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Chapter 10

THE ROLE OF STRESS IN PSYCHOSTIMULANT ADDICTION: TREATMENT APPROACHES BASED ON ANIMAL MODELS

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ABSTRACT

Drug addiction is a chronic relapsing multifactorial disorder arising as a result of the interaction between biological and environmental factors and characterized by a loss of control over use of the drug. It has been repeatedly demonstrated that stress is a risk factor for the initiation and maintenance of drug consumption and for relapse after detoxification periods. Several animal models have been developed to study the neurobiology of drug addiction, among which the self-administration (SA) and conditioned place preference (CPP) paradigms are the most used. The extinction /reinstatement procedures of SA and CPP allow a situation similar to relapse - the main problem in the treatment of drug addiction - to be modeled. Stressful experiences can increase drug-seeking, compulsive drug-taking and reinstatement after long-term withdrawal in rodents. The objective of this chapter is to provide an up-to-date review of studies regarding the role of stress in the development of addiction to psychostimulant drugs in these animal models. First, we describe the physiological response to stress and the relationship between the brain systems involved in addiction and stress. Next, we describe SA and CPP animal models of addiction and the different kind of stressors used in experiments in these models, with special reference to social defeat stress. Later we discuss the results of studies showing how different stressors modify the acquisition and reinstatement of SA and CPP. Finally, we focus on studies that have evaluated the capacity of different drugs to reduce the effects of stress on the acquisition and

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reinstatement of SA and CPP, such as NA, CRF, kappa, DA and hypocretin antagonists. We hope to offer a perspective of potential treatment approaches based on the data obtained in studies with these animal models and propose new priorities for future work in the field.

Keywords: Amphetamine, cocaine, conditioned place preference, corticotropin-releasing factor, crowding, dopamine, environmental enrichment, food restriction, footshock, forced swim, isolation, kappa opioid receptors, maternal separation, methamphetamine, noradrenaline, reinstatement, restraint, rodents, self-administration, social defeat, social interaction, stress, tail pinch, yohimbine

ABBREVIATIONS

α2AR: alpha 2 adrenergic receptor
ACTH: adrenocorticotropin hormone
AMPH: amphetamine
β 1AR: beta 1 adrenergic receptor
β 2AR: beta 2 adrenergic receptor
BLA: basolateral nucleus of amygdala
BNST: bed nucleus of stria terminalis
CB: cannabinoid
CeA: central nucleus of amygdala
COC: cocaine
CPP: conditioned place preference
CRF: corticotropin-releasing factor
DA: dopamine
EE: environmental enrichment
HPA: Hypothalamus-Pituitary-Adrenal
KOR: kappa opioid receptor
LC: locus coeruleus
MDMA: 3,4-methylenedioxymethamphetamine
METH: methamphetamine
NA: noradrenaline
NAcc: nucleus accumbens
PFC: prefrontal cortex
POMC: proopiomelanocortin
SA: self-administration
VTA: ventral tegmental area

INTRODUCTION

Drug addiction is a chronic multifactorial relapsing disorder that is a result of the interaction between biological and environmental factors (Ellenbroek, van der Kam, van der Elst, and Cools, 2005; Enoch, 2006). It is a chronic and recurrent illness characterized by a

loss of control over use of the drug and by relapse (Koob, 2010; Koob and Volkow, 2010). Even following a successful detoxification process and after long-term abstinence, relapse can appear when individuals are exposed to stimuli such as the drug of abuse, stress, or cues associated with drug consumption (Koob, 2009; Sinha, 2011). Thus, relapse to compulsive drug-taking is the main problem in the treatment of drug addiction. This trend towards relapse in addiction suggests that drugs of abuse produce permanent alterations in the brain (Nestler, 2004; Sun, 2011; Van den Oever, Spijker, Smit, and De Vries, 2010).

Several animal models have been developed to study the neurobiology of addiction, among which the self-administration (SA) and conditioned place preference (CPP) paradigms are the most used. These models allow the rewarding effects of drugs of abuse to be evaluated and have been designed to accurately reflect the characteristics of drug addiction. The extinction/reinstatement procedures of SA and CPP reproduce a situation similar to relapse. Reinstatement is an operant event that can be measured directly when a laboratory animal reinitiates a particular behaviour after extinction (Aguilar, Rodríguez-Arias, and Miñarro, 2009; Shaham, Shalev, Lu, De Wit, and Stewart, 2003).

It has been repeatedly demonstrated that stress is a risk factor for the initiation, maintenance and escalation of drug consumption and for relapse after periods of detoxification (Koob, 2010; Logrip, Koob, and Zorrilla, 2011; Logrip, Zorrilla, and Koob, 2012; Sinha, 2008; Sinha, Shaham and Heilig, 2011). There is a narrow relationship between stress and addiction brain systems, and stressful experiences modify the activity of brain areas involved in the rewarding effects of psychostimulants (Belujon and Grace, 2011; Koob, 2009; Sinha, 2008). There is a positive association between stress and increased drug intake and relapse to drug use (for a review see Sinha et al., 2011). In rodents, exposure to stressors (e.g., footshock, immobilization, forced swim, maternal separation, social isolation, social defeat stress) and activation of neural and hormonal stress mechanisms can produce behavioral and neurochemical adaptations that render individuals more prone to drug-seeking and drug-taking behaviours (Goeders, 2002a; Koob and Kreek 2007; Logrip et al., 2012; Marinelli and Piazza 2002; Miczek et al. 2008; Moffett et al., 2007).

The relationship between stress and psychostimulant addiction has been evaluated mainly using the SA paradigm and somewhat less so using the CPP paradigm. Many studies have focused on acquisition, but fewer on reinstatement. Most previous studies have employed morphine or COC (COC) to evaluate the effects of stress on acquisition and reinstatement of drug-taking, although a few have employed other psychostimulants. Similarly, social stressors have seldom been used, even though it is more relevant to humans. Finally, studies of which drugs mitigate the effects of stress on drug consumption and reinstatement have only recently appeared.

The main objective of this chapter is to provide an up-to-date review of published studies regarding the role of stress in the development of addiction to psychostimulant drugs in animal models. First, we describe the physiological response to stress and the relationship between the brain systems involved in addiction and stress, particularly the circuit of extended amygdala. Next, we describe SA and CPP animal models of addiction and the different stressors used in the experiments performed with these models, with special reference to social stress. Later we discuss the results of studies showing how different stressors modify the acquisition and reinstatement of psychostimulant SA and CPP. We then focus on studies that have evaluated the capacity of different drugs to reduce the effects of stress on the acquisition and reinstatement of SA and CPP, such as noradrenaline (NA),

corticotropin-releasing factor (CRF), kappa opioid and dopamine (DA) antagonists. We aim to offer a perspective of potential treatment approaches to drug addiction based on the data obtained in studies with these animal models, primarily with the drugs that have proven effective in reducing the effects of stress on reinstatement. Finally, we explain the protective factors that can reduce the effects of stress on addiction. To end the review we will propose new priorities for future work in the field.

NEUROBIOLOGY OF STRESS RESPONSE

Organisms work for the body's welfare throughout life and are biologically prepared to compensate for deficits that may disrupt our natural homeostasis. When we are hungry, our body prepares to hunt for food, as if we have no other biological necessity. The imbalance created in our bodies by both internal and external stimuli can be compensated biologically or through our behavior.

Stress is one of the conditions that can alter the biology of organisms. Faced with a stressful situation, there is a break in the homeostasis of individuals that needs to be compensated. Therefore, different neurobiological, chemical and behavioural actions are initiated to resolve this situation. In this way, stress is an essential condition of life and is an important factor in the maintenance of health and development of illness.

The physician Hans Selye defined theterm "stress"for the first time as a non-specific response of the body to any demand characterized by the action of neurobiological systems such as glucocorticoids (Selye, 1975). Selye developed a new concept in this area - "the general adaptation syndrome" - which encompasses an alarm reaction, a stage of resistance, and finally a stage of exhaustion. Many have attempted to describe the stress concept and it has been difficult to establish a consensus, as each investigator has emphasized different aspects of stress, whether it be cognition, motivation, emotion, behavior or biological aspects. However, the different definitions are in agreement with respect about the response to stress; different regulatory systems of the body are activated to adapt the organism to internal or external challenges, such as the Hypothalamus-Pituitary-Adrenal (HPA) system, a central control and regulatory system of the organism that is involved in the stress response with hormones such as corticotropin-releasing factor (CRF), adrenocorticotropin hormone (ACTH) and glucocorticoids; or the symphatic-adrenal system, with catecholamines (adrenaline and NA) (Kupfermann, 1991). There are other important systems involved in the stress response, such as the immune system (for a review see Capuron and Miller, 2011; Costa-Pinto and Palermo-Neto, 2010). Different brain areas are activated depending on the type of stress invoked: physical or social. For example, stimuli of social stress do not present an immediate threat for the organism and needs to be processed by the prefrontal cortex (PFC). Although stressors can elicit different responses in different individuals depending on "conditioning" or interaction with the environment, it is the sympathetic nervous system and the HPA system that are usually activated (Stratakis and Chrousos, 1995). As can be seen in Figure 1, in a situation of stress, the HPA axis is activated by the secretion of CRF from the hypothalamus (Goeders, 2002b; Sarnyai, Shaham, and Heinrichs, 2001; Turnbull and Rivier, 1997). CRF-containing neurons projecting from the paraventricular nucleus to the median eminence release the peptide into the adenohypophyseal portal circulation. The binding of CRF to

receptors located in the anterior hypophysis results in the synthesis of proopiomelanocortin (POMC), a large precursor protein that produces several smaller peptides, including ACTH and β-endorphin. ACTH diffuses through the general circulation until it reaches the adrenal glands, where it stimulates the biosynthesis and secretion of adrenocorticosteroids (e.g. cortisol in humans or corticosterone in rats), which act at diffuse body sites to assure the overall response to stress (Goeders, 2003). Under stress, cortisol redirects energy utilization to the various organs, simultaneously amplifying energy-mobilizing mechanisms and inhibiting less relevant organ functions (Chrousos and Gold, 1992; McEwen, 2003). The general function of the HPA axis is controlled by several negative feedback loops (Herman, McKlveen, Solomon, Carvalho-Netto, and Myers, 2012) regulated by mineralocorticoid and glucocorticoid receptors (Harris, Holmes, de Kloet, Chapman, and Seckl, 2012). Glucocorticoids act in a negative feedback mode by decreasing production and release of CRF in the hypothalamus and of POMC and its neuropeptides in the anterior pituitary (Zhou et al., 2006). The sympathetic nervous system activated the adrenal medulla by inducing adrenaline and NA release (see Figure 1), which leads to a variety of physiological processes that prepare the organism for flight or fight, or in other words to face the stressor or to escape it: increase in heart rate, a rise in blood pressure, a shift in blood flow to the skeletal muscles, an increase in blood glucose, dilation of the pupils and stimulation of respiration (Goeders, 2003).

Drug addiction is often characterized as a chronic cycle of drug intoxication, withdrawal and relapse (Koob, 2010). The mesocorticolimbic DA system, originating in the ventral tegmental area (VTA) and projecting to the nucleus accumbens (NAcc) and PFC (see Figure 2), is known to play a major role in appetitive behaviors (Carlezon and Thomas, 2009; Dalley and Everitt, 2009; Kelley and Berridge, 2002; Wise, 2008) and is the main neural substrate of the rewarding effects produced by drugs (McBride, Murphy, and Ikemoto, 1999; Wise et al., 1998).

There is a positive relation between psychostimulant SA behaviour and the level of activation of the mesolimbic DA brain system (Cadoni et al., 2005; Calipari et al., 2012; Chevrette, Stellar, Hesse, and Markou, 2002; Di Chiara et al., 2004; Everitt and Wolf, 2002; Franken, Booij and van den Brink, 2005; Wise, 2005), with animals with heightened DA transmission being more likely to develop psychostimulant SA behaviour (Hooks, Jones, Smith, Neill, and Justice, 1991; Hooks, Colvin, Juncos, and Justice, 1992; Marinelli and White, 2000; Rouge-Pont, Piazza, Kharouby, Le Moal, and Simon, 1993). Moreover, reductions in DA function have been implicated in the reduced reward function reflected in increases in the threshold for intracranial self-stimulation that accompanies withdrawal from COC use (Antkiewicz-Michaluk, 2006; Markou and Koob, 1992).

Manipulation of the main afferents to the mesolimbic DA system also modifies the rewarding effects of psychostimulants. The systemic administration of the γ-aminobutyric acid $(GABA)_B$ receptor agonists, such as baclofen, at doses that inhibit DA release reduces SA of psychostimulants under different schedules of reinforcement (Brebner, Phelan, and Roberts, 2000; Brebner, Froestl, and Roberts, 2002; Di Ciano and Everitt, 2003; Roberts, Andrews, and Vickers, 1996; Shoaib, Swanner, Beyer, Goldberg, and Schindler, 1998; Xi and Stein, 1999, 2000) and psychostimulant-induced CPP (Halbout, Quarta, Valerio, Heidbreder, and Hutcheson, 2011). Glutamate antagonists also reduce the rewarding effects of psychostimulants in SA and CPP (Hyytia, Bäckström, and Liljequist, 1999; Maldonado,

Rodríguez-Arias, M., Castillo, A., Aguilar, M.A., and Miñarro, 2007; Osborne and Olive, 2008) paradigms.

Activation of brain stress systems seems to be a key element of the negative emotional state produced by dependence and which drives drug-seeking through negative reinforcement mechanisms (Koob, 2009).

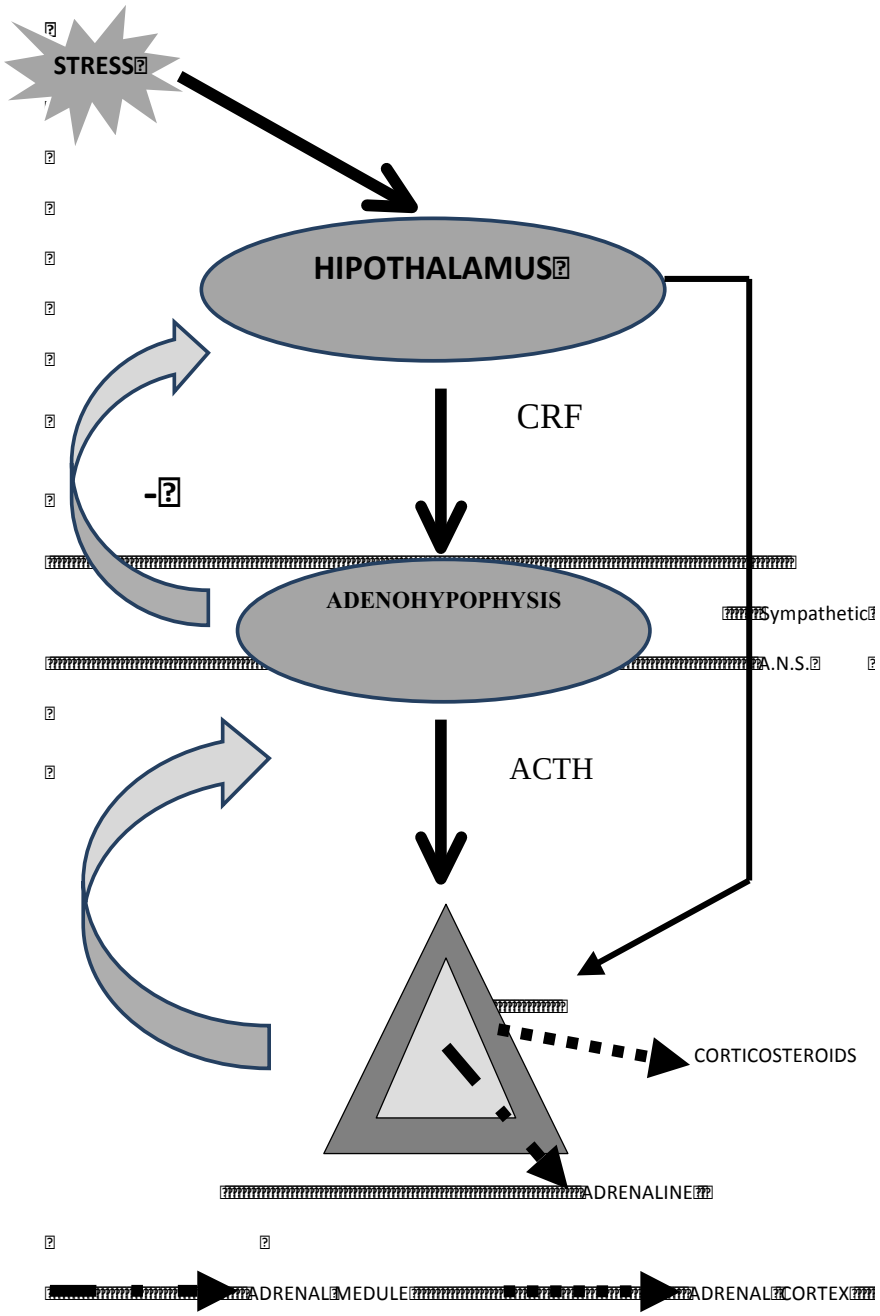

Figure 1. Physiology of the response to stress.

