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The impact of stress on addiction

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Abstract

This article will review data obtained from both clinical and preclinical investigations demonstrating that exposure to stress has a significant impact on drug addiction. The preclinical literature suggests that stress increases reward associated with psychomotor stimulants, possibly through a process similar to sensitization. While it is not conclusive that a similar process occurs in humans, a growing clinical literature indicates that there is a link between substance abuse and stress. One explanation for the high concordance between stress-related disorders and drug addiction is the self-medication hypothesis, which suggests that a dually diagnosed person often uses the abused substance to cope with tension associated with life stressors or to relieve symptoms of anxiety and depression resulting from a traumatic event. However, another characteristic of self-administration is that drug delivery and its subsequent effects on the hypothalamo–pituitary–adrenal (HPA) axis are under the direct control of the individual. This controlled activation of the HPA axis may result in the production of an internal state of arousal or stimulation that is actually sought by the individual (i.e., the sensation-seeking hypothesis). During abstinence, exposure to stressors or drug-associated cues can stimulate the HPA axis to remind the individual about the effects of the abused substance, thus producing craving and promoting relapse. Continued investigations into how stress and the subsequent activation of the HPA axis impact addiction will result in the identification of more effective and efficient treatment for substance abuse in humans. Stress reduction, either alone or in combination with pharmacotherapies targeting the HPA axis may prove beneficial in reducing cravings and promoting abstinence in individuals seeking treatment for addiction.
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1. Introduction

According to Dr. Hans Selye, stress can be defined as the nonspecific response of the body to any demand placed upon it to adapt, whether that demand produces pleasure or pain (Selye, 1975). Although stressors can elicit different responses in different individuals depending on "conditioning" or interactions with the environment, the sympathetic nervous system and the hypothalamo–pituitary–adrenal (HPA) axis are typically activated (Stratakis and Chrousos, 1995). This stress response or "stress cascade" is responsible for allowing the body to make the necessary physiological and metabolic changes required to cope with the demands of a homeostatic challenge (Miller and O'Callaghan, 2002). Sympathetic nervous system responses include an increase in heart rate, a rise in blood pressure, a shift in blood flow to skeletal muscles, an increase in blood glucose, dilation of the pupils and a stimulation of respiration. Thus, the activation of the sympathetic nervous system results in a variety of physiological processes which prepare the organism for flight or fight, whether to face the stressor or attempt to escape it, to maintain homeostasis.

The HPA axis is initially activated by the secretion of corticotropin-releasing hormone (CRH) from the hypothalamus (Sarnyai et al., 2001; Turnbull and Rivier, 1997; Goeders, 2002). CRH-containing neurons projecting from the parvocellular division of the paraventricular nucleus to the external zone of the median eminence release the peptide into the adenohypophyseal portal circulation in response to stress. The binding of CRH to receptors located in the anterior pituitary results in the synthesis of proopiomelanocortin, a large precursor protein that is cleaved to produce several smaller biologically active peptides, including β-endorphin and adrenocorticotropin hormone (ACTH). ACTH diffuses through the general circulation until it reaches the adrenal glands, where it stimulates the biosynthesis and secretion of adrenocorticosteroids (i.e., cortisol in humans or corticosterone in rats). The Type I mineralocorticoid receptor has a high affinity for corticosterone and is usually fully occupied at basal concentrations of the hormone. This receptor also displays a high affinity for the

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mineralocorticoid, aldosterone. The Type II glucocorticoid receptor has a lower affinity for corticosterone and is more likely to be occupied when plasma corticosterone is elevated (e.g., during "stress"). This receptor also has a high affinity for the synthetic glucocorticoid, dexamethasone.

When one considers the impact of stress on drug addiction and how activation of the HPA axis augments the motivation and/or vulnerability for drug use, a number of questions come to mind. How can a stimulus (i.e., stress) that is generally regarded as something to avoid or escape actually increase the perception of drug reward? Furthermore, how can drugs (e.g., cocaine, amphetamine) that result in the activation of the HPA axis be among the most reinforcing drugs ever studied? This article will address these questions in the context of both clinical and preclinical data.

2. Stress and vulnerability to addiction

During the acquisition of drug self-administration, an animal comes into contact with a drug and its potentially rewarding effects for the first time (Goeders, 2002). This is also when the animal learns to make the response that leads to drug delivery, thereby producing reinforcement. Environmental events that decrease the lowest dose of a drug that is recognized by the animal as a reinforcer are considered to be events that increase vulnerability or the propensity for an animal to acquire self-administration. Acquisition can also be facilitated by events that decrease the time required to reach a specified behavioral criterion indicative of self-administration.

