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Social defeat stress: mechanisms underlying the increase in rewarding effects of drugs of abuse

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Abstract

Social interaction is known to be the main source of stress in human beings, which explains the translational importance of this research in animals. Evidence reported over the last decade has revealed that, when exposed to social defeat experiences (brief episodes of social confrontations during adolescence and adulthood), the rodent brain undergoes remodeling and functional modifications, which in turn lead to an increase in the rewarding and reinstating effects of different drugs of abuse. The mechanisms by which social stress cause changes in the brain and behavior are unknown, and so the objective of this review is to contemplate how social defeat stress induces long-lasting consequences that modify the reward system. First of all, we will describe the most characteristic results of the short- and long-term consequences of social defeat stress on the rewarding effects of drugs of abuse such as psychostimulants and alcohol. Secondly, and throughout the review, we will carefully assess the neurobiological mechanisms underlying these effects, including changes in the dopaminergic system, corticotrophin releasing factor signaling, epigenetic modifications and the neuroinflammatory response. To conclude, we will consider the advantages and disadvantages and the translational value of the social defeat stress model, and will discuss challenges and future directions.

Introduction

Social relations are crucial for human development and other species that live according to social hierarchies. In addition, the environment in which individuals develop is critical due to its impact on wellness, health maintenance and survival (Kessler et al., 2010). One of the key factors in maintaining human health is the stress response, which depends on the interaction between the environment and regulatory body systems, such as the sympathetic nervous

system and the hypothalamic-pituitary-adrenal axis (HPA) (Stratakis and Chrousos, 1995). Different types of stress (physical or psychological) can induce qualitatively different behavioral patterns and physiological responses. Over the last two decades ago, an important number of studies have focused on the phenomenon of social and psychological stress and its consequences (e.g. Miczek et al., 2008; Burke and Miczek, 2014), a subject of increasing relevance, as people currently experience highly stressful life styles that induce short and long-term negative behavioral and psychological consequences.

Stress is one of the main risk factors in several diseases, including depression, anxiety or addiction (Sinha et al., 2011; Logrip et al., 2012), and there is a close association between the brain systems involved in the response to drugs of abuse and stress. Therefore, environmental stressors can cause long-term changes in the brain's reward system function, inducing relapses in drug-seeking and -taking. Activation of the stress system also seems to be crucial for the negative emotional state induced by dependence, which drives drug-seeking through negative reinforcement mechanisms (Koob, 2010).

According to the last World Drug Report (UNODC, 2017), 29.5 million people globally suffer from drug use disorders, thus constituting a health problem with serious social and economic consequences (EMCDDA, 2017), and affecting, not only drug addicts, but also their families and social environment. Stress is a prevalent condition that affects human beings during their lifetime and the knowledge of the neurobiological basis of addiction, specifically the role of stress, allows prevention and treatment strategies to be developed. Animal models are a crucial tool for experimental research to improve our understanding of the neurobiology of addiction, and its behavioural and physiological consequences, and to

explore future approaches to treatment. Social defeat (SD) is considered the most representative animal model for studying the consequences of social stress (Hammels et al., 2015). It involves an agonistic encounter between conspecifics of the same specie (Tornatzky and Miczek, 1993), and mimics a subordinate vs. outsider position in human relations (Selten et al., 2013). Preclinical studies of social stress employ mainly territorial male resident rats or mice confronting a conspecific intruder. The social defeat model - or the so-called resident-intruder paradigm - allows the natural expression of offensive and defensive behaviors in laboratory rodents. By recording the frequency, duration, latency and temporal and sequential patterns of the behavioral acts and postures of both animals during these confrontations, a detailed quantitative picture of offensive (resident) and defensive (intruder) aggression is obtained (Koolhaas et al., 2013). The most commonly used resident-intruder paradigm is that proposed by Miczek and co-workers (2008), where the experimental animal is confronted with an aggressive opponent in its own home cage in a repeated and intermittent manner. Animals are exposed to four episodes of social defeat, each lasting 25 minutes. Each episode consists of three phases and begins by placing the experimental animal or intruder in the home cage of the aggressive opponent or resident for 10 minutes. During this initial phase, the intruder is protected from attack by a wire mesh wall that allows social interaction and species-typical threats from the male aggressive resident (Covington & Miczek, 2001). In the second phase, the wire mesh is removed, and a 5-minute period of confrontation begins. In the third phase, the wire mesh is replaced for a further 10 minutes to allow social threats from the resident. Threat and attack behaviors are scored in resident mice, and avoidance/flee and defensive/submissive behaviors are evaluated in intruder mice. According to Burke and co-workers (2016), the social encounter is terminated earlier (before 5 min) if the intruder displays a submissive supine posture for more than 8 seconds or if 13 attack bites are inflicted.

SD stress induces pronounced physiological and endocrine responses, such as circadian rhythm disturbances and elevated levels of corticosterone (Lumley et al., 2000; Meerlo et al., 2002; Montagud-Romero et al., 2016b; Rodríguez-Arias et al., 2017), and alteration of serotoninergic and dopaminergic neurotransmission (Hammels et al., 2015), among others.

To date, there is conclusive work evaluating the consequences of SD for subsequent drug intake (e.g. Burke and Miczek, 2014). Exposure to different procedures of SD increases the reinforcing effects of cocaine, amphetamine and alcohol. Most studies have used the intravenous self-administration (SA) paradigm (Neisewander et al., 2012; Holly et al 2016; Han et al., 2017); moreover, consistent results have also been obtained in the conditioned place preference (CPP) paradigm (Montagud-Romero et al., 2015; Rodríguez-Arias et al., 2016; 2017).

The main aim of this review is to illustrate how SD stress induces long-lasting consequences that modify the reward system. Firstly, we will briefly review the most representative results of the short- and long-term consequences of social stress on the rewarding effects of psychostimulants and alcohol. Most importantly, we will review the neurobiological mechanisms involved in these actions, such as the dopaminergic system, corticotrophin releasing factor (CRF) signaling, epigenetic changesand neuroinflammatory processes. Finally, we will consider the translational value of this model, its strengths and limitations, as well as challenges and future directions.

Effects of social defeat on psychostimulant and alcohol reward

The main methodology employed to assess vulnerability to cocaine and alcohol-rewarding effects is the operant SA procedure and the CPP paradigm. CPP is the most commonly used test to evaluate the environmental cues that condition the rewarding effects of a drug (Aguilar et al., 2009), while the SA procedure directly evaluates the animals' motivation to obtain the substance of abuse. Both models provide a complete scenario of vulnerability to drug abuse, since they allow both external and individual cues to be measured.

Self-Administration studies

The SA is an experimental model that evaluates the primary reinforcing effect of drugs according to the effort made by the animal to obtain the drug. To evaluate the rewarding properties of a drug, operant procedures involve a fixed-ratio program in which the animal performs a determined number of non-variable responses in order to achieve an infusion of the drug (Moser et al., 2010). Besides this, there are also progressive ratio programs, where the number of responses required to obtain the drug increases gradually, thus providing a measure of the animal's motivation to obtain the drug (Depoortere et al., 1993; Tabakoff and Hoffman, 2000). Another index is the so-called 'breaking point', which determines the point at which the animal reaches the maximum responses to get an infusion (Yap and Miczek, 2008).