RELATIONSHIP BETWEEN BRAIN SYSTEMS INVOLVED IN STRESS AND DRUG ADDICTION

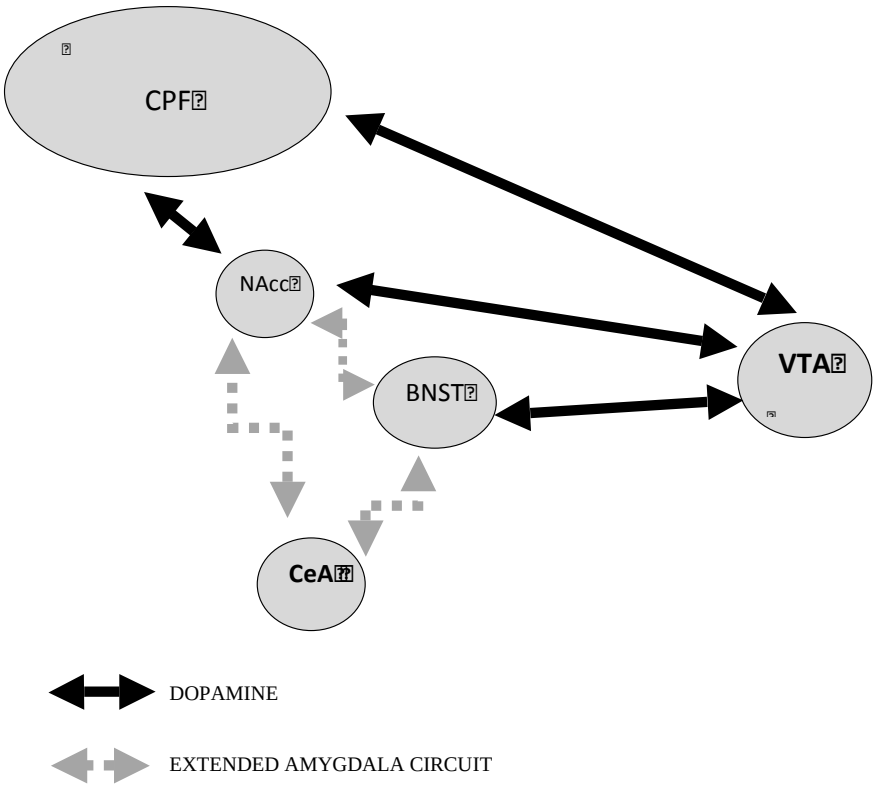

Figure 2. The mesocorticolimbic DA system and the extended amygdala circuit.

Many of the motivational effects of drugs may involve a common neural circuitry that forms a separate entity within the basal forebrain, termed the "extended amygdala" (Alheid and Heimer, 1988). The extended amygdala circuitry extends from the shell of the NAcc to the bed nucleus of the stria terminalis (BNST) and central nucleus of the amygdala (CeA) (Alheid and Heimer, 1988; de Olmos and Heimer, 1999; Koob, 2009), where neurotransmitters such as CRF, NA, and DA interact (see Figure 2).

The extended amygdala is innervated by the dorsal and ventral NA pathway originating in the locus coeruleus (LC) (Aston-Jones, Rajkowski, Kubiak, Valentino, and Shipley, 1996; Moore and Bloom, 1979), The CeA and BNST are also innervated by DA neurons originating from regions of the midbrain, including the VTA (Hasue and Shammah-Lagnado, 2002). Both NA and DA neurons synapse with, or in close proximity to, CRF neurons in the CeA and BNST (Eliava, Yilmazer-Hanke, and Asan, 2003; Phelix, Liposits, and Paull, 1994). CRF neurons in the CeA project to the BNST (Sakanaka, Shibasaki, and Lederis, 1986) and VTA (Rodaros, Caruana, Amir, and Stewart, 2007) and CRF neurons in the BNST provide a local source of CRF and also project to the VTA (Rodaros et al., 2007). CRF in the VTA has an excitatory effect on DA and glutamate transmission in the region (Wang et al., 2005).

DA has been found to play an important role in the neurobiology of fear and anxiety (de Oliveira, Reimer, and Brandão, 2006; Macedo, Martinez, Albrechet-Souza, Molina, and

Brandão, 2007; Pezze andFeldon, 2004; Reis, Masson, de Oliveira, and Brandão, 2004). Moreover, the PFC has been shown to be a potent regulator of the stress response, in part via attenuation of responses in the amygdala (Rosenkranz and Grace, 2002a, b; Rosenkranz, Moore, and Grace, 2003), which is the brain region in which fear and anxiety are expressed (LeDoux, 2000). Another brain region that has been shown to be particularly susceptible to the deleterious effects of maintained stress is the hippocampus (Sapolsky, Uno, Rebert, and Finch, 1990; Sapolsky, 2000; Lee, Ogle, and Sapolsky, 2002).

Similarly to repeated administration of psychostimulants and other drugs of abuse, repeated exposure to stress can heighten sensitivity to drug-induced psychomotor stimulation. In some cases, this sensitized behavioral response is correlated with enhanced drug-induced DA and glutamate responses in the NAcc and increased cellular activation of reward-associated brain regions (Deroche et al., 1995; Miczek, Covington, Nikulina, and Hammer, 2004; Nikulina, Covington, Ganschow, Hammer, and Miczek, 2004; Pacchioni, Gioino, Assis, and Cancela, 2002; Rouge-Pont, Marinelli, Le Moal, Simon, and Piazza, 1995). For example, the exposure to a brief, intermittent episode of social defeat stress activates mesolimbic DA pathways that project from the VTA to the NAcc and medial PFC (Anstrom, Miczek, and Budygin, 2009; Di Chiara and Imperato, 1988; Tidey and Mizek, 1997). Single or repeated exposure to stress or drugs can also induce neurochemical sensitization, as demonstrated by augmented drug-induced DA responses in the NAcc (del Rosario, Pacchioni, and Cancela, 2002; Grimm et al., 2003; Miczek, Mutschler, van Erp, Blank, and McInerney, 1999a; Rouge-Pont et al., 1995), which are often accompanied by enhanced drug-induced psychomotor responses (del Rosario et al., 2002; Deroche et al., 1992; Deroche et al., 1995; Leyton and Stewart, 1990; Nikulina, Miczek, and Hammer, 2005; Stohr et al., 1999). These results suggest that environmental stressors can activate long-term changes in the function of brain reward pathways, just as drugs of abuse do (Quadros and Miczek, 2009). Different stressors increase DA activity in the VTA via potentiation of the ventral subiculum-NAcc pathway, which underlies the increase in the behavioral response to psychostimulants. This pathway can be activated by the LC-NA system and/or the basolateral amygdala (BLA) (Belujon and Grace, 2011).

Brain stress systems, CRF and NA in the extended amygdala also play a key role in the transition to and maintenance of dependence (Koob et al., 2009). Both the mesocorticolimbic DA system and the extended amygdala circuit have been implicated in stress-induced reinstatement of COC seeking (Koob, 2010: McFarland, Davidge, Lapish, and Kalivas, 2004; Shaham et al., 2003). The ventral NA pathway projecting to the extended amygdala has been specifically related to the effects of NA on stress-induced reinstatement of drug seeking (Shaham, Erb and Stewart, 2000; Wang, Cen, and Lu, 2001). Footshock stress causes initial activation of lateral tegmental NA neurons, which in turn activates CRF projection neurons from CeA to BNST, and local CRF interneurons in the BNST (Erb, Salmaso, Rodaros, and Stewart, 2001; Shaham et al., 2000; Wang et al., 2001). Thus, stress-induced reinstatement appears to involve the lateral tegmental NA nuclei (Highfield et al., 2000; Shaham et al., 2000) and their NA projections through the ventral NA bundle (Moore and Bloom, 1979) to the CeA, BNST, hypothalamus, medial septum and NAcc (Shaham et al., 2003). In addition to the CRF-containing pathway from the CeA to the BNST (Erb et al., 2001), VTA glutamate (Wise, 2009) plays an important role in stress-induced reinstatement of COC seeking in rats. It has been proposed that footshock activates limbic circuitry in the CeA, which in turn activates a VTA DA projection to the dorsal PFC, with the subsequent rise in DA producing

reinstatement via a glutamatergic projection to the NAcc core (McFarland et al., 2004). The administration of the nonselective CRF receptor antagonist into the VTA blocks footshock-induced VTA glutamate release, DA activation and reinstatement, suggesting that footshock reinstates COC seeking by inducing CRF and glutamate release in the VTA and activating VTA DA neurons as a result (Wang, You, Rice, and Wise, 2007). More recent studies have demonstrated the involvement of CRF2 receptors in the VTA and the CRF1 receptors in the BNST in stress-induced reinstatement (Gysling, 2012; Wang, You, and Wise, 2009). Activation of the BNST is necessary for reinstatement of COC seeking, since its inactivation with lidocaine blocks forced swim-induced reinstatement of COC CPP (Briand, Vassoler, Pierce, Valentino, and Blendy, 2010). The study in question also demonstrated that CREB is required for the activation of the circuit that converges on the DA reward pathway in order to elicit reinstatement of drug reward, with the BNST constituting a key intersection between stress and reward circuits (Briand et al., 2010).

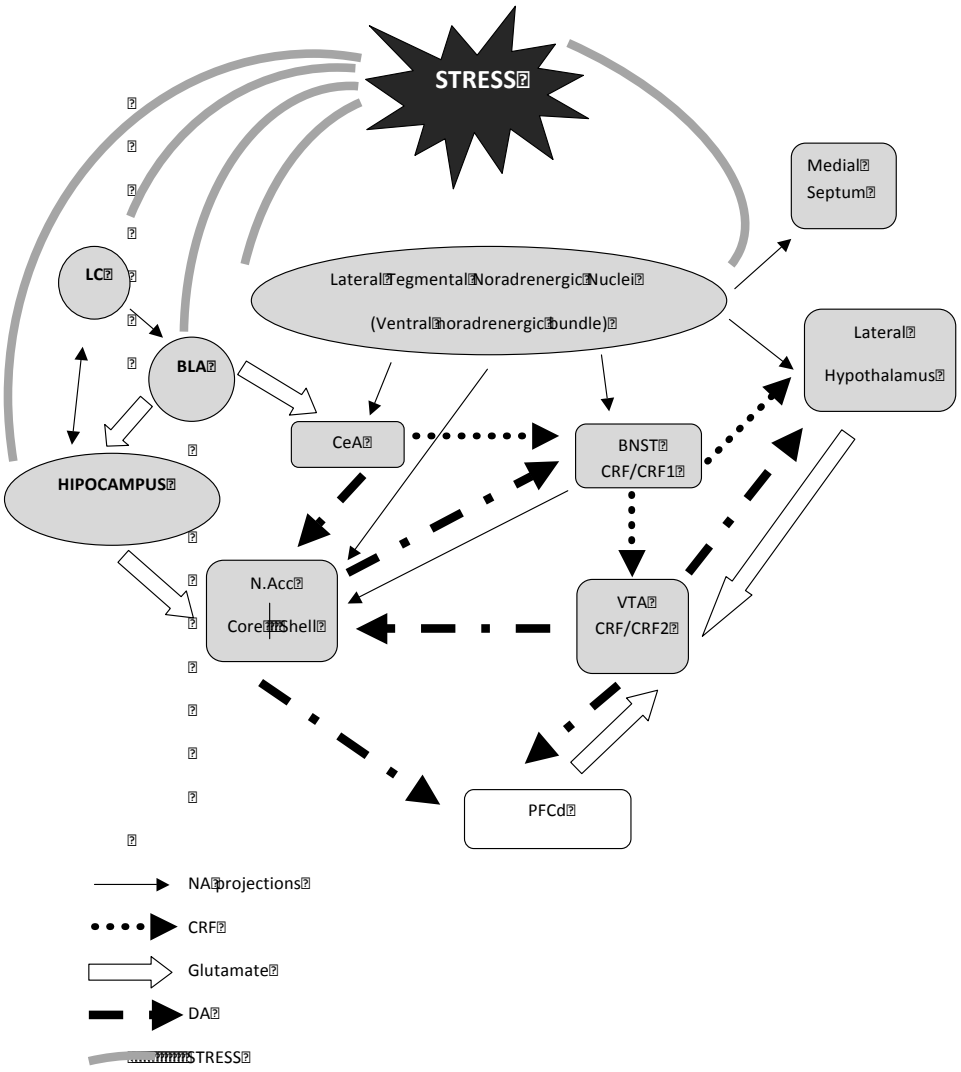

Figure 3. Neural substrates of stress induced reinstatement.

The NAcc is also involved in COC-seeking behavior triggered by footshock stress or by COC priming and drug-associated conditioned stimuli (Fuchs, Ramirez, and Bell, 2008). Similarly, NA transmission in the extended amygdala plays an important role in increased drug seeking and stress-induced reinstatement (Smith and Aston-Jones, 2008). Experience with COC induces an alteration of the complex interaction of CRF, glutamate and the mesocorticolimbic DA system, which appears to contribute to the transition from casual to compulsive COC-seeking (Wise and Morales, 2010).

Adrenal activity during repeated long-access COC SA is also required for stressor-induced reinstatement (Graf et al., 2011), and the existence of a CRF/kappa opioid receptor (KOR) connection that mediates stress-induced reinstatement has been proposed (Bruchas, Land, and Chavkin, 2010).

Two main afferents to the NAc, the BLA and the ventral subiculum of the hippocampus, and their interactions with the LC-NA system have also been associated with stress-induced reinstatement (Belujon and Grace, 2010). Increases in NA release in the BLA and PFC have also been related with the potentiation of cue-induced reinstatement induced by yohimbine, which seems to enhance the motivational salience of conditioned cues (Buffalari and Grace, 2009). Increases in CRF in the amygdala are also responsible for reinstatement of methamphetamine (METH) seeking behavior induced by shock (Nawata, Kitaichi, and Yamamoto, 2012).

Therefore, in addition to the activation of the mesolimbic DA system, aversive events and triggering of stress systems play key roles in modulating addictive behavior (Sinha, 2008). A key element of the addiction process involves the activation of brain stress systems that are localized in the circuitry of the extended amygdala and which produce a negative emotional state that becomes a powerful motivation for the drug-seeking associated with compulsive use.

The CRF and NA have an important role in addiction as central elements of a complex system that maintains emotional homeostasis (Koob, 2010). COC and stress interact directly with DA neurons in the VTA, with these interactions having an impact on stress-induced relapse (Ungless, Argilli, and Bonci, 2010).

MOST USED ANIMAL MODELS OF ADDICTION

Most of the recent progress gained regarding knowledge of the underlying mechanisms of addiction and relapse has been a result of studies with animal models. The use of animal models has the advantage of greater control of experimental variables (age of initial exposure, drug, dose, duration, timing of exposure, etc.) and has provided much valuable information. The main drawback to animal studies is that any model reproduces all the stages in the development of drug addiction. Results obtained with multiple behavioural and neurobiological models are necessary to achieve a deeper understanding of this disorder (Ahmed, 2010; Sanchis-Segura and Spanagel, 2006; Schramm-Sapyta, Walker, Caster, Levin, and Kuhn, 2009; Shippenberg and Koob, 2002; Weiss, 2010). Although several animal models have a high predictive value, most studies have been performed with the SA or the CPP paradigms.

Drug Self-Administration (SA)

The technique of SA is essential in drug addiction research, as nearly all drugs that are addictive in humans are self-administered by laboratory animals, which show patterns of drug intake that mimic those of human users (Caine and Koob, 1993; Collins, Weeks, Cooper, Good, and Russell, 1984; Deroche-Gamonet, Belin, and Piazza, 2004; Yap and Miczek, 2008). SA models human drug-taking behavior and is the most straightforward procedure for evaluating the intrinsic primary reinforcing properties of a substance (by testing whether animals will work to obtain the substance) (Yahyavi-Firouz-Abadi and See, 2009; Moser, Wolinsky, Duxon, and Porsolt, 2010). In this procedure, laboratory animals are trained to emit a response, such as pressing a lever or performing a nose-poke, to self-administer a drug. If the animal responds, it is rewarded with the drug. As a consequence, the animal acquires the new operant behavior (Yahyavi-Firouz-Abadi, 2009). As SA measures the animal's behavior according to its search for the drug, this technique can be used to study the neurobiological mechanisms involved in drug taking and drug seeking (Fuchs, Feltenstein, and See, 2006a; See, 2005; Stewart, 2000). Compared to other models of addiction, SA models the abuse of drugs by humans more closely in both the route of drug administration (iv) and the response-contingent mode of administration (O´Connor, Chapman, Butler, and Mead, 2011).

The main shortcoming of the SA paradigm is the complexity of the technique, as it involves surgery to implant an iv or intracerebral catheter that allows the animal to self-administer the drug freely (Graf et al., 2011). Another disadvantage of SA is the lack of a standardized procedure for evaluating substances with different potencies, reinforcement properties and pharmacokinetics. The choice of training substance, species and procedural parameters can radically affect the results obtained (Moser et al., 2011). Animals that acquire drug-taking behaviour more quickly or indulge in it more frequently can be considered to resemble human drug addicts. However, drug taking, even when acquired quickly, is not equivalent to drug dependence (Ahmed, 2010).

As rodents learn to self-administer drugs, there are time- and experience-dependent changes in the frequency and intensity of their behavior (Yap and Miczek, 2008). Thus, acquisition is a process whose defining feature is an increase in drug use over time. Indeed, acquisition is just one example of SA behavior in transition (Yap and Miczek, 2008); others include the escalation of drug use during extended access or “binge” conditions as physical dependence develops (Dai, Corrigall, Coen, and Kalant, 1989) or as brain reward systems are altered (Ahmed and Koob, 1998; Ahmed, Kenny, Koob, and Markou, 2002; Covington and Miczek, 2001; Covington, Tropea, Rajadhyaksha, Kosofsky, and Miczek, 2008; Paterson and Markou, 2003, 2004; Tornatzky and Miczek, 2000).

