Drug withdrawal conceptualized as a stressor

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Abstract

Drug withdrawal is often conceptualized as an aversive state that motivates drug-seeking and drug-taking behaviors in humans. Stress is more difficult to define, but is also frequently associated with aversive states. Here we describe evidence for the simple theory that drug withdrawal is a stress-like state, on the basis of common effects on behavioral, neurochemical, and molecular endpoints. We also describe data suggesting a more complex relationship between drug withdrawal and stress. As one example, we will highlight evidence that, depending on drug class, components of withdrawal can produce effects that have characteristics consistent with mood elevation. In addition, some stressors can act as positive reinforcers, defined as having the ability to increase the probability of a behavior that produces it. As such, accumulating evidence supports the general principles of opponent process theory, whereby processes that have an affective valence are followed in time by an opponent process that has the opposite valence. Throughout, we identify gaps in knowledge and propose future directions for research. A better understanding of the similarities, differences, and overlaps between drug withdrawal and stress will lead to the development of improved treatments for addiction, as well as for a vast array of neuropsychiatric conditions that are triggered or exacerbated by stress.

Keywords

addiction; corticotropin-releasing factor; cyclic AMP response element binding protein; dynorphin; glutamate; opiate; opponent process; psychostimulant

Introduction

Stress is a complex construct with interdependent biological and psychological components. By definition, it is the nonspecific response of an organism to any demand (stressor) placed upon it that requires adaptation (Selye, 1936; McEwen and Gianaros, 2011). Stressors typically engage the hypothalamic–pituitary–adrenal (HPA) axis to produce physiological and emotional responses. The biological effects of stress are relatively hardwired and can be measured objectively (changes in hormone release, heart rate), whereas emotional effects

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can depend on an individual's perception of their ability to cope with the stressor (Coyne *et al.*, 1981; Maier and Watkins, 2005) and are therefore more subjective. The same stressor may trigger pleasure in one individual but aversion in another. A popular conceptualization of stress is that it is a constellation of negative, depressive-like emotions (anhedonia, anxiety, irritability, feeling overwhelmed) that should be avoided, although stimuli that would seem to qualify as stressors can be experienced as euphoric and thrilling (e.g. skydiving). In laboratory animals, some forms of stress can produce 'anomalous' responses that are not easily conceptualized as reflecting depressive-like effects (Willner, 2005). Key to our understanding of how stressors affect emotion is the concept of allostasis, in which stability of homeostatic systems is maintained through adaptive plasticity (i.e. opponent processes). Here we will discuss how both the onset and the offset of drugs of abuse can be considered stressors that trigger adaptive plasticity within neural circuits that regulate motivation and emotion. These neuroadaptive responses contribute to the pathophysiology of drug addiction, defined here as a chronic, relapsing disease characterized by compulsive drug seeking and use despite harmful consequences (Koob and Volkow, 2010).

Reinforcement is a process by which a response-contingent delivery or removal of a stimulus increases the probability of a subsequent response. There are two forms: positive reinforcement, which is associated with euphoria, and negative reinforcement, which is associated with cessation of an aversive state. Both forms contribute to the addiction process (Wise and Koob, 2014), although positive reinforcement is often associated with the development of addiction and negative reinforcement is associated with the maintenance of addiction. As an individual repeatedly uses a drug, a shift occurs such that cessation of withdrawal-induced dysphoria (a stressful state) drives continued drug use and relapse (Koob and Le Moal, 2008; Wise and Koob, 2014). The neurobiological basis of this shift, which has been conceptualized as an opponent process theory (Solomon and Corbit, 1974; below), is the focus of considerable research. This framework holds true for all drugs considered to be addictive, although each class of drug engenders unique patterns of use and progression to addiction. Here we will focus on the similarities and differences between stress and dependence on opioids and psychostimulants. With opioids (e.g. heroin, prescription painkillers), the progression from impulsive to compulsive intake often starts with misuse to get high and relieve tension (i.e. self-medication) followed by development of tolerance (Chartoff and Connery, 2014). Only 3–13% of first-time users of prescription painkillers or heroin, respectively, develop dependence within the first year, suggesting that addiction is not inevitable (NSDUH, 2008). With psychostimulants (cocaine, amphetamine), people typically start with low-level sporadic use, often in social settings. For 5–10% of users, drug binges of hours or days (until supply is depleted) become frequent (NSDUH, 2008). The end of a binge is characterized by profound dysphoria, general depression of activity, and intense drug craving (Gawin, 1991).

The mesocorticolimbic system, comprising the ventral tegmental area (VTA), the nucleus accumbens (NAc), and the prefrontal cortex (PfC), is considered a primary mediator of acute drug reward (Wise and Rompre, 1989; Iremonger and Bains, 2009; Sesack and Grace, 2010). Direct actions of drugs of abuse within this neural circuit trigger molecular, physiological, and neurochemical events that produce reward and reinforce drug-seeking

behavior. Repeated drug use engages additional compensatory events that serve to oppose reward and, paradoxically, reinforce drug-seeking behavior. For example, the acute stress response originates with HPA axis activation, but direct and indirect connections with elements of the mesocorticolimbic system mediate affective components of stress (Van't Veer and Carlezon, 2013). We will focus on a restricted set of changes that occur in response to drugs of abuse and stress within the mesocorticolimbic system, as this system is known to play a role in addiction, as well as in regulation of mood states (Nestler and Carlezon, 2006; Russo and Nestler, 2013). We will discuss representative examples of excitatory transmitters, peptides, and intracellular factors, as it is impossible to be comprehensive in an article of this type. Our thesis is that the impact of repeated drug administration and stress on the brain and behavior produces similar alternating cycles (waveforms) of hedonic state such that robust aversive states emerge upon stimulus withdrawal. We will also provide evidence for and against a novel corollary – that is, these aversive states trigger similar opponent processes such that their cessation is followed by elevations in reward function.

The opponent process

Because external and internal stimuli are constantly changing, motivational states have a temporal dynamic. This concept is articulated in the opponent process theory, which posits that 'Hedonic states are automatically opposed by central nervous system mechanisms which reduce the intensity of hedonic feelings, both pleasant and aversive' (Solomon and Corbit, 1974). Opponent processes are conceptualized as defending hedonic equilibrium, and specific structures within the brain are responsible for regulating these processes. This model has been used as a framework to understand the transition from occasional drug use to addiction (Koob *et al*., 1989). In this context, the immediate rewarding effects of a drug of abuse (State 'A', the 'high') are followed by delayed aversive effects (State 'B', the 'crash') that are due to drug-dependent recruitment of opponent processes. However, this theory also applies to stimuli that are initially aversive, such as stress, fear, and anxiety (Solomon and Corbit, 1974). We will discuss evidence that the temporal dynamics of drug withdrawal and stress include negative states, but also that these states can in themselves represent aversive stimuli that trigger opponent processes leading to rebound increases in reward function (Fig. 1) and additional cycles of reverberation.

Dependent animals quickly learn that the simplest and most effective way to stop drug withdrawal-induced negative affective states is to administer the drug (Wikler and Pescor, 1967), which produces a rapid and robust elevation in reward, which is highly reinforcing (Hutcheson *et al*., 2001). Related to this, humans often learn that a relatively simple way to alleviate negative affective states due to stress or anxiety disorders is to self-medicate with drugs of abuse. A much more difficult approach for addicts – one that fails more often than not–would be to let withdrawal-induced negative affective states end naturally, which (as discussed below) would theoretically produce a slow and mild elevation in mood that may manifest as increased confidence in the ability to cope with the stress of abstinence. This approach is likely too gradual to be reinforcing *per se* and may include subtle reverberations that include periods of dysphoria, making a conscious decision to take this path challenging.

Similarities between drug withdrawal and stress

Acute versus repeated exposure

Both acute drug administration and stress elicit states of arousal and engage many of the same neural circuits (Koob, 2008; McEwen and Gianaros, 2011). Both activate the HPA axis, which consists of the paraventricular nucleus (PVN) of the hypothalamus, the anterior lobe of the pituitary gland, and the adrenal gland (Herman *et al*., 2005), resulting in release of stress hormones and peptides [e.g. corticotropin-releasing factor (CRF), corticosterone, glucocorticoids, endogenous opioids] (Sarnyai *et al*., 2001; Koob and Volkow, 2010). Release of these molecules has immediate and delayed effects on limbic circuit function, including activation of the mesocorticolimbic system (Thierry *et al*., 1976; Deutch *et al*., 1991; Marinelli and Piazza, 2002; Sheline, 2003; Pittenger and Duman, 2008). For example, corticosterone facilitates dopamine effects and potentiates drug reward (Piazza *et al*., 1993), and CRF injected into the VTA stimulates dopamine neurons (Kalivas *et al*., 1987). Rodents will self-administer glucocorticoids if the activity state of dopamine neurons is high (under conditions of novelty, during the active phase of their circadian cycle; Piazza *et al*., 1993). Stress also causes cross-sensitization to drugs of abuse (Kalivas and Stewart, 1991), providing a potential biological explanation for comorbidity of stress-related and addiction disorders (Sinha *et al*., 2006; Koob, 2008). The initial response to acute drug administration or stress is activation, which increases vigilance and goal-directed behavior. This state of arousal is protective in the short-term (Keay and Bandler, 2001) but disruptive with increasing intensity, duration, and frequency (Buydens-Branchey *et al*., 1990; Sapolsky, 1996; Miczek *et al*., 2008).