There are numerous studies demonstrating that physical (tail pinch or foot shock) and social (isolation, social defeat, maternal separation) stressors facilitate the acquisition of cocaine SA (see eg. Goeders and Guerin, 1994; Haney et al, 1995; Miczek and Mutschler, 1996; Ramsey

and Van Ree, 1993; Campbell and Carroll, 2001; Kosten et al, 2000; Schenk et al, 1987; Mantsch and Katz, 2007).

The effects of SD on cocaine SA have been extensively studied in adult rats (Miczek et al., 2008). Miczek's laboratory has persistently reported that SD increases both acquisition of cocaine SA and motivation to take the drug, raising the breaking point in the progressive ratio program (Covington et al., 2005; Quadros and Miczek, 2009; Boyson et al., 2014; Han et al., 2017). Studies use short-term access to the drug, resulting in very controlled and stable levels of drug SA. Nevertheless, prolonged access (a 24-hour binge) leads to a progressive acceleration and escalation of drug intake over the course of two or more weeks. Bingeing for 24 h induces a higher number of infusions, a shorter inter-infusion interval, and greater quantities of cocaine consumed in socially defeated rats relative to non-stressed ones as long as two months after the last agonistic encounter (Covington and Miczek, 2005; Quadros and Miczek, 2009; Boyson et al., 2011; Boyson et al., 2014; Yap et al., 2015).

In the same way, brief episodes of acute SD stress prior to the SA session have been shown to significantly increase the rate of cocaine intake (Miczek and Mutschler, 1996; Holly et al., 2016). However, if there is a delay between exposure to the acute episode of SD and the SA sessions, the effects of stress are dissipated (Covington and Miczek, 2001).

The extinction – reinstatement process is employed to study relapse into drug seeking. During extinction, animals press a lever (or nose-poke) to self-administer the drug, but they do not obtain any infusion. The reinstatement of SA after extinction implies the restoration of a

concrete operant response, and the ability of different stimuli to reinstate the response is determined. Using the intravenous SA procedure, reinstatement can be induced by re-exposure to the drug, to the environmental cues previously associated with the drug or by exposure to a stressful event.

Regarding this, reinstatement of alcohol and cocaine seeking has been demonstrated after exposure to environmental cues paired with the SD experience (Funk et al., 2005; Manvich et al., 2016). Even after a period of 15 days of abstinence from cocaine, socially defeated animals show an increase of drug seeking during reinstatement testing (Covington and Miczek, 2001; Holly et al., 2016). Several studies have demonstrated that physical and social stress reinstates extinguished cocaine-seeking behavior (Erb et al, 1996; Ahmed and Koob, 1997; Mantsch and Goeders, 1999a; Shalev et al, 2003). A detailed description of these studies is provided in Table 1.

Conditioned Place Preference studies

The CPP paradigm in conjunction with the SA provides a comprehensive assessment of the rewarding effects of drugs of abuse, as both models measure the role of motivation and environmental cues (Aguilar et al., 2009). Specifically, this procedure aims to evaluate the relevance of the environmental cues associated with the drug (Tzschentke, 2007), based on the change from initially neutral environmental cues to conditioned stimuli with secondary motivational properties (Aguilar et al., 2009).

Animals are first trained to acquire CPP, and studies are in line with those using SA, with both types showing that SD increases the conditioned reinforcing properties of psychostimulants. Both acute and repeated SD induce short-and long-lasting increases in the conditioned rewarding effects of cocaine in mice (McLaughlin et al., 2006; Land et al., 2009; Hymel et al., 2014; Montagud-Romero et al., 2016b; Reguilón et al., 2017).

Later, animals undergo a process of extinction of this preference. Subsequently, the extinguished CPP can be firmly reinstated by non-contingent administration of a priming dose of the drug, or by exposure to stressful stimuli like social defeat. The reinstatement of CPP consists of the reappearance of the approach behavior to a drug-associated context. Moreover, defeated animals require more sessions than non-stressed animals for the CPP to be extinguished (Montagud-Romero et al., 2016b). More information about these studies is presented in Table 2.

Social defeat studies with Alcohol.

Although there is agreement among SA and CPP studies that social stress increases the rewarding effects of psychostimulants, the effects of SD on alcohol intake are vary depending on the paradigm that is employed. While some studies have shown that acute exposure toSD during ethanol SA does not produce any change in alcohol consumption (van Erp and Miczek, 2001; Funk et al., 2004), others show that rats enhance their alcohol intake 2 hours after SD (Caldwell and Riccio, 2010). In the CPP paradigm, acute SD before ethanol CPP procedure has been shown to enhance its rewarding effects with respect to control conditions (Funk et al., 2004), while SD also increments the short- and long-term conditioning rewarding effects of ethanol (Croft et al., 2005; Macedo et al., 2018). For more details, see Table 2.

Social defeat stress during adolescence

The literature shows that suffering social stress during adolescence increases the risk to drug consumption (Hoffman et al., 2000; King and Chassin, 2008). Adolescence is a critical period of brain maturation marked by numerous cognitive, behavioral and biological developments (Pickles et al., 1998; Spear, 2000; Bava and Tapert, 2010). For example, the adolescent brain experiences a massive loss of gray matter and synapses in the neocortex (Gogtay et al., 2004), while the pruning process during adolescence involves the loss of approximately 50% of synaptic connections (Spear, 2013). Myelination and synaptic pruning help to reconfigure and re-wire brain connections into adult patterns, contributing to the thinning of the neocortex. As a result of this maturingprocess, the adolescent brain operates in a promotivational state, with a limited inhibitory capacity, poor control regulation, hyperactivity of the amygdala, and dopamine (DA) hyperactivity in the nucleus accumbens (NAc) when processing appetitive stimuli (Rodríguez-Arias and Aguilar, 2012).

Drug use during this critical period of development often predisposes to an increased likelihood of continued use into adulthood (Arteaga et al., 2010). Moreover, social (e.g. peer influence), economic (e.g. low social status), hormonal (increase in adrenal and gonadal hormones), neurochemical (changes in DA neurotransmission) and dietary (high-fat/sugar diets) conditions during adolescence also contribute to increased vulnerability to drug use (Spear, 2000; Blanco-Gandia et al, 2017). Social stress in early life, such as bullying at school or child abuse, can have several consequences in adulthood (de Groot et al., 1999; Lumley et al., 1999). The SD model is considered a model of bullying in adolescent mice, producing an emotional state of defeat (Björkqvist, 2001; Koolhaas et al., 2013; Rodríguez-Arias et al., 2016; 2017). Adolescent rodents, housed with males of similar age, are

confronted with an aggressive adult male, allowing physical aggression during 5 minutes, similarly to that which occurs between adult animals. According to Buwalda and co-workers (2013), defeat experience during adolescence affects play behavior, with defeated rodents adopting more submissive postures during play fighting.

Although adolescents display a higher release of adrenocorticotropic hormone (ACTH) and corticosterone in response to an acute stressor than adults (Doremus-Fitzwater et al., 2010; Bingham et al., 2011), their response to SD evolves with the repetition of the encounters. Adolescent mice experience the first SD as play-fighting rather than social stress, as male aggression during this phase is not experienced in the same way as during maturity (Montagud-Romero et al., 2017; Rodriguez-Arias et al., 2017). With the repetition of the defeat experience and the maturation of their hormonal profile, adolescent animals exhibit higher corticosterone responses with respect to their first agonistic encounter, thus displaying an increasingly adult response (Romeo et al., 2006; Lui et al., 2012; Wright et al., 2012). Changes in the ACTH/corticosterone neuroendocrine axis and hormonal alterations precipitated by puberty (e.g. an increase in testosterone levels) may underlie the progression in the social defeat experience that takes place during adolescence.