There are many pharmacological and environmental factors to be considered when evaluating SA of substances and acquisition (Ator and Griffiths, 2003), including dose (Campbell Thompson, and Carroll, 1998; Carroll and Lac, 1997), availability of alternative reinforcement (Carroll et al, 1996), sex (Donny et al., 2000; Lynch, Kushner, Rawleigh, Fiszdon, and Carroll, 1999), animal strain (Shoaib, Schindler, and Goldberg, 1997), developmental stage (Adriani, Macrì, Pacifici, and Laviola, 2002) and the presence of drug-paired sensory stimuli (Caggiula et al., 2002). However, these elements are not all equally important. Indeed, available data suggest that the choice of training substance may not be the most important variable in a SA study, but rather that other factors, such as session length or

the response requirement for drug infusion, are more important determinants (Moser et al., 2010). Most operant SA procedures employ a FR schedule of reinforcement whereby the animal must perform a fixed number of responses to receive an intravenous drug infusion. The number of responses an animal will emit to obtain an infusion generally increases for substances possessing markedly positive reinforcing properties (Moser et al., 2010).

Variations of the SA model have been developed to study the main features of addiction. Time-out and punished responding both model compulsive use (Deroche-Gamonet et al., 2004; Vanderschuren and Everitt, 2004), and long-access training schedules model high-level use (Knackstedt and Kalivas, 2007). Additionally, models of habitual drug-seeking have also been developed (Everitt et al., 2008). On the other hand, studies using SA sessions of continuous access to the drug for an extended period of time or the progressive ratio schedule highlight different aspects of drug taking behavior (Yap and Miczek, 2008). Specifically, rodent models of prolonged access to COC indicate an apparent shift from controlled, regulated drug intake to out-of-control or dysregulated intake (Tornatzky and Miczek, 2000). SA models of continuous access "binges" allow the animal to control the rate of consumption (Markou et al., 1993).

One commonly used schedule employed to investigate the effects of stress on motivation to consume a drug is the progressive ratio schedule, designed by Hodos (1961), who varied the sweetness and volume of milk in order to measure reward strength. With the progressive ratio method, motivational (desire/wanting) rather than consummatory (taking) components of SA behavior can be measured (Tabakoff and Hoffman, 2000), since rates of response to the drug provide an index of the animal's motivation to obtain it (Depoortere, Li, Lane, Emmett-Oglesby, 1993). In the progressive ratio paradigm the instrumental response requirement to obtain a drug reinforcer progressively increases until the animal ceases to respond (Brown, Jackson, and Stephens, 1998; Moser et al., 2010). The last response that the animal performs to obtain the drug is known as the "break point" (Yap and Miczek, 2008). By varying the schedule of reinforcement, it is possible to measure different aspects of motivation (Ripley and Stephens, 2011) other than the initial motivation of the animal to self-administer the drug (Oleson and Roberts, 2009).

A major clinical problem in treating drug abusers or addicts is the high rate of relapse to abuse, even long after abstinence (Hunt, Barnett, and Branch, 1971; Kalivas, Volkow, and Seamans, 2005; O'Brien et al., 1997). A variation of the SA paradigm, including the extinction and reinstatement of the instrumental response after acquisition of SA, has been developed to model relapse. The extinction-reinstatement model of the iv SA paradigm is the most widely used animal model in the study of relapse to drug-seeking (Epstein, Preston, Stewart, and Shaham, 2006; Shaham et al., 2003) and for a long time was practically the only paradigm employed to study relapse (Carroll et al. 1996). Relapse to a prior behavioural response following extinction is known as reinstatement, and the stimuli that induce it are called "primers" (Self, 1998). The most powerful "primers" are injection of the self-administered drug, drug-associated stimuli or cues, and exposure to stress (De Vries, Schoffelmeer, Binnekade, Mulder, and Vanderschuren, 1998; Ettenberg, MacConell, and Geist, 1996; McFarland and Ettenberg, 1997; Shaham, Rajabi, and Stewart 1996; Shaham, Erb, Leung, Buczek, and Stewart, 1998). Therefore, reinstatement of drug-seeking after extinction, which implies the restoration of a concrete operant response (Yahyavi-Firouz-Abadi and See, 2009), is an animal model of the propensity to relapse to drug taking (Goeders, 2003; Epstein et al., 2006; Shaham et al., 2003).

Drug SA studies about the effects of stress on drug addiction are typically divided into four temporally distinct phases: acquisition, maintenance, extinction and reinstatement. The acquisition phase is defined as the period of time required to attain a stable rate of drug SA. This phase is followed by a maintenance phase of days or weeks. Extinction training is usually introduced prior to reinstatement tests, and is carried out to achieve an operationally defined criterion that can involve within-session parameters on a single test trial, or multiple daily sessions where no drug reinforcement is available. Extinction refers to a progressive decrease in drug-associated operant responding when the drug is no longer available (Epstein et al., 2006; Shaham et al., 2003; Stewart, 2000). In the reinstatement phase, after extinction of SA behaviour, the ability of several stimuli to reinstate the response is determined. Alternatively, subjects may be tested after a period of withdrawal in the absence of explicit extinction trials (abstinence) when returned to the environment where drug was previously available (Fuchs, Branham, and See, 2006b). Relapse is an operant event that can be measured directly when a laboratory animal reinitiates a particular behavioural response, such as the lever-press (Shaham et al., 2003; Stewart, 2000). The reinstatement phase occurs when the persistence of drug-seeking behavior is measured by responding to an operandum (usually a lever or a poke) where the drug was previously available (See et al., 2011). The drug SA version of the extinction-reinstatement procedure is based on the similarities in the development of drug dependence/addiction between humans and laboratory animals (Yan and Nabeshima, 2008). Clinical and epidemiological evidence documents the relapsing nature of drug addiction, thus, adequate experimental models are required to gain further insight into the factors that promote and trigger relapse (Yap and Miczek, 2008).

Conditioned Place Preference (CPP)

The CPP paradigm offers a simple method of assessing the conditioned reward induced by different stimuli (Bardo and Bevins, 2000; Tzschentke, 1998, 2007) and has been widely used to study the conditioned rewarding effects of addictive drugs (Aguilar et al., 2009). It is a simple and fast procedure, and was the first to assess positive rewarding properties of stimuli (Moser et al., 2010). In this paradigm, contextual or environmental stimuli acquire secondary appetitive properties (conditioned rewarding effects) when paired with a primary reinforcer (Tzschentke, 1998, 2007). For example, an initial neutral environment (such as the colour of one compartment in the CPP box) is associated with the specific effects of a drug of abuse during several conditioning sessions (Manzanedo et al., 2001), while another compartment is associated with the injection of a vehicle. Following conditioning, if the animal spends more time in the compartment previously associated with the drug, it is assumed that CPP has developed (Aguilar et. al., 2009). Conditioned reward implies that the animal attributes positive incentive value to the cues associated with the primary reinforcer, and will thus perform flexible or voluntary responses to obtain access to such cues (Robbins, 1978). Under appropriate conditions, CPP can be sensitive to a wide range of substances, including psychostimulants (Moser et al., 2010).

In this paradigm itis considered that animals have acquired CPP when there is a difference between the neutral preference of animals for each of the CPP compartments in the pre-conditioning test and the time animals spend in each CPP compartment after the conditioning phase (Parker and McDonald, 2000; Wang, Luo, Zhang, and Han, 2000; Wang,

Luo, Ge, Fu, and Han, 2002). Generally, the CPP paradigm consisted of three phases. The first phase, known as "preconditioning", confirms the lack of an innate preference for a given compartment of the CPP box. In the second phase, called "acquisition", conditioning itself takes place. The main objective of this phase is that the animal associates the reinforcing effect of the drug with a specific compartment and the lack of effects of a vehicle injection with the other compartment. This association is developed during several conditioning sessions (generally four with the drug and four with saline) that animals undergo daily (both drug and vehicle conditioning sessions every day, separated by an interval of several hours), or every two days (drug and vehicle administered on alternate days). In the last stage of the procedure, the "post-conditioning" phase, the presence of CPP is evaluated. If the animal spends more time in the compartment where the drug was administered than during the pre-conditioning phase or than that spent in the vehicle-paired compartment, the animal is considered to have acquired CPP.

As with the SA model, the CPP paradigm has been adapted to study the main features of addiction. For example, the number of conditioning training sessions can be increased in order to augment exposure to contextual cues associated with the effects of COC in order to model human conditions of extended access to the drug (Rodriguez-Arias, Castillo, Daza-Losada, Aguilar, and Miñarro, 2009). Another variation of the CPP including extinction /reinstatement has been developed as an animal model to study relapse (Aguilar et al., 2009). In this model, the animals are first trained to acquire a CPP (as explained before) and later undergo a process of extinction of the CPP. Extinction is defined as the decrease in the frequency or intensity of learned responses after removal of the unconditioned stimulus (i.e. a drug) that has reinforced the learning (Pavlov, 1927). During an extinction phase, the acquired preference for the drug-paired context is extinguished by pairing injections of the vehicle with both compartments (drug-associated and vehicle-associated), or by allowing subjects to explore the drug- and vehicle-associated compartments during daily sessions in the absence of the drug. Either procedure will produce extinction of the original drug-induced CPP (Yahyavi-Firouz-Abadi and See, 2009).

After extinction, re-exposure to a low dose of the conditioning drug (known as priming) and exposure to a stressful event induce reinstatement of the CPP (Shaham et al., 2003; Shalev, Grimm, and Shaham, 2002; Tzschentke, 2007; Weiss, 2005). For example, amphetamine (AMPH) (Cruz, Marin, and Planeta, 2008; Li, Ren, and Zheng, 2002) and 3,4-methylenedioxymethamphetamine (MDMA) (Daza-Losada et al., 2007) priming induces the reinstatement of AMPH or MDMA CPP, respectively. Similarly, COC CPP is reinstated by intermittent footshock (Lu, Zhang, Liu, and Zhang, 2002), restraint stress (Sanchez, Bailie, Wu, Li, and Sorg, 2003), conditioned fear stimuli, such as a tone or an odor previously associated with footshock (Sanchez and Sorg, 2001), among other stressful events.

KINDS OF STRESSORS USED IN EXPERIMENTAL MODELS

As discussed previously, stress is a well-known risk factor in the development of addiction and in vulnerability to relapse in drug addiction (Sinha, 2008). Studies with laboratory animals reported a significant association between acute and chronic stress and an increase in motivation to initiate use and augment the consumption of addictive substances

(Sinha, 2001; Sinha, Garcia, Paliwal, Kreek, and Rounsaville, 2006; Koob and Kreek, 2007; Miczek, Yap, and Covington, 2008). Relapse during abstinence, which constitutes the main problem in drug addiction treatment, is often associated with stress exposure, which can provoke a subjective state of drug craving. Stress-induced relapse and craving in humans can be modeled in mice, rats and monkeys using the reinstatement model, in which drug-taking behaviors are extinguished and then reinstated by acute exposure to certain stressors (Sinha et al., 2011).

In animal models, drug craving and reinstatement following extended periods of abstinence are reliably triggered by exposure to stressful events (Shaham et al., 2000; Sinha, 2001; Sinha 2005; Yahyavi-Firouz-Abadi and See, 2009).

Stress is a complex construct (Cannon, 1935; Selye, 1956) that is not yet well defined operationally (Chrousos and Gold, 1992). However, different authors have defined the term "stress" as forced exposure to events or conditions that are normally avoided by an animal (Piazza and LeMoal, 1998). Different types of stressors have been used in studies about the role of stress in drug addiction in animal models (Lu, Shepard, Hall, and Shaham, 2003; Aguilar et al., 2009). We have classified these stressors in four categories: pharmacological, physical, emotional and social stressors.

Pharmacological Stressors

Various pharmacological agents are able to induce a stress response and subsequent craving or drug-seeking for psychostimulants. The advantages of employing a pharmacological stressor are that the same stressor can be used in different species, the level of stress can be varied by modifying the dose of compound, and the pathways it activates are well identified. The most used pharmacological stressors are noradrenergic compounds and CRF, but there are other agents, such as neuroactive peptides related to central stress responses (vasopressin and substance P) and inverse benzodiazepine agonists, can also be employed (See and Waters, 2010).

Yohimbine

Some studies have used the pharmacological stressor yohimbine (YOH) to induce stress in animals (Buffalari and See, 2011; See and Waters, 2010). YOH enhances anxiety-like behaviors in several paradigms in experimental animals (File, 1986; Johnston and File, 1989; Bijlsma, de Jongh, Olivier, and Groenink, 2010), increases levels of cortisol (Banihashemi and Rinaman, 2006) and has well-characterized stress and anxiety effects in humans (Southwick, Morgan, Charney, and High, 1999).

The use of YOH as a stressor in animal models of drug addiction offers two main experimental and translational advantages. Firstly, it is a homologous method of stress activation across species. Secondly, it has a relatively long half-life of several hours (Hubbard, Pfister, Biediger, Herzig, and Keeton, 1988), allowing the stress to be maintained across the duration of other experimental procedures, such as a session of SA or CPP, as well as during a reinstatement test (Buffalari and See, 2011).

Several studies have successfully used systemic injections of YOH to trigger stress-induced reinstatement of COC and METH seeking in rats (Bongiovanni and See, 2008; Lee et al., 2004; Le, Harding, Juzytsch, Funk, and Shaham, 2005; Shepard, Bossert, Liu, and

Shaham, 2004). Moreover, YOH potentiates conditioned cue-induced reinstatement of COC seeking (Feltenstein and See, 2006; Buffalari and See, 2009a; Buffalari and See, 2011), and increases NA in the amygdala and BNST through the antagonism of α-2 NA receptors (Buffalari and Grace, 2009; Forray, Bustos, and Gysling, 1997; Galvez,Mesches, McGaugh, 1996; Khoshbouei, Cecchi, Dove, Javors, and Morilak, 2002; Tjurmina, Goldstein, Palkovits, and Kopin, 1999). It has been suggested that stress activation via YOH may rely on intact BNST function, since NE receptor blockade in the BNST disrupts COC seeking caused by stress (Leri, Flores, Rodaros, and Stewart, 2002). Alternative mechanisms in the BNST and other brain regions may contribute to the effects of YOH on reinstatement of drug seeking, since it has been shown to have affinity for serotonin (Millan et al., 2000) and DA (Scatton, Zivkovic, and Dedek, 1980) receptors and increases prefrontal NA tone (Garcia et al., 2004). Moreover, the administration of NA in the BNST and CeA also induces the reinstatement of COC SA in rats (Brown, Tribe, D'souza, and Erb, 2009; Brown, Nobrega, and Erb,2010).

Corticotropin-Releasing Factor (CRF)

As explained previously, in the anterior pituitary CRF is the primary neurohormone from which ACTH is released in response to stress, while CRF-containing axon terminals and receptors are present outside the pituitary. Administration of CRF mimics many of the autonomic and behavioral aspects of the stress response (Bale and Vale, 2004; Owens and Nemeroff, 1991). Similarly, centrally-administered CRF (icv or into the VTA) has been reported to induce reinstatement of COC SA (Blacktop et al., 2011; Brown et al., 2009; Brown, Kupferschmidt, and Erb, 2012; Buffalari, Baldwin, Feltenstein, and See, 2012; Erb, Kayyali, and Romero, 2006; Graf et al., 2011; Mantsch et al., 2008; Wang et al., 2005), though not when administered in the CeA (Erb and Stewart, 1999). The CRF2 receptor agonist urocortin II located in the VTA also induces reinstatement of COC SA (Wang et al., 2007).

Other Drugs

The reinstatement of COC SA is achieved by administration of other drugs such as hypocretin (orexin) 1 (Boutrel et al., 2005; Wang et al., 2009), KOR agonists such as U50,488 (Redila and Chavkin, 2008) or spiradoline and enadoline (Valdez, Platt, Rowlett, Rüedi-Bettschen, and Spealman, 2007), and neuropeptide S (Pañeda et al., 2009).

Physical Stressors

Experimental manipulations that consist of exposing the subject to an aversive environmental event, such as footshock, restraint or tail pinch, are considered physical stressors.

Intermittent Shock

Footshock is one of the most commonly used methods of inducing stress (Lu et. al., 2003) and is the primary stimulus for aversive Pavlovian conditioning in rodents (Logrip et al., 2012). The main advantage of this type of stressor is that it is discretely manipulable, since the experimenter can regulate its duration, frequency, intensity, predictability and

controllability (Logrip et al., 2012). Different authors have used intermittent, inescapable footshock in rats and mice to study the effects of stress exposure on the rewarding properties of psychostimulants in the SA and CPP paradigms (for a review see Lu et al., 2003; Shalev, Highfield, Yap, and Shaham, 2000; Shalev, Erb, and Shaham, 2010). The intensity and duration of footshock are variable, although values are generally between 0.1 and 1 mA and 0.1-0.5s, respectively. Frequency of footshock delivery is the total number of shocks or the total time during which shocks are administered (for example 15 min). Exposure to footshock prior to SA and CPP sessions can enhance acquisition, maintenance and reinstatement of psychostimulant intake (Logrip et al., 2012; Lu et al., 2003; Shalev et al., 2010).

