

TWO INTERCONNECTED WORLDS

How exposure to social stress makes us more vulnerable to drug use

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Stress is one of the main risk factors that can induce humans to develop disorders such as depression, anxiety, or drug use. One of the main sources of stress is social interaction, which can lead to situations like bullying at school or work. In this article we will review the close relationship between exposure to stressful situations and increased cocaine or alcohol use. We will also present the main results obtained with animal models, which have allowed researchers to study the brain mechanisms involved in the impact of stress on drug use. To conclude, we will detail the main mechanisms that explain the powerful effect that stress has on substance use.

Keywords: **social stress, addiction, alcohol, cocaine, drugs.**

■ STRESS IS PART OF OUR DAILY LIVES

Social relationships are critical not only to the development of humans, but also to other animal species that live together in social hierarchies. The environment in which individuals grow has an impact on their well-being, health, and even survival. However, maintaining an individual's homeostasis and health can depend on a key factor in today's society: stress. The term *stress* was defined by Hans Selye (1975) as a non-specific biological response to any challenging situation. Facing a stressful situation (such as having the flu, running a marathon, or taking a public examination), represents a disturbance in the individual's homeostasis, which must be restored. The individual response to this situation will depend on their interaction with the environment and the activity of some of our regulatory systems. The hypothalamic-pituitary-adrenal axis is one of the main regulatory systems activated in response to stress. It releases hormones such as corticotropin-releasing factor,

«Stress is one of the main risk factors involved in drug use»

adrenocorticotrophic hormone, and glucocorticoids (Figure 1). The sympathoadrenal system is also activated, leading to the release of catecholamines (adrenaline and noradrenaline). More recently, the immune system has also been shown to be involved in this process (Costa-Pinto & Palermo-Neto, 2010). Although stress responses are initially adaptive and represent an attempt to maintain homeostatic balance, if prolonged over the long term, they can end up damaging the organism.

Psychological or social stress is the most studied type of stress due to its significant influence on our daily lives. Phenomena such as workplace mobbing and school bullying have been on the rise worldwide in recent years. These types of harassment take place in important areas of people's lives and can be devastating for the victims from a clinical point of view. Indeed, they can lead to anxiety, depression, or substance use disorders.

Thus, stress is one of the main risk factors involved in drug use. It plays a key role not only in relapse,

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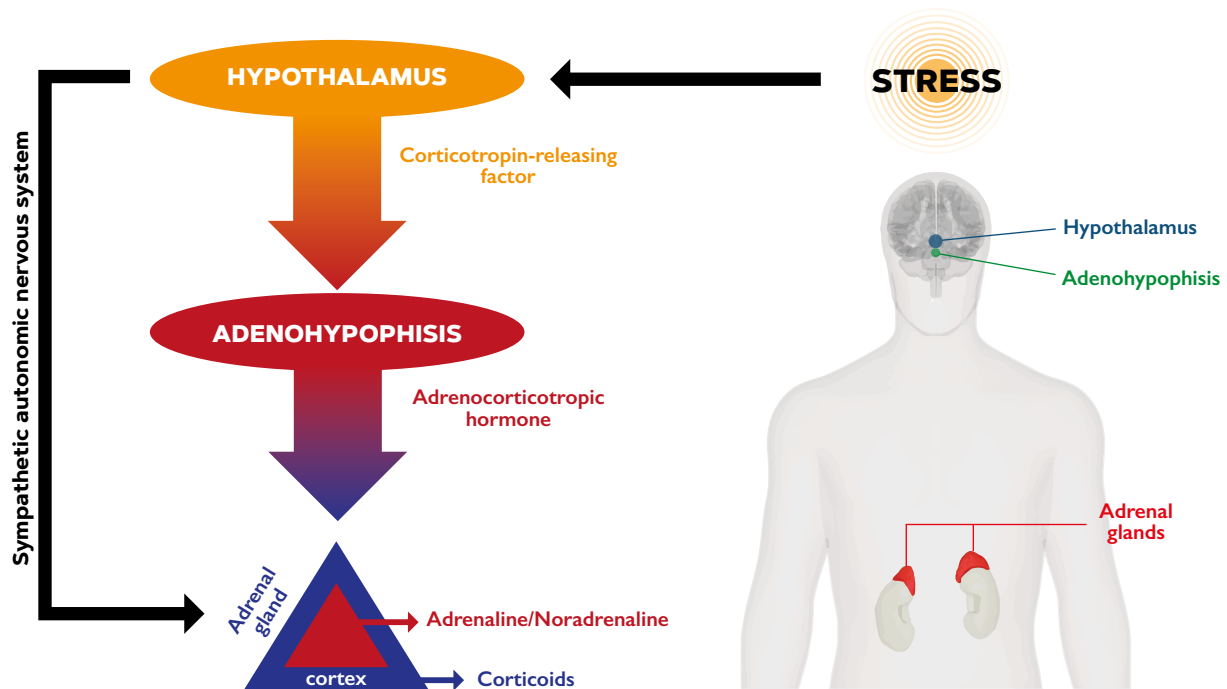