The ability of stressors to alter the acquisition of drug self-administration in rats has received considerable attention (Goeders, 2002; Piazza and Le Moal, 1998). The acquisition of amphetamine and cocaine self-administration is enhanced in rats exposed to tail pinch (Piazza et al., 1990), social defeat (Haney et al., 1995; Tidey and Miczek, 1997; Kabbaj et al., 2001) or neonatal isolation (Kosten et al., 2000). Exposure to electric footshock also increases the subsequent reinforcing efficacy of heroin (Shaham and Stewart, 1994) and morphine (Will et al., 1998) in rats.

We have investigated the effects of exposure to response-contingent ("controllable stress") and noncontingent ("uncontrollable stress") electric footshock on the acquisition of intravenous cocaine self-administration in rats (Goeders and Guerin, 1994; Goeders, 2002). In these experiments, one rat from a group of three randomly received an electric footshock when it pressed a response lever that also resulted in the presentation of food (response-contingent shock). Although this resulted in a conflict between obtaining food reinforcement and avoiding footshock, these animals controlled whether or not and when shock was delivered. Shock presentation for the second rat in each triad was yoked to the first rat, so that the second rat received footshock regardless of whether or not it had pressed its food response lever at all (noncontingent shock). Therefore, these rats had no control over the delivery of the stressor. The third rat in each triad responded under the same schedule of food reinforcement as the other two rats but was never shocked. Self-administration was trained with an extremely low dose of cocaine during the first week of testing, and this concentration was subsequently doubled each week. When a full range of doses is investigated in this way, an inverted "U"-shaped dose–response curve is typically generated. In general, lower doses contained within the ascending portion of this curve are believed to be more related to cocaine reward than those falling on the descending limb, which is also affected by the unconditioned, nonspecific effects of these higher doses of cocaine (Woods et al., 1986). Exposure to uncontrollable footshock shifted the ascending limb of the cocaine dose–response curve upward and to the left, indicating that these rats were more sensitive to low doses of cocaine than rats exposed to response-contingent or no shock. These results emphasize the importance of controllability over stressor presentation on the effects of that stressor on drug reward (Goeders and Guerin, 1994; Goeders, 2002). Interestingly, footshock did not affect responding maintained by higher doses of cocaine that fell on the descending limb of the dose–response curve. Furthermore, this phenomenon appears to be relatively specific for the acquisition of cocaine self-administration since in our hands, neither exposure to footshock (Goeders and Guerin, 1996a) nor exogenous injections of corticosterone (Goeders and Guerin, 1999) affect ongoing self-administration.

We next investigated the effects of exogenous injections of corticosterone, which is secreted during the final step of HPA axis activation, on the acquisition of cocaine self-administration (Mantsch et al., 1998). Rats were treated daily, 15 min prior to each self-administration session, with corticosterone (2.0 mg/kg, ip, suspended in saline) or saline. These injections began 2 weeks prior to the start of self-administration testing to mimic the stress experiment described above as closely as possible. Similar to what we observed with electric footshock, daily pretreatment with corticosterone also produced a leftward shift in the ascending limb of the dose–response curve for the acquisition of self-administration, indicating that corticosterone-treated rats were more sensitive to low doses of cocaine than were rats pretreated with saline. In a related experiment, rats were bilaterally adrenalectomized prior to acquisition testing (Goeders and Guerin, 1996b). This surgery effectively removed the final step in HPA axis activation. These adrenalectomized rats did not self-administer cocaine at any dose tested even though they quickly learned to respond on another lever for food pellets, indicating that the rats could still learn and perform the necessary lever-pressing response. In another series of experiments, pretreatment with the corticosterone synthesis inhibitor ketoconazole also reduced both the rate of acquisition of cocaine self-administration and the number of rats reaching the criterion for acquisition under conditions of food restriction (Campbell and Carroll, 2001). Taken together,

these preclinical data suggest an important role for stress and the subsequent activation of the HPA axis in the acquisition of drug self-administration.