It has been suggested that footshock-induced corticosterone secretion mediates the effect of this stressor on psychostimulant SA (Piazza and LeMoal, 1998). Acquisition of COC SA is enhanced in rats exposed to shocks (Goeders and Guerin, 1994) and plasma levels of the corticosterone prior to the test correlate with the initiation of COC SA behavior (Goeders and Guerin, 1996). Moreover, manipulations that reduce or eliminate corticosterone have been shown to decrease COC SA, which can be interpreted as an undermining of the reinforcing efficacy of this drug (Goeders and Guerin, 1996; Marinelli and Piazza, 2002; Piazza and Le Moal, 1997). Similar manipulations of corticosterone secretion decrease psychostimulant-induced locomotor activity and extracellular DA levels in the NAc (Marinelli and Piazza, 2002; Piazza and LeMoal, 1998). In addition, exposure to chronic stressors may involve long-term adaptations in neural mechanisms outside the HPA axis, such as the mesolimbic DA system and extended amygdala (Lu et al., 2003; Shalev et al., 2010).

Restraint or Immobilization

Different studies have employed immobilization or restraint to evaluate the effects of stress on the rewarding properties of psychostimulants and reinstatement after extinction (Lu et al., 2003; Shalev et al., 2000, 2010). In these studies, rats or mice are restrained for several minutes or hours for either 1 day (acute) or several days (repeated daily) in a glass or Plexiglas restraining device.

It has been observed that acute, but not repeated (7 days), restraint one day before CPP training with AMPH enhances the CPP produced by a medium dose (1.5 mg/kg) but not that produced by high or low doses (Capriles and Cancela, 1999, 2002). This enhancement of AMPH CPP by acute restraint is blocked when D2 receptor antagonists are administered prior to exposure to restraint (Capriles and Cancela, 1999). Cancela and colleagues showed that acute restraint enhances AMPH-induced increases in motor activity and extracellular DA levels in the striatum, and that NMDA glutamatergic receptors are involved in these effects (Pacchioni et. al., 2002). Acute exposure to restraint before the reinstatement test also induces the reinstatement of COC (Sanchez et al., 2003) and METH (Qi et al., 2009) CPP.

Restraint of pregnant female rats has been used to study the effects of prenatal stress on the subsequent response of adult offspring to psychostimulants. For example, in one study, restraint stress exposure three times per day for the last 7 days of gestation induced an enhancement in the effects of COC in offspring of 10 weeks of age. Prenatal stressed rats exhibited elevated locomotor activity, enhanced DA levels in the NAcc and PFC, and higher levels of glutamate in the NAcc in response to COC administration. Moreover, although no effects were observed on COC SA, a greater lever response was observed during extinction and COC-primed reinstatement (Kippin, Szumlinski, Kapasova, Rezner, and See, 2008).

Tail Pinch

Although the term "tail pinch" originally referred to a momentary application of pressure (Antelman, Szechtman, Chin, and Fisher, 1975), it now refers to continuous pressure for a period of several minutes (generally between 10 and 20 min) that induces a stress response in rats (Brake, Zhang, Diorio, Meaney, and Gratton, 2004; Marinelli, Quirion, and Gianoulakis, 2004) and mice (Ribeiro Do Couto et al., 2006). Typically animals receive a single session of tail pinch, although the intensity and frequency can vary. For example, in one study in our laboratory mice were individually placed in a transparent plastic cage (23 × 13.5 ×13 cm) and a plastic clothespeg (creating a pressure of 800 g) was fastened to their tails (at 1–1.5 cm from the body) for 15 min (Ribeiro Do Couto et al., 2006).

Tail pinch is considered a mild stressor, and although animals occasionally attempt (without success) to remove the peg, no tissue damage is produced. Stress induced by tail pinch has been found to enhance the initiation of psychostimulant SA (Lu et al., 2003; Piazza, Deminiere, Le Moal, and Simon, 1990; Rougé-Pont et al., 1993).

Tail pinch induces cortisol release (Ribeiro Do Couto et al., 2006) and can also increase DA levels (Keller, Maisonneuve, Nuccio, Carlson, and Glick, 1994; Rougé-Pont et al., 1993). Moreover, it has been reported that COC administration enhances the increase in DA evoked by tailpinch (Kiyatkin, 1993).

Emotional Stressors

This category includes discrete stressors, such as food restriction/deprivation and forced swim, or a combination of multiple stressors known as the chronic unpredictable stress paradigm. These events have been used to study how exposure to stress affects rodent behavioral responses in the CPP and SA paradigms (Aguilar et al., 2009; Lu et al., 2003).

Food Deprivation/Restriction

To induce stress with this procedure, animals are exposed to a regimen that reduces their body weight to an average of 90-80% of free-feeding weight by the beginning of experimental manipulations and maintains it at that level throughout the experiment. This paradigm works by applying acute food deprivation/restriction (typically 24 h of either deprivation or restriction by providing a small 5–8 g ration) or chronic food restriction (several days or weeks of limited access to food) (Lu et al., 2003).

Acute or chronic food restriction significantly increases the initiation and maintenance of psychostimulant SA (Carroll, 1984, 1985; Carroll and Meisch, 1981; Carroll, France, and Meisch, 1981; Carroll, Lac, Walker, Kragh, and Newman, 1986; Glick, Hinds, and Carlson, 1987; Lu et al., 2003; Takahashi et al.. 1978) and enhances COC and AMPH CPP (Bell, Stewart, Thompson, and Meisch, 1997; Stuber, Evans, Higgins, Pu, and Figlewicz, 2002). Acute food deprivation also induces the reinstatement of psychostimulant seeking (Carroll, 1985; Comer, Lac, Wyvell, Curtis, and Carroll, 1995; Shalev, Marinelli, Baumann, Piazza, and Shaham, 2003).

Forced Swim

In this procedure animals are placed in a deep cylindrical container (made of poly-propylene, glass, etc.) filled with water (at 20-25º C) and are forced to swim during a period of several minutes (5-10). In some studies the procedure consists of a single exposure to forced swim (Kreibich et al., 2009; Mantsch et al., 2010), while others submit subjects to chronic exposure prior to the SA or CPP sessions (Kreibich et al., 2009). Chronic forced swim stress enhances acquisition of the CPP induced by COC and a single exposure to forced swim reinstates the extinguished CPP (Kreibich et al., 2009).

The Chronic Unpredictable Stress Paradigm

One model of emotional behavior is the chronic unpredictable stress (CUS) paradigm, which involves exposing mice to a variety of mild stressors in an unpredictable manner.

Following habituation to individual housing, mice undergo two weeks of exposure to different stressors: 1h in a restraint tube, inversion of the light/dark cycle, 2h of access to an empty water bottle, 15h of food restriction, 30 min forced swim 32+/-2ºC water, and 10 min paired housing with damp bedding. During the two weeks of CUS, mice are exposed to 1-3 stressors per day, and are never exposed to the same stressor more than once on the same day (Miller, Ward, and Dykstra, 2008).

Varying results have been reported with the CUS paradigm, including a decrease in the consumption of/preference for sweet foods, disruption of grooming, increase of aggression, more immobility in the forced swim test and increased learned helplessness (reviewed in Willner, 2005). In light of these results, the CUS paradigm is often used as a model of depression, as these effects are reversible by antidepressant treatment (Willner, Towell, Sampson, Sophokleous, and Muscat, 1987). In addition, it has been reported that exposure to CUS may alter the rewarding effects of COC in the CPP paradigm (Miller et al., 2008).

Social Stressors

Considerable evidence points to different kinds of social stress as risk factors for initiation, escalating and relapse to drug abuse (Brady and Sinha, 2005; Brady, Dansky, Sonne, and Saladin, 1998; Shaham et al., 2000; Sinha et al., 2006).

There are different social experiences and conditions which induce social stress in animals, such as maternal deprivation, acute (brief) social stress, intermittent repeated social stress, subordination, crowding and isolation (Lu et al., 2003; Miczek et al., 2008; Ribeiro Do Couto, Aguilar, Lluch, Rodríguez-Arias, and Miñarro, 2009; Shaham et al., 2003). These manipulations can be performed at different ages (adolescence or adulthood) and at different phases of experimental procedures of SA and CPP (acquisition, maintenance, extinction and reinstatement).

Maternal Separation

Early life stress can profoundly affect adult behavior, and childhood trauma is closely associated with the severity of drug dependence (Enoch et al., 2010; Triffleman, Marmar, Delucchi, and Ronfeldt, 1995). Maternal separation/deprivation provides a good model with which to study the protracted effects of childhood trauma in rodents and to observe later

responses to addictive drugs in the SA and CPP paradigms (Logrip et al., 2012; Lu et al., 2003). There are different models of maternal separation/deprivation, and studies vary in the way they enforce separation. One common model involves repeated separation of pre-weaning pups from their mothers for varying periods of minutes (15-180 min) or hours (for example 6h) every day on several consecutive postnatal days (PND), generally on PND 1-2 and PND12-15 (Campbell and Spear, 1999; Faure, Stein, and Daniels, 2009; Kosten, Miserendino, and Kehoe, 2000; Matthews, Robbins, Everitt, and Caine, 1999; Moffett et al., 2006). Other studies have employed a single 24 h period of maternal deprivation on PND9-10 (Llorente-Berzal et al., in press; Martini and Valverde, 2012).

Different studies have been performed to study the effects of maternal separation on acquisition of COC (Kosten et al., 2000; Martini and Valverde, 2012; Matthews et al. 1999; Moffett et al., 2006) and AMPH (Der-Avakian and Markou, 2010) SA and the CPP induced by AMPH (Campbell and Spear, 1999), methamphetamine (Faure et al., 2009) and MDMA (Llorente-Berzal et al., in press). Reinstatement of psychostimulant-seeking may also be modulated by a history of maternal separation (Lynch, Mangini, and Taylor, 2005).

Social Isolation

Some authors use social isolation to induce stress and then compare the effects of this manipulation on behavioural responses to drugs of abuse with those in animals living in groups and interacting socially. The effect of chronic isolation is highly dependent on the age of onset and length of exposure. Social housing at different stages of the SA and CPP procedures can influence the response to drugs of abuse (Ribeiro Do Couto et al., 2009; Schenk, Lacelle, Gorman, and Amit, 1987), with isolated rats showing a greater propensity to self-administered COC (Ding et al, 2005; Kosten et al., 2000; Schenk et al., 1987) and more sensitivity to the reinforcing properties of this drug (Smith, Neill, and Costall, 1997). Neonatal isolation increases the acquisition, maintenance (Lynch et al., 2005; Zhang, Sanchez, Kehoe, and Kosten, 2005), and cue-induced reinstatement of COC SA in adults rats (Lynch et al., 2005). Similarly, isolation during the period just after weaning (termed 'isolation rearing') potentiates DA-dependent behaviours, such as locomotor activity induced by psychostimulant drugs (Hall et al., 1998), and reinstatement of CPP induced by COC priming (Ribeiro Do Couto et al., 2009).

Crowding

Another condition that can induce stress in adult animals is crowding. In one study carried out in our laboratory we induced stress in animals by housing eight mice together in small plastic cages (25x25x14cm). On PND 21, male mice were housed in groups of four (experimental animals), and from PND 60 onwards, a new mouse was introduced into the cage every 2 days until each cage housed a total of eight mice (including four that were not used in the subsequent experimental procedures). We observed that crowding increased the reinstating effects of COC priming on the CPP induced by COC (Ribeiro Do Couto et al., 2009). It is important to note that crowding is not experienced as a stressful experience in adolescent mice (Ribeiro Do Couto et al., 2009).

Acute/Brief Social Defeat

A rodent model of social stress is the paradigm of social defeat. In this model, the effects of suffering a social defeat on the subsequent response of the defeated animal to drugs of abuse are evaluated. There are two main variations of this model according to the paradigm of aggression used: resident/intruder or agonistic encounter in a neutral environment.

In the first, which is more common, a territorial resident rat or mouse confronts and dominates an intruder, which is generally the experimental animal (Miczek et al., 2008). To study the effects of a brief episode of social defeat, an "intruder" is introduced into the home cage of an experienced aggressive male resident, where it is threatened and attacked by the resident until it shows clear signs of submission, usually after a few minutes of confrontation. In other studies, repeated, intermittent agonistic encounters ending in social defeat for the experimental animal are staged. In this case, each brief episode of social defeat consists of three phases. During the initial phase, the intruder's (smaller) home cage is placed inside the resident's cage. The cage protects the intruder from attacks bythe resident but allows social contactand species-typical threats from the male aggressive resident, thus instigating provocation (Covington and Miczek, 2001; Fish, Faccidomo, and Miczek, 1999). In the second phase, the protective cage is removed and the intruder is placed directly into the resident´s chamber for the confrontation, which should last no more than 5 min. A defeat is defined when the intruder displays a supine posture for five consecutive seconds, a response that typically occurs after three to five biting attacks from the resident, at which point the confrontation is terminated. In the third and final phase, the intruder is immediately returned to its protective home cage, which is once more placed inside the larger resident's cage for another 10 min to allow social threats from the resident. Socially defeat-stressed animal are exposed to four episodes of social defeat separated by intervals of 2 days (for example on days 1, 4, 7 and 10) (Torntzky and Miczek, 1993; Quadros and Miczek, 2009). Repeated, intermittent exposure to brief episodes of social defeat stress can produce persistent long-term consequences in rats and mice, including faster acquisition of drug SA (Kabbaj, Isgor, Watson, and Akil, 2001; Tidey and Miczek, 1997).

Although both resident and intruder usually exhibit increased corticosterone secretion, only stressed intruders engage in escalated patterns of psychostimulant SA; for example, with COC (Covington and Miczek 2001, 2005; Covington et al., 2005; Kabbaj et al., 2001; Miczek and Mutschler, 1996; Nikulina, Marchand, Kream, and Miczek, 1998) and AMPH (Miczek et al., 1999a; Yap and Miczek, 2007). On the other hand, it has been demonstrated that brief episodes of social defeat engender neural, physiological and behavioral effects which contrast with those caused by continuous subordination stress (Covington and Miczek, 2005; Fuchs, Czéh, and Flügge, 2004; Kozorovitskiy and Gould, 2004; Miczek, Nikulina, Kream, Carter, and Espejo, 1999b; Sgoifo, Koolhaas, Alleva, Musso, and Parmigiani, 2001; Razzoli, Carboni, Guidi, Gerrard, and Arban, 2007; Tornatzky and Miczek, 1993, 2001). Besides the increase in plasma corticosterone levels (Hucklebridge and Nowell, 1974; Miczek et al., 1999b), brief episodes of social defeat stress produce long-lasting sensitized neural responses to psychomotor stimulant challenge, particularly in the VTA, and decrease activation in the medial PFC (Covington et al., 2005; Nikulina et al., 2004).

In the second paradigm the experimental animal suffers social defeat in an aggressive social encounter with a conspecific of equal age and body weight (Ribeiro Do Couto et al., 2006). Aggressive opponents are housed individually for a month prior to encounter, since this isolation schedule heightens aggression in mice (Rodriguez-Arias, Miñarro, Aguilar,

Pinazo, and Simón, 1998). An agonistic encounter of 15 min takes place in a neutral transparent plastic cage. Experimental mice exhibit avoidance/flee and defensive/submissive behaviours after suffering the aggressive behaviours (threat and attack) of the opponent, which has been individually housed, has had previous fighting experience, and has been screened for a high level of aggression. The criterion used to define an animal as defeated is the adoption of a specific posture of defeat, characterized by an upright position, limp forepaws, upwardly angled head, and retracted ears (Miczek, Thompson, and Shuster, 1982). Defeated mice always exhibit this extreme form of "upright submissive" behaviour (Rodríguez-Arias et al., 1998). This type of social defeat produces an increase in corticosterone levels and enhanced priming-induced reinstatement of the CPP induced by COC (Ribeiro Do Couto et al., 2009).

EFFECTS OF STRESS ON THE ACQUISITION AND REINSTATEMENT OF PSYCHOSTIMULANT SELF-ADMINISTRATION

In experimental models, acute exposure to different stressful experiences can promote psychostimulant use and increase the escalation of consumption (Covington and Miczek 2001, 2005: Goeders and Guerin 1994; Haney, Maccari, Le Moal, Simon, and Piazza, 1995; Kosten et al., 2000; Miczek and Mutschler, 1996; Piazza et al., 1990; Ramsey and van Ree, 1993; Shaham and Stewart, 1994). Moreover, chronic stress exposure increases drug craving (Shaham et al., 2000, 2003; Sanchez et al., 2003). Animal models of stress-induced reinstatement of drug-seeking also allow the neuropharmacological and neurobiological features of stress-induced relapse to be determined (See and Waters, 2011). As discussed previously, these stressful experiences can enhance SA of COC and AMPH and induce reinstatement of psychostimulant seeking by acting on the VTA-NAcc-medial PFC-extended amygdala circuit (Yap and Miczek, 2008; Koob, 2010).

Effects of Stress on Acquisition of Psychostimulant Self-Administration

The ability of stressors to alter the acquisition of psychostimulant SA in rats has received considerable attention (Goeders, 2003; Lu et al., 2003; Piazza and Le Moal, 1998). In the present chapter, we summarize the data obtained by studies of the effects of environmental stressors on acquisition of psychostimulant SA conducted during the last ten years (see Table 1).