Figure 1. The stress response of the hypothalamic–pituitary–adrenal axis. Activation of the autonomic nervous system (comprising the sympathetic autonomic nervous system) occurs primarily via nuclei located in the hypothalamus and is considered the main organisational structure because it controls all vital functions. First, stress activates the sympathetic autonomic nervous system (via the hypothalamic nucleus), resulting in the release of catecholamines (adrenaline and noradrenaline) from the adrenal medulla (shown in black). Next, the hypothalamic–pituitary–adrenal axis is activated and the hypothalamus releases corticotropin-releasing factor which, in turn, activates the adenohypophysis and thereby stimulates the adrenocorticotrophic hormone. Stimulation by this hormone results in the increased release of corticosteroids by the cortex of the adrenal medulla (shown in shades of orange and blue).

SOURCE: Authors

but also in the initiation, escalation, and maintenance of drug use (Rodríguez-Arias et al., 2013). Given the close relationship between the brain systems involved in addiction and stress, environmental stressors can lead to long-term changes in the function of the brain reward system (Rodríguez-Arias et al., 2013). The neurobiological system involved in stress response is related to drug-responsive brain areas; the common link between the two is the so-called *extended amygdala*. This circuit comprises the shell of the nucleus accumbens, the bed nucleus of the stria terminalis, and the central nucleus of the amygdala where neurotransmitters such as corticotropin-releasing factor, noradrenaline, and dopamine interact (Figure 2).

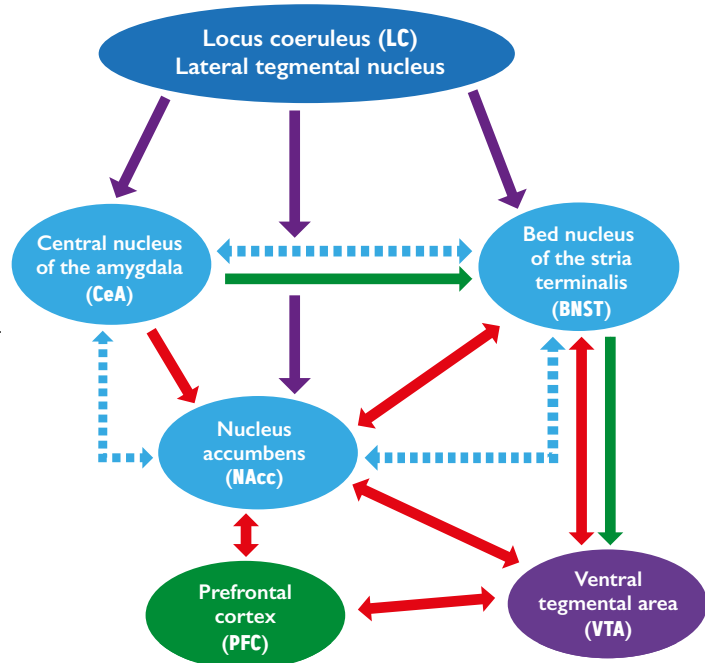
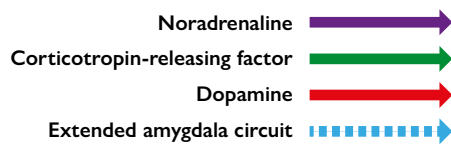
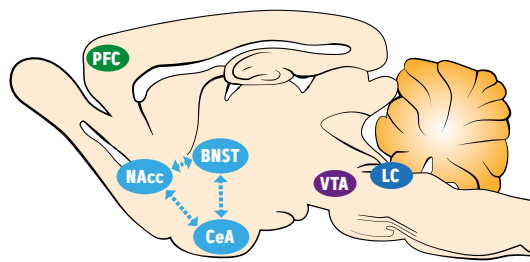
The brain mechanisms involved in the impact of stress on drug use are very complex and require the use of preclinical studies to allow us to study the different factors involved. Among the different animal models designed to represent the social experiences or conditions that induce social stress in humans, the one with the most phenomenological and pathophysiological similarities is the paradigm