As occurs in adult defeated rodents and with other stressors, recent studies show that animals defeated intermittently during adolescence self-administer more cocaine in the SA paradigm when they become adults (Burke and Miczek, 2015; Burke et al., 2016).

Moreover, these animals present an increased breaking point in the progressive ratio, and ingest a higher number of infusions in a 24h binge access. In contrast, it was recently found that suffering defeat during adolescence delays cocaine SA acquisition in adulthood, which calls into question the perception that repeated SD also increases cocaine SA in adult animals, (Rodríguez-Arias et al., 2017). Amphetamine and cocaine-induced CPP were also shown to be enhanced in mice defeated during adolescence and evaluated in adulthood, confirming that social stress in this period of development has long-lasting consequences in later life (Burke et al., 2011; Montagud-Romero et al., 2015; Rodríguez-Arias et al., 2017). Only one study has evaluated the effects of SD on ethanol ingestion. Socially defeated adolescent mice consume more ethanol and show increased motivation for the drug three weeks after the last SD experience (Rodríguez-Arias et al., 2016). A detailed description is provided in Table 1 and 2.

To sum up, although the experience of SD is different in adolescent animals, there is an increase in the rewarding effects of cocaine and ethanol regardless of the age at which exposure to the stress occurs (Le et al., 1998; Funk et al., 2005; Montagud-Romero et al., 2016b; Rodríguez-Arias et al., 2017).

Mechanisms underlying the effects of social defeat stress on reward

Stress response system: corticotrophin releasing factor (CRF)

One of the mechanisms that explains how social stress increases vulnerability to drug addiction are changes in the CRF system. Physiological response to stress consists of a neuroendocrine cascade initiated by CRF, which integrates the adaptive response to stress

(Owens and Nemeroff, 1991). In a stressful situation, the HPA axis is triggered by secretion of CRF from the paraventricular nucleus of the hypothalamus (PVN) (Goeders, 2002; Bale and Vale, 2004). In parallel, CRF axons project to extrahypothalamic areas such as the extended amygdala and ventral tegmental area (VTA), thereby modulating DA function and causing neuroadaptations in DA neurons in the corticolimbic pathway (Wanat et al., 2008; Haass-Koffler and Barlett, 2012).

VTA is a key structure for the effects of drug reinforcement and the site at which interaction between DA and the CRF system occurs (Borgland et al. 2010; Boyson et al., 2011). Social stress promotes the release of CRF in the VTA when there is both acute and repeated social stress (Holly et al., 2016). Recently, researchers have related this increase in basal levels of CRF in the VTA with the escalation on cocaine SA and the development of behavioral and neural cross-sensitization that takes place in defeated animals (Boyson et al., 2014; Holly et al., 2016; Han et al., 2017). These CRF effects are mediated by two receptors, namely CRF receptor type 1 (CRFR1) and CRF receptor type 2 (CRFR2), both positively coupled to adenylate cyclase through stimulatory G proteins (Hauger et al., 2009; Binder and Nemeroff, 2010; Zorrilla and Koob, 2010). Thus, antagonism of CRFR1 and CRFR2 could be an interesting tool in the study of the neurobiological mechanisms through which SD stress modulates the response to cocaine and a pharmacological approach in the prevention of relapse induced by stress (see Table 3). Indeed, the results of pre-clinical research using CRF1 receptor antagonists are very promising. When administered before SD episodes, the CRF1 receptor antagonist CP-154,526 reversed the effects of stress on cocaine-induced CPP (Ferrer-Pérez et al., 2018). When administered before physical stress (footshock), it blocked the reinstatement of cocaine CPP, while failing to block reinstatement induced by a priming dose of the drug (Lu et al., 2001). Regarding the effects of CRF1 antagonists on the SA

procedure, central and peripheral VTA injections of CRF1 antagonist before stress reduced the escalation of cocaine, heroin, and ethanol SA after SD (Le et al., 2000; Boyson et al., 2011; 2014) or a physical stressor (footshocks) (Shaham et al., 1998).

On the other hand, the antagonism of CRF2 produces less consistent effects. Some researchers have found that blockade of CRF2 receptors with a peripheral peptidic antagonist induces a stress response comparable to the effect of SD on control animals and an enhancement of the effects of SD (Ferrer-Perez et al., 2018). In line with these reports, knockout CRFR2 mice have higher ACTH and corticosterone levels in the blood due to hypersensitivity of the stress system (Bale et al., 2000; Bale and Vale, 2004). Conversely, other studies point in the opposite direction, revealing a protective effect of CRF2 antagonists when administered intra VTA on the escalation (Boyson et al., 2014) and reinstatement of cocaine SA (Wang et al., 2007). Different routes of administration of the corticotropin-releasing factor CRF2 receptor antagonist (VTA vs peripherally) and variations in the stress procedures employed could explain these divergent results. Additionally, several authors have speculated that this receptor plays a dual role of activation and inhibition of the stress response (Reul and Holsboer, 2002), with the effect being modulated by the moment at which the response takes place and also by the location of the structure containing the receptor. Activation of corticotropin-releasing factor CRF2 receptor induces an anxiogenic effect in the early phases of the response and an anxiolytic effect in the recuperation phase, thus antagonizing the effects of corticotropin-releasing factor CRF1 receptor in structures like the paraventricular nucleus of hypothalamus, the bed nucleus of the stria-terminalis, the septal nuclei or the amygdala (Rivier et al., 2003).

In conclusion, the CRF system is involved in the short and long-lasting effects of SD stress on drug response. Thus, CRF1 and CRF2 receptors should be considered possible research targets for preventing or reversing the effects of stress in psychostimulant addiction disorder.

Dopaminergic system

DA is a neurotransmitter involved in the control of multiple functions as well as the experience of punishment and reward (Pierce and Kalivas, 1997; Polter and Kauer, 2014). The mesolimbic dopaminergic system has been implicated in the rewarding effects of drugs of abuse (Koob and Le Moal, 2001; Wise and Koob, 2014), and specifically, cocaine administration has been shown to increase extracellular concentrations of DA in the NAc (Di Chiara and Imperato, 1988). However, the dopaminergic system is also activated by aversive stimuli such as social isolation (Han et al., 2015), foot-shock (Brischoux et al., 2009) or SD, which produce an increase in extracellular DA release (Imperato et al., 1989; Tidey and Miczek 1996; Holly and Miczek, 2016). DA neurons respond to salient and arousing events, including appetitive, aversive, and novel stimuli. The increase in DA transmission and consequent activation of DA receptors in striatal regions is critically important for behavioral excitation (Tidey and Miczek 1996; Anstrom et al., 2009). This enhanced phasic dopaminergic signaling represents an essential component in the process of switching attention and behavioral selection to unexpected, important stimuli (Robinson et al., 2002).