Intermittent *footshock* can increase COC SA behavior in adult rats subjected to different training procedures (Ramsey and Van Ree, 1993; Sanchez and Sorg, 2001). One study reported enhanced acquisition of COC SA in rats administered footshock during sessions of food SA immediately prior to sessions of COC SA (Goeders and Guerin, 1994). Ramsey and Van Ree (1998) found that when rats observed another rat receiving a footshock just before acquisition sessions initiated COC SA with a very low dose (0.031 mg/kg/infusion). Thus, footshock stress itself or the psychosocial experience of witnessing a conspecific receive footshock appears to enhance acquisition of COC SA.

Table 1. Effect of stress on psychostimulant self-administration

Authors	Year	Drug	Stressor	Process	Animal	Effects
Anker & Carroll	2010	COC	YOH	reinstatement	rat	Reinstatement of drug seeking
Beardsley et al.	2010	COC	footshock	reinstatement	rat	Reinstatement of drug seeking (RTI-194 blocks reinstatement).
Beardsley et al.	2005	COC	footshock	reinstatement	rat	Reinstatement of drug seeking (JDTic reduces reinstatement)
Blacktop et al.	2011	COC	footshock	reinstatement	rat	Reinstatement of drug seeking (Bilateral intra-VTA CRF produced reinstatement in long-acces)
Bongiovanni & See	2008	COC	YOH	reinstatement	rat	Reinstatement of drug seeking (YOH increases cue-induced reintatement)
Boutrel et al.	2005	COC	hypocretin	reinstatement	rat	Reinstatement of drug seeking (blockade of NA and CRF blocks reinstatement)
Brown & Erb	2007	COC	footshock	reinstatement	rat	Reinstatement of drug seeking
Brown et al.	2012	COC	YOH	reinstatement	rat	Reinstatement of drug seeking (SCH23390 and SCH31966, but not raclopride, blocked reinstatement
Buffalari & See	2009	COC	footshock	reinstatement	rat	Reinstatement of drug seeking
Buffalari & See	2011	COC	YOH	reinstatement	rat	Reinstatement of drug seeking (YOH increases cue-induced reintatement)
Campbell & Carroll	2001	COC	food restriction	acquisition	rat	Speed up acquisition of SA
Capriles et al.	2003	COC	footshock	reinstatement	rat	Reinstatement of drug seeking (SCH 23390 prevents reinstatement)
Carroll	1985	COC	food restriction	acquisition	rat	Increase the maintenance of cocaine SA
				reinstatement		Reinstatement of drug seeking
Carroll et al.	1981	COC	food restriction	acquisition	rat	Increases SA
Carroll et. al.	1986	COC	food restriction	acquistion	rat	Increases SA
Conrad et al.	2010	COC	forced swim	reinstatement	rat	Reinstatement of drug seeking
Covington & Miczek	2001	COC	social defeat	acquisition	rats	Increased SA and breaking point.
Covington et al.	2005	COC	social defeat	acquisition	rat	Escalated pattern of SA
Cruz et al.	2011	COC	social defeat	acquisition	rat	Escalated pattern of SA
de Guglielmo et al.	2012	COC	YOH	reinstatement	rat	Reinstatement of drug seeking (pregabalin abolishes reinstatement)
De Vry et al.	1989	COC	food restriction	acquisition	rat	Speed up acquisition of SA
Ding et al.	2005	COC	isolation	acquisition	rat	Increases SA
Erb et al.	1996	COC	footshock	reinstatement	rat	Increases SA
Erb et al.,	2000	COC	footshock	reinstatement	rat	Reinstatement of drug seeking (Clonidine and lofexidine attenuate reinstatement)
Erb et al.,	2001	COC	footshock	reinstatement	rat	Reinstatement of drug seeking
Erb et. al.,	2004	COC	footshock	reinstatement	rat	Reinstatement of drug seeking
Feltenstein & See	2006	COC	YOH	reinstatement	rat	Reinstatement of drug seeking (exposure to drug-paired cues potentiates reinstatement)
Feltenstein et al.	2011	COC	YOH	reinstatement	rat	Reinstatement of drug seeking (females demostrated higher reinstatement)
Figueroa-Guzman et al.	2011	COC	footshock	reinstatement	rat	Reinstatement of drug seeking (l-THP attenuates reinstatement)
Fuchs et al.	2008	COC	footshock	reinstatement	rat	Reinstatement of drug seeking (inactivation of NAC attenuated reinstatement)
Glick et al.	1987	COC	food restriction	acquisition	rat	Increases SA
		AMPH				Increases SA
Goddard & Leri	2006	COC	footshock	reinstatement	rat	Reinstatement of drug seeking
Goeders & Guerin	1994	COC	footshock	acquisition	rat	Increases SA
Graf et al.,	2011	COC	footshock	reinstatement	rat	Reinstatement of drug seeking (Alpha-helical CRF9-41 blocks reinstatement)
			CRF			
Haney et al.,	1995	COC	social defeat	acquisition	rat	Increases SA
Highfield et al.	2002	COC	food restriction	reinstatement	rat	Reinstatement of drug seeking
Howes et al.	2000	COC	isolation	acquisition	rat	Increases SA at low doses but slows it at high dose
Kabbaj et al.	2001	COC	social defeat	acquisition	rat	Increases SA
Kippin et al.	2008	COC	prenatal stress	acquisition	rat	No effects
				reinstatement		Increase reinstatement of drug seeking
Kosten et al.	2000	COC	neonatal isolation	acquisition	rat	No effects
Kupferschmidt et al.	2012	COC	footshock	reinstatement	rat	Reinstatement of drug seeking (AM251 does not block reinstatement)
			CRF			Reinstatement of drug seeking (AM251 prevents reinstatement)
Kupferschmidt et al. (a)	2011	COC	footshock	reinstatement	rat	Reinstatement of drug seeking (influence of the intensity and duration of footschock)
Kupferschmidt et al. (b)	2011	COC	footshock	reinstatement	rat	Reinstatement of drug seeking (TCAP-1 does not block reinstatement)
			CRF			Reinstatement of drug seeking (TCAP-1 blocks reinstatement)
Kupferschmidt et al.	2009	COC	YOH and footshock	reinstatement	rat	Reinstatement of drug seeking (influence of exposure to stress during extinction)
Land et al.	2009	COC	social defeat	reinstatement	mice	Reinstatement of drug seeking
Leri et al.	2002	COC	footshock	reinstatement	rat	Reinstatement of drug seeking (B1/B2 antagonists attenuates reinstatement)
Lynch et al.	2005	COC	neonatal isolation	acquisition	rats	Increases SA
				reinstatement		Reinstatement of drug seeking
Mahler et al.	2012	METH	YOH	reinstatement	rat	Reinstatement of drug seeking
Mantsch & Katz	2007	COC	footshock	acquisition	rat	Escalated pattern of SA
Mantsch et al.	2008	COC	footshock and CRF	reinstatement	rat	Reinstatement of drug seeking (greater in long-access)
Martin-Fardor & Weiss	2012	COC	footshock	reinstatement	rat	Reinstatement of drug seeking (LY379268 and MTEP prevent reinstatement)
Martini & Valverde	2012	COC	maternal separation	acquisition	mice	Increases SA
Matthews et al.	1999	COC	maternal separation	acquisition	rat	Increases SA in male and decreases in female rats
Miczek et. al.	2011	COC	social defeat	acquisition	rat	Increases SA
Moffett & Goeders	2005	METH	footshock	acqusition	rat	Decreases SA
Moffett et al.	2006	COC	maternal separation	acquisition	rat	Increaes SA (low doses)
Nawata et al.	2012	METH	footshock	reinstatement	rat	Reinstatement of drug seeking (CRF receptor antagonist block reintatement)
Papasava & Singer	1985	COC	food restriction	acquisition	rat	Increases SA
Piazza et al.	1990	AMPH	tail pinch	acquisition	rat	Increases SA
Piazza et al.	1989	AMPH	prenatal stress	acquisition	rat	Increases SA
Quadros & Mizcek	2009	COC	social defeat	acquisition	rat	Escalated pattern of SA, increased break points
Ramsey & van Ree	1993	COC	footshock	acquisition	rat	Increases SA
Ribeiro Do Couto et al.	2009	COC	social defeat	reinstatement	mice	Increases reinstatement induced by priming
Rougé-Pont et al.	1993	AMPH	tail pinch	acquisition	rat	Increases SA
Sanchez & Sorg	2001	COC	footshock	reinstatement	rat	Reinstatement of drug seeking
Shaham et al.	1998	COC	footshock	reinstatement	rat	Reinstatement of drug seeking
Shalev et al.	2003	COC	food restriction	reinstatement	rat	Reinstatement of drug seeking (CP-154,526 attenuates reinstatement)
Shepard et al.	2004	METH	YOH and footschock	reinstatement	rat	Reinstatement of drug seeking
Sorge et al.	2005	COC	footshock	reinstatement	rat	Reinstatement of drug seeking (buprenorphine does not affect reinstatement)
Soria et al.	2008	COC	footshock	reinstatement	mice	Reinstatement of drug seeking
Tidey & Miczek	1997	COC	social defeat	acquisition	rat	Increases SA
Wang et al.	2009	COC	hypocretin	reinstatement	rat	Reinstatement of drug seeking
Wang et al.	2007	COC	footshock	reinstatement	rat	Reinstatement of drug seeking (CRF2 antagonists prevent reinstatement)
Wang et al	2005	COC	footshock	reinstatement	rat	Reinstatement of drug seeking (CRF is necessary)
Xi et al.	2004	COC	footshock	reinstatement	rat	Reinstatement of drug seeking (SB-277011A attenuates reinstatement)
Yap & Miczek	2008	COC	different stressors	acquisition	rat	Increases SA
		AMPH				
				reinstatement		Reinstatement of drug seeking
Yoon et al.	2012	COC	footshock	reinstatement	rat	Reinstatement of drug seeking (acupuncture reduces reinstatement)
Zhang et al.	2005	COC	neonatal isolation	acquisition	rat	Enhances maintenance of SA
Zhou et al.	2012	COC	YOH	reinstatement	rat	Reinstatement of drug seeking (orexin antagonists block reinstatement)

The capacity of repeated daily exposure to electric footshocks to escalate COC SA has been also investigated. Male Sprague-Dawley rats were trained to self-administer COC during 2-h sessions comprised of four 30-min SA components. Repeated daily footshock was delivered 5 min before each of the four SA components over 14 days of SA testing. Daily exposure to 4 alternating blocks of 5-min footshock / 30-min COCSA triggered a significant escalation in COC SA that lasted for the whole 14-day experimental period (Mantsch and Katz, 2007). In the study in question, it was also observed that adrenalectomy plus

corticosterone replacement prevented footshock-induced escalation of COC SA, indicating that the escalating effects of footshock were dependent on increases in circulating levels of glucocorticoids.

Elevation of corticosterone through repeated daily injections failed to reproduce the effects of repeated daily footshock on SA, but restored the effects of footshock on escalated COC SA in adrenalectomized rats receiving corticosterone replacement, suggesting that a rise in glucocorticoid levels was necessary but not enoughon its own to produce said escalation (Mantsch and Katz, 2007). These studies indicate that exposure to footshock can increase both acquisition and maintenance of COC intake, although further investigation is required to differentiate between the short- and long-term effects of this stressor on psychostimulant SA. In contrast with that observed with COC, electric footshock exposure does not increase METH SA in adult male Wistar rats (Moffett and Goeders, 2005). Following initial food training, rats were allowed to self-administer METH at doses that were doubled weekly. Neither non-contingent electric footshock nor treatment with corticosterone altered the lowest dose at which the rats first acquired METH SA. These results suggest that the HPA axis does not have a major role in the acquisition of METH SA.

In addition, several studies have shown that acute food deprivation or restriction (24-hr deprivation of food or restriction of food supply to 5–8 g per day in rats) or chronic food restriction (i.e., multiple days or weeks of limited access to food) significantly increases the initiation and maintenance of psychostimulant SA (Yap and Miczek, 2008). Takahashi et al. (1978) reported that chronic restricted feeding to 80% of free feeding body weight brought forward AMPH SA over a range of unit doses (0.05–0.8 mg/kg). These findings have been extended to the initiation and maintenance of COC SA (De Vry, Donselaar, and Van Ree, 1989; Papasava and Singer, 1985), and it has been reported that the effect of food deprivation is much more pronounced on COC than on AMPH SA (Glick et al., 1987). Carroll and colleagues reported that acute food restriction (8 g of food every third day) increased COC SA during the maintenance phase (Carroll, 1985; Carroll et. al., 1981, 1986). Moreover, mild chronic deprivation (20 g/day) also speeded up COC SA (Campbell and Carroll, 2001).

Stress induced by tail pinch also enhances AMPH SA in rats (Piazza et al., 1990). Rougé-Pont et al. (1993) observed that this stressor induced an increase in DA levels and suggested that this biochemical modification was related with the enhanced predisposition to acquire psychostimulant SA in animals with higher DA activity in the NAcc (Rougé-Pont et al., 1993). In another study tail pinch produced a significant increase in DA in rats that had been exposed prenatally to COC (Keller et al., 1994).

Prenatal and neonatal stress also increases psychostimulant SA. The group of Piazza et al. performed a study in which female dams were restrained during the last week of pregnancy (45 min per day, for 3 days). Subsequently, adult offspring were trained to self-administer a low dose of AMPH (0.03 mg/kg/infusion) in five daily sessions. The authors observed drug SA only in rats in the prenatal stress group, and not in control animals (Piazza, Deminière, Le Moal, and Simon, 1989; Piazza and LeMoal, 1998). On the other hand, Kippin et al. (2008) assessed the influence of maternal stress during gestation (restraint stress three times per day for the last 7 days of gestation) on COC SA behavior in offspring at 10 weeks of age. Prenatal stress did not increase active lever pressing or alter intake of COC during SA, though it did enhance motivational responsiveness to COC during extinction and reinstatement (Kipping et al., 2008).

Neonatal isolation increases the acquisition and maintenance of COC SA in adult rats (Lynch et al., 2005; Zhang et al., 2005). Maternal separation also differentially modulates adult responses to psychostimulants in accordance of the severity of said separation. Neonatal handling blunts male rats' locomotor responses to acute doses of COC (Brake et al., 2004), while mice with a history of extended maternal separation display higher locomotor sensitization to COC (Kikusui, Faccidomo, and Miczek, 2005), an effect not observed in the case of AMPH, strangely enough (Weiss, Domeney, Heidbreder, Moreau, and Feldon, 2001). Matthews et al. studied the effect of maternal separation (3-6 h/day for 10 days, between PND 5 and 20) on the initiation of COC SA in male and female rats. Maternally deprived male rats showed a downward shift in the dose–response curve for the rate of intravenous COC self-administration in adulthood, while their female counterparts self-administered more COC than their respective controls (Matthews et al., 1999). In a similar line, Kosten et al. (2000) reported that maternal separation (for 1 h/day between the age of 2 and 9 days) increased the acquisition of COC SA. Longer periods of maternal separation (180 min, PND2-15) increase the rewarding effects of COC, while shorter periods of maternal separation (15 min, PND2-15) blunts the reinforcing effects of this drug, which suggests that extended maternal separation heightens sensitivity to the reinforcing effects of low doses of COC (Moffett et al., 2006). Recently, Martini and Valverde (2012) observed that 24h of MD on PND9 increased the time required for meeting the acquisition criteria of COC SA and reduced breaking point values in a progressive schedule in maternally deprived adolescent mice, pointing to an impairment of rewarding functions. Behavioural tests have also confirmed an increase in anxiety- and depression-related behaviours in these animals, which exhibit a decrease in BDNF levels in the amygdala and hippocampus (Martini and Valverde, 2012).Research also indicates an enhancement of the facilitatory effect of psychostimulants on brain reward function following a history of extended maternal separation. AMPH treatment reduces threshold currents for intracranial self-stimulation of the lateral hypothalamus to a greater degree in rats with a history of maternal separation than in controls (Der-Avakian and Markou, 2010).

Since the main source of stress in humans is social interaction, stress induced in rodents by *social defeat* in an agonistic encounter may represent a stressor of ecological and ethological validity (Tornatzky and Miczek, 1993) that increases vulnerability to acquiring and maintaining COC SA and reinstatement of drug-seeking behaviours in these animals (Miczek et al., 2008). Social defeat promotes and intensifies COC SA when assessed by performance in a progressive ratio schedule and in conditions of extended binge-like access (Boyson, Miguel, Quadros, Debold, and Miczek, 2011; Covington and Miczek, 2001, 2005; Covington et al., 2008; Cruz, Quadros, Hogenelst, Planeta, and Miczek, 2011; Haney et al., 1995; Kabbaj et al., 2001; Miczek and Mutschler, 1996; Miczek et al., 2008; Nikulina et al. 1998; Tidey and Miczek, 1997). Four brief episodes of social defeat stress over the course of one week increase the acquisition of a low dose of COC iv SA in both male (Haney et al., 1995, Tidey and Miczek, 1997) and female rats (Haney et al., 1995). Under conditions of unlimited access to COC for 24 h (binge), socially defeated rats self-administer COC with shorter inter-infusion intervals, thus consuming higher quantities (Covington and Miczek, 2005). Once COC SA is established, brief episodes of social defeat stress prior to each experimental session can increase the rate of drug intake significantly, particularly at lower doses (Miczek and Mutschler, 1996). While defeat immediately prior to operant sessions increases COC SA, progressively longer delays between social defeat exposure and COC SA

training dissipates the effects of stress on acquisition (Covington and Miczek, 2001; Covington et al., 2005). More recently, it has been demonstrated that intermittent defeats increase COC consumption and rates of response during binges (Covington et al., 2008). Moreover, it has been reported that previous exposure to brief episodes of social defeat stress intensifies the escalation of COC SA associated with extended access conditions in rats. In one study, four episodes of social defeat stress induced cross-sensitization to a COC challenge, increased breaking points for COC SA, and produced persistent, escalated COC taking during a 24-h binge (Quadros and Miczek, 2009).