Repeated administration of drugs of abuse or stressors triggers allostasis – defined as the process of maintaining stability (i.e. homeostasis) through change – in neural circuits that control motivated behavior (Koob and Le Moal, 2008). One hypothesis is that, at a point that differs for each individual, chronic drug administration or stress ultimately leads to 'allostatic load' (McEwen and Gianaros, 2011), a pathological state in which homeostasis is no longer maintained. In this state, the brain and behavior are altered, perhaps irreparably.

Consequences of chronic exposure to drugs or stress

Withdrawal from most classes of abused drugs produces behavioral and emotional responses that are similar to those observed with chronic stress. Importantly, even low-intensity stressors can be perceived as highly aversive if they are unpredictable or uncontrollable (Adell *et al*., 1988; Foa *et al*., 1992). This is particularly relevant to addiction, where the knowledge that the drug will be attainable at a later time (after work, on the weekend) gives the user a sense of control that can allay the sense of panic and anxiety that, coupled with withdrawal signs, often comes with a lack of drug availability.

Drug withdrawal includes acute and protracted aversive states including anxiety, anhedonia, irritability, and depressed moods that resemble major depressive disorder (O'Brien *et al*., 1977; Wikler, 1980; Gawin, 1991; Barr *et al*., 2002; Koob and Le Moal, 2008). The neural mechanisms underlying acute versus protracted withdrawal signs are likely distinct but not mutually exclusive. For example, it is thought that drug-induced within-system adaptations

might produce aversive states during early withdrawal, whereas between-system adaptations might emerge over time and contribute to protracted aversive states (Koob and Volkow, 2010). In clinical studies, most people report negative emotional states just before relapse, with anxiety and depression being the most common (Brownell *et al*., 1986; Markou and Koob, 1991; Sarnyai *et al*., 2001; Kenny and Markou, 2005; Iremonger and Bains, 2009). Repeated, prolonged, or severe stressors often precede the development of anxiety disorders, depression, and substance abuse (Kessler, 1997; Pine and Charney, 2002; Kendler *et al*., 2003; Volkow and Li, 2004; Fox *et al*., 2007). Conversely, substance abuse can also precede or exacerbate mood disorders (Kessler, 1997). Depression is characterized by anhedonia and lack of energy, whereas excessive worrying and problems concentrating are hallmark symptoms of anxiety. Many of these same negative affective states can be recapitulated in animal models that utilize chronic stress, allowing researchers to identify their underlying substrates. There are behavioral tests that quantify hedonic state, concentration, avoidance, and escape, all of which enable quantification of depressive-like and anxiety-like behaviors. Discrete stressors such as foot-shock, maternal deprivation, and restraint induce depressive-like behaviors including increased immobility in the forced swim test (Platt and Stone, 1982; Aisa *et al*., 2008), as well as elevations in brain reward thresholds (Zacharko and Anisman, 1991), which indicate anhedonia. Stress-related states can disrupt performance in the five-choice serial reaction time task, a procedure that quantifies attention in rodents (Van't Veer *et al*., 2013). Repeated stressors such as chronic social defeat stress – an ethologically relevant stressor involving daily exposure to an aggressor – produce anhedonia (Berton *et al*., 2006; Golden *et al*., 2011; Donahue *et al*., 2014) and anxiogenic-like responses in subordinate mice in tests such as the elevated plus maze (Keeney and Hogg, 1999; Slattery *et al*., 2012), as well as decreases in social interaction with conspecifics (Avgustinovich *et al*., 2005; Berton *et al*., 2006). Although some behavioral signs of chronic social defeat stress become evident after the first exposure, they require several exposures to reach their full intensity and persist after the stress is terminated (Donahue *et al*., 2014), suggesting an allostatic shift in set point.

A hallmark of addiction to psychostimulants and opioids is that tolerance can develop to acute drug-induced euphoria, which is thought to be due to the strengthening of within-system and between-system opponent processes (Nestler, 2004; Koob and Le Moal, 2008). A parallel increase in the magnitude of drug offset-induced dysphoria drives negative reinforcement processes (Koob, 2008; Koob and Le Moal, 2008). If drug withdrawal and stress are similar, then tolerance should develop to the activating effects of acute stressors concomitant with an increased emergence of negative affective states upon repeated exposure to stressors. However, as the type and the timing of stressors can vary markedly, the pattern of stress-driven oscillations in affective states is not as clear-cut as with drugs of abuse. For example, habituation to the activating effects of repeated yet varied stressors may not occur, whereas tolerance typically develops to repeated and identical stressors (McEwen and Gianaros, 2011). This observation has led to the development of chronic unpredictable stress procedures (Hill *et al*., 2012). Traumatic or chronic uncontrollable stress that blunts the HPA axis through negative feedback can lead to depressive-like behaviors in which stressors normally coded as arousing lose their motivational properties. This occurs in part through a decrease in PfC function and an increase in extended amygdalar function

[basolateral amygdala and bed nucleus of the stria terminalis (BNST)], which engenders low cognitive and behavioral control (Sinha, 2008).

In contrast to the weakening of arousal/reward and strengthening of negative affect, drugs of abuse and stressors can also produce sensitization, as reflected by amplification of their stimulant and reward-related effects (Carlezon and Nestler, 2002). A discussion of drug and stress sensitization is outside the scope of this review, but it is important to emphasize that repeated exposure to a stressor often elicits sensitization of stress-induced behaviors and may promote the transition from active to passive coping strategies (Keay and Bandler, 2001) by triggering dysphoria and anhedonia, and by the induction of active or passive coping strategies that may terminate the stress or blunt the impact of an inescapable stressor (Keay and Bandler, 2001).

Neural mechanisms common to drug withdrawal and stress

The mesocorticolimbic system has long been associated with reward states (Wise and Bozarth, 1987). However, accumulating evidence implicates these structures in both positive and negative affective states (Roitman *et al.*, 2005; Carlezon and Thomas, 2009; McCutcheon *et al.*, 2012; Volman *et al.*, 2013). Aversive stimuli increase dopamine neuron population activity (Valenti *et al.*, 2011) and dopamine release (Thierry *et al.*, 1976; Abercrombie *et al.*, 1989; Imperato *et al.*, 1993; Piazza and Le Moal, 1998; Pascucci *et al.*, 2007), which may promote or antagonize stress effects on behavior. Interestingly, aversive stimuli can also suppress dopamine release in the NAc (Maisonneuve *et al.*, 1995; Ebner *et al.*, 2010; McCutcheon *et al.*, 2012). The fact that dopaminergic neurons originating in the VTA project not only to the NAc and PfC, but also to the hippocampus, amygdala, and BNST (Swanson, 1982), which play important roles in fear, anxiety, reward, and stress, supports the concept that the mesocorticolimbic system integrates and processes salient stimuli (Salamone, 1994; Pezze and Feldon, 2004; Carlezon and Thomas, 2009). Here, we describe a small set of molecular adaptations that play particularly important roles in both drug withdrawal and stress, based primarily upon our own work.

Role of glutamate systems

Overview

Glutamatergic afferents to the NAc come from brain regions known to be important for processing both positive and negative emotional stimuli, such as the basolateral amygdala (Kelley *et al.*, 1982), and for goal-directed behavior, including the orbitofrontal cortex, insula, and cingulate cortex (Berendse *et al.*, 1992). In addition, the NAc receives innervation from the ventral subiculum of the hippocampus (Kelley and Domesick, 1982; Groenewegen *et al.*, 1987), which likely provides spatial and contextual information about the stimuli [for review of NAc afferents, see Brog *et al.* (1993); Sesack and Grace (2010)].

Drug withdrawal

Available data suggest that psychostimulant and opioid withdrawal have opposite effects on glutamatergic transmission in the NAc. Withdrawal from chronic cocaine is associated with suppression of presynaptic and postsynaptic glutamate transmission (Kalivas, 2004),

whereas opiate withdrawal is associated with increased levels of extracellular glutamate in the NAc (Aghajanian *et al*., 1994; Desole *et al*., 1996; Sepulveda *et al*., 1998, 2004; Kalivas, 2004). Repeated cocaine use causes reductions in basal glutamate transmission in the NAc (Pierce *et al*., 1996; Bell *et al*., 2000; Hotsenpiller *et al*., 2001) and decreased responsiveness to ionotropic and group I metabotropic glutamate receptor (mGluR) stimulation (Swanson *et al*., 2001; Thomas *et al*., 2001). This is related, at least in part, to the reduced activity of the cystine–glutamate exchanger: restoration of this process normalizes extracellular glutamate levels (Baker *et al*., 2003), raising the possibility that medications targeting this process may be therapeutic. However, a cocaine injection (contingent or noncontingent) or a cue associated with repeated cocaine causes an increase in glutamate release (Pierce *et al*., 1996; Bell *et al*., 2000; Hotsenpiller *et al*., 2001; Miguens *et al*., 2008). One hypothesis is that the reduced baseline levels of gluta-mate after chronic cocaine may accentuate synaptic transmission within PfC–NAc connections following cocaine challenge (Boudreau and Wolf, 2005; Boudreau *et al*., 2007; Kourrich *et al*., 2007; Iremonger and Bains, 2009). Consistent with this, virus-mediated gene transfer experiments demonstrate that elevated expression of GluR2 in the NAc enhances cocaine reward (Kelz *et al*., 1999). It has been proposed that this PfC–NAc synaptic enhancement is necessary for reinstatement of operant responding on levers previously paired with cocaine or heroin delivery (McFarland *et al*., 2003; LaLumiere and Kalivas, 2008).