Numerous studies have demonstrated that SD alters dopaminergic receptors in different brain areas (see Table 4). DA effects are mediated by five DA receptor subtypes divided into two separate families: D1-like receptors (D1R) (D1 and D5), which activate Gs proteins, and D2-

like receptors (D2R) (D2, D3, D4), which stimulate G0/Gi proteins. There are contrasting results regarding the effects of SD on D1R. Several studies indicate that SD reduces the affinity (Avgustinovich and Alekseyenko, 2010) and the levels of D1R in the prefrontal cortex (PFC) (Huang et al., 2016), amygdala (Huang et al., 2016) and hippocampus (Montagud-Romero et al., 2016b). Moreover, excitatory synaptic input frequency decreases in NAc D1-medium spiny neurons (MSNs) in mice with depressive-like behaviors after SD, and the enhancement in activity in D1-MSNs results in resilient behavioral outcomes (Francis et al., 2015; Muir et al., 2018). In line with this, a recent study found that SD reduces the expression of D1R in the medial prefrontal cortex (mPFC) only in susceptible mice (Shinohara et al., 2017). On the other hand, a number of studies have failed to find differences in the regulation of D1R after SD (Lucas et al., 2004; Burke et al., 2011; Bagalkot et al., 2015; Jin et al., 2015). Finally, data show that when SD occurs during adolescence, there is an increase in the levels of D1R in the caudate and putamen nucleus when the animals became adults (Novick et al., 2011).

DA D2R are probably the most important postsynaptic receptors mediating behavioral and extrapyramidal activity. D2R are linked to different subtypes of impulsiveness (see review by Jentsch et al., 2014), with excessive eating in obese subjects (see review Wang et al., 2002), and with the development of adequate social behavior (Manduca et al., 2016). SD has been shown to induce a long-lasting increased expression of these receptors in the PFC and hippocampus of adult rodents (Lucas et al., 2005; Bagalkot et al., 2015; Montagud-Romero et al., 2016b). However, SD during adolescence undermines the maturation of cortical DA through D2R regulation of DA synthesis or the glucocorticoid-facilitated pruning of cortical DA fibers (Burke et al., 2011; Naneix et al., 2013; Burke and Miczek, 2014). Sustained mPFC DA release during repeated adolescent defeat results in prolonged over-activation of

presynaptic D2 autoreceptors, ultimately causing long-term reductions in mPFC DA activity (Watt et al., 2014). Therefore, D2R appears to be a potential neural mechanism underlying the reduction of cortical stress-induced DA (Burke and Miczek, 2014). Moreover, SD in adolescence alters the way in which later amphetamine exposure in adulthood negatively regulates D2R (Burke et al., 2011).

Considering that there is no agreement regarding the changes to DA receptors after exposure to SD, pharmacological studies could provide more information. Use of the non-specific DA D1/D2R antagonist cis (z) flupenthixol in the NAc demonstrated that activation of these receptors modulates the acquisition and expression of aggressive behavior after SD in Syrian hamsters (Gray et al., 2015). Pharmacological studies have also confirmed that both DA receptors are involved in the increase of the conditioned rewarding effects of cocaine induced by SD. Blockade of D1R prior to each SD completely abolishes the increase in the CPP induced by cocaine (Montagud-Romero et al., 2016b). In line with this, several studies support a critical role for D1R during acute stress, as blockade of these receptors prevented the reinstatement of cocaine-seeking behavior (Capriles et al., 2003; Sánchez et al., 2003; Brown et al., 2012).

On the other hand, it has been observed that administration of the antagonist D2R (sulpiride) before SD drastically reduces defensive behaviors and stimulates social investigation (Puglisi-Allegra and Cabib, 1988). Similar results have been described in defeated adolescents, in which the blockade of mPFC D2R prevented the decrease of dopaminergic activity in adulthood (Watt et al., 2014). Raclopride, a D2R antagonist, completely abolishes the long-lasting increase in cocaine-induced CPP when administered before each SD in adult

mice (Montagud-Romero et al., 2016b), and also reverses the acute effects of SD on the rewarding effects of cocaine (Reguilón et al., 2017). These results suggest that both DA receptors (D1R and D2R) are involved in the effects induced by social stress on the rewarding effects of several drugs, although further studies would be needed to specifically evaluate the role of DA receptors in relation to stress-induced drug-seeking and taking behavior.

For the development and maintenance of the dopaminergic phenotype throughout the life of an organism, several transcription factors, including Pitx3 and Nurr1, are of vital importance (Smits and Smidt, 2006; Kadkhodaei et al., 2009; Bissonette and Roesch, 2015). Pitx3 is essential for Nurr1-mediated transcription of its target genes, which include tyrosine hydroxylase, D2R, DA transporter (DAT) and vesicular monoamine transporter 2 (Vmat2) (Jacobs et al., 2009). A recent study found that mice exhibited decreased levels of the transcription actors Pitx3 and Nurr1 in the VTA when they were defeated during adolescence, but not in adulthood. This confirms that the genetic control of DA markers is altered only when social stress occurs during adolescence (Montagud-Romero et al., 2017). The molecular processes underlying the different effects of SD on transcriptional factors are difficult to determine. During critical periods of development, like adolescence or the early stages of life, individuals are highly vulnerable to the effects of stress in such that these transcriptional factors could be less affected by stress in adulthood. Coppens and co-workers (2011) observed that SD during adolescence upregulates the expression of BDNF and other genes in several brain areas, while no changes are observed in adulthood. In response to a stressful experience, CRF release in the VTA can cause synaptic neuroadaptations of DA neurons along the mesolimbic pathway (Saal et al., 2003; Ungless et al., 2003; Borgland et al., 2004). The greater plasticity of the adolescent brain explains why mice exposed to repeated social

stress during adolescence and cocaine exhibit lower expression of Pitx3 in the VTA (Montagud-Romero et al., 2017). In line with this, mice separated from their mother and treated with cocaine exhibit decreased Nurr1 and Pitx3 protein expression levels in the VTA (Garcia-Rubio et al., 2016). Finally, epigenetic mechanisms may also play a role, although no studies have evaluated this issue to date. Using HDAC inhibitors, Green and co-workers (2017) observed increases of DAT mRNA expression in rat N27 mesencephalic cells, accompanied by significant increases in Nurr1 and Pitx3 mRNA expression. A detailed description is provided in Table 5.

Brain-derived neurotrophic factor (BDNF) is strongly linked to the mesolimbic pathway, promoting the release of DA through activation of tropomyosin receptor kinase B (TrkB), and there is interaction among neural mechanisms in response to cocaine or stress affecting DA and BDNF (Goggi et al., 2003; McCarthy et al., 2012; Vasconcelos et al., 2015). Some studies associate genetic changes and the expression of BDNF with the depressive-like symptoms induced by SD in adult rodents (Berton et al., 2006; Woo Koo et al., 2016). Extracellular-signal-regulated kinase (ERK) and the cyclic adenosine monophosphate response element binding protein (CREB) pathway stimulate the expression of BDNF (Kandel, 2001; Barco et al., 2002; Bramham and Messaoudi, 2005), enhancing the expression of proBDNF in the dentate gyrus (DG) and basolateral amigdala (BLA) in adult and adolescent mice subjected to SD (Montagud-Romero et al., 2017). Extracellular signal-regulated kinase (ERK/MAPK) plays a crucial role in long-term adaptive changes that occur during cognitive processes, and is activated in numerous physiological conditions by a variety of stimuli (see Ciccarelli and Giustetto, 2014). There are not many studies evaluating the effects of SD on the expression of pERK1 and pERK2 in DG. Iio and coworkers (2011) found that pMEK1/2 and pERK1/2 were decreased in the hippocampus of rats exposed to

chronic social defeat. However, an increase in the expression of pERK1 and pERK2 in the hippocampus has been detected only in defeated adult mice (Pardon et al., 2005). This activation of pERK1/2 and CREB in the DG might generate behaviors similar to depression or anxiety (Cameron and Schoenfeld, 2018; Gass and Riva, 2007). These results may throw light on the relationship of modifications of dopaminergic neurotransmission in the reward circuit (Nikulina et al., 2012; Yang et al., 2016; Xu et al., 2018).