The capacity of social defeat to heighten sensitivity to a drug's stimulant effects and escalation of drug intake has been associated with stress-induced neuroadaptations in brain reward pathways (Miczek et al., 2008; Shalev et al., 2002). Brief social stress can produce enduring neural sensitization expressed through immediate early gene activation in the mesocorticolimbic circuit, and this defeat stress-induced sensitization can be responsible for increased COC SA (Covington and Miczek, 2001). Cross-sensitization between these brief stressors and stimulant drugs suggests shared neural mechanisms in rodents (Covington and Miczek, 2001; Pacchioni, Cador, Bregonzio, and Cancela, 2007; Yap and Miczek, 2007). In one study, the relationship between behavioral sensitization, induced by either social defeat or an AMPH, and intravenous COCSA was explored in mice. Male mice were exposed to a defeat experience, an AMPH or saline injection every day for 10 days. Ten days after the last defeat or injection, mice were challenged with AMPH and then trained to nose poke for iv COC. Repeated social defeat produced a sensitized motor response to AMPH challenge. AMPH-pretreated mice exhibited increased COC SA during acquisition and elevated breaking points during their performance in a progressive ratio schedule of reinforcement when compared to stress-sensitized and control animals. Thus, contrary to that seen in rats, increased levels of COC SA are seen in AMPH-pretreated mice but not after repeated defeat stress (Yap and Miczek, 2008). On the other hand, in spite of strong evidence suggesting that social defeat promotes escalated COC SA, it remains to be determined whether or not the consequences of social defeat are generalized in escalated patterns of intake of psychostimulants besides COC (Cruz et al., 2011).

Subordination, an alternative type of social stress, induces the opposite effects to episodic social defeat (Miczek, Nikulina, Shimamoto, and Covington, 2011). The latter stress consists of four brief confrontations between the experimental rat and an aggressive resident rat over the course of 10 days. The former stress involves continuous exposure to an aggressive resident for five weeks while living in a protective cage within the resident's home cage, with the brief daily confrontations that this provokes. While episodically defeated intruder rats exhibit increased iv COC SA under a fixed ratio schedule with prolonged binge-like access, subordination stress suppresses COC intake. Moreover, a sensitized DA response in the NAcc and increased tegmental BDNF has been observed in episodically defeated rats, whereas the DA and BDNF responses of continuously subordinated rats were inhibited (Miczek et al., 2011). It is likely that intermittency and controllability of social stress experience contributes to the effects observed.

An important factor that can influence the effects of stress on psychostimulant SA is the age of the animal, since the impact of social stressors during adolescence can dramatically influence neural development. In adult rodents, repeated intermittent exposures to a psychomotor stimulant progressively augment behavioral effects (i.e. behavioral sensitization), whereas adolescents are far less sensitive to the effects of repeated COC or

AMPH administration (Bolanos, Glatt, and Jackson, 1998; Collins and Izenwasser, 2002; Lanier and Isaacson, 1977). Social isolation during adolescence enhances the acquisition of iv COC SA at low unit doses but decreases the acquisition of high unit doses, which points to a leftward shift in the dose–response curve for COC response (Howes, Dalley, Morrison, Robbins, and Everitt, 2000). Using a fixed ratio schedule of reinforcements, it has been observed that adolescent rats deprived of social interactions self-administered more COC than non-isolated rats (Ding, Belin, and Piazza, 2005). The effects of social defeat can also differ between adolescent and adult animals. Social defeat stress attenuates the induction of behavioral sensitization to a subsequent COC challenge in adolescent hamsters (Trzcinska, Bergh, DeLeon, Stellar, and Melloni, 2002). Moreover, the induction of behavioral sensitization to AMPH in adult rats is attenuated by repeated experience of social defeat at the hands of an older and larger aggressor during adolescence (Kabbaj et al., 2002).

Effects of Stress on the Reinstatement of Pyschostimulant Self-Administration

Stressful life experiences, as well as promoting drug abuse, can trigger relapse after long-term periods of abstinence (Brady and Sinha, 2005; Shaham et al., 2000). Reinstatement of drug seeking after extinction of SA is the most used animal model of the propensity to relapse to drug taking after prolonged drug use and discontinuation (Lu et al., 2003; See, Fuchs, Ledford, and McLaughlin, 2003; Shaham et al., 2000; Shaham et al., 2003) and involves mechanisms related to the development and expression of craving (Gerber and Stretch, 1975; Stewart and Wit, 1987).

Many studies have employed the reinstatement procedure of the SA paradigm to explore the relationship between stress and relapse, demonstrating that stress is clearly associated with increased reinstatement of psychostimulant seeking (Yap and Miczek, 2008; Anker and Carroll, 2010a). In this procedure, mice and rats are trained to respond in order to access drug infusions, typically by pressing a lever. Subsequently, following extinction of the drug-reinforced response, the ability of certain stressors to induce non-reinforced pressing of the drug-associated lever (reinstatement) is determined. A number of excellent reviews on the reinstatement of extinguished drug seeking have been published (Goeders, 2002a; Goeders, 2003; Shaham et al., 2003; Lu et al., 2003; Shalev et al., 2002), and so we wish to merely summarize the data obtained by studies of the effects of environmental stressors on reinstatement of drug seeking previously reinforced by psychostimulant drugs conducted during the last ten years (see Table 1).

Previously published studies have tended to employ intermittent *footshock* to induce reinstatement of psychostimulant-seeking behavior (Ahmed and Koob, 1997; Beardsley, Howard, Shelton, and Carroll, 2005; Beardsley, Shelton, Hendrick, and Johnson, 2010; Blacktop et al., 2011; Boutrel et al., 2005; Erb, Shaham, and Stewart, 1996; Erb, Lopak, and Smith, 2004; Figueroa-Guzman et al., 2011; Graf et al., 2011; Kupferschmidt, Klas, and Erb, 2012; Martin-Fardor and Weiss, 2012; Nawata et al., 2012; Shaham et al., 2000; Stewart, 2000; Wang et al., 2007; Xi et al., 2004; Yoon et al., 2012) and to study the neural substrates of stress-induced reinstatement (Erb et al., 2001; McFarland et al., 2004).

In fact, footshock stress has been was found to be as effective as priming injections of drugs in inducing high response levels in reinstatement tests employing different

psychostimulants, doses, schedule requirements, footshock parameters, and strains of rats (Lu et al., 2003; Shaham et al., 2000, 2003). Footshock has also been shown to induce reinstatement of COC SA in mice (Soria, Barbano, Maldonado, and Valverde, 2008).

Although footshock-induced reinstatement of psychostimulant seeking can be achieved reliably and robustly, it can be sensitive to certain procedural variables, such as the procedure of extinction and reinstatement test sessions, the intensity and duration of the footshock stress, and the presence of drug-associated cues during extinction and reinstatement (Kupferschmidt, Brown, and Erb, 2011).

For example, footshock stress-induced reinstatement of COC may be affected by the history of drug use, the time since drug taking ceased and the interval between stress exposure and reinstatement test.

Exposure to 15 min of intermittent, inescapable, footshock stress induces suppression of response at early time points (after 1 day of extinction) but enhances reinstatement progressively over time in rats with more exposure to COC, in whom reinstatement is stronger 60 days after extinction (Sorge and Stewart, 2005).

The reinstating effects of acute footshock have been shown to persist for up to 40 min (but not 60 min) after a single session of intermittent footshock (Brown and Erb, 2007). Rats self-administered COC under long-access (6h daily) conditions for 14 days are more susceptible to footshock induced reinstatement than those exposed to short-access conditions (2h daily) (Mantsch et al., 2008).

Footshock stress can induce reinstatement by reactivating the motivational value of COC-conditioned cues. In this sense, Goddard and Leri (2006) reported that footshock stress can induce the reinstatement of operant responding maintained by a COC-conditioned stimulus in rats never trained to actively self-administer COC.

More recently, Buffalari and See (2009) examined whether three different levels of intermittent footshock would trigger reinstatement or potentiate reinstatement of COC-seeking caused by conditioned cues.

In their study, male rats underwent daily i.v. COC SA, followed by extinction of lever responding in the absence of previously COC-paired cues. Reinstatement of COC-seeking was measured during presentation of COC-paired cues, following pretreatment with three levels of intermittent footshock (0.25, 0.5, and 0.75 mA) or footshock plus cues.

Footshock at the 0.5 and 0.75 mA levels (without cues) led to significant reinstatement and also potentiated the reinstatement triggered by the presentation of conditioned cues. These results demonstrate that stress and drug-paired cues interaction leads to stronger reinstatement (Buffalari and See, 2009).

YOH induces reinstatement of COC SA in rats (Anker and Carroll, 2010b; Brown et al., 2012; de Guglielmo et al., 2012; Zhou et al., 2012) and markedly increases cue-induced reintatement of COC seeking in rats (Bongiovanni and See, 2008; Feltenstein and See, 2006; Feltenstein, Henderson, and See, 2011; Lee et al., 2004), with a greater increase being noted in females (Feltenstein et al., 2011).

In addition, it reinstates METH SA (Shepard et al., 2004; Mahler et al., 2012). Different studies have shown that YOH potentiates conditioned cue-induced reinstatement of COC seeking (Feltenstein and See, 2006; Buffalari and See 2009a; Buffalari and See, 2011).

In another study, Kupferschmidt et al. (2009) investigated whether repeated exposure to YOH during extinction training affects the time-course of extinction and the magnitude of subsequent YOH- or footshock-induced reinstatement of COC seeking. Rats trained to self-

administer COC were given five days of extinction training, during which they were injected with YOH. Following additional extinction training in the absence of YOH, animals were tested for YOH- or footshock- induced reinstatement Animals injected with YOH during extinction showed an attenuated rate of extinction, and, following additional extinction training in the absence of YOH, a marked attenuation of YOH-induced reinstatement of COC seeking.

YOH treatment during extinction did not, however, affect the magnitude of reinstatement induced by footshock. These findings demonstrate that repeated exposure to a stressor during extinction training can modulate extinction learning and the subsequent reinstatement of drug seeking induced by that stressor (Kupferschmidt, Tribe, and Erb, 2009).

Dietary restriction is another method used to promote appetitive drug-seeking in the operant context.

Acute (1 day) food restriction and/or deprivation (no food) can act as a stressor to facilitate the reinstatement of COC seeking behavior (Bongiovanni and See, 2008; Carroll, 1985; Highfield, Mead, Grimm, Rocha, and Shaham, 2002; Shaham et al., 2003; Shalev et al., 2003).

Cold swim stress also induces the reinstatement of COC-seeking behavior in rats trained to self-administer COC after 16 days of extinction. Indeed, the reinstating effects of stress are evident even 3 days after stress exposure (Conrad et al., 2010). A previous study has reported that a history of COC consumption and prolonged (14 days) abstinence can increase the endocrine response to stress (enhanced corticosterone levels after cold swim in COC vs. saline treated rats), which may facilitate the reinstatement of drug-seeking behavior (Cleck, Ecke, and Blendy, 2008).

Maternal stress during gestation (restraint stress three times per day for the last 7 days of gestation) also can affect the reinstatement of COC SA. In offspring of 10 weeks of age, prenatal stress promotes active lever responding both during extinction and COC-primed reinstatement, but not during conditioned-cued reinstatement (Kippin et al., 2008). A history of *maternal separation* can also modulate the reinstatement of psychostimulant-seeking. Zhang and colleagues (2005) found no significant alteration of COC-induced reinstatement in adult rats that had experienced 1-h maternal isolation, a paradigm involving not only maternal separation but also isolation from littermates.

However, the same isolation paradigm has been shown to yield increased cue-induced reinstatement (Lynch et al., 2005). Additional studies employing maternal separation and brief handling are required to fully understand the impact of neonatal handling on reinstatement and the magnitude of relapse to drug-seeking after periods of abstinence.

To date, no studies have employed stressful events of a more ethological relevance, such as social defeat, to evaluate the effect of stress on reinstatement of psychostimulant SA. Only two studies have used social defeat stress as a trigger for reinstatement of the CPP induced by morphine (Ribeiro Do Couto et al., 2006) or COC (Land et al., 2009).

Similarly, only one study in the CPP paradigm has evaluated the effects of social stressors such as isolation, crowding and social defeat to modulate the priming-induced reinstatement of COC CPP (Ribeiro Do Couto et al., 2009). These studies are described in the following section. In this way, the capacity of social stressors to reinstate psychostimulant SA has yet to be determined.

EFFECTS OF STRESS ON THE ACQUISITION AND REINSTATEMENT OF PSYCHOSTIMULANT CONDITIONED PLACE PREFERENCE

Effects of Stress on the Acquisition of the Conditioned Place Preference Induced by Psychostimulants

Several studies have found that exposure to different stressors (forced swim, maternal deprivation, social defeat, etc.) can modify the rewarding effects of psychostimulants in the CPP paradigm (see Table 2). However, in contrast to the results observed with the SA paradigm, stress induced by tail or foot shock does not modify the rewarding effects of COC or AMPH in the CPP paradigm. For example, a single session of an uncontrollable, inescapable tailshock prior to CPP has been shown to have no effect on the CPP responses to COC in male rats (Der-Avakian et al., 2007). In a similar way, footshock stress in adolescence does not alter adult AMPH CPP (Burke, Watt, and Forster, 2011), while exposure to restraint stress (during 2h) in adolescence (PND 35) undermines the subsequent acquisition of CPP induced by a low dose of AMPH (0.5 mg/kg), in adulthood (Richtand et al., 2012). These results suggest that emotional or social stressors may have a greater impact than footshock on the response to drugs in the CPP paradigm.

Using the chronic unpredictable stress (CUS) paradigm, a model of emotional behavior, it has been reported that mice exposed to a variety of mild stressors (restraining, inversion of the light/dark cycle, access to an empty water bottle, food restriction, forced swim and housing with damp bedding) in an unpredictable manner can modify the rewarding effects of COC in the CPP paradigm. Exposure to CUS significantly increases COC CPP in CB1-KO mice, but tends to decrease it in wild-type mice with respect to untreated mice (Miller et al., 2008).

Chronic food restriction also increases the acquisition of psychostimulant CPP, although the effects seem to be in function of the dose used. Food restriction to 80% of free-feeding body weight modestly increases COC CPP for a medium dose (5 mg/kg), but not for lower (2.5 mg/kg) or higher (10 mg/kg) doses (Bell et al., 1997). Mild chronic food restriction of 15 g/day (90% of free-feeding body weight) enhances AMPH CPP for a moderate dose (0.85 mg/kg), but decreases preference for two higher doses (1.7 and 3.4 mg/kg) (Stuber et al., 2002). Mice previously exposed to repeated forced swim show a significantly greater preference for the side paired with COC (Mc Laughlin et al., 2003, 2006a; Kreibich et al., 2009).

Thus, stress induced by forced swim before COC conditioning augments the rewarding effects of this drug in the CPP paradigm. In addition, Schindler et al. (2010) found that previous exposure to repeated forced swim stress before the final preference test was enough to produce a potentiation of COC CPP. In their study, mice exposed to a 15 min swim 2-4h after completion of COC training on day 3, and those exposed to four 6 min swims 10 minutes before the final preference test on day 4 showed an increased acquisition of the CPP induced by COC, an effect that was not observed in mice exposed to acute forced swim stress (one 15 min swim on day 4, 10 or 45 min before the final preference test) (Schindler, Li, and Chavkin, 2010).