It is not inherently intuitive how exposure to a stressor can increase vulnerability to drug self-administration in rats (Goeders, 2002). This phenomenon likely occurs via a process analogous to sensitization (Piazza and Le Moal, 1998), whereby repeated intermittent injections of cocaine increase the behavioral and neurochemical responses to subsequent exposure to the drug. In fact, our acquisition experiments were specifically designed to test cocaine doses in an ascending order since exposure to higher doses of psychomotor stimulants can sensitize rats to lower doses, resulting in the acquisition of self-administration at doses of these drugs that would not otherwise maintain responding (Goeders, 2002). Interestingly, exposure to stressors or injections of corticosterone can also result in sensitization to the behavioral and neurochemical (e.g., nucleus accumbens dopamine) responses to cocaine (Prasad et al., 1998; Rouge-Pont et al., 1995), and these effects are attenuated in adrenalectomized rats (Prasad et al., 1998; Przegalinski et al., 2000) or when corticosterone synthesis is inhibited (Rouge-Pont et al., 1995). The ability of stressors to facilitate the acquisition of drug self-administration may therefore result from a similar sensitization phenomenon, perhaps involving dopamine (Goeders, 1997; Piazza and Le Moal, 1998). Although exposure to the stressor itself may be aversive, the net result is reflected as an increased sensitivity to the drug. Therefore, if certain individuals are more sensitive to stress (Piazza and Le Moal, 1998) and/or if they find themselves in an environment where they do not feel that they have adequate control over this stress (Levine, 2000), then these individuals may be more likely to engage in substance abuse.

However, it is not ethically possible to conduct the types of experiments reviewed above in humans; no one would consider placing drug-free individuals at risk for addiction to determine how stress affects the development of that addiction. Nevertheless, there is a growing clinical literature that suggests a possible linkage between stress and addiction. An obvious group of individuals who may be at greater risk for substance abuse are combat veterans, especially those suffering from post traumatic stress disorder (PTSD). In fact, a number of studies have identified individuals with the dual diagnosis of combat-related PTSD and substance abuse (Penk et al., 1988, 1989; Zaslav, 1994; Donovan et al., 2001). Although a causal relationship between exposure to combat-related stress and substance abuse has not been clearly established, veterans with PTSD typically report a higher lifetime use of alcohol, cocaine and heroin than veterans screening negative for PTSD (Saxon et al., 2001).

Alcoholism has also been associated with exposure to stressors other than combat. Stressors such as an unhappy marriage or even dissatisfaction with employment have been associated with increased alcohol use (Jose et al., 2000). Harassment (Richman et al., 1996; Rospenda et al., 2000) or other work-related stressors (Vasse et al., 1998) also increase the risk of alcoholism, although sexual abuse and sexual harassment were more likely to produce symptoms of PTSD and affect drinking in women than in men (Richman et al., 1996; Newton-Taylor et al., 1998). In many instances, alcohol is used to cope with the tension associated with stress in the environment (Tyssen et al., 1998) or to relieve symptoms of anxiety, irritability and depression resulting from a traumatic life event in individuals with PTSD (Volpicelli et al., 1999). Other studies have reported a link between PTSD and the use of substances other than alcohol (Zweben et al., 1994; Brown et al., 1998), including cocaine (Dansky et al., 1999; Brady et al., 2001) and opioids (Clark et al., 2001). A common theme in these reports is that sexual abuse and trauma are associated with the development of PTSD and substance abuse in women to a greater extent than men (Bollerud, 1990; Richman et al., 1996; Newton-Taylor et al., 1998), which is similar to the literature on alcohol. Finally, adolescents are especially susceptible to social stressors and traumatic life events, and exposure to these stressors can significantly impact their substance use. Addiction during adolescence or even later in adulthood has been associated with childhood sexual abuse (Teusch, 2001; Walker et al., 1998) or other childhood trauma (Triffleman et al., 1995; DeWit et al., 1999). The inability to effectively cope with everyday social stressors has also been related to adolescent substance abuse (Wills, 1986; Mates and Allison, 1992; Wagner et al., 1999). Even cigarette smoking (Siqueira et al., 2001) and cannabis use (Butters, 2002) have been linked to stress in family life or social situations and the inability of the adolescent to cope with the demand produced by these stressors.

However, it is difficult to determine if stressors, sexual trauma and/or PTSD actually led to subsequent substance use in the instances reviewed above or if substance use contributed to the traumatic events and/or the development of PTSD in the first place. Obviously, not everyone who experiences trauma and PTSD is a substance abuser and not every drug addict can trace the etiology of his or her addiction to some specific stressor or traumatic event. However, prevalence estimates suggest that rates of substance abuse among individuals with PTSD may be as high as 60–80%, while the rates of PTSD among substance abusers is between 40% and 60% (Donovan et al., 2001), indicating that there is a clear relationship between stress and increased substance use in some cases. This relationship should be evaluated on an individual basis when determining the most appropriate treatment for an addiction (Lamon and Alonzo, 1997; Brady and Sonne, 1999; Winhusen and Somoza, 2001).