Although there is no general agreement, the above-mentioned results confirm the dopaminergic system as a critical neural link between aversive stress experiences and the rewarding properties of drugs of abuse (Koob and Le Moal, 2001; Wise and Koob, 2014; Hammels et al., 2015; Han et al., 2015).

Epigenetic mechanisms

Epigenetic modifications to chromatin represent mechanistic pathways through which stress exposure can affect the brain, and provide the missing link between environmental stimuli and genetic response. However, little attention has been focused on the long-term epigenetic changes induced by SD stress. Changes to chromatin structure can occur at many levels, the main mechanisms being histone acetylation, phosphorylation and methylation, together with alterations in DNA methylation levels in the brain. While DNA methylation often represses gene transcription (Jones and Takai, 2001; Guibert and Weber, 2013), histone acethylation, which undermines histone interaction with DNA, has been closely related with a rise in levels of gene transcription (Morris et al., 2010; Biliński et al., 2012; Peixoto and Abel, 2013). On the other hand, histone deacetylation promotes a state of transcriptional repression (Forsberg

and Bresnick, 2001; Ito and Adcock, 2002; Tsankova et al., 2006). In terms of histone methylation, downstream effects on gene regulation depend largely on the specific amino acid modified. All these epigenetic mechanisms may mediate the impact of stress on the function of neural circuits (Tsankova et al., 2006; Sananbenesi and Fischer, 2009; Nelson and Monteggia, 2011).

Acetylation of histones, and specifically an increase in histone H3 acetylation, is the most frequently reported epigenetic mechanism induced by SD. In brain structures such as the NAc, mPFC, dorsal raphe (DR) or hippocampus, an increase in H3/K14 acetylation (K refers to the lysine amino acid residues within the N-terminal tail protruding from the histone core of the nucleosome) has been detected up to 10 days after the last exposure to chronic SD stress (Covington et al., 2009; Hinwood et al., 2011; Hollis et al., 2010, 2011; Kenworthy et al., 2014). Similar long-lasting hyperacethylation has been found in histone H3/K9 and K27 in the promoter of the sodium dependent D-serine transporter gene ASCT2 (Kanai and Hediger, 2003; Wang et al., 2017). Furthermore, the response to novelty modulates the epigenetics induced by SD exposure, since H3K14 acetylation augments only in low-responding rats (Hollis et al., 2011). Interestingly, the increase in histone H3 in the hippocampus acetylation induced by SD can be reverted by physical exercise (Patki et al., 2014). Contrasting results have been reported regarding H4 acetylation after SD, with no changes (Tsankova et al., 2006; Hollis et al., 2010) and increases both being reported in defeated mice (Erburu et al., 2015; Montagud-Romero et al., 2016a). Epigenetic mechanisms also seem to play a role in resilience to the effects of SD, since susceptible rats display higher levels of histone H3 (K9,14,18) and total H3 and H4(K5,12,16) acetylation (Tsankova et al., 2006; Hollis et al., 2011; Kenworthy et al., 2014). Recent studies have reported SD-induced epigenetic changes in particular genes. In adult mice socially defeated during adolescence,

Xu and co-workers (2018) observed increased levels of dimethylation of histone H3 at lysine K9 immediately downstream from the BDNF IV promoter. Equally, an upregulation of ASCT2 (D-serine transporter) expression in chronic social defeat stress was regulated through histone hyper-acetylation in its promoter region (Wang et al., 2017).

In accordance with these results, the enzymes that control epigenetic processes are altered after SD. For example, short- and long-term reductions in the histone deacetylase (HDAC) levels (specifically HDAC 2), in the NAc and hippocampus have been observed in defeated mice. On the contrary, increases in histone acetyltransferase (HAT) activity have been described in the same structure (Covington et al., 2009; Montagud-Romero et al., 2016a; Martin et al., 2017). In addition, a downregulation of HDAC6 (in raphe neurons and in the hippocampus) and HDAC5 (in NAc and PFC) has been reported a few weeks after the last SD, changes that were reverted by the HDAC inhibitor imipramine (Renthal et al., 2007; Espallergues et al., 2012; Fuchikami et al., 2016; Martin et al., 2017). However, in a long-term evaluation, the level of HDAC6 continued to be significantly elevated more than one month after the last agonistic encounter (Jianhua et al., 2017), with an increase in the mRNA expression of different classes of HDAC enzymes in the PFC (Erburu et al., 2015).

Other epigenetic changes induced by SD described in the literature include a three methylation in H3(K4) (H3(K4)me3), which is closely associated with transcriptional initiation. In one study, an increase was detected in the hippocampus three weeks after the last defeat experience (Montagud-Romero et al., 2016a). In another, an increment of H3K9me2/me3 in the NAc and of the promoter of the BDNF IV gene in the mPFC were produced by SD, and were associated with a repression of transcription (Pathak et al., 2017,

Xu et al., 2018). Although long-term changes in DNA methylation have not been described after SD (Wang et al, 2017; Xu et al., 2018;), DNA methyltransferases 3a and 3b have been shown to undergo a significant acute decrease in their mRNA expression a few hours after SD (Jung et al., 2015).

Finally, several studies have highlighted how epigenetic changes are associated with the behavioral response of socially defeated rodents to stress. Infusion of HDAC inhibitors into the NAc (e.g. MS-275 or SAHA) reverses stress-induced social avoidance in defeated mice and restores the time in which animals are engaged in social interaction (Covington et al., 2009). These drugs also reverse social avoidance when administered to the amygdala and PFC (Covington et al., 2011, 2015). Inhibition of HDAC with valproic acid not only increases the effects induced by SD (McCann et al., 2017), but also the conditioning rewarding effects of cocaine, since HDAC inhibitors increase associative learning (Ploense et al., 2013; Montagud-Romero et al., 2016a). On the contrary, inhibition of HAT activity with the HAT inhibitor curcuma longa, or through viral-mediated transfer and overexpression of specific HDACs in the NAc, markedly inhibits the increase in cocaine-induced CPP in defeated animals (Renthal et al., 2007; Hui et al., 2010). These results confirm that the alterations in histone acetylation induced by SD correlate with the increase in the conditioned rewarding effects of cocaine (Montagud-Romero et al., 2016a).

To summarize, there is a large body of evidence to show that SD induces long-term chromatin remodeling, up-regulating levels of histone acetylation H3 and increasing HAT activity, while results concerning HDAC levels are controversial (see Figure 1). These epigenetic modifications seem to be responsible, at least partially, for the behavioral effects

induced by SD, including stronger rewarding effects of cocaine. Epigenetic mechanisms should be viewed as potential avenues leading to innovative treatments for the long-term effects of social stress on drug addiction.

