Stress, Motivation, and Drug Addiction

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ABSTRACT—*A growing clinical literature indicates that there is a link between substance abuse and stress. One explanation for the high co-occurrence of 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 hypothalamic-pituitary-adrenal (HPA) axis are under the direct control of the individual. This controlled activation of the HPA axis may produce an internal state of arousal or stimulation that is actually sought by the individual. During abstinence, exposure to stressors or drug-associated cues can stimulate the HPA axis and thereby remind the individual about the effects of the abused substance, thus producing craving and promoting relapse. 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.*

KEYWORDS—*HPA axis; reward; vulnerability; stress; relapse*

The mere mention of the word *stress* often conjures up images of heart disease, ulcers, and serious psychiatric disorders triggered through negative interactions with the environment. In reality, however, stress is not always associated with negative events. Selye (1975), who is generally accepted as the father of modern stress-related research, defined stress as the nonspecific response of the body to any demand placed upon it to adapt, whether that demand produces pleasure or pain. Accordingly, stress can result from a job promotion or the loss of a job, the birth of a child or the loss of a loved one, or any number of events, both positive and negative, that affect the daily life of an individual.

The two primary biological systems that are typically activated during and immediately after exposure to a stressor are the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis (Stratakis & Chrousos, 1995). The activation of these systems produces a stress response, or *stress cascade*, that is responsible for allowing the body to make the changes required to cope with the demands of a challenge. Sympathetic nervous system responses often include the release of the neurotransmitter norepinephrine, an increase in heart rate, a shift in blood flow to skeletal muscles, an increase in blood glucose, and a dilation of the pupils (for better vision), all in preparation for fight or flight (i.e., facing the stressor or attempting to escape from it). The HPA axis is initially activated by the secretion of corticotropin-releasing hormone (CRH) from the hypothalamus in response to a stressor (Goeders, 2002). CRH binds to receptors located in the anterior pituitary, causing the production of several substances, including adrenocorticotropin hormone (ACTH). When ACTH reaches the adrenal glands, it stimulates the biosynthesis and secretion of adrenocorticosteroids (i.e., cortisol in humans or corticosterone in rats). Cortisol travels through the bloodstream to produce a variety of effects throughout the body.

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STRESS AND VULNERABILITY TO ADDICTION IN HUMANS

It is not ethical to conduct clinical studies on the effects of stress on the vulnerability for addiction in people without a history of drug abuse because no one should be intentionally put at risk for developing an addiction by being exposed to a substance with the potential for abuse. Therefore, scientists must rely on retrospective studies, and there is a growing body of clinical studies suggesting a link between stress and addiction. Combat veterans, especially those with posttraumatic stress disorder (PTSD), appear to have an elevated risk for substance abuse. Veterans with PTSD typically report more use of alcohol, cocaine, and heroin than veterans who do not meet the criteria for diagnosis of PTSD (Zaslav, 1994). However, people exposed to stressors other than combat, such as an unhappy marriage, dissatisfaction with employment, or harassment, also report higher-than-average rates of addiction. Sexual abuse, trauma, and sexual harassment are more likely to produce symptoms of PTSD and alcoholism or other addictions in women than in men (Newton-Taylor, DeWit, & Gliksman, 1998).

Despite these findings, however, it is difficult to determine if stressors, sexual trauma, or PTSD actually lead to subsequent substance use or if substance use contributes to the traumatic events 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 his or her addiction to some specific stressor or traumatic event. Nevertheless, prevalence estimates suggest that the rate of substance abuse among individuals with PTSD may be as high as 60 to 80%, and the rate of PTSD among substance

abusers is between 40 and 60% (Donovan, Padin-Rivera, & Kowaliw, 2001). These numbers show a clear relationship between PTSD and substance abuse. One explanation for the high co-occurrence of PTSD and drug addiction (i.e., dual diagnosis) is the self-medication hypothesis. 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, irritability, and depression resulting from a traumatic event (Khantzian, 1985).