«The neurobiological system involved in stress response is related to drug-responsive brain areas»

of social defeat stress in rodents, which has a high translational value because of its ecological and ethological validity. In this model, an experimental animal (intruder) is introduced into the cage of a mouse or rat who is dominant in that territory (resident) and will threaten and attack the intruder. Behavioural changes have been observed in the intruder

animal after this experience, including decreased social interaction and anhedonia, and physiological, neuroendocrine, and neurobiological alterations (Miczek et al., 2008). In the following sections, we will describe the main effects observed in this social stress

model related to drug use, especially focusing on cocaine and alcohol. Several paradigms exist to study the effects of social defeat on drug use, with two of the most common ones being oral or intravenous self-administration and conditioned place preference (CPP). Self-administration is a reinforcement model based on the primary hedonic effect of substance use, while CPP is based on associative learning and the cognitive ability to make predictions about the attainment of future reinforcement in an associated context.



■ SOCIAL STRESS AND COCAINE USE

The use of psychostimulants is highly prevalent in our society, and cocaine is currently the illegal psychostimulant with the highest consumption rates in the population aged 15–64 in Spain (Delegación del Gobierno para el Plan Nacional sobre Drogas, 2019). In a study by Furnari et al. (2015), participants reported stressful events in the three days prior to cocaine use.

In line with this study, numerous experiments in rodents have shown that experiencing social defeat was associated with increased cocaine use. Social defeat resulted in increased intravenous self-administration of cocaine even at low doses, as well as increased cocaine seeking behaviour, even when the animals were required to work harder to obtain the reinforcer (Newman et al., 2018). When the animals were exposed to a situation where they were given unlimited access to cocaine for 24 hours (a binge model), those that had previously been defeated self-administered greater amounts of cocaine at shorter intervals (Holly et al., 2015). Increased long-term cocaine self-administration was also observed, even one month after their last social defeat (Ferrer-Pérez et al., 2019). Once cocaine self-administration is established, brief episodes of social stress before each experimental session could lead to a significant increase in the rate of cocaine use.

Drug use relapse can also be studied in animal models. In these paradigms, after eliminating a behaviour that was previously maintained due to the reinforcing effects of the substance, it can be restored by exposing the animal to a subthreshold drug dose (priming dose), a contextual cue associated with drug

Figure 2. Relationship between brain systems mediating addiction and stress. The locus coeruleus is the most important noradrenergic neuronal area of the central nervous system, involved in many of the sympathetic effects caused by stress due to the increased production of noradrenaline. In turn, this increase in noradrenaline by the locus coeruleus is related to the activation of drug-responsive brain areas, such as the extended amygdala circuit, consisting of the central nucleus of the amygdala, the nucleus accumbens, and the bed nucleus of the stria terminalis. Neurotransmitters such as noradrenaline, corticotropin-releasing factor, and dopamine interact in this circuit, where nuclei such as the prefrontal cortex and ventral tegmental area are also involved.

SOURCE: Authors

use, or a stressful situation. Similarly, craving and reinstatement of drug use after prolonged periods of abstinence was very strongly triggered by exposure to stressful events such as social defeat (Montagud-Romero et al., 2018).