Neuroinflammation response

The term neuroinflammation refers to the cascade of events that generate cellular (microglia, astroglia and infiltrated immune cells) and molecular (cytokines and chemokines) modifications in the form of an immune response within the central nervous system (CNS). The neuroimmune response relays in microglia, which increase in number (Kettenmann et al., 2011) and recruit monocytes from the peripheral blood (Wohleb et al., 2014) in response to harmful stimuli. An inflammatory microglial response also involves the production of pro-inflammatory cytokines and the expression of several cell surface antigens. Numerous studies have demonstrated that neuroinflammation may not only be provoked by pathological conditions, but can also be trigged by psychological stress (Xanthos and Sandkuhler, 2014). Although the effect of SD on neuroinflammation is clearly demonstrated, results regarding acute exposure to social stress are controversial. Some authors have found that acute social stress is not effective in producing either peripheral or central inflammation (Hueston et al., 2011), while others have determined that a single exposure to social stress can promote enhanced neuroinflammation in response to subsequent exposure to stress (Audet et al., 2011).

In animal studies, SD-induced neuroinflammation has been well characterized, with long-lasting increases in the number of macrophages and activated microglia in the brain (Stankiewicz et al., 2015). Immediate or delayed (up to 7 days) increases in pro-inflammatory cytokines such as interleukin IL-1β, IL-6 and the tumor necrosis factor alpha (TNFα)

(Wohleb et al., 2011, 2012, 2014) have been described in several brain regions (Audet et al., 2011; Patki et al., 2013). More importantly, there is a relation between individual differences in stress susceptibility and the neuroinflammatory response; studies reveal that stress-susceptible rodents exhibit increased pro-inflammatory cytokines such as IL-6, IL-15, IL-7, monocyte chemoattractant protein (MCP-1), and IL-1β (Hodes et al., 2014; Stewart et al., 2015; Wood et al., 2015). These alterations are region-specific, as susceptible rats exhibit a higher release of IL-1β within the locus coeruleus (LC) (Wood et al., 2015), but not within the DR. In contrast, stress-resilient rats or mice do not exhibit elevated pro-inflammatory cytokine expression in the plasma, but do exhibit enhanced expression of anti-inflammatory IL-4 and IL-10 (Hodes et al., 2014; Stewart et al., 2015). Resilient rats exhibit a decrease of IL-1β in the DR (Wood et al., 2015), although an increase in IL-1β mRNA has also been reported in the hypothalamus of resilient mice after two exposures to stress (De Miguel et al., 2011).

The chemical and electrical signaling between the neurons requires a controlled microenvironment to function effectively. The blood-brain barrier (BBB) separates the cerebral interstitial fluid from the blood and regulates the movement of substances between the blood and CNS cells (Abbott, 2013). Adolescent mice exposed to SD undergo significant changes in BBB structure. SD reduces the expression of the tight junction protein claudin-5 and produces an increase in basal laminin degradation in the NAc and hippocampus. Consequently, there is an increase in IgG extravasation, indicating that social defeat increases BBB permeability, probably through alterations in structural proteins (Rodríguez-Arias et al., 2017). As a result of BBB deterioration, peripheral immune cells can penetrate the CNS, causing or enhancing existing neuroinflammation (Bhattacharya et al., 2016).

In addition, social stress leads to the release of inflammatory monocytes into the circulation (Wohleb et al., 2012, 2014; Goto et al., 2015), accompanied by an increase in their number and a greater release of pro-inflammatory cytokines within the spleen (Kinsey et al., 2008). Although the individual differences in splenic inflammation in response to social-stress is largely uncharacterized, susceptible mice generally exhibit increased splenic release of pro-inflammatory cytokines when stimulated with the T-cell stimulating agent concanavalin A (Gomez-Lazaro et al. 2011), indicating that the spleen plays a major role in neuroinflammation in response to social stress.

Social defeat-induced neuroinflammatory processes are also related to learning and memory deficits, and to hippocampal neurogenesis. Mice exposed to SD show neurogenesis deficits in the hippocampus with respect to unstressed controls (McKim et al., 2017). An impaired differentiation of neural progenitor cells into mature neurons, accompanied by behavioral changes in memory and mood, has been observed in SD mice. Increased hippocampal cytokines, enhanced microglial Iba-1 immunoreactivity in the DG, and an increase in DG cluster of differentiation 45 (CD45)-positive cells in SD mice suggest recruitment of peripheral monocytes by the brain (McKim et al., 2017). Administration of the anti-inflammatory minocycline prior to SD exposure prevents the increase in Iba-1 immunoreactivity and monocyte recruitment and spatial memory recall deficits that it induces. These results highlight the role of neuroinflammation in stress-induced behavioral changes and point to a potential therapy for patients experiencing stress-related cognitive impairment (Pfau and Russo, 2016).

Is has been demonstrated that both susceptible and resilient rats display differential regulation of gene expression within the LC and DR with respect to control rats (Wood et al., 2015). In the LC, susceptible rats exhibit higher IL-1β mRNA levels and resilient rats exhibit decreased IL-1β and TNFα. Altered expression of several other genes, many of which play a role in immune or inflammatory processes, has also been identified after SD (Finnell and Wood, 2016). Interestingly, inducible nitric oxide synthase (iNOS), a signaling molecule involved in the pathogenesis of inflammatory disorders, was found to be reduced six-fold in resilient rats versus controls, which may constitute a protective mechanism (Wong et al., 1996), as iNOS suppression has been shown to promote anti-inflammatory type microglia (Franco and Fernandez-Suarez, 2015).

Scientific evidence clearly demonstrates that vulnerability to substance abuse disorder is linked to alterations in inflammatory parameters (Hutchinson and Watkins, 2014; Rodrigues, 2014; Reus et al., 2015). An enhanced inflammatory state could be considered a risk factor, as immune signaling in the CNS contributes considerably to mesolimbic DA reward signaling, thereby conditioning reward behaviors (Rodrigues, 2014; Harricharan et al., 2017). Although the exact mechanisms of the genesis of addiction are not well understood, there is a growing body of literature relating alteration of the immune system and inflammatory markers to vulnerability to substance abuse disorders (Hutchinson and Watkins, 2014; Rodrigues, 2014). Inflammatory processes could be the pathway between stress and disease, modulating behavioral and neuroendocrine functions that contribute to the vulnerability and enhanced sensibility to drugs after social stress procedures (see Figure 2).

Conclusion: limitations and future directions

SD is one of the most common stressors faced by humans, and causes or aggravates a high number of mental pathologies, including drug abuse. However, the mechanisms by which social stress produces changes in the brain and behavior are largely a mystery. Although human behavior cannot be completely represented by preclinical studies, animal models are responsible for more than 90% of all neurodevelopmental research (Clancy et al., 2007). The SD paradigm has permitted great scientific advances in the field of drug addiction, but also has important limitations. Knowledge of these limitations is critical for improving this animal model.

One of the main advantages of the SD model is that the hormonal response is stronger than with other stress models (Koolhaas et al., 1997). Corticosterone reaches higher peaks during encounters and there is no habituation with repeated exposure to the aggressive opponent (Covington and Miczek, 2005; Watt et al., 2009). On the other hand, the major drawback of the SD paradigm is that it is designed principally for male rodents. Because most female rodents do not express spontaneous aggression, the majority of basic research examines the physiological and behavioral outcomes of social conflict in male rodents. However, aggression is not an exclusively masculine characteristic driven by male sex hormones. There are many situations in which female experimental animals can act aggressively, showing responses that are not attributable to testosterone (Brain et al., 1992). For example, there are cases in which female rodents exhibit territorial and maternal aggression, which constitutes an avenue for examining sex differences in physiology and behavior in response to stress (Solomon et al., 2017). Female rodents are capable of displaying threat and attack behavior, and in some species are more aggressive than males during agonistic encounters (Huhman et

al., 2003; McCann et al., 2017). Defeated females respond to a caged opponent with similar social avoidance to that observed in males, but research some decades ago showed that female rats do not become "permanently" submissive after losing an aggressive encounter (Brain et al., 1992; Schotens et al., 1998; Swanson 1990). In the human population, although men are more affected at a physiological level by social stress (Lee et al., 2013), women show higher rates of anxiety and fear. This crucial issue needs to be assessed in the future to make the SD a more valid and translational animal model. In this context a recent study applied the SD procedure in females, but more research is needed (Harris et al., 2017).