VULNERABILITY TO ADDICTION: ANIMAL STUDIES

It is much easier to conduct prospective studies on the effects of stress on the vulnerability for addiction in animals than in humans. These animal studies typically investigate the effects of stress on the propensity to learn drug-taking behavior (which is often referred to as the "acquisition" of drug taking). In a typical experiment, the animals come into contact with a drug and its potentially rewarding effects for the first time (Goeders, 2002), and the researcher investigates what dose or how much time is necessary for them to learn to make the response (e.g., a lever press) that leads to drug delivery, thereby producing reinforcement. Environmental events (e.g., stressors) that decrease the lowest dose that is recognized by an animal as a reinforcer (i.e., that leads to acquisition of the response) are considered to increase vulnerability to acquire drug-taking behavior. Another measure of acquisition is the time required for the animal to reach a specified behavioral criterion (e.g., a specified frequency of the response that leads to drug delivery).

The ability of stressors to alter the acquisition of drug taking in rats has received considerable attention (Goeders, 2002; Piazza & Le Moal, 1998). For example, studies have shown that sensitivity to amphetamine and cocaine is enhanced in rats exposed to stressors such as tail pinch and neonatal isolation. Electric shock to the feet is another stressor used in rat experiments. In a study on the effects of controllable versus uncontrollable stress, my colleagues and I modeled controllable stress by administering shocks whenever the rats made a particular response, and uncontrollable stress by administering shocks that were not contingent on the rats' behavior (Goeders, 2002). Rats that were exposed to uncontrollable stress were more sensitive to low doses of cocaine than rats that were exposed to controllable stress or that were not shocked at all; this finding demonstrates that control over a stressor can change the effects of that stressor on the vulnerability for drug taking (Goeders, 2002).

Given that uncontrollable stress made animals more sensitive to cocaine, my colleagues and I hypothesized that this process may have resulted from the stress-induced activation of the HPA axis. Because corticosterone (cortisol) is secreted as the final step of HPA-axis activation, we next studied the effects of daily injections of corticosterone on the acquisition of cocaine taking. These injections produced an increase in sensitivity to cocaine that was almost identical to what we saw with uncontrollable stress. In a related experiment, rats' adrenal glands were surgically removed (i.e., adrenalectomy) to effectively eliminate the final step in HPA-axis activation. These rats did not self-administer cocaine at any dose tested, even though they quickly learned to respond to obtain food pellets. Thus, the rats could still learn and perform the necessary lever-pressing response, but cocaine was apparently no longer rewarding. In another series of experiments, the synthesis of corticosterone was blocked with daily injections of ketoconazole, and this reduced both the rate of acquisition of cocaine self-administration and the number of rats that eventually reached the criterion for acquisition of this behavior. Taken together, these data suggest an important role for stress and the subsequent activation of the HPA axis in the vulnerability for drug taking.

How does exposure to a stressor increase the vulnerability for drug taking? This biological phenomenon likely occurs via a process analogous to sensitization, whereby repeated but intermittent injections of cocaine increase the behavioral and neurochemical responses to subsequent exposure to the drug (Piazza & Le Moal, 1998). Exposure to stressors or injections of corticosterone can also result in a sensitization to cocaine, and these effects are attenuated in rats that have had their adrenal glands removed or corticosterone synthesis inhibited. Although exposure to the stressor itself may be aversive in many cases, the net result is reflected as an increased sensitivity to the drug. This suggests that if individuals are particularly sensitive to stress or find themselves in an environment where they do not feel that they have adequate control over their stress, they may be especially likely to engage in substance abuse.

STRESS AND RELAPSE TO ADDICTION

Clinical studies of drug addicts have demonstrated that reexposure to the abused substance, exposure to stressors, or simply the presentation of stress-related imagery is a potent event for provoking relapse. However, simply exposing an addict to environmental stimuli or cues previously associated with drug taking can also produce intense drug craving (Robbins, Ehrman, Childress, & O'Brien, 1999). Such environmental stimuli include locations where the drug was purchased or used, the individuals the drug was purchased from or used with, and 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 have been previously paired with drug use. Presumably, the repeated pairing of these cues with the chronic use of the drug can lead to a classical conditioning of the drug's effects, so that exposure to these stimuli following abstinence produces responses reminiscent of responses to the drug itself. These conditioned responses elicit increased desire or craving, thus leading to relapse.