The results obtained using CPP were broadly similar to those obtained after self-administration. Social defeat increased the conditioned reinforcing effects of cocaine, and this increase lasted up to one month after the last experience of social stress (Ferrer-Pérez et al., 2019). Once cocaine CPP has been established and cocaine-seeking behaviour has been extinguished, an agonistic social interaction was sufficient to restore cocaine-induced preference and to increase susceptibility to reinstatement induced by a priming dose of the same drug.

Very few studies have assessed the effect of social defeat during adolescence (bullying model) on drug use in adulthood. Although CPP results are fairly consistent with those observed in adults, intravenous

self-administration results are less clear. Some studies showed an increased motivation for cocaine use in adult rodents defeated during adolescence, as well as an increase in infusions during a cocaine binge (Burke et al., 2017). However, other studies indicate that stress during adolescence may produce deficits in learning and memory processes, because defeated mice required more sessions to discriminate the behaviour that allowed them to consume cocaine (Rodríguez-Arias et al., 2016).

Therefore, we can conclude that social defeat during adulthood leads to an increase in cocaine use and cocaine seeking; nonetheless, further studies will be needed to examine the effects of social defeat during adolescence.

■ SOCIAL STRESS MAKES US DRINK MORE ALCOHOL

Alcohol is the most widely consumed legal drug in our society: moderate alcohol consumption is fairly widespread and accepted by the general population. Human studies indicate that social stress is a strong predictor of alcohol dependence, especially when these experiences take place during one's childhood or adolescence. Another critical time is during the rehabilitation process, where social stress can easily induce relapse.

Preclinical studies support the outcomes observed in humans and show that exposure to social defeat increases alcohol intake compared to non-stressed animals (Reguilón et al., 2020). Using the oral alcohol self-administration paradigm, an increase in consumption and motivation to obtain the substance have been observed in defeated animals. Moreover, this effect is maintained several months after the last social defeat (Reguilón et al., 2020). Similar results have been shown in mice subjected to social defeat during adolescence (Rodríguez-Arias et al., 2016). Moreover, it has been reported that exposure to social stress facilitates the acquisition of alcohol CPP, delays the termination of memories associated with alcohol consumption, and induces the reinstatement of place preference associated with alcohol consumption (Macedo et al., 2018).

Thus, as with cocaine, the results obtained in animal models indicate that social stress increases alcohol consumption as well as the motivation to obtain alcohol when experiencing social defeat, both in adolescence and in adulthood.

■ WHY DOES SOCIAL STRESS INCREASE CONSUMPTION?

At this point, there is no doubt that social stress increases cocaine and alcohol consumption. The question we should be able to answer is through what mechanisms it induces this powerful effect. Social stress can modulate different neurotransmitter systems, alter the expression of several transcription factors, and thus modify the expression of different genes. In addition, it produces changes in the immune response (Montagud-Romero et al., 2018). When stress is experienced chronically, the interaction of these mechanisms will result in structural and functional changes in our brain. In the following section, we will review the most important alterations associated with social stress that can affect the addictive process.

As we have already mentioned, social stress induces an increase in the corticotropin-releasing factor, which directly modulates dopamine neurotransmission in both the ventral tegmental area and the nucleus accumbens (Montagud-Romero et al., 2018). The mesocorticolimbic dopaminergic system is a key pathway for experiencing the reinforcing effects of alcohol, cocaine, and other drugs of abuse. We now know that dopamine neurons in this

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pathway play a critical role in behavioural responses to stress. Furthermore, animals subjected to social defeat experience an increase in extracellular dopamine in the nucleus accumbens and medial prefrontal cortex after occasional exposure to social stress. Interestingly, this increased dopamine was also found after affiliative social interactions, demonstrating that any type of social experience affects the function of the mesolimbic dopamine system and elicits associative learning, thus shaping responses to this learning. Chronic exposure to social stress leads to permanent changes in the activity of these neurons and may be responsible for an increased intake of alcohol and psychostimulants (Montagud-Romero et al., 2018). There is a decrease in the usual activity of the dopaminergic system, with a change in dopamine D1 and D2 receptors. As a consequence of a reduction in D1 receptor affinity, the levels of this receptor in the prefrontal cortex, amygdala, and hippocampus also decrease. Regarding the D2 receptor, increased expression has been observed in the prefrontal cortex of adult mice. When social defeat was experienced during adolescence, there are alterations in