In addition to the above-mentioned limitation, most studies today evaluate the stress response in adult subjects. However, humans suffer stress throughout life, and so SD stress should also be studied in adolescent animals, as they present particular responses to stress and their greater brain plasticity makes the long-term consequences more severe. Although in recent years research have increasingly focused on the effects of SD during adolescence, further work is necessary to confirm existing data.

Another characteristic of the SD paradigm is the wide range of species and strains that can be employed. Although this has been considered a weakness, as it could, in theory, compromise comparison of data, it actually allows more valuable information to be obtained. Some rodent strains are more susceptible to the effects of SD or show more aggression toward their conspecifics than others (Osadchuk et al., 2009; Dow et al., 2011; Heinla et al., 2014), it being well established that genotype has a strong influence on social dominance and patterns of agonistic behavior (Kudryavtseva et al., 2006; Nevison et al., 1999). On the other hand, studies in other species offer valuable information that cannot be obtained with mice or rats.

For instance, the brain functions of tree shrews are closer to those of humans, and depression induced by social defeat in this species shows high construct, face and predicted validity as an animal model (Wang et al., 2012). Another example is the mandarin vole, which has been increasingly used in recent years to investigate social disorders (Tai and Wang, 2001; Jia et al., 2009). One of the advantages afforded by this species is that females exhibit high levels of spontaneous aggression towards same-sex conspecifics (Tai and Wang, 2001), which provides an opportunity to measure the physiological and psychological effects of chronic social defeat.

The SD model emphasizes the social aspect of stress; however, it produces both physical and social stress and is not purely psychological, as often occurs in a human context of social stress. We need to take into account that the physical stress suffered by the animal also has a bearing, and that it is difficult to separate the two types of stress within this model (Hammel et al., 2015).

The heterogeneity of methodologies, SD paradigm variations, doses of drugs administered and time intervals between exposures, pharmacological treatments and neurochemical measurements after stress, as well as the age of the animals employed, are sure to influence the diversity of the results obtained. It is important to continue conducting studies to more effectively determine the role of the different mechanisms and markers involved in the reward circuits of mice exposed to SD. Furthermore, it should be taken into account that the response to SD is not homogenous, since the susceptibility of each individual varies, an issue that has been addressed in more recent resilience studies. Socially defeated mice do not exhibit a homogenous response, as they belong to two different populations: susceptible and

non-susceptible/resilient mice, with the former showing higher anxiety or more HPA-axis reactivity than the latter (Krishnan et al., 2007; Cao et al., 2010; Vialou et al., 2010; Berube et al., 2013; Mineur et al., 2013; Der-Avakian et al., 2014; Tse et al., 2014). Thus, it is important to identify specific mechanisms underlying resilience to stress in order to discover new approaches to the treatment of depressive, anxiety and drug use disorders (Daskalakis and Yehuda, 2014).

In this review, we have summarized the main systems affected by social defeat and which could be responsible for increases in the rewarding effects of cocaine and alcohol. To date, studies have mainly focused on the particular role of each of these systems, but a tentative common hypothesis can already be drawn. Social stress strongly activates the HPA axis, leading to increases in CRF levels. VTA neurons express an elevated number of glucocorticoid, CRF and adrenergic receptors, and by activating them, stress induces further changes in the DA pathway. Tovar-Díaz and co-workers have recently demonstrated that CRF and α1 adrenergic receptor signaling enhance the plasticity of NMDA-receptor-mediated glutamatergic transmission in VTA DA neurons through distinct effects on inositol 1,4,5-triphosphate (IP3)-dependent Ca2+ signaling. In this way, acute social defeat stress engages similar cooperative CRF and α1AR signaling in the VTA to reinforce learning of cocaine-paired cues.

Social defeat also activates neuronal intracellular signaling governed by the extracellular signal-regulated kinase (ERK/MAPK), as occurs in numerous other physiological conditions (see Ciccarelli and Giustetto, 2014). ERK signaling may control transcription by targeting several different regulators of gene expression, such as transcription factors and histone

proteins. Activation of the ERK/MAPK pathway could phosphorylate substrates (e.g. CREB) that regulate genes, such as BDNF, which can promote the release of DA, among many other effects (Goggi et al., 2003; McCarthy et al., 2012; Vasconcelos et al., 2015). On the other hand, epigenetic mechanisms induced by social stress could be responsible for the changes observed in DA receptors. For instance, rats exposed to maternal separation and social isolation show downregulation of the D1 receptor in the NAc due to hypermethylation of the Drd1a promoter region (Sasagawa et al., 2017).

Social stress also affects microglia through their glucocorticoid and adrenergic receptors (Fujita et al. 1998; Sierra et al. 2008; Markus et al. 2010), which when stimulated, induce proliferation, recruitment of monocytes from the peripheral blood, release of pro-inflammatory cytokines and expression of several cell surface antigens (e.g. Iba1)(Kettenmann et al. 2011; Wohleb et al. 2013). The well-known stress-induced depression effect induced through microglial activation (Tong et al., 2017) is hypothesized to involve inflammation of neurons, neurodegeneration and apoptosis, impaired neurogenesis, production of stress proteins, or alteration in neurotrophin metabolisms (see Singhal and Baune, 2017).

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Abbreviations

ACTH: adrenocorticotropic hormone

BBB: blood-brain barrier.

BDNF: brain-derived neurotrophic factor

BLA: basolateral amygdala

CD45: cluster of differentiation 45.

CNS: central nervous system.

CREB: cyclic adenosine monophosphate response element binding protein

CRF: corticotrophin-releasing factor

CRFR1: CRF receptor type 1

CRFR2: CRF receptor type 2

D1R: D1-like receptor

D2R: D2-like receptor

DA: dopamine

DAT: dopamine transporter

DG: dentate gyrus

DR: dorsal raphe.

ERK: extracellular-signal-regulated kinase

HAT: histone acetyltransferase

HDAC: histone deacetylase

HPA: hypothalamic-pituitary-adrenal axis

IL-10: Interleukin 10.

IL-15: Interleukin 15.

IL-1r2: IL-1 receptor type 2.

IL-1β: Interleukin 1 beta.

IL-4: Interleukin 4.

IL-6: Interleukin 6.

IL-7: Interleukin 7.

iNOS: inducible Nitric Oxide Synthase.

LC: locus coeruleus.

MCP-1: monocyte chemoattractant protein 1.

mPFC: medial prefrontal cortex

MSNs: medium spiny neurons

NAc: nucleus accumbens

PFC: prefrontal cortex

PVN: paraventricular nuclei

SA: self-administration

CPP: conditioned place preference

SD: social defeat

TNFα: tumor necrosis factor alpha.