In the VTA, glutamatergic transmission is enhanced for a short time period (~24 h) after chronic cocaine administration (Pierce *et al*., 1996; Reid *et al*., 1997; Kalivas and Duffy, 1998), but it returns to baseline levels by 3 weeks after cessation of cocaine (White *et al*., 1995; Zhang *et al*., 1997; Churchill *et al*., 1999; Ungless *et al*., 2001). This is partly because of alterations in the expression of AMPA and NMDA receptor subunits (Fitzgerald *et al*., 1996; Carlezon *et al*., 1997; Churchill *et al*., 1999; Loftis and Janowsky, 2000; Lu *et al*., 2002; Lane *et al*., 2008; Choi *et al*., 2011).

The acute effect of opioids occurs through activation of μ-opioid receptors (MORs), which are inhibitory Gαi-coupled G-protein-coupled receptors (Giacchino and Henriksen, 1996; Williams *et al*., 2001). MOR activation suppresses basal and evoked increases in extracellular glutamate in the NAc and dorsal striatum (Desole *et al*., 1996; Enrico *et al*., 1998; Sepulveda *et al*., 2004). Spontaneous or naloxone-precipitated withdrawal from chronic opioids leads to increases in neuronal activity and transmitter release due to the removal of inhibitory MORs (Williams *et al*., 2001). Glutamate release has also been shown to increase, and numerous studies have shown that systemic or intracerebroventricular administration of NMDA or AMPA receptor antagonists reduces morphine tolerance and withdrawal signs (Trujillo and Akil, 1991; Tokuyama *et al*., 1996; Gonzalez *et al*., 1997).

Extracellular glutamate levels are significantly increased in the NAc during morphine withdrawal (Aghajanian *et al*., 1994; Desole *et al*., 1996; Sepulveda *et al*., 1998, 2004), although excitatory synaptic transmission is not necessarily increased (Kalivas, 2009). It has been shown that presynaptic mGluR2/3 inhibitory autoreceptor function is increased during morphine withdrawal, and mGluR2/3 receptor agonists attenuate behavioral signs of morphine withdrawal (Robbe *et al*., 2002) and context-induced reinstatement of operant responding on levers previously paired with heroin self-administration (Bossert *et al*., 2006),

raising the possibility that despite increases in glutamate levels, synaptic transmission may decrease. Regardless, we have demonstrated that intra-NAc microinjections of the selective AMPA receptor antagonist NBQX into morphine-dependent rats block withdrawal-induced conditioned place aversions (Sawyer *et al.*, 2009), suggesting that activation of AMPA receptors in the NAc is necessary for withdrawal-induced negative affective states.

In the VTA, the immediate effect of opioid withdrawal is loss of MOR-mediated inhibition of glutamatergic and GABAergic afferents to dopamine neurons and an increase in glutamate and γ-aminobutyric acid (GABA) release. Subsequently, glutamate and GABA engage the more slowly acting metabotropic mGluR2/3 and GABA$_B$ receptors on glutamatergic terminals, resulting in decreased glutamatergic synaptic transmission (Manzoni and Williams, 1999). These effects lead to a strong suppression of dopamine activity (Diana *et al.*, 1995).

These findings suggest that psychostimulant withdrawal is associated with decreased, and opioid withdrawal with increased, glutamatergic transmission in the NAc. In the VTA, psychostimulant withdrawal is associated with increased levels and availability of ionotropic glutamate receptors, whereas opioid withdrawal triggers inhibition of glutamate release. We acknowledge that this highly simplified summary does not fully address the complexities of glutamatergic transmission (Kalivas *et al.*, 2009; Chartoff and Connery, 2014) and reflects a major gap in our understanding of the neural mechanisms of aversion. It has been proposed that aversive states are associated with activation, whereas rewarding states are associated with inhibition of NAc medium spiny neurons (Carlezon and Thomas, 2009); the development of increasingly sophisticated methods to control these systems will provide important new insights.

Stress

Similar to findings with opioid withdrawal, stress (restraint, forced swimming) increases extracellular glutamate levels in the NAc, as well as in the PfC and hippocampus (Moghaddam, 1993). Similar to findings with psychostimulant withdrawal, stress enhances synaptic strength in the NAc shell. Cold water stress causes an increase in AMPA/NMDA ratios in medium spiny neurons of the NAc shell that is glucocorticoid receptor-dependent (Campioni *et al.*, 2009), and exogenous treatment with corticosterone is sufficient to enhance PfC-NAc synaptic strength. Further similarities to drug withdrawal include stress-induced increases in the number and function of GluR2-containing AMPA receptors in the NAc (Campioni *et al.*, 2009). Both stress and drug withdrawal can evoke reinstatement of responding at a lever previously paired with drug administration (often interpreted as drug 'seeking') in animals that have undergone extinction training (Shaham *et al.*, 2003). Further, intra-NAc infusions of AMPA can induce reinstatement (Suto *et al.*, 2004). Taken together, synaptic plasticity of glutamatergic transmission in the NAc may be a common mechanism by which stress and withdrawal influence behavior.

As with psychostimulants and opioids, chronic restraint stress and repeated social defeat stress both increase the spontaneous and burst firing of VTA dopamine neurons (Anstrom and Woodward, 2005; Cao *et al.*, 2010). For stress, this is thought to be due to CRF-dependent increases in glutamatergic VTA afferents. Stressors elevate CRF in the BNST

(Erb and Stewart, 1999; Erb *et al*., 2001; Jasnow *et al*., 2004), a brain region that has been implicated in anxiety states (Hammack *et al*., 2004) and in drug withdrawal-induced negative affective states (Koob, 2008), and that sends glutamatergic projections to brain regions including the VTA (Rodaros *et al*., 2007). Footshock enhances BNST–VTA neuronal activity, and selective optogenetic stimulation of BNST–VTA gluta-matergic fibers produces aversion and anxiety-like behavior (Jennings *et al*., 2013). Through the actions of CRF, stress sensitizes VTA dopamine neurons to glutamatergic inputs through a postsynaptic mechanism that involves increasing the AMPA/NMDA ratio (Ungless *et al*., 2001, 2003; Saal *et al*., 2003). One mechanism for increased synaptic strength could be that stress, in common with drugs of abuse, increases GluR1 (AMPA) and NR1 (NMDA) receptor subunits in the VTA (Fitzgerald *et al*., 1996).

The idea that drugs of abuse and stress strengthen synaptic connections through enhanced glutamatergic transmission and potentiated dopamine neuron activity is consistent with observations that stress can enhance drug-taking and drug-seeking behaviors. However, it does not fit well with the idea that stress and drug withdrawal are aversive states that produce depressive-like and anxiety-like behaviors. Withdrawal from chronic regimens of psychostimulants and opioids – specifically, those expected to produce tolerance rather than sensitization (Carlezon and Nestler, 2002) – suppresses dopamine neuron activity, although this does not preclude the existence of strengthened glutamate–dopamine neuron synapses. The effects of chronic stress on dopamine neuron activity are not as well studied, but evidence suggests that, under some circumstances, mesocortico-limbic dopamine activity is increased (Miczek *et al*., 2008). Social defeat experiments in which an intruder rat is threatened by an aggressor reveal increases in extracellular dopamine in the NAc and PfC (Tidey and Miczek, 1996). Repeated social defeat also potentiates amphetamine-induced dopamine release in the NAc (Miczek *et al*., 1999), likely due to stress-induced increases in cortical–VTA glutamatergic transmission (Miczek *et al*., 2008). How stress-induced elevations in dopamine can be reconciled with negative affective states remains a gap in knowledge.

Implications

There have been considerable efforts to utilize drugs that alter glutamate function as treatments for addiction (Chartoff and Connery, 2014). Drugs that act at NMDA receptors (memantine) and the glutamate–cystine anti-porter (*N*-acetylcysteine) have generated significant enthusiasm (Bridges *et al*., 2012; Tomek *et al*., 2013). One concern with these types of treatments is that glutamate and its receptor targets are ubiquitous in the brain and that actions that are beneficial in one region may have disruptive effects in another, making the treatments unpleasant or debilitating.

Role of corticotropin-releasing factor

Overview

CRF is the principal regulator of the stress response (Vale *et al*., 1981). It is produced by cells in the PVN of the hypothalamus and triggers hormonal stress responses by activating the HPA axis (Herman *et al*., 2005). CRF and its two receptor subtypes, CRFR1 and

CRFR2, have widespread and overlapping expression in the cortex, extended amygdala (including the NAc), medial septum, hypothalamus, thalamus, cerebellum, and midbrain and hindbrain nuclei (Swanson and Sawchenko, 1983; Lemos *et al*., 2012).

