlying stress induced drug behavior would prove useful in creating successful pharmacotherapy for drug addiction. Clinical consideration of therapy aimed at reducing the stress component of addiction may lead to more effective solutions for treatment programs. Developing a better understanding of the molecular mechanisms underlying the ability of stress to modulate these different aspects of addiction could help us develop targeted pharmacological interventions.

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