Table 2. Effect of stress on psychostimulant conditioned place preference

Authors	Year	Drug	Stressor	Process	Animal	Effect
Aldrich et al.	2009	COC	forced swim	reinstatement	mice	Reinstates CPP (Zyklophin prevents reinstatement)
Briand et al.	2010	COC	forced swim	reinstatement	mice	Reinstates CPP
Burke et al.	2011	AMPH	social defeat	acquisition	rats	Enhances CPP
Capriles & Cancela	1999	AMPH	restraint stress	acquisition	rat	Enhances CPP (haloperidol abolished this effect)
Carey et al.	2007	COC	forced swim	reinstatement	mice	Reinstates CPP (Arodyn prevents reinstatement)
Cruz et al.	2010	AMPH	restraint	reinstatement	rats	Reinstates CPP
Der-Avakian et al.	2007	COC	tailshock	acquisition	rats	Inhibits CPP
Faure et al.	2009	METH	maternal separation	acquisition	rats	No modify METH CPP
Grimwood et al.	2011	COC	forced swim	reinstatement	mice	Reinstates CPP (PF-04455242 prevents reinstatement)
Hays et al.	2012	COC	maternal separation	acquisition	mice	Reduces CPP
Kreibich et al.	2009	COC	forced swim	acquisition	mice	Enhances CPP (antalarmin prevents reinstatement)
Kreibich et al.	2004	COC	forced swim	reinstatement	mice	Reinstates CPP (not in CREB mutant mice)
Land et al.	2009	COC	social defeat	reinstatement	mice	Reinstates CPP (KOR antagonists prevents reinstatement)
Lu et al.	2001	COC	footshock	reinstatement	rat	Reinstates CPP (alpha-helical CRF 9-41 prevents reinstatement)
Lu et al.	2002	COC	footshock	reinstatement	rat	Reinstates CPP (L365,260 in Nacc s or amygdala prevents reinstatement)
Mantsch et al.	2010	COC	forced swim	reinstatement	mice	Reinstates CPP (clonidine prevents reinstatement)
McLaughlin et al.	2003	COC	forced swim	acquisition	mice	Enhances CPP (nor-binaltorphimine prevents reinstatement)
McLaughlin et al. (a)	2006	COC	forced swim	acquisition	mice	Enhances CPP (U50,488 15 blocks this effect)
McLaughlin et al. (b)	2006	COC	social defeat	acquisition	mice	Enhances CPP (nor-binaltorphimine blocks this effect)
Miller et al.	2008	COC	CUS	acquisition	mice	Enhanced CPP in CB1 KO
Qi et al.	2009	METH	restraint stress	reinstatement	mice	Reinstates CPP (oxytocin prevents reinstatement)
Redila & Chavkin	2008	COC	footshock forced swim	reinstatement	mice	Reinstates CPP (KOR antagonists prevents reinstatement)
Ribeiro Do Couto et al.	2009	COC	social defeat	acquisition	mice	No modify COC CPP
				reinstatement		Enhanced priming-induced reinstatement
Richtand et al.	2012	AMPH	restraint	acquisition	rats	Inhibits CPP
Ross et al.	2011	COC	forced swim	reinstatement	mice	Reinstates CPP (D-Trp isomer prevents reinstatement)
Sanchez et al.	2003	COC	restraint	reinstatement	rat	Reinstates CPP (SKF 81297 and SCH 23390 prevents reinstatement)
Schindler et al.	2010	COC	forced swim	acquisition	mice	Enhances CPP (nor-binaltorphimine blocks this effect)
Vaughn et al.	2012	COC	forced swim	reinstatement	mice	Reinstates CPP (CB1 antagonist prevents reinstatement)
Vranjkovic et al.	2012	COC	forced swim	reinstatement	mice	Reinstates CPP (NA antagonist prevent reinstatement)

Neonatal stress (8h maternal separation per day from P5 to P9) in mice undermines adult COC CPP learning and increases adult hippocampal neurogenesis, effects that could be associated with a diminishing of adult arousal by neonatal stress (Hays et al., 2012). Moreover, stress during childhood in the form of maternal deprivation (3 h per day from PND 2 to PND 14) does not lead to a stronger METH CPP in adulthood. Rats exposed to stress in early life and normally reared controls have been shown to develop CPP after repeated METH exposure (Faure et al., 2009). This lack of a difference between deprived and non-deprived animals in the rewarding effects of METH could have been a result of the dose of METH used. According to the hypothesis that stress induced by maternal deprivation alters the motivational brain system, thereby reducing arousal and reward, a decreased CPP would only be observed with lower sub-threshold doses of drugs of abuse. In line with this, in a recent study in our laboratory we have observed that maternal deprivation impairs the rewarding effects of MDMA in rats (Llorente-Berzal et al., in press).

The rearing environment can also modify acquisition of CPP. Studies have housed rodents in isolation, in crowded conditions, or in an enriched environment and compared their acquisition of CPP with that of rodents reared in a standard environment. For example, it has been observed that COCCPP is maintained over long periods of abstinence in mice housed in a standard environment but disappears in mice housed in an enriched environment (Solinas, Chauvet, Thiriet, El Rawas, and Jaber, 2008). Studies carried out to explore the protective effects of different social environments are reviewed later on.

The chronic social stress induced by isolation during adolescence was shown to enhance the preference for AMPH in females at a dose of 1.0 mg/kg and induce a trend toward stronger preference in males at a dose of 0.25 mg/kg relative to control animals. When tested several weeks after adolescent stress, rats (both sexes) showed a decrease in preference for the 0.5 mg/kg dose of AMPH when compared to controls. These results suggest that the nature of the effects of chronic stress may depend in part on the developmental period in which the stress occurs, as well as the time lapse between stress exposure and testing (Mathews, Mills, and McCormick, 2008). On the other hand, Ribeiro Do Couto et al. (2009) found that housing conditions and social experiences do not affect the acquisition of CPP induced by COC in mice, though these experiences did produce effects on the reinstatement of COC CPP after extinction (see following section).

Social defeat stress-exposed mice (12-16 weeks old) conditioned with COC were found to exhibit significantly stronger CPP for the drug–paired chamber than unstressed mice (McLaughlin et al., 2006b). Another more recent study has investigated the effects of social defeat during adolescence on adult CPP induced by AMPH in male rats. Adolescent social defeat stress increases preference for AMPH-paired cues in adulthood, suggesting that social stress has a great impact on later drug behaviors (Burke et al., 2011). The rewarding efficacy of MDMA seems not to be modulated by social stress, since low and moderate doses are capable of inducing CPP in both non-confronted mice and mice exposed to aggressive social interactions (Rodriguez-Alarcon, Canales, and Salvador, 2007).

Effects of Stress on Reinstatement of the Conditioned Place Preference Induced by Psychostimulants

As many studies have confirmed, stress is a potent trigger for returning to drug use after long-term abstinence. In this context, we are going to examine evidence of how stress exposure promotes reinstatement of a previously extinguished psychostimulant-induced CPP. Studies have shown that exposing rodents to a variety of stressors, including electric footshock, forced swim and social stress, reinstates drug-induced CPP (see Table 2), which suggests that this procedure can be used to examine the neurobiological processes that contribute to stress-induced relapse (Aguilar et al., 2009).

Administration of 15-min footshock sessions prior to CPP testing reinstates preference for the previously COC-paired chamber in mice (Redila and Chavkin, 2008) and rats (Wang et al., 2000). Restraint, another kind of physical stressor, also induces reinstatement of psychostimulant CPP. Immobilization stress (15-min, administered within the CPP chamber) produces reinstatement of COC-seeking behavior in males rats (Sanchez et al., 2003). Acute exposure to restraint stress also reinstatesAMPH-induced CPP when tests are performed during adolescence (1 day following extinction), but not when animals are tested in adulthood (30 days after extinction) (Cruz, Leão, Marin, and Planeta, 2010). Restraint stress (15 min. immobilization) induces reinstatement of METH CPP in male mice (Qi et al., 2009), and, similarly, stress induced by forced swim reinstates COC CPP in male mice (Carey, Borozny, Aldrich, and McLaughlin, 2007; Grimwood et al., 2011; Kreibich and Blendy, 2004; Manstch et al., 2010; Redila and Chavkin, 2008; Ross, Reilley, Murray, Aldrich, and McLaughlin, 2012; Vaughn et al., 2012; Vranjkovic, Hang, Baker, and Mantsch, 2012).

Ribeiro Do Couto et al. (2009) reported that housing conditions and social experiences alter the reinstatement of COC CPP induced by COC priming. Isolation of animals or social defeat in an agonistic encounter prior to the reinstatement test increased susceptibility to COC-induced reinstatement (Ribeiro Do Couto et al., 2009). Indeed, a single social defeat has been shown to reinstate COC CPP in mice (Land et al. 2009, Titomanlio et al., submitted). Conversely, reinstatement of COC CPP is prevented by manipulation of housing conditions during acquisition of CPP or prior to the reinstatement test. Crowding in adolescent mice, isolation in adult mice, and cohabitation with a female in both age groups (when the animals were in the same conditions throughout the whole procedure) prevents COC-induced reinstatement. Cohabitating with a female or social interaction with another male before the reinstatement test also reduces priming-induced reinstatement of COC CPP (for more information about preventive factors, see section 9).

PHARMACOLOGICAL BLOCKADE OF THE POTENTIATING EFFECTS OF STRESS ON PSYCHOSTIMULANT REWARD

Stress exposure increases the risk of addictive drug use in human and animal models of drug addiction through mechanisms that are not completely understood. Some years ago, Capriles and Cancela (1999) demonstrated that restraint stress increases the rewarding effects of AMPH in the CPP and that the administration of D1 and D2 DA receptor antagonists (SCH 23390, sulpiride and haloperidol) abolished the sensitising effects of restraint stress on the reinforcing properties of AMPH. Later, McLaughlin et al. (2003, 2006a, b) showed that stress induced by social defeat enhanced the acquisition of COC CPP in mice (McLaughlin, Marton-Popovici, and Chavkin, 2003; McLaughlin, Land, Li, Pintar, and Chavkin, 2006a; McLaughlin, Li, Valdez, Chavkin, and Chavkin, 2006b). In addition, they found that daily pretreatment with the KOR antagonist norbinaltorphimine (nor-BNI) blocked stress-induced potentiation of COC CPP in male mice (McLaughlin et al., 2006a). Similarly, mice subjected to repeated forced swim stress before COC conditioning showed significantly stronger CPP than unstressed mice, and the same effect was observed when forced swim stress or the KOR agonist U50,488 were administered before testing for preference. Both effects were shown to be blocked by the KOR antagonist nor-BNI. These results suggest that stress enhances the rewarding value of COC-associated cues through a dynorphin-dependent mechanism (Schindler et al., 2010). In fact, accumulated evidence directly links the endogenous opioid neuropeptide dynorphin and the activation of dynorphin/KOR with the enhancing effect of stress on the rewarding properties of drugs of abuse (Bruchas et al., 2010). CRF and glutamate systems are also involved in the effects of stress on acquisition of COC SA. Intermittent social defeats augment COC SA and response rates during binges, and these effects are prevented when NMDA or AMPA receptor antagonists (Covington et al., 2008) or CRF1 receptor antagonists (Boyson et al., 2011) are administered before defeat.

With respect to the effects of stress on reinstatement, NA, CRF, kappa opioid, DA and cannabinoid receptors have been implicated, among other neurotransmitter receptors. Administration of the alpha2 adrenergic receptor (α2AR̤antagonist YOH induces the reinstatement of COC seeking. Some years ago, Erb et al. (2000) reported that footshock-induced reinstatement of COC SA was weakened by the α2AR agonists clonidine, lofexidine

and guanabenz, while Leri et al. (2002) demonstrated that footshock-induced reinstatement of COC SA was attenuated by administration of a mixture of the beta(1)- and beta(2)-adrenergic receptor (β1AR, β2AR, respectively) antagonists betaxolol and ICI-118,551 to the BNST and CeA (Leri et al., 2002). The role of the different adrenergic receptors in stress-induced reinstatement has been studied by Mantsch et al. (2010). The most selective α2ARantagonist, BRL-44,408, induced the reinstatement of COC CPP. Suppression of noradrenergic neurotransmission by administration of the nonselective βAR antagonist propranolol, blocked reinstatement of COC CPP induced by both YOH and forced swim, an effect that was not achieved with the α-1 AR antagonist prazosin. The α2AR agonist clonidine and the β2AR antagonist ICI-118,551 also suppressed forced swim-induced reinstatement, while the selective β1AR antagonist betaxolol did not (Mantsch et al., 2010). More recently, Vranjkovic et al. (2012) reported that the administration of ICI-118,551 blocked reinstatement of COC CPP induced by forced swim, while betaxolol (at a high dose) interfered with swim-induced reinstatement. These data suggest that stress-induced reinstatement depends on NA signalling through β2ARs (Mantsch et al., 2010; Vranjkovic et al., 2012).

As occurs with YOH, the administration of *CRF* induces reinstatement of COC seeking (Erb et al., 2006, 2010). The non-selective CRF receptor antagonist, alpha-helical CRF_{9-41}, decreases footshock-induced reactivation of COC CPP reactivation (Lu, Liu, and Ceng, 2001), and administration of alpha-helical CRF_{9-41} to the VTA (but not to the SN) decreases footshock-induced reinstatement of COC CPP (Wang et al., 2005). Similarly, the non-selective CRF antagonist D-Phe CRF_{12-41} reducesCOC SA induced by footshock when administered icv (Erb et al., 2008), and to the BNST but not to the CeA (Erb and Stewart, 1999). However, it does not affect the reinstatement of COC SA induced by YOH (Brown et al., 2009). Recently, alpha helical CRF_{9-41} was found to block footshock-induced reinstatement in rats with long-term access to COC SA (Graf et al., 2011) in a study which also demonstrated that when the adrenal response to SA was blocked before acquisition of SA by adrenalectomy with diurnal corticosterone replacement, subsequent footshock- and CRF-induced reinstatement was also blocked. However, adrenalectomy plus corticosterone before extinction and reinstatement failed to reduce reinstatement. The study in question suggested that adrenal-dependent neuroadaptations in CRF responsiveness underlie the increased susceptibility to stress-induced relapse that emerges with repeated COC use (Graf et al., 2011).

Similarly, stress-induced reinstatement of COC seeking is blocked by selective CRF1 receptor antagonists. CP-154,526 decreases footshock-induced reinstatement of COC SA (Shaham, 1998) and antalarmin blocks forced swim-induced reinstatement of COC CPP (Kreibich et al., 2009). However, in a study by Wang et al. administration of the selective CRF1 antagonists NBI-27914 and R121919 to the VTA did not block footshock-induced reinstatement of COC seeking (Wang et al., 2007). The same study also highlighted the important role of CRF2 receptors in the VTA in reinstatement of COC seeking, as antisauvagine-30, one such receptor antagonist decreased footshock-induced reinstatement of COC SA (Wang et al., 2007). Both CRF1 and CRF2 receptors seem to be important in CRF-dependent neuroadaptations, establishing stress-induced relapse to drug seeking behavior (Gysling, 2012).

In the last five years, data obtained regarding stress-induced reinstatement have corroborated the stress-like effect of KOR agonists (Wee and Koob, 2010) and demonstrated

that KOR antagonists suppress stress-induced reinstatement of COC-seeking behavior in the CPP and SA paradigms. The KOR antagonists JDTic, nor-BNI and RTI-194 decrease footshock- or forced swim-induced reinstatement of COC SA (Beardsley et al., 2005, Beardsley, Shelton, Hendrick, and Johnson, 2010; Redila and Chavkin, 2008), while the KOR antagonists arodyn, zyklophin and PF-04455242 and the D-Trp isomer of CJ-15,208 diminish forced swim-induced reinstatement of COC CPP (Aldrich, Patkar, and McLaughlin, 2009; Carey et al., 2007; Grimwood et al., 2011; Ross et al., 2012). The inactivation of serotonergic KORs by injection of the KOR antagonist nor-BNI into the dorsal raphe nucleus also blocks social defeat-induced reinstatement of COC CPP (Land et al., 2009). Conversely, mu receptors are not involved in stress-induced reinstatement of COC seeking, since buprenorphine has no effect on footshock stress-induced reinstatement of COC SA (Sorge, Rajabi, and Stewart, 2005).

Transmission at DA receptors also seems to mediate the reinstatement of COC seeking CPP. The D1/5 receptor antagonist SCH23390 blocks reinstatement of COC SA induced by footshock when injected into the medial PFC and OFC (Capriles, Rodaros, Sorge, and Stewart, 2003) and the reinstatement of COC CPP induced by immobilization when injected into the medial FPC (Sanchez et al., 2003). The same effect is observed on CRF- and YOH-induced reinstatement when peripheral SCH23390 is administered (Brown et al., 2012). Similarly, the D1/D5 antagonist SCH31966 blocks YOH-induced reinstatement of COC SA (Brown et al., 2012), and the selective D3 antagonist SB-277011A attenuates footshock-induced reinstatement of COC seeking behavior when microinjected into the NAcc, but not into the dorsal striatum, of male rats (Xi et al., 2004). However, the D2/3 receptor antagonist raclopide does not block CRF- or YOH-induced reinstatement of COC seeking (Brown et al., 2012). In contrast, reinstatement of COC SA by footshock is undermined by administration of levo-tetrahydropalmatine, a tetrahydroprotoberberine isoquinoline with a pharmacological profile that includes antagonism of D1, D2 and D3 DA receptors (Figueroa-Guzman et al., 2011).

The role of endocannabinoid signaling has been studied in only two recent studies (Kupferschmidt et al., 2012; Vaughn et al., 2012). The cannabinoid CB1 receptor antagonist AM251 was found to block CRF-induced reinstatement of COC SA (Kupferschmidt et al. 2012) and forced swim-induced reinstatement of COC CPP (Vaughn et al., 2012). However, AM251 had no effect on footshock-induced reinstatement of COC SA (Kupferschmidt et al., 2012). On the other hand, the cannabinoid agonist CP 55,940 increases the reinstating effects of a low dose of the β2AR antagonist BRL-44408. Reinstatement COC CPP is observed when the two compounds are co-administered, but not when administered alone (Vaughn et al., 2012).