There is increasing evidence that CRF acts within the mesocorticolimbic system to influence motivated behavior. CRF-immunoreactive fibers and CRF receptors are found in the VTA (Swanson and Sawchenko, 1983; Van Pett *et al*., 2000) and NAc (Lemos *et al*., 2012). CRF is released in response to stressors in an activity-dependent manner, and its effect on neurotransmission is dependent on the type of stress and prior history of stress exposure (Lemos *et al*., 2012). Moderate stressors that activate both the HPA axis and the extrahypothalamic circuits are arousing and can facilitate goal-directed behavior. For example, footshock increases CRF release in the VTA, which then selectively facilitates glutamate release in rats that are drug-experienced (Wang *et al*., 2005). Traumatic or chronic uncontrollable stress that blunts the HPA axis through negative feedback can lead to depressive-like behaviors in which stressors normally coded as arousing lose their motivational properties. For example, intracerebroventricular infusion of relatively high CRF doses produces conditioned place aversions (Cador *et al*., 1992) and disrupts cognition (Van't Veer *et al*., 2013).

Drug withdrawal

Acute administration of most drugs of abuse activates the HPA axis to elicit corticosterone secretion, as well as stimulates extrahypothalamic systems to release CRF (Piazza and Le Moal, 1997; Kash *et al*., 2008). Corticosterone and CRF can potentiate dopamine release in terminal fields and dopamine neuron excitability (Piazza *et al*., 1993; Piazza and Le Moal, 1997; Marinelli and Piazza, 2002; Kash *et al*., 2008). Acute withdrawal (following single-drug treatment) from drugs of abuse also results in activation of the HPA stress response. Although it may seem contradictory that acute drug effects (typically associated with euphoria) can have the same molecular consequences as acute drug withdrawal (typically associated with dysphoria), it is important to remember that people often report that initial drug use has aversive aspects. For example, psychostimulants can elicit anxiety, panic, and overwhelming autonomic symptoms (Yamamoto *et al*., 2007), whereas opioids can produce nausea and sluggishness (Coluzzi *et al*., 2012). For only a small percentage of users are the euphoric effects strong enough to drive continued drug use into dependence and addiction. Similarly, acute stressors are not exhilarating and euphorogenic for everyone.

In contrast, the HPA response is blunted during withdrawal from chronic drug administration due to negative feedback mechanisms (Basso *et al*., 1999), whereas the extrahypothalamic CRF stress system response is sensitized (Koob, 2008). Extracellular CRF is increased in the extended amygdala during drug withdrawal (Merlo Pich *et al*., 1995; Richter and Weiss, 1999; Weiss *et al*., 2001). Further, CRFR1 receptor antagonists block withdrawal-induced negative affective states, including anxiogenic effects in the elevated plus maze and defensive burying test, anhedonia in the intracranial self-stimulation (ICSS) test, and naloxone-precipitated conditioned place aversions in morphine-dependent rats (Basso *et al*., 1999; Knapp *et al*., 2004; Overstreet *et al*., 2004; Smith and Aston-Jones, 2008). Given that the actions of CRF in the VTA are excitatory and most likely contribute to

arousal and the reinforcing aspects of stress, drug withdrawal-induced CRF release in the amygdala and BNST may play a more important role in negative affective states.

Stress

Similar to the effects of acute drug administration, stressors activate the HPA axis and increase CRF expression in the extended amygdala (Merlo Pich *et al.*, 1995; Koob, 1999). Extrahypothalamic CRF released from the central amygdala and BNST is part of a feedforward system that activates an animal to mobilize the body for appropriate (e.g. 'fight or flight') behavioral responses. In the NAc of naive mice, CRF released in response to an acute, moderate stressor acts to increase dopamine release through coactivation of CRFR1 and CRFR2, providing a putative mechanism for stress-induced enhancement of drug effects. It has been recently reported that CRF acting through CRFR1 and protein kinase C enhances hyperpolarization-activated *(Ih)* currents to increase the firing rate of dopamine neurons (Wanat *et al.*, 2008). Prolonged acute (10–20 min) exposure to CRF also activates CRFR2 to increase glutamate-dependent transmission in dopamine neurons (Ungless *et al.*, 2003). However, severe stress exposure abolishes this stimulatory effect on dopamine release in the NAc, an effect that lasts up to 90 days (Lemos *et al.*, 2012). Loss of the capacity of CRF to facilitate dopamine release in the NAc is consistent with stress-induced depressive-like states, and is accompanied by a switch in the emotional response to CRF from appetitive to aversive (Lemos *et al.*, 2012).

As with drug withdrawal, chronic activation of the extrahypothalamic CRF system can trigger pathological states (Koob, 1999; Lemos *et al.*, 2012). When animals are exposed to chronic, unpredictable, or more severe stressors, the effects of CRF on behavior change; for example, a dose of CRF that produces robust behavioral activation in the home cage produces behavioral suppression in a novel (i.e. stressful) environment (Sutton *et al.*, 1982; Takahashi *et al.*, 1989). Exogenously administered CRF has dose-dependent anxiogenic and fearful effects in the elevated plus maze (Baldwin *et al.*, 1991), as well as the acoustic startle (Swerdlow *et al.*, 1989), conditioned fear (Cole and Koob, 1988), and stress-induced freezing (Sherman and Kalin, 1988) tests. Finally, high doses of CRF can produce both taste and place aversions (Heinrichs *et al.*, 1991; Cador *et al.*, 1992).

Implications

Drug withdrawal and stress have many of the same effects on CRF. These observations have led to interest in the development of CRF antagonists to treat addiction. Thus far, the development of CRF receptor antagonists as therapeutics has been hindered by the high lipophilicity of initial drugs, although novel compounds are of continued interest (Zorrilla and Koob, 2010). More research on how CRF receptor activation affects other systems downstream may provide additional targets for new treatments.

Role of cyclic AMP response element binding protein

Overview

Cyclic AMP response element binding protein (CREB) is a transcriptional regulator expressed in the nucleus of all cells in the brain. It is constitutively expressed and bound to

the promoter regions of genes that contain cAMP response elements. CREB becomes transcriptionally active when the Ser[133] residue is phosphorylated in response to various stimuli, including adenylate cyclase-mediated increases in cAMP (Lonze and Ginty, 2002). As such, CREB is critical for coupling the transmission of events that occur at cell membranes into alterations in gene expression. Some examples of CREB-regulated gene-products that have been implicated in mood regulation include CRF (Itoi *et al*., 1996), BDNF (Finkbeiner *et al*., 1997), dynorphin (Cole *et al*., 1995), and the GluR1 AMPA receptor subunit (Borges and Dingledine, 2001). Interestingly, alterations in the expression of these target genes and the proteins they encode can, in turn, cause changes in neural activity that would be expected to further elevate CREB activity, a notable exception being the actions of dynorphin at κ-opioid receptors (KORs). There are numerous comprehensive reviews that describe the molecular mechanisms involved in CREB-mediated gene transcription (Abel and Kandel, 1998; West *et al*., 2001; Carlezon *et al*., 2005).

Drug withdrawal

Evidence suggests that CREB within the mesocorticolimbic system regulates drug reward-induced and drug withdrawal-induced aversive states. The rewarding effects of a single exposure to psychostimulants or opioids are associated with decreased P-CREB levels in the striatum, including the NAc (Turgeon *et al*., 1997; Tenayuca and Nazarian, 2012). In contrast, chronic morphine causes a compensatory increase in adenylate cyclase activity in MOR-expressing cells (Sharma *et al*., 1975a,b; Van Vliet *et al*., 1990). When morphine is discontinued, or withdrawal is precipitated with naloxone, cAMP levels markedly increase (Nestler and Aghajanian, 1997), which leads to intracellular adaptations including activation of cAMP-dependent protein kinase (PKA) and phosphorylation of CREB at Ser[133] (Chartoff *et al*., 2003, 2006). Correlations between the timing of upregulated activity within cAMP pathways and signs of withdrawal support the idea that CREB contributes to aversive or dysphoric states associated with drug withdrawal.

Accumulating evidence indicates that CREB activation is part of a process that opposes the actions of drugs of abuse (Carlezon *et al*., 2005). Stimulation of PKA and virus-mediated elevation of CREB in the NAc both decrease cocaine reward, whereas antagonism of PKA and overexpression of a dominant-negative form of CREB in the NAc increase cocaine and morphine reward (Carlezon *et al*., 1998; Self *et al*., 1998; Pliakas *et al*., 2001; Barrot *et al*., 2002). Elevated expression of CREB in the NAc is associated with increased depressive-like behaviors, which may be qualitatively similar to depressive-like behaviors and dysphoria observed during drug withdrawal (Pliakas *et al*., 2001; Muschamp *et al*., 2011). For example, opioid withdrawal triggers PKA-dependent phosphorylation of CREB *in vivo* and in dissociated striatal neurons, suggesting that CREB activation results from direct morphine action in the NAc and striatum (Chartoff *et al*., 2003, 2006; Edwards *et al*., 2009). Further, mice with a targeted disruption of CREB α and iso-forms (CREBα) show reductions in signs of precipitated withdrawal after chronic morphine administration (Maldonado *et al*., 1996; Walters and Blendy, 2001). Together, these findings suggest that CREB activation in the NAc may reduce acute drug reward and lead to aversive or depressive-like motivational states that accompany drug withdrawal.