TrkB: tropomyosin receptor kinase B

Vmat2: vesicular monoamine transporter 2

VTA: ventral tegmental area

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Table 1. The effects of social defeat (SD) on the rewarding effects of cocaine and alcohol using the self-administration (SA) procedure.

Animal	Age	Sex	Type of SD	Drug	Effect	Reference
Mouse	Adults	Male	Repeated	Cocaine	Increased SA	Han et al., 2017
Mouse	Adults	Male	Repeated	Cocaine	Delayed SA acquisition	Rodríguez-Arias et al., 2017
Rat	Adults	Male	Repeated	Cocaine	Increased binge	Covington et al. 2005; Quadros and Miczek, 2009; Boyson et al., 2014; Covington and Miczek, 2005; Boyson et al., 2011; Yap et al, 2015; Miczek and Mutschler, 1996; Covington and Miczek,
Rat	Adolescents	Male	Repeated	Cocaine	Increased SA	Burke and Miczek, 2015; Burke et al., 2016
Rat	Adults	Male	Repeated	Cocaine	induces SA reinstatement	Manvich et al., 2016
Mouse	Adolescents	Male	Repeated	Alcohol	Increased alcohol intake	Rodríguez-Arias et al., 2016
Mouse	Adults	Male	Repeated	Alcohol	Increased intake	Croft et al., 2005
Rat	Adults	Male	acute	Alcohol	Decreased SA	Funk et al., 2005
Rat	Adults	Male	Repeated	Alcohol	No changes	van Erp and Miczek, 2001
Rat	Adults	Male	Acute	Alcohol	Moderate increase	Funk et al., 2004
Rat	Adults	Male	Repeated	Alcohol	Increased alcohol intake	Caldwell and Riccio, 2010

Table 2. The effects of social defeat on the rewarding effects of cocaine and alcohol using the conditioned place preference (CPP) procedure.

Animal	Age	Sex	Type of SD	Paradigm	Drug	Effect	Reference
Mouse	Adults	Male	Acute	CPP	cocaine	increased preference	Montagud-Romero et al., 2015; Reguilón et al., 2017
Mouse	Adolescents	Male	Acute	CPP	cocaine	reduced preference	Montagud-Romero et al., 2015
Mouse	Adults	Male	Repeated	CPP	cocaine	increased preference	McLaughlin et al., 2006; Hymel et al., 2014
Mouse	Adults	Male	Acute	CPP	cocaine	induces reinstatement	Land et al., 2009
Mouse	Adults	Male	Repeated	CPP	cocaine	Increased preference and more sessions required to extinguish the preference	Montagud-Romero et al., 2016b
Rat	Adults	Male	Acute	CPP	alcohol	reduces place aversion	Funk et al., 2004
Mouse	Adults	Male	Repeated	CPP	alcohol	increased preference	Macedo et al., 2018

Table 3. Social defeat (SD) stress promotes CRF (corticotrophin-releasing factor) release. Effect of different CRF receptor antagonists on the enhanced reward response induced by social defeat stress

CRF Receptor	Drug	oute of administratio	Effect/Experimental paradigm	References	
CRF1 antagonist	CP-154,526	Peripheral	↓ subthreshold cocaine CPP	Ferrer-Pérez et al., 2018	
	CP-376,395	Bilateral intra-VTA	↓ cocaine taking during SA bing	Boyson et al., 2014	
	CP-154,526	Peripheral	↓ cocaine taking during SA bing	Boyson et al., 2011	
CRF2 antagonist	Astressin2-B	Peripheral	↑ subthreshold cocaine CPP	Ferrer-Pérez et al., 2018	
	Astressin2-B	Bilateral intra-VTA	↓ cocaine taking during SA bing	Boyson et al., 2011; 2014	

Table 4. Effects of social defeat (SD) on the DA receptor expression. DA dopamine; PFC prefrontal cortex; mPFC media prefrontal cortex.

DA receptor	Animal age	Brain structure	Receptor expression	References	
D1	Adolescence mice	Caudate and putamen	Increase	Novick et al., 2011	
	Adult mice	PFC	Decrease	Huang et al., 2016	
		Amygdala	Decrease	Huang et al., 2016	
		Hippocampus	Decrease	Montagud-Romero et al., 2016b	
D2	Adolescence mice	mPFC	Decrease	Watt et al., 2014	
	Adult mice	PFC	Increase	Lucas et al., 2011; Bagalkot et al., 2015; Montagud-Romero et al., 2016b	

Table 5. Effects of social defeat (SD) on the expression of different family factors (Pitx3, Nurr1, ΔFosB, pCREB, Fos, proBDNF, pERK1/2). BLA basolateral amygdala; DG dentate gyrus; NAc shell nucleus accumbens shell; VTA ventral tegmental area.

Family factor	Expression	Brain structure	Animal age	Reference
Pitx3	Decrease	VTA	Adolescent mice	Montagud-Romero et al., 2017
Nurr1	Decrease	VTA	Adolescent mice	Montagud-Romero et al., 2017
ΔFosB	Decrease	Nac shell	Adult (susceptible) mice	Vialou et al., 2010
Fos	Increase	BLA	Adult mice	Yang et al., 2016
pCREB	Increase	BLA	Adult mice	Yang et al., 2016
proBDNF	Increase	DG, BLA	Adolescent mice	Montagud-Romero et al., 2017
pERK 1/2	Increase	Hippocampus	Adult mice	Pardon et al., 2005

Figures legend.

Figure 1. Epigenetic mechanisms modifications may influence the impact of stress on exposure to addictive drugs and mediate vulnerability to addictive disorders. Histone (H), histone deacetylase (HDAC), histone acetyltrasferase (HAT), methylation (me), methyltransferase (Mtase), SD (social defeat).

Figure 2. Social stress promotes the activation of microglia an increase pro-inflammatory cytokine and chemokine expression. The increase permeability of the blood brain barrier allows the trafficking of monocytes into the CNS from the peripheral circulation.Interleukin (IL), tumor necrosis factor α (TNFα), monocyte chemoattractant protein 1 (MPC1).

Figure 1.

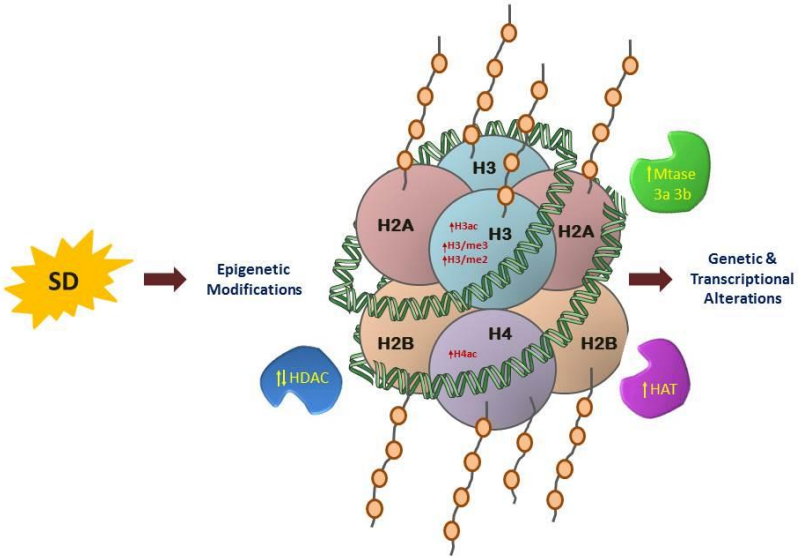

Figure 2.