Other neurotransmitter systems, including brain neuropeptides, glutamate and GABA, have also been implicated in stress-induced reinstatement of COC seeking. The administration of the cholecystokinin (CCK) receptor antagonist L365, 260 to the amygdala and NAcc blocks stress-induced reinstatement of COC CPP (Lu et al., 2002). Similarly, the hypocretin type 1 receptor antagonist SB 334867 prevents footshock-induced reinstatement of COC SA (Boutrel et al., 2005). However, the administration of SB 408124, another hypocretin type 1 receptor antagonist, to the VTA has no effect on footshock-induced reinstatement (Wang et al., 2009) and YOH-induced reinstatement (Zhou et al., 2012) of COC SA. The neuropeptide oxytocin also obstructs the reinstatement of COC CPP induced by restraint stress (Qi et al., 2009), and an analog of theteneurin C-terminal-associated

peptides (TCAP) blocks CRF-induced reinstatement of COC SA, though it has no effect on footshock-induced reinstatement of COC seeking (Kupferschmidt, Lovejoy, Rotzinger, and Erb, 2011). Recently, it has been demonstrated that footshock stress-induced reinstatement of COC SA is attenuated by the selective metbotropic glutamate receptor (mGluR)2/3 agonist LY379268 and by the selective mGluR5 antagonist MTEP (Martin-Fardon and Weiss, 2012). Moreover, the structural analog of GABA pregabalin suppresses the reinstatement of COC seeking induced by YOH (de Guglielmo et al., 2012). Finally, acupuncture applied for 1 min at bilateral Shenmen points after footshock stress suppresses the reinstatement of COC seeking behavior (Shoon Yoon et al., 2012).

PREVENTIVE FACTORS IN ANIMAL MODELS OF DRUG ADDICTION

The use of experimental animal models is essential to the study of the factors that determine vulnerability to drug addiction, such as stress, as they make it possible to isolate and control the genetic, environmental and social variables that contribute to the development of drug addiction. Similarly, the preventive effects of some variables, such as environmental enrichment, social interaction or cohabitation with females, and access to alternative rewards, on the vulnerability to drug addiction can be studied in animals.

Environmental Enrichment

An environmental factor that influences the behavioral and neurochemical effects of drugs of abuse and may provide protection against drug addiction is environmental enrichment (Bardo, Klebaur, Valone, and Deaton, 2001; Carroll, Anker, and Perry, 2009; El Rawas, Thiriet, Lardeux, Jaber, and Solinas, 2009; Jessor and Jessor, 1980; Solinas, Thiriet, El Rawas, Lardeux and Jaber, 2009; Solinas, Thiriet, Chauvet, and Jaber, 2010; Stairs and Bardo, 2009; Xu, Hou, Gao, He, and Zhang, 2007), which has been defined as ‘‘a combination of complex inanimate and social stimulation’’ (Rosenzweig, Bennett, Hebert, and Morimoto, 1978). With EE, animals are generally housed in large cages with running wheels and a few toys that are periodically changed to stimulate the curiosity of the animals and increase exploration (Laviola, Hannan, Macrì, Solinas, and Jaber, 2008; Nithianantharajah and Hannan, 2006; Rosenzweig and Bennett, 1996; van Praag, Kempermann, and Gage, 2000). In some cases, animals are exposed to EE for only a few hours for one or several days, in contrast to their normal housing conditions (Rampon et al., 2000). It has been hypothesized that EE provides animals with control and choice over their social and spatial environment (Baumans, 2005; Hutchinson, Avery, and Vandewoude, 2005).

To study the preventive effects of environmental enrichment (EE), animals are exposed before having any contact with the drug (Solinas et al., 2010). Accumulating evidence indicates that EE mimics positive life experiences and helps to prevent the development of drug addiction (Carroll, Anker, and Perry, 2009; Stairs and Bardo, 2009). In the SA paradigm, the reinforcing effects of the psychostimulants AMPH and COC are less pronounced in EE rats (Bardo et al., 2001; Green, Gehrke, and Bardo, 2002; Green et al.,

2010; Stairs, Klein, and Bardo, 2006). Rats reared with EE exhibit less drug taking behavior when measured by fixed ratio (FR1) schedules and less motivation for the drug when measured by progressive ratio (PR) schedules (Bardo et al., 2001; Green et al., 2002). A review of studies investigating the preventive effects of EE on drug addiction has been written by Stairs and Bardo (2009).

Other studies have shown that EE, as well as having preventive effects, is "curative" in cases of psychostimulant addiction. EE has also been shown to eliminate already developed addiction-related behaviours, decreasing resistance to the extinction of AMPH SA and reducing the propensity to relapse (Stairs et al., 2006). Exposure to EE during long periods of abstinence from COC SA also reduces drug seeking and attenuates reinstatement induced by conditioned cues and stress (Chauvet, Lardeux, Goldberg, Jaber, and Solinas, 2009).

The preventive and curative effects of EE have also been observed in the CPP paradigm. AMPH and COC produce CPP in EE rats but not in their isolated counterparts (Bardo et al., 1995a; Bowling and Bardo, 1994; Bowling, Rowlett, and Bardo, 1993; Green et al., 2009). The rewarding effects of COC in the CPP are blunted in mice reared with EE from weaning through to adulthood when compared with animals reared in standard environments (Solinas et al., 2009). Using in vivo microdialysis in mice, it has been demonstrated that EE does not exert its protective effects by reducing COC-induced increases in DA levels in the ventral or dorsal striatum, but rather by undermining COC-induced expression of the immediate early gene zif-268 in the NAcc (shell and core) and Delta-Fos B levels in the striatum (Solinas et al.,2009).

When mice are housed in an enriched environment after acquisition of COC CPP the reinstatement of CPP induced by COC priming is prevented, suggesting that environmental stimulation is a fundamental to facilitating abstinence and preventing relapse to COC addiction (Solinas et al., 2008). Moreover, EE reduces activation of the brain circuitry involved in COC-induced reinstatement. After CPP, COC increases c-FOS expression in the NAcc shell, VTA and BLA in mice housed in a standard environment but not in EE mice. In fact, COC-induced expression of c-FOS is significantly reduced in the NAcc core and infralimbic cortex of EE mice (Solinas et al., 2008). More recently, it has been demonstrated that EE undermines the maintenance of COC CPP, which is long-lasting in mice reared in a standard environment, and is associated with reduced expression of Fos in the anterior cingulate cortex, the lateral caudate putamen, the NAcc shell, the dentate gyrus of the hippocampus, the BLA and CeA, the BNST, and the VTA with respect to mice conditioned with COC and reared in a standard environment (Chauvet, Lardeux, Jaber, and Solinas, 2011).

Recent studies have shown that the expression of genes of the endocannabinoid system differ in mice reared with EE from the weaning stage until adulthood and those reared in a standard environment. EE increases CB1 mRNA levels in the hypothalamus and in the BLA, but decreases them in the basomedial amygdala. Similarly, FAAH mRNA levels are higher in the hypothalamus and the BLA of EE mice. Such changes in the endocannabinoid system could result in a reduced response to stress and, consequently, in a greater resistance to addiction (El Rawas, Thiriet, Nader, Lardeux, Jaber, and Solinas, 2011).

It is important to note that, contrary to that observed with COC, EE is incapable of reducing the rewarding effects of METH; mice reared with EE for 2 months during early stages of life develop CPP after conditioning with METH in adulthood (Thiriet et al., 2011). On the other hand, it has recently been demonstrated that if EE is not maintained into

adulthood the risk of developing drug addiction increases. Mice reared with EE but then switched to a non-enriched standard environment experience stronger rewarding effects of COC and exhibit higher levels of CRF mRNA in the BNST and of CREB phosphorylation in the BNST and the NAcc shell. Indeed, increased sensitivity to the rewarding effects of COC is completely blocked by the CRF antagonist antalarmin, which points to the role of the CRF system in the negative consequences of environmental changes (Nader et al., 2012).

As discussed in the course of the present chapter, stress is known to play a crucial role in drug addiction (Goeders, 2003; Koob, 2008; Sinha, 2007, 2008) by increasing the rewarding effects of drugs and creating a negative emotional state that renders ex-users more vulnerable to relapse (Koob, 2008; Sinha, 2007, 2008). Studies showing that EE reverses already-established COC addiction suggest that levels of stress during abstinence influence the risk of relapse dramatically (Chauvet et al., 2009; Solinas et al., 2008; Thiel, Sanabria, Pentkowski, and Neisewander, 2009) and that EE acts as an anti-stress (Mora, Segovia, and del Arco, 2007; Segovia, del Arco, and Mora, 2009) or antidepressant (Laviola et al., 2008) mechanism whose function is to create a positive emotional state that protects against relapse. A recent study has demonstrated increased AMPH SA in socially isolated rats when compared to rats living in groups or with EE, and that this increase may involve enhanced reactivity of the HPA stress axis (Stairs et al., 2011). EE can be considered a functional opposite of stress. For example, in what is a protective role, the anti-stress effects of EE reduce the reinforcing effects of drugs and their ability to induce long-lasting neuroplastic changes, thus helping to prevent the development of drug addiction. In the case of the curative effects of EE, restoration of the normal, pre-drug functioning of the stress system facilitatesthe individual's resisting of the desire to take the drug, therefore lowering the risk of relapse (Solinas et al., 2010).

Another important mechanism that could underlie the positive effects of EE in facilitating abstinence and reducing COC seeking and reinstatement is its reversal of the cognitive deficits induced by chronic consumption of COC (Solinas et al., 2010). Psychostimulant addiction appears to be associated with deficits in decision making and other cognitive tasks that play an important role in relapse, such as behavioral inflexibility and perseverative behaviours (Verdejo-García and Bechara, 2009; Stalnaker, Takahashi, Roesch, and Schoenbaum, 2009). Therefore, environmental stimulation together with pharmacological treatment and behavioral therapy may be of fundamental importance to the success of drug addiction treatment programmes (Chauvet et al., 2009).

Social Interactions

There is compelling evidence that social experiences modify vulnerability to reinstatement, acting as prevention or risk factors in the development of drug addiction (Swadi, 1999). If negative environmental conditions render subjects more vulnerable to drug abuse, positive environmental conditions are likely to have protective effects against addiction. The presence of alternative nondrug reinforcers undermines acquisition and maintenance of COC use and abuse (for a review, see Higgins, 1997). Using animal models, several studies have investigated how different types of social interaction, if experienced in parallel to drug use, can prevent drug abuse and substance dependence (Fritz et al., 2011; Thiel, Okun, and Neisewander, 2008; Ribeiro Do Couto et al., 2009).

Social interaction with a coespecific animal is a rewarding experience. An environment previously paired with the presence of a rat induces CPP in adolescent rats, and social reward-CPP increases as the number of social pairings rises (Thiel et al., 2008). In addition, interaction between social and COC reward has been demonstrated; a low dose of COC (2 mg/kg, IP) and a low number of social pairings (2 pairings of an environment with a rat), insufficient for producing CPP in adolescent rats when administered alone, have been shown to produce a robust CPP when administered together (Thiel et al., 2008). On the other hand, in rats in the CPP paradigm concurrently trained to pair COC with one compartment and social interaction with the other, it has been demonstrated that four 15-min episodes of social interaction with a gender- and weight-matched male conspecific reversed CPP from COC to social interaction (Fritz et al., 2011a, b). Social interaction also reverses COC CPP-induced expression of the immediate-early gene zif268 in the NAcc shell, VTA, CeA and BLA (Fritz et al., 2011a), and the antagonism of sigma receptors with BD1047 decreased COC CPP in favour of social reward CPP (Fritz et al., 2011b). In addition, excitotoxic lesions of the NAcc core or the BLA shift CPP toward social interaction, whereas inactivation of the NAcc shell shifts CPP toward COC, demonstrating the differential involvement of these divisions of the NAcc in COC and social reward (Fritz et al., 2011c).

In our laboratory we have demonstrated that priming-induced reinstatement of a previously extinguished COC-induced CPP is blocked by exposing mice to different kinds of social interaction, such as exposure to a female, crowding during adolescence and a non-aggressive agonistic encounter (Ribeiro Do Couto et al., 2009). Cohabitation with a female seems to act as an alternative reinforcer by decreasing vulnerability to reinstatement, and contact with a female prior to a reinstatement test prevents reinstatement of heroine SA in rats (Shaham, Puddicombe, and Stewart, 1997). Similarly, we have observed that cohabitation with a female of the same age has a protective effect and reduces vulnerability to reinstatement of a COC CPP (Ribeiro Do Couto et al., 2009). Mating throughout the experimental procedure (during acquisition, extinction, and reinstatement of CPP) blocks the reinstatement induced by COC in adolescent and adult animals. Similarly, a brief mating episode 48 h before the reinstatement test blocks the reinstating effects of COC priming in adult male rats. However, no protective effects of mating are observed in adult grouped mice that are mated after acquisition of CPP (and which, thus, lived with a female for 9 days, during which extinction and reinstatement took place). These results suggest that exposure to female company only exerts a protective effect against reinstatement when cohabitation occurs during the acquisition, extinction and reinstatement of CPP, or before reinstatement. In the first case, mating may act as a natural reward that competes with the rewarding effects of COC, while in the second, the novelty of this natural reward interferes with the reinstating effects of COC. Therefore, the lack of reinstatement in mice with a mate could be due to the presence of an alternative reinforcer (the female) that prevents reinstatement after COC priming.

Crowding in adolescent mice (housing in groups of four from PND 21-PND 23 and from PND 24 onwards, and introducing another mouse into the cage every 2 days, until the cage houses eight mice) acts as a protective factor against reinstatement of COC CPP, but has the opposite effect in adult animals (Ribeiro Do Couto et al., 2009). In this way, crowded housing conditions produce different effects in adolescent and adult mice, blocking reinstatement in the former and increasing susceptibility to reinstatement in the latter. These differential effects may be due to the way in which animals perceive this housing condition and how it

affects their emotional reactivity. It has been observed that crowding stresses adult male rats and increases their corticosterone levels (Brown and Grunberg, 1995) and ACTH response to noise, thus increasing their emotional reactivity (Armario, Castellanos, and Balasch, 1984). Stress induced in adult mice by crowding increases susceptibility to reinstatement, since CPP is reinstated in adult animals not only with 25 mg/kg but also with 12.5 mg/kg of COC, a dose that does not produce reinstatement in grouped animals. Conversely, it appears that crowded conditions are rewarding rather than stressing for adolescent mice. Periadolescent rodents are generally associated with a peculiar behavioral profile characterized by affiliative and playful behaviors. While crowding strengthens the corticosterone response to an acute stress challenge in adult male mice, a trend towards lower corticosterone levels is observed in periadolescent male mice (Laviola, Adriani, Morley-Fletcher, and Terranova, 2002). Indeed, a recent study has shown that social proximity is rewarding for juvenile mice (Panksepp and Lahvis, 2007). In this context, the rewarding effect of crowded conditions for adolescent mice may act as an alternative reinforcer that prevents reinstatement after COC priming (Ribeiro Do Couto, et al., 2009).

Social interaction with another male also decreases vulnerability to reinstatement of a COC CPP in rats (El Rawas et al., 2012; Fritz et al., 2011a, b) and mice (Ribeiro Do Couto et al., 2009). Four 15 min episodes of social interaction with a gender-and weight-matched male early-adult conspecific has been shown to inhibit COC-induced reinstatement of COC CPP (El Rawas et al., 2012; Fritz et al., 2011a, b). Similarly, we have observed that a single non-aggressive social encounter with a conspecific mouse (of equal age and body weight) in a neutral cage 30 min before the reinstatement test reduces priming-induced reinstatement of COC CPP. In the agonistic encounter in question experimental animals were confronted with opponents that had been housed in a group and made temporarily anosmic by intranasal lavage with 4% zinc sulfate solution one day before (Smoothy, Brain, Berry, and Haug, 1986). Since this type of opponent elicits attack but never initiates it, experimental animals do not suffer the experience of defeat. Thus, this type of agonistic encounter can be viewed as a normal social interaction between two conspecific animals with a similar low level of aggression. In fact, no aggressive behaviours were observed in these encounters. The fact that an agonistic encounter with a non-aggressive male before the reinstatement test blocks the reinstating effects of COC priming suggests that a brief social interaction also acts as an alternative reinforcer that prevents reinstatement of COC CPP (Ribeiro Do Couto et al., 2009).

CONCLUSION

As discussed throughout this chapter, exposure to stress stimulates psychostimulant consumption and vulnerability to relapse in animal models of addiction. Different types of stressors (physical, emotional and social) potentiate the rewarding effects of psychostimulants in the SA and CPP paradigms and induce reinstatement of drug seeking after extinction. However, it is important to note that a great number of the studies published about this subject have employed the SA paradigm, the footshock as stressor and adult rats as experimental subjects. In fact, current knowledge of the neural substrates of stress-induced reinstatement is derived mainly from this type of study, which may have created a somewhat

limited perspective. In the last ten years, the use of the CPP paradigm, the application of stressful stimuli with more ethological relevance, such as emotional or social stressors, and the inclusion of mice as experimental animals have contributed to extending our understanding of how stress enhances vulnerability to relapse. It is now clear that SA and CPP evaluate different aspects of reward and that the results obtained with one paradigm must be complemented by studies performed in the other. Another limitation that becomes patent when reviewing the literature about the effects of stress on psychostimulant addiction is that most studies have been performed with COC, while the effects of stress on the rewarding properties of other psychostimulants have received little attention. Future work exploring the role of stress in psychostimulant addiction should focus on AMPH, METH or psychostimulant-related drugs such as MDMA. The way in which stress differentially affects adult and adolescent animals should also be an area of future research.

Pharmacological manipulation, particularly the antagonism of NA, CRF and kappa receptors, has shown potential in blocking stress-induced potentiation of acquisition of psychostimulant SA and CPP and stress-induced reinstatement of psychostimulant seeking. Future studies should test new drugs that act on the neurotransmitters and neuromodulator systems involved in stress and brain reward. The data obtained may be of great use in developing effective pharmacological treatments for addiction based on the mediation of stress triggers.

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