SOCIAL DEFEAT

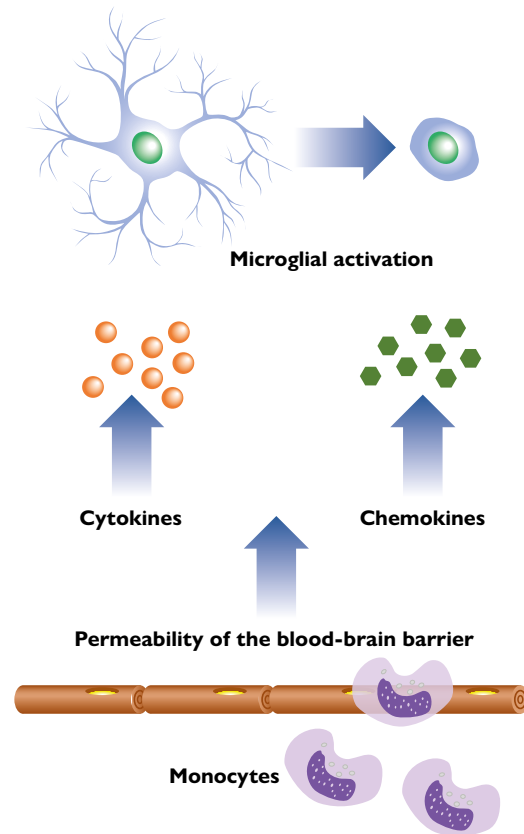


Figure 3. Social stress promotes the activation of microglia and increases the production of proinflammatory cytokines and chemokines, increasing the permeability of the blood-brain barrier and leading to the augmented transfer of monocytes (peripheral inflammatory cells) from peripheral circulation into the central nervous system. Disruption of this barrier can result in an immune system response to repair the central nervous system damage, which can induce structural changes in the brain. In the last decade, these changes have been linked to vulnerability to developing an addictive disorder.

SOURCE: Authors

transcription factors that modulate the dopaminergic system (such as Pitx3 and Nurr1) and which are essential for the transcription of genes such as tyrosine hydroxylase or the D2 receptor. Thus, unlike stressed animals in adulthood, social defeat during adolescence produces an increase in D1 receptors in the caudate and putamen and a decrease in D2 receptors in the prefrontal cortex (Montagud-Romero et al., 2018).

Social stress can also interfere with dopaminergic activity via brain-derived neurotrophic factor (BDNF). Acute social stress increases BDNF levels in the nucleus accumbens and ventral tegmental area, which affects the mesocorticolimbic pathway and leads to increased dopamine release (Miczek et al., 2011). However, chronic social stress is accompanied by a decrease in both BDNF and dopamine expression in the nucleus accumbens which is associated with depressive symptomatology (Miczek et al., 2011).

Social stress induced activation of the hypothalamic-pituitary-adrenal axis also leads to changes in the expression of NMDA and AMPA glutamate receptors. These changes contribute to

the emergence of the neuroadaptations underlying the addictive process which are perpetuated through memory and learning of drug-associated stimuli (Stelly et al., 2016).

Finally, we will address one of the mechanisms most extensively studied nowadays – the neuroinflammatory response. The term neuroinflammation refers to a series of events that produce molecular and cellular modifications in an immune response from the central nervous system. Neuroinflammation has become increasingly important in recent decades because it has been associated with the development of mental and neurodegenerative diseases. In fact, the so-called neuroinflammatory theory of depression was outlined in the 1990s (see Maes et al., 2009). This theory is based on the increase in inflammatory mediators observed in patients with depression and the occurrence of depression or anxiety in individuals injected with cytokines (proteins that coordinate inflammatory responses). Thus, the role of the immune system has become increasingly important