CREB activation in the VTA also regulates drug-induced affective states. The VTA has a distinct rostral to caudal neurochemical and functional topography; increased CREB function in rostral portions of the VTA increases the rewarding effects of cocaine and morphine, whereas similar changes in more caudal regions have opposite effects (Olson *et al*., 2005). Irrespective of rostral–caudal placement, intra-VTA injection of a dopamine D1 receptor agonist, which activates CREB, blocks morphine withdrawal-induced conditioned place aversions (Chartoff *et al*., 2009a), consistent with the idea that elevated CREB in the VTA increases reward-like states under some conditions.

A persistent gap in knowledge, however, is related to understanding the effect that NAc CREB-mediated aversive states has on drug-seeking and drug-taking behaviors. The negative reinforcement hypothesis would predict that CREB contributes to maintenance of drug-taking behavior and relapse because negative affective states motivate these behaviors. This view is supported by a study demonstrating that CREB over-expression in the NAc potentiates the rewarding and reinforcing aspects of cocaine self-administration (Larson *et al*., 2011). In contrast, a separate study showed that chronic cocaine self-administration upregulates a microRNA (miR-212) in striatal regions that enhances CREB activity, and yet prevents the escalation of cocaine self-administration when rats are allowed extended access to cocaine (Hollander *et al*., 2010). Even a third outcome was described by Green *et al*. (2010): rats raised in an enriched environment have reduced levels of P-CREB in the NAc and show an enhanced sensitivity to cocaine-induced conditioned place preferences, consistent with early virus-mediated gene transfer studies (Carlezon *et al*., 1998); however, reduced CREB activation in environmentally enriched rats is also associated with a downward and rightward shift in the cocaine self-administration dose–effect curve (Green *et al*., 2010), suggesting a decrease in the reinforcing efficacy of cocaine. There are sufficient methodological differences among these studies to account for the seemingly incongruous results, including the timing of the experiments; regardless, the ways in which NAc CREB contributes to drug dependence and addiction are not fully understood and may require resolution of CREB activation at a cellular level (i.e. discriminating CREB activation in either dopamine D1 or dopamine D2 receptor-expressing medium spiny neurons in the NAc).

Stress

The effects of stress on CREB have been most thoroughly studied in the NAc. Swim stress increases CREB activity in the NAc (Pliakas *et al*., 2001) and decreases the latency to immobility when rats are exposed to a second day of swim stress (Porsolt *et al*., 1977). Mimicking these changes by virus-mediated gene transfer of CREB in rats not previously exposed to forced swimming decreases the latency to immobility compared with that in rats treated with a control virus. In contrast, disruption of CREB function produces the opposite effect – that is, increased latency to immobility (Pliakas *et al*., 2001; Barrot *et al*., 2002) – which resembles the effects of standard anti-depressants in this assay. Footshock produces similar effects on CREB, and rats with viral vector-induced elevations in CREB show resistance to the extinction of fear conditioning (Muschamp *et al*., 2011), a hallmark of post-traumatic stress disorder in humans (Parsons and Ressler, 2013). Collectively, these data indicate that stress-induced elevations in CREB function within the NAc produce

depressive-like signs, suggesting that stimulus-induced elevations in this region represent an allostatic adaptation that opposes the reinforcing effects of drugs and other types of rewards (Carlezon *et al.*, 2005). Elevations in CREB function within the amygdala, a brain region often associated with aversive states, also potentiate fear responses in rats (Josselyn *et al.*, 2001), whereas elevations in CREB function in the hippocampus are associated with beneficial effects of anti-depressants (Chen *et al.*, 2001).

Implications

CREB regulates many genes that can contribute to addiction and stress-like states. CREB itself is unlikely to be a feasible target for therapeutic intervention because broad and unselective activation or inhibition of CREB throughout the brain would be expected to produce a mixture of beneficial and detrimental effects (Carlezon *et al.*, 2005). However, interest remains in the development of medications that can affect systems that are regulated by CREB but have more limited brain distribution. Below, we focus on dynorphin and brain KOR systems, as efforts to develop medications that alter signaling through this system have advanced to clinical trials (see Carroll and Carlezon, 2013). However, it is important to note that BDNF systems have been implicated in addiction (Graham *et al.*, 2007; Vassoler and Sadri-Vakili, 2014) and stress (Berton *et al.*, 2006; Duman and Monteggia, 2006) despite the challenges associated with the current lack of pharmacological agents available to study BDNF, making it necessary to work with the peptide itself or peptide-blocking antibodies.

Role of dynorphin and κ-opioid receptor systems

Overview

The endogenous opioid dynorphin is cleaved from the precursor protein preprodynorphin and predominantly activates KORs (Chavkin *et al.*, 1982), which are Gαi-coupled (Law *et al.*, 2000). Dynorphin and KORs are expressed throughout limbic brain areas implicated in the pathophysiology of stress and drug addiction in humans and rodents (Fallon and Leslie, 1986; Mansour *et al.*, 1995; Sukhov *et al.*, 1995; Hurd, 1996; Peckys and Landwehrmeyer, 1999; Shuster *et al.*, 2000; Alheid, 2003; Nestler and Carlezon, 2006; Koob and Le Moal, 2008). Within the NAc, dynorphin is expressed in medium spiny neurons and KORs are expressed on dopaminergic nerve terminals, as well as on nerve terminals that contain either GABA or glutamate, where they act to inhibit transmitter release (Fallon *et al.*, 1985; Simmons and Chavkin, 1996; Rusin *et al.*, 1997; Svingos *et al.*, 1999; Meshul and McGinty, 2000; Hjelmstad and Fields, 2003; Margolis *et al.*, 2006). There is also evidence for postsynaptic colocalization of KORs and dynorphin on dendritic spines in the NAc (Arvidsson *et al.*, 1995; Svingos *et al.*, 1999), although evidence for functional effects of these postsynaptic receptors is lacking. Dynorphin is released from dense core vesicles upon high levels of sustained neuronal activity (Weisskopf *et al.*, 1993; Simmons *et al.*, 1997); new evidence indicates that dynorphin is copackaged in vesicles with orexin, a peptide with opposing effects (Muschamp *et al.*, 2014). Activity-dependent dynorphin release, especially from dendritic sites, can then serve as an effective mechanism by which neurons regulate their own activity (Drake *et al.*, 1994; Brown and Bourque, 2004; Ludwig and Leng, 2006; Kreibich *et al.*, 2008; Iremonger and Bains, 2009). Within the VTA, KORs are expressed on both the cell bodies and the terminals of dopamine neurons (Svingos *et al.*, 1999, 2001),

resulting in inhibition of dopamine release in areas that receive VTA input (e.g. NAc and PfC; Margolis *et al*., 2003; Margolis *et al*., 2006; Ford *et al*., 2007).

Drug withdrawal

Chronic exposure to drugs of abuse increases the activity of the KOR system within mesocorticolimbic circuits (Hurd and Herkenham, 1993; Spangler *et al*., 1993; Mathieu-Kia and Besson, 1998; Shippenberg *et al*., 2007; Zhou *et al*., 2008; Piras *et al*., 2010). In general, KOR activation produces aversive states that, at least in laboratory animals, have characteristics of both withdrawal and stress (Bals-Kubik *et al*., 1993; Newton *et al*., 2002; McLaughlin *et al*., 2003, 2006a; Bruchas *et al*., 2010; Knoll and Carlezon, 2010; Muschamp *et al*., 2011). Further, KOR activation is crucial in facilitating stress-induced reinstatement of operant responding in animals with substantial self-administration experience that have undergone extinction of operant responding for drug (Beardsley *et al*., 2005; Land *et al*., 2009; Bruchas *et al*., 2010; Sun *et al*., 2010; Schank *et al*., 2012; Graziane *et al*., 2013; Grella *et al*., 2014; Sedki *et al*., 2014) or reinstatement of drug-induced conditioned place preference (Carey *et al*., 2007; Redila and Chavkin, 2008; Cordery *et al*., 2012; Al-Hasani *et al*., 2013; Jackson *et al*., 2013; Aldrich *et al*., 2014). An implicit assumption in these studies is that stress-induced dynorphin release produces negative affective states that drive reinstatement (Koob, 2008). However, this has not been empirically determined because there are as yet no published studies that directly demonstrate that KOR blockade inhibits both drug withdrawal-induced negative affective states and reinstatement of drug seeking in the same animal. Further, it has been shown that KOR agonists actually decrease, and the KOR antagonist JDTic potentiates, cocaine-primed reinstatement of operant responding on a lever previously paired with cocaine delivery in animals that have undergone extinction training (Beardsley *et al*., 2005; Morani *et al*., 2009; Ruedi-Bettschen *et al*., 2010). These findings suggest that endogenous dynorphin decreases the effects of the cocaine prime such that it is a weaker stimulus for reinstatement.