Reinstatement is generally accepted as an animal model of the propensity to relapse to drug taking (Stewart, 2000). With this model, animals are taught to self-administer a drug until they reach a stable level of drug intake; they are then subjected to prolonged periods during which the response that previously resulted in drug delivery no longer does so (i.e., extinction). Once drug-taking behavior has extinguished, or following a specified period of abstinence, the rats are tested to see if specific stimuli will reinstate the response previously associated with drug taking (Goeders, 2002). Such reinstatement of drug-seeking behavior can be elicited by injections of the drug itself or by exposure to brief periods of intermittent electric shock to the feet (i.e., stress). In her review of reinstatement, Stewart (2000) described how norepinephrine and CRH are important for stress-induced reinstatement, which should be no surprise because norepinephrine and CRH are produced during the activation of the sympathetic nervous system and HPA axis, respectively.

Stimuli that were paired with the drug during self-administration can become environmental cues that can be presented following extinction to reinstate responding (See, 2002). Reinstatement that occurs under these conditions is referred to as cue-induced reinstatement. The fact that cue-induced reinstatement occurs suggests that exposure to a

physical stressor or a "taste" of cocaine itself is not a necessary prerequisite for relapse. My colleagues and I have reported that the corticosterone synthesis inhibitor ketoconazole reverses the cue-induced reinstatement of cocaine seeking and also decreases the increases in corticosterone observed in the blood during reinstatement (Goeders, 2002). The CRH receptor blocker CP-154,526 also attenuates 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 and relapse in humans. Treatment for relapse may therefore be improved by developing behavioral or pharmacological therapies that reduce HPA-axis responses induced by environmental cues previously associated with drug use.

IMPLICATIONS

Data obtained from both human and animal investigations indicate that exposure to stress increases the vulnerability for addiction. The animal literature suggests that stress increases reward associated with drugs such as cocaine and amphetamine through a process similar to sensitization. The growing literature on drug addiction indicates that there is a similar link between substance abuse and stress, as reflected in the high co-occurrence of PTSD and drug addiction. One explanation for this link is the self-medication hypothesis (Khantzian, 1985), according to which 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. On the surface, however, this hypothesis may appear somewhat counterintuitive. Many abused substances (especially cocaine) can induce anxiety and panic in humans and anxiety-like responses in animals through direct effects on CRH release (Goeders, 1997, 2002). One might expect that this augmented HPA-axis activity would increase the aversive effects of the drug and reduce the motivation for it. During the acquisition of drug-taking behavior, however, exposure to aversive, stressful stimuli may actually sensitize individuals, making them more sensitive to the rewarding properties of the drug. Once drug taking has been acquired, the positive aspects of drug reward likely mitigate the drug's potential anxiety-like 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 because controllability and predictability of a stressor significantly decrease its aversive effects (Levine, 2000). If the individual controls when the drug is administered, he or she also controls when the activation of the HPA axis occurs. This controlled activation of the HPA axis may result in an internal state of arousal or stimulation that is rewarding to the individual (Goeders, 2002). This internal state may be analogous to the one produced during novelty or sensation seeking (e.g., in thrill seekers or sensation seekers), which may also be involved in drug reward (Wagner, 2001). Drug taking by some substance abusers may therefore be an attempt to seek out specific sensations, and the internal state produced may be very similar to that perceived by individuals who engage in risky, thrill-seeking behavior. Such sensation seekers have been reported to be at elevated risk for abusing a variety of substances, including cocaine, opioids, alcohol, cannabis, and nicotine.

Once an individual has stopped using a drug, exposure to stressors or drug-associated cues can stimulate the sympathetic nervous system and the HPA axis and thereby 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 play a role in addiction will result in more effective and efficient treatments 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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