in recent years, and numerous studies have been published demonstrating its role in the effects induced by social stress (Figure 3). Social stress stimulates leukocytes and microglia (cells that coordinate immune defences and the phagocytosis of harmful elements) and increases brain and peripheral levels of cytokines and chemokines (Calcia et al., 2016). This neuroinflammatory response is also accompanied by an increase in blood-brain barrier permeability. The structural and functional integrity of the blood-brain barrier is vital for the maintenance of central nervous system homeostasis. Dysfunction of this barrier has been observed in numerous neurological diseases such as multiple sclerosis, Parkinson's disease, and Alzheimer's disease. When an inflammatory process occurs, the tight junction between endothelial cells in the brain capillaries may be altered as a result of the release of cytokines and other pro-inflammatory agents. This will allow leukocytes, monocytes, and macrophages to penetrate the central nervous system, thereby enhancing the inflammatory response. In turn, the release of pro-inflammatory cytokines and chemokines, leads to microglial activation and astrogliosis, a defence mechanism activated to minimise or repair damage to the central nervous system, leading to structural and functional changes in the brain (Calcia et al., 2016). In the last decade, these changes have been linked to increased vulnerability to the development of addictive disorders. The immune response in the central nervous system affects dopaminergic signalling in the mesolimbic pathway by modifying reward behaviours. Because of this relationship between neuroinflammation, stress, and substance abuse, some researchers have used non-steroidal anti-inflammatory drugs such as indomethacin to reverse the increased conditioned reinforcing effects of cocaine induced by social stress (Ferrer-Pérez et al., 2018).

Other components of the neuroinflammatory response that have been extensively studied in relation to substance abuse and stress exposure are the TLR4 receptors of the innate immune system, which are responsible for recognising pathogen-associated molecular patterns. Stress exposure results in the activation of these receptors, which modulate transcription factors linked to neuronal plasticity, memory, and neurotoxicity. For example, an increase in the NFκ transcription factor—involved in various stages of the addictive processes—has been observed in the nucleus accumbens, striatum, and hippocampus

«Gender significantly modulates stress experiences, coping, and the impact it has on the organism»

of animals exposed to social stress. Furthermore, knockout mice lacking the TLR4 receptor do not show the increase in cocaine or alcohol consumption induced by social defeat (Montagud-Romero et al., 2021). Therefore, the results obtained to date suggest that the immune system may be an important therapeutic target for treating problems resulting from exposure to social stress.

■ A LOT OF WORK STILL REMAINS

Although the social defeat model has led to great advances in our understanding of the influence of social stress on the development of drug addiction, it also has important limitations. First, we must bear in mind that the model, despite emphasising the social aspects of stress, also produces physical stress associated with the agonistic encounter itself, and so it is not purely a psychological stressor, as in the human context.

Second, in our opinion, the main shortcoming of this paradigm is that it induces stress only in male rodents given that the agonistic encounter is produced by territorial defence (spontaneous aggression) – a characteristic of male rodents. Although females may exhibit certain types of aggressive behaviour, translating the social

defeat model to females is complex. The few studies that have investigated socially stressed female rodents provided similar results to those obtained with males (Holly et al., 2012). However, in humans, gender significantly modulates stress experiences, coping, and the impact it has on the organism. In general, women seem to experience the negative effects of stress more intensely, with these effects being associated with a higher risk of anxiety-depressive disorders compared to men (WHO, 2019). Therefore, preclinical studies in females are particularly relevant.

Third, to date, most studies have evaluated the response to stress in adults; however, humans are exposed to stressful situations all their lives. Thus, studies should also focus on other stages such as adolescence when the impact on the brain can be more severe because of the high levels of neural plasticity that characterise this period.

Despite all these limitations, the studies performed so far agree that social stress is one of the main risk factors in the development of substance-use disorder. Environmental stressors can cause short- and long-term changes in different brain systems and can induce relapses in drug seeking and use. Although preclinical

studies cannot fully model human behaviour, they can help us to uncover the behavioural consequences of stress, as well as its mechanisms of action. Finally, insights from basic studies help point towards new therapeutic targets for the treatment of stress-induced disorders, such as anti-inflammatory drugs. ☺

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