The reinstatement paradigm, which is thought to model craving and relapse, does not specifically address how dynorphin or KORs affect the strength of withdrawal-induced stress-like states. We recently demonstrated that intracerebroventricular administration of the long-lasting KOR antagonist norBNI before initiation of an experimenter-administered binge cocaine regimen [three intraperitoneal injections of 15 mg/kg cocaine per day for 14 days, as described by Spangler *et al*. (1993)] blocks the development and expression of cocaine withdrawal-induced anhedonia, as measured using the ICSS test (Chartoff *et al*., 2012). Similarly, the KOR antagonists JDTic and norBNI attenuate the expression of nicotine withdrawal signs (Jackson *et al*., 2010). Both somatic withdrawal signs and hyperalgesia, as well as anxiety-related behavior and conditioned place aversion, were blocked. In contrast, several studies have shown that KOR antagonism can potentiate aversive states associated with morphine withdrawal: norBNI increased naloxone-induced conditioned place aversions and somatic withdrawal signs in morphine-dependent rats (Maldonado *et al*., 1992; Spanagel *et al*., 1994). Together, these findings raise the possibility that the role of dynorphin in drug withdrawal depends on the drug of abuse.

Stress

Just as swim stress elevates CREB function within the NAc, it also elevates prodynorphin expression (Chartoff *et al*., 2009b). Levels of footshock that produce fear conditioning elevate prodynorphin within the amygdala, and these increases are correlated with expression of fear (Knoll *et al*., 2011). Systemic administration of KOR agonists produces dysphoria in humans (Pfeiffer *et al*., 1986) and has aversive and stress-like effects in rodents in a variety of tests (Mague *et al*., 2003; McLaughlin *et al*., 2003, 2006b; Todtenkopf *et al*., 2004; Land *et al*., 2008; Bruchas *et al*., 2010). These effects are blocked by KOR antagonists and disrupted in mutant mice in which dynorphin or KORs are ablated (Mague *et al*., 2003; McLaughlin *et al*., 2003; Todtenkopf *et al*., 2004; Land *et al*., 2008; Van't Veer *et al*., 2013). Activation of KORs in the NAc is sufficient to produce many of these aversive effects, although roles for other regions including VTA, PfC, amygdala, hippocampus, and raphe nucleus have been described (Bals-Kubik *et al*., 1989; Shirayama *et al*., 2004; Bruchas *et al*., 2011; Knoll *et al*., 2011; Muschamp *et al*., 2011). Administered on their own, KOR antagonists have combined antidepressant (Pliakas *et al*., 2001; Newton *et al*., 2002; Mague *et al*., 2003) and anxiolytic (Knoll *et al*., 2007) effects in rodents and block the acute and chronic effects of stressful stimuli (Beardsley *et al*., 2005; Knoll *et al*., 2007). Interestingly, KOR antagonists prevent the cognition-disrupting effects of CRF itself (Van't Veer *et al*., 2012), consistent with other reports that the dysphoric effects of CRF involve KORs (Land *et al*., 2008). In the context of addiction, KOR antagonists block reinstatement of 'cocaine-seeking' behavior triggered by stress, but not by cocaine itself (Beardsley *et al*., 2005). Accumulating evidence suggests that KOR antagonists are most effective when administered before a stressor (Van't Veer and Carlezon, 2013). To the extent that cocaine withdrawal can be considered a stressor, this concept is exemplified in studies examining the effects of cocaine withdrawal on ICSS. As described above, pretreatment with a KOR antagonist before a 'binge' regimen of cocaine attenuated the development of withdrawal-induced anhedonia, but administration after withdrawal effects had become detectable was ineffective (Chartoff *et al*., 2012). A similar prophylactic effect has been reported in rats self-administering heroin in long-access sessions, where pretreatment with KOR antagonists prevents escalation of drug intake that normally develops over time (Schlosburg *et al*., 2013). One interpretation of these data is that stress triggers a cascade of neuroadaptations that recruit other systems that are insensitive to alterations in KOR function.

Implications

There is considerable enthusiasm for the development of KOR antagonists for the treatment conditions ranging from addiction to depression and anxiety (Carroll and Carlezon, 2013). The broad ability to reduce the impact of stress may explain how KOR antagonists can have efficacy in such a wide variety of animal models that represent different disease states. However, the fact that KOR antagonists seem most efficacious if administered before a stressor – suggesting that they block a cascade of events that, once initiated, are difficult to reverse – represents a limitation that may narrow their utility.

Differences between drug withdrawal and stress

Stress, but not drug withdrawal, triggers opponent reward states

Stressful, painful, and aversive stimuli can be reinforcing or perceived as rewarding (Solomon and Corbit, 1974). Under some circumstances, nonhuman primates will self-administer shock (Laurence *et al*., 1994). In addition, mice that are exposed to an inescapable stressor (elevated stand) demonstrate a rewarding after-effect, measured as a conditioned place preference to stand exposure, which is correlated with an increase in NAc dopamine (Shen *et al*., 2011). In humans, termination of painful stimuli can produce pleasure (Becerra and Borsook, 2008; Leknes *et al*., 2011). Finally, there are numerous examples of stress (sensation)-seeking behaviors including racecar driving, skydiving, and roller coaster riding (Zuckerman, 1990). It is thought that sensation seekers requiring higher levels of arousal to feel positive emotion, alertness, and interest (Hebb, 1955; Piazza *et al*., 1993), although this fails to explain how more consistent effects can be observed in laboratory animals.

The idea that aversive stimuli can trigger opponent processes to subsequently produce positive affective states (Solomon and Corbit, 1974) is important in the context of stress-related disorders and addiction. It has been difficult to pinpoint neural mechanisms because it is not clear how factors such as the type, magnitude, frequency, or timing of stressors interact with baseline affective states to modulate reward function and mood. For example, chronic mild stress has been shown to reduce brain stimulation reward when rats press for electrical stimulation of the VTA (Moreau *et al*., 1992) but has no effect when the stimulation is in the lateral hypothalamus (Lin *et al*., 2002). Interestingly, ICSS thresholds actually decreased below baseline (indicating increased reward function) in the days following cessation of chronic mild stress (Lin *et al*., 2002), reminiscent of the proposed oscillations in affective state shown in Fig. 1. In contrast, chronic social defeat stress produces robust elevations in ICSS thresholds (indicating decreased reward function) in mice, which remain elevated several days after the defeat sessions are halted (Donahue *et al*., 2014).

A more reductionist approach is to isolate specific components of the stress response and track their impact on hedonic state and neural plasticity over time. We found that activation of KORs with the highly selective and potent KOR agonist salvinorin A (salvA; Roth *et al*., 2002) produces an immediate (0–2 h) anhedonic response and a delayed (23–24 h) hedonic response as measured with ICSS (Fig. 2a; Potter *et al*., 2011). KOR-mediated anhedonia has been well documented (Muschamp *et al*., 2011), but the delayed (and transient) increase in reward function 24 h after salvA administration is relatively novel and suggests that KOR activation triggers opponent processes within reward circuits. Consistent with this, there are reports that dynorphin and KOR agonists can be reinforcing. For example, rats can be trained to self-administer the KOR agonist RU-51599 (Marinelli *et al*., 1998), and dynorphin can produce conditioned place preferences and sustain self-administration behavior under some conditions (Khazan *et al*., 1983; Iwamoto, 1988). Humans self-administer salvA, although generally not compulsively (Zawilska and Wojcieszak, 2013), just as they use a

variety of other chemicals (lysergic acid diethylamide, organic solvents) that may have aversive or hallucinogenic effects.

KOR activation, as might occur with drug withdrawal, stress, or administration of a potent agonist such as salvA, triggers opponent neuroadaptations in dopamine-mediated signaling and dopamine neurotransmission. Acute administration of salvA causes long-lasting (~2 h) decreases in dopamine levels in the extracellular NAc (Carlezon *et al.*, 2006; Ebner *et al.*, 2010), which likely initiates compensatory changes in dopamine signaling (Acri *et al.*, 2001; Chefer *et al.*, 2005). Consistent with this, repeated treatment of rats with the KOR agonist U69593 potentiates locomotor sensitization to a D2 receptor agonist (Perreault *et al.*, 2005), and the D2 receptor number is significantly increased after withdrawal from repeated U69593 administration (Izenwasser *et al.*, 1998). We have shown that prior, repeated salvA treatment potentiates the locomotor response to a D1 receptor agonist (Chartoff *et al.*, 2008). Taken together, these data raise the possibility that as the KOR-related component of the aversive response to stress or drug withdrawal diminishes, an upregulated dopamine system is unmasked, allowing for higher baseline reward function and an altered hedonic response to drugs of abuse.