3. Stress and relapse to addiction

Reinstatement is a preclinical approach that is widely regarded as an animal model of the propensity to relapse to

drug taking, involving mechanisms related to the development and expression of craving (Gerber and Stretch, 1975; Stewart and de Wit, 1987). A number of excellent reviews on the reinstatement of extinguished drug seeking have recently been published (Stewart, 2000; Weiss et al., 2001; See, 2002; Shaham et al., 2003), including specific reviews on the reinstatement of cocaine (Spealman et al., 1999; Shaham et al., 2000; Shalev et al., 2002), heroin (Shaham et al., 2000; Shalev et al., 2002), ethanol (McBride et al., 2002) and nicotine (Mathieu-Kia et al., 2002) seeking, and the reader is encouraged to consult these articles for a more thorough understanding of the subject. With this model, animals are taught to self-administer a drug until stable drug intake is maintained, and are then subjected to prolonged periods of extinction training or abstinence. Once the criteria for extinction are met, or following a specified period of abstinence, the ability of specific stimuli to reinstate responding on the manipulandum previously associated with the delivery of drug infusions is taken as a measure of drug seeking (Goeders, 2002). This reinstatement of drug-seeking behavior can be elicited by priming injections of the drug itself in rats and monkeys (Spealman et al., 1999; Stewart, 2000) or by exposure to brief periods of intermittent electric footshock stress in rats (Shaham et al., 2000; Stewart, 2000). Acute re-exposure to the self-administered drug (de Wit, 1996) and exposure to stress (Shiffman and Wills, 1985; Lamon and Alonzo, 1997; Brady and Sonne, 1999; Sinha, 2001; Sinha et al., 1999), or simply the presentation of stress-related imagery (Sinha et al., 2000), have also been identified as potent events for provoking relapse to drug seeking in humans. It is no surprise that norepinephrine and CRH, mediators of the activation of the sympathetic nervous system and HPA axis, respectively, are involved in stress-induced reinstatement (Stewart, 2000; Weiss et al., 2001; Liu and Weiss, 2002). However, CRH and the HPA axis do not appear to be involved in drug-induced reinstatement (Mantsch and Goeders, 1999; Stewart, 2000; Shaham et al., 2003).

Clinical studies have demonstrated that simple exposure to environmental stimuli or cues previously associated with drug taking can produce intense drug craving (O'Brien et al., 1992; Robbins et al., 1999), suggesting that exposure to a physical stressor or a "taste" of cocaine itself are not necessary prerequisites for the development of craving in humans (Goeders and Clampitt, 2002; Goeders, 2002). Examples of such environmental stimuli include locations where the drug was purchased and/or used, the individuals that the drug was purchased from or used with as well as associated drug paraphernalia. In fact, the cycling, relapsing nature of addiction has been proposed to result, at least in part, from exposure to environmental cues that had been previously paired with drug use (Gawin, 1991). Presumably, the repeated pairing of these cues during the chronic use of the drug can lead to a classical conditioning of the drug's effects whereby exposure to these stimuli following abstinence produces responses reminiscent of the drug itself. These conditioned responses elicit increased desire or craving, thus leading to relapse (O'Brien et al., 1992). In addition to these subjective increases in craving, exposure to conditioned environmental stimuli also induces biological effects such as physiological changes in arousal (Johnson et al., 1998) and the activation of limbic areas of the brain (Childress et al., 1999). Preclinical investigations have also demonstrated that cue-induced reinstatement may indeed be an important and valid animal model of drug craving (See, 2002). Therefore, the remainder of this section will focus on the involvement of the HPA axis in the cue-induced reinstatement of extinguished drug seeking.

Rats were trained to self-administer cocaine, with cocaine delivery paired with the presentation of a tone and the illumination of a house light (Meil and See, 1996; Goeders and Clampitt, 2002). Once a stable baseline of cocaine self-administration was observed, lever pressing was extinguished to less than 20% of baseline rates. During reinstatement testing, responding resulted in the presentation of a conditioned cue or reinforcer (i.e., the house light and tone previously paired with self-administered cocaine). The response-contingent presentation of the conditioned reinforcer reliably reinstated extinguished cocaine-seeking behavior, while the noncontingent presentation of the same stimulus did not. Increases in plasma corticosterone were evident during cocaine self-administration as well as during extinction and reinstatement testing. However, while plasma corticosterone returned to basal levels by the end of the session during extinction, it remained elevated through the end of the session during reinstatement, suggesting that cue-induced reinstatement was associated with HPA axis activation. Pretreatment with the corticosterone synthesis inhibitor ketoconazole reversed the conditioned reinforcer-induced reinstatement of extinguished cocaine-seeking behavior and also attenuated the conditioned increases in plasma corticosterone observed during reinstatement. Pretreatment with the CRH1 receptor antagonist CP-154,526 resulted in a similar decrease in cocaine seeking (Goeders and Clampitt, 2002). Recent preliminary data suggest that benzodiazepines such as alprazolam (Clampitt et al., 2001) and oxazepam also attenuate cue-induced reinstatement. Taken together, these data suggest an important role for the HPA axis in the ability of environmental cues to stimulate cocaine-seeking behavior in rats. Improved treatment for relapse may therefore result from the development of behavioral and pharmacological therapies that reduce the activation of the HPA axis induced by environmental cues previously associated with drug use (Winhusen and Somoza, 2001; Goeders, 2002).