In contrast, there is little direct evidence that drug withdrawal-induced negative affective states trigger an opponent reward state. Rats administered a binge-like regimen of cocaine (Fig. 2b) or allowed to self-administer cocaine or heroin for an extended period each day (6 h/day) show a progressive decrease in brain stimulation reward (Ahmed and Koob, 1998; Kenny *et al.*, 2006; Chartoff *et al.*, 2012). When drug access is stopped, reward thresholds return to baseline over the course of a week, but do not fall below predrug baseline levels (Chartoff *et al.*, 2012). This suggests that drug withdrawal-induced negative affective states do not result in overt increases in reward that are expressed once withdrawal signs end. Alternatively, drug withdrawal may trigger a variety of neuroadaptations that simultaneously increase and decrease reward function, as has been demonstrated with chronic drug use (Nestler and Aghajanian, 1997; Koob, 2009). Indirect support for this idea comes from findings that, with sustained cessation of drug administration, mesolimbic dopamine transmission normalizes from a depressed level (Weiss *et al.*, 1992) and the ability of acute exposure to drugs of abuse to increase NAc dopamine levels is enhanced (Kalivas and Duffy, 1993; Heidbreder *et al.*, 1996). The time course of this enhancement parallels the progressive increase in the locomotor-activating (i.e. sensitization) and reinforcing (i.e. incubation of craving) effects of cocaine that occur as the time after the last drug administration increases (Kalivas and Duffy, 1993; Heidbreder *et al.*, 1996; Lu *et al.*, 2004).

Stress, but not drug withdrawal, can act as a positive reinforcer

Animals will self-administer electrical stimulation into brain areas (i.e. dorsal mesencephalic central gray area, lateral tegmentum, reticular formation) that, when stimulated noncontingently, elicit vigorous escape responses (Cazala *et al.*, 1985). Similarly, nonhuman primates will self-administer mild electric shocks under some conditions (Barrett *et al.*, 1978; Malagodi *et al.*, 1981; Laurence *et al.*, 1994). One explanation for these behaviors is that the rewarding effects of stimulation offset are perceived as more reinforcing than the aversive effects of the stimulation itself. A more nuanced view is that the way in which the

temporal dynamics of stress onset, duration, and offset coincide with operant behavior determines whether approach or avoidance behavior will be observed. This has been elegantly demonstrated in fruit flies; a shock can condition approach or avoidance to an odor depending on the relative timing of the shock and the conditioning odor (Tanimoto *et al.*, 2004). If the conditioning odor comes after the shock, it can come to signify shock offset, and flies will learn to approach that odor.

In contrast, direct evidence that drug withdrawal *per se* can serve as a positive reinforcer is lacking, perhaps owing to challenges in the design of studies that would address this issue.

Inconsistencies and gaps in knowledge

Impact of stress and drug withdrawal on reinstatement of drug taking

The idea that drug withdrawal and stress elicit similar negative affective states through similar mechanisms is not novel (Kreek and Koob, 1998; Koob, 2008). An important and unresolved question is how drug withdrawal as a stressor influences the motivation to self-administer drugs of abuse, because blocking stress may be a feasible intervention (Van't Veer and Carlezon, 2013). In the case of stress, there is evidence supporting both facilitative and suppressive effects on drug taking and relapse. Brief exposure to stressors or injections of corticosterone can sensitize the mesocorticolimbic dopamine system to the activating (Antelman *et al.*, 1980; Kalivas and Stewart, 1991; Rouge-Pont *et al.*, 1995; Prasad *et al.*, 1998) and rewarding (Lett, 1989; Piazza *et al.*, 1990) effects of cocaine and other addictive drugs. Likewise, stress can trigger craving in drug-dependent humans (Sinha *et al.*, 1999) and facilitate the acquisition and reinstatement of drug self-administration (Piazza *et al.*, 1990; Goeders and Guerin, 1996; Shaham *et al.*, 2003). Stress-induced reinstatement of operant responding on a lever previously paired with cocaine delivery requires CRF release into the VTA, which activates glutamatergic inputs to dopamine neurons (Wang *et al.*, 2005). Although exposure to a stressor itself may be aversive, there is considerable evidence that the net result is an increased sensitivity to the reinforcing effects of the drug (McLaughlin *et al.*, 2006a; Bruchas *et al.*, 2010). For instance, people who are more sensitive to stress (Piazza and Le Moal, 1997) or who do not feel that they have adequate control over stress may be more likely to abuse drugs. In contrast, there is evidence that prolonged or uncontrollable stress suppresses the mesocorticolimbic dopamine system, reward function, and drug intake (Willner *et al.*, 1992; Miczek *et al.*, 2008; Miczek *et al.*, 2011). The complexity of this issue stems mainly from the infinite stress permutations that can be invoked.

The case for drug withdrawal motivating continued drug taking and relapse appears to be more complex. The central tenet of negative reinforcement as it applies to addiction is that drug withdrawal-induced negative affective states motivate behaviors that terminate the negative affect. This has been difficult to demonstrate unequivocally in animal models. It has been shown that rats allowed extended access to self-administration of drugs of abuse progressively escalate drug intake in parallel with an escalation of anhedonia as measured with ICSS (Koob, 2009), suggesting that withdrawal-induced negative affective states drive drug intake, which is perfectly consistent with the opponent process theory. Although powerful because both drug intake and affect were measured in the same animals, these

findings are correlative. Early studies in morphine-dependent rodents and nonhuman primates trained to self-administer morphine reported that μ-opioid receptor antagonist treatment precipitated withdrawal and increased rates of morphine self-administration (Schuster and Thompson, 1969). A more recent study that controlled for dependence, withdrawal state, dose of self-administered opioid (remifentanil), and reinforcement history showed that morphine-withdrawn rats initiated remifentanil self-administration at much lower doses and at much earlier time points than nondependent rats (Cooper *et al*., 2008). These findings support the idea that drug withdrawal-induced negative affective states serve as negative reinforcers.

However, the studies described above did not directly address whether withdrawal could precipitate relapse. Rats trained to self-administer heroin that underwent extinction training could be motivated to reinstate lever pressing when administered a morphine prime but not when administered the opioid antagonist naltrexone (Stewart and Wise, 1992), suggesting that proponent, rather than opponent, processes drive reinstatement. A subsequent study demonstrated that rats required previous experience with heroin self-administration during withdrawal in order for drug 'seeking' to be enhanced during subsequent bouts of withdrawal (Hutcheson *et al*., 2001). The implications of these findings on drug addiction are important because they suggest that self-medication is a learned rather than an inherent process. If true, then it may be possible to take advantage of this learning process for treatment. For example, the memory that heroin is more rewarding during withdrawal could potentially be disrupted during reconsolidation processes. Alternatively, treatments that alleviate withdrawal states could be purposefully paired with precipitated withdrawal to help stamp in the memory that therapeutic alleviation of withdrawal can serve as a reinforcer to remain abstinent.

Another major gap in current knowledge is related to understanding how aversive state-mediated increases in reward function might contribute to addictive behavior (Fig. 1). For example, KOR activation has been shown to modulate aspects of dopamine signaling in the NAc. Repeated administration of KOR agonists decreases dopamine uptake in the NAc (Thompson *et al*., 2000), which subsequently increases basal and cocaine-potentiated levels of extracellular dopamine (Heidbreder *et al*., 1998). In addition, postsynaptic dopamine D2 receptor levels are increased in the NAc after repeated KOR activation (Izenwasser *et al*., 1998), an effect that could be considered proreward. We have shown that repeated administration of salvA increases the locomotor stimulant effects of cocaine (Potter *et al*., 2011), but effects on reward-related or reinforcement-related effects of cocaine have not been tested.

Conclusion

Preventing disease tends to be easier than reversing it (Van't Veer and Carlezon, 2013). The idea of preventing addiction is appealing but provocative. Considering that stress can play a role in causing new cases of addiction and comorbid psychiatric illnesses, and can exacerbate existing cases, one strategy may be to mitigate the effects of stress. As described above, CRF antagonists and KOR antagonists have attracted interest as medications that reduce illness by targeting stress. There have been practical limitations in the development

of CRF antagonists (Zorrilla and Koob, 2010), and KOR antagonists seem most efficacious if administered before a stressor (Van't Veer and Carlezon, 2013). Importantly, some of the most traumatic and costly forms of stress (e.g. combat, responding to a disaster) can be predicted in advance; hence, intervention with these types of agents may be effective in preventing addiction or psychiatric conditions that are highly comorbid with addiction (e.g. depressive and anxiety-related illnesses; Kessler *et al*., 2008). These agents may also be effective for treating individuals who have been in recovery for long periods of time, by preventing stress-induced relapse of drug-seeking behavior.

A more effective strategy for faster intervention would be to find treatments that can cause lateral or vertical shifts in the affective oscillations triggered by repeated drug use; shortening or flattening the negative dips in the hedonic state (Fig. 1). Conceptualized in this way, some of the most highly effective (but still controversial) treatments for addiction (such as methadone, nicotine patch) work through this mechanism. The most tenable strategy may be to find treatments that reverse drug-induced neuroadapations, both antireward and proreward, to cure the disease rather than to treat its symptoms; however, this requires a more thorough understanding of the neurobiology of addiction.

Acknowledgements

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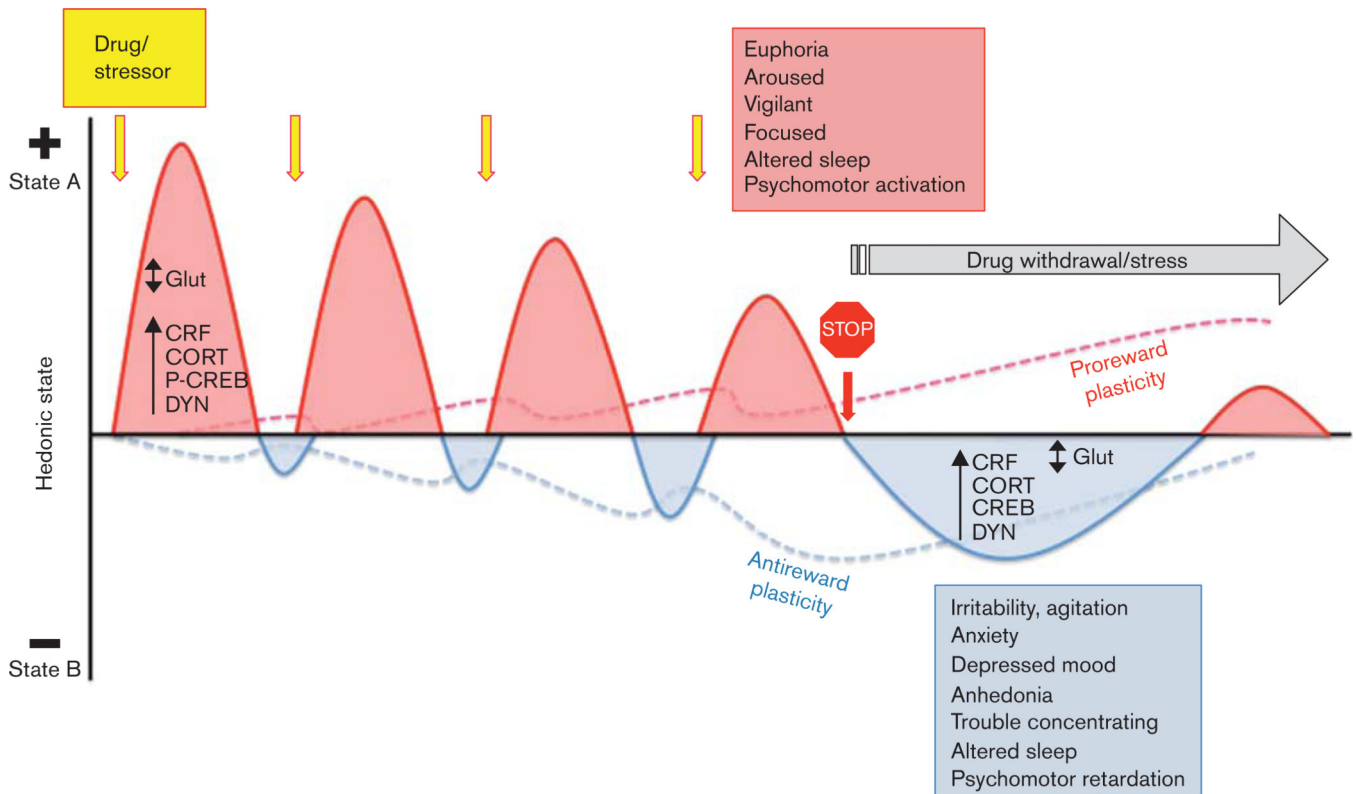
Fig. 1.

Conceptualization of drug withdrawal and stress triggering similar neuroplastic mechanisms to maintain allostasis of hedonic state. Acute exposures to drugs of abuse and stressors (yellow arrows) activate stress and reward pathways (HPA axis and mesocorticolimbic system, respectively) that are arousing (State "A": positive deflections on hedonic axis, red curves; signs listed in red box). Each stimulus-induced increase in hedonic state is followed by a decrease in hedonic state (State "B": negative deflections on hedonic axis, blue curves), which grows in strength with repeated presentation of the drug or stressor. Allostasis-driven neural plasticity occurs within stress and reward circuitry that oppose both the arousal/ rewarding effects of repeated stimuli (red dashed line) and the depressive/anhedonic effects of stimulus offset (blue dashed line). Drug withdrawal (stop sign) eliminates the positive effects of acute drug administration on hedonic state, resulting in marked decreases in hedonic state (signs listed in blue box). This abrupt withdrawal state results in depressive-like mood states similar to those observed with chronic stress. There is evidence that withdrawal-induced increases in at least some factors (e.g. dynorphin) can themselves trigger subsequent positive deflections on the hedonic axis (red curve, far right). A gap in our knowledge is with regard to how drug withdrawal and stress impact addictive behaviors such as craving and relapse over time, as hedonic states oscillate. CORT, corticosterone; CRF, corticotropin-releasing factor; DYN, dynorphin; Glut, glutamate; HPA, hypothalamic–pituitary–adrenal; P-CREB, phosphorylated cAMP response element binding protein.
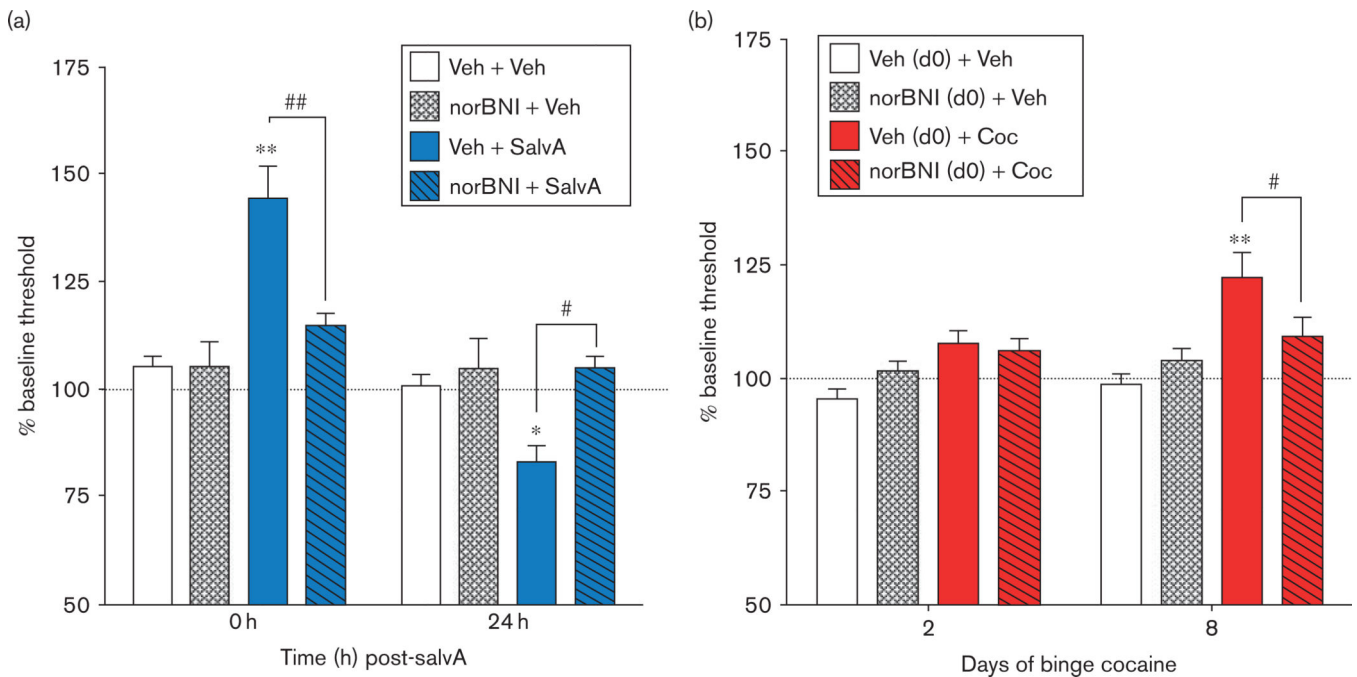
Fig. 2.
Evidence that processes that have an affective valence are followed in time by an opponent process that has the opposite valence. Hedonic states are determined by intracranial self-stimulation (ICSS). An increase in % baseline threshold [lowest frequency (Hz) of stimulation at which rats will perform operant behavior] reflects a decrease in sensitivity to brain stimulation reward (i.e. anhedonia), whereas a decrease in % baseline threshold reflects an increase in sensitivity to brain stimulation reward. (a) Rats treated with salvinorin A (salvA, 2.0 mg/kg, intraperitoneally) show an immediate (0 h post injection) increase in ICSS thresholds and a delayed (24 h post injection) decrease in ICSS thresholds compared with vehicle-treated rats (Veh, 75% dimethyl sulfoxide). Both are sensitive to blockade by the κ-opioid receptor (KOR) antagonist norBNI (10 mg/kg, intraperitoneally, given 24 h before salvA; adapted with permission from Potter *et al*., 2011). (b) Rats treated with cocaine (Coc) in a binge-like regimen (3× 15 mg/kg/day for 14 days, intraperitoneally) show normal ICSS thresholds 21 h after the first day of cocaine injection but develop increased ICSS thresholds compared with vehicle-treated rats (Veh, 0.9% saline), which plateau after ~8 days of binge treatment. Treatment with norBNI [20 μg, intracerebroventricularly, day 0 (d0), 24 h before the start of the cocaine binge regimen] prevents cocaine withdrawal-induced anhedonia (adapted with permission from Chartoff *et al*., 2012). *$P < 0.05$, **$P < 0.01$ compared with Veh +Veh; #$P < 0.05$, ##$P < 0.01$ comparing groups under the bars.