4. Conclusions

Data obtained from clinical and preclinical investigations indicate that exposure to stress increases the vulnerability for

addiction. The preclinical literature suggests that stress increases reward associated with psychomotor stimulants, possibly through a process similar to sensitization (Piazza and Le Moal, 1998; Goeders, 2002). It is not conclusive that a similar process occurs in humans, but a growing clinical literature indicates that there is a link between substance abuse and stress. Prevalence estimates suggest that rates of substance abuse among individuals with PTSD may be as high as 60–80%, while the rates of PTSD among substance abusers is between 40% and 60% (Donovan et al., 2001). One explanation for the high concordance between PTSD (and related disorders) and drug addiction (i.e., dual diagnosis) is the self-medication hypothesis (Stanton, 1976; Khantzian, 1985; Gelkopf et al., 2002). According to this hypothesis, a dually diagnosed person often uses the abused substance to cope with tension associated with life stressors or to relieve or suppress symptoms of anxiety and depression resulting from a traumatic event (Tyssen et al., 1998; Volpicelli et al., 1999). Others may also engage in substance abuse to manage symptoms of anxiety and/or depression that are unrelated to a specific life event. On the surface, however, this may appear somewhat counterintuitive. Many abused substances (especially psychomotor stimulants such as cocaine) can induce anxiety and panic in humans and anxiogenic-like responses in animals through effects on CRH release (Goeders, 1997, 2002). Accordingly, one might expect that augmenting HPA axis activity would increase the aversive effects of the drug and reduce the motivation for it. During acquisition, however, exposure to aversive, stressful stimuli may actually sensitize individuals, making them more sensitive to drug reward. Once self-administration has been acquired, the positive aspects of drug reward likely mitigate the drug's potential anxiogenic effects (Goeders, 2002).

However, another characteristic of self-administration is that drug delivery and its subsequent effects on the HPA axis are under the direct control of the individual. This is an important consideration since the controllability and predictability of a stressor significantly decrease its aversive effects (Levine, 2000). The individual controls when the drug is administered and, therefore, when the activation of the HPA axis also occurs. This controlled activation of the HPA axis may result in the production of an internal state of arousal or stimulation that is actually sought by the individual (Goeders, 2002). This internal state may be analogous to novelty or sensation seeking that has been reported in humans (e.g., thrill seekers or sensation seekers) and suggested to be involved in drug reward (Bardo et al., 1996; Dellu et al., 1996; Scourfield et al., 1996). Drug self-administration by this subgroup of substance abusers may represent an attempt to seek out specific sensations, with the internal state produced being very similar to that perceived by individuals who engage in risky, thrill-seeking behavior (Wagner, 2001; Goeders, 2002; Franques et al., 2003). These sensation seekers have been reported to be at greater risk for abusing a variety of substances including cocaine (Ball et al., 1994; McKay et al., 1995; Patkar et al., 2002), opioids (Franques et al., 2003), alcohol (Henry et al., 2001) and nicotine (Pedersen et al., 1989; Carton et al., 1994). Sensation-seeking adolescents are also at increased risk for nicotine, alcohol and cannabis use (Martin et al., 2002). Once drug use has terminated during abstinence, exposure to stressors or drug-associated cues can stimulate the HPA axis to remind the individual about the effects of the abused substance, thus producing craving and promoting relapse (Goeders, 2002). Therefore, continued investigations into how stress and the subsequent activation of the HPA axis impact addiction will result in the identification of more effective and efficient treatment for substance abuse in humans. Stress reduction and coping strategies, either alone or in combination with pharmacotherapies targeting the HPA axis may prove beneficial in reducing cravings and promoting abstinence in individuals seeking treatment for addiction.

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