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Stress and Drug Use

Neil E. Grunberg, Sarah Shafer Berger, and Kristen R. Hamilton

INTRODUCTION

Stress clearly has profound psychological and biological effects, as revealed by the many and diverse chapters in this *Handbook*. Of these many effects, the association between stress and recreational drug use is fascinating and particularly complex because it involves the interplay of behaviors, cognitions, and motivations with biochemical, physiological, and molecular biological responses to stress and to drug actions. The fact that stress is positively correlated with the self-administration of various recreational drugs suggests that there are common, underlying mechanisms to explain this association. Yet the fact that recreational drugs have markedly different biological actions stalls the rush to a single principle or overarching explanation for the stress–drug use relationship. The fact that drug self-administration involves biologically active substances that affect the brain, autonomic nervous system (ANS), and viscera in ways that mimic, offset, or interact with stress responses further complicates understanding of the stress–drug use relationship. This chapter is focused on particular drugs that are commonly self-administered, legal (nicotine, alcohol, caffeine) or illegal (cocaine, heroin), central nervous stimulants (caffeine, cocaine), central nervous depressants (alcohol, heroin), or both (nicotine; see Table 22.1). The chapter begins with separate, brief discussions of stress, substance use, and each of the five substances to provide background information relevant to the stress–drug relationship. Next, the relationship between stress and each substance is reviewed. Then, many of the explanations that have been offered to account for the stress–drug use relationship are catalogued into four separate groups: (1) drug use decreases stress (“self-medication hypotheses”), (2) abstinence from drug use is altered by or resembles stress (“withdrawal hypotheses”), (3) stress alters drug actions (“pharmacodynamic hypotheses”), and (4) drug use increases stress (“positive feedback loop hypotheses”).

WHAT IS STRESS?

Stress is the process by which environmental demands tax or exceed the adaptive capacity of the organism (Baum, Gatchel, & Krantz, 1997). The stress response may constitute eustress (stress resulting from positive stimuli) or distress (stress resulting from negative stimuli; Selye, 1976). Stress causes physiological responses in the body that help an organism to maintain homeostasis during the demands of the stressor, including activation of the ANS. Sympathetic nervous system (SNS) arousal (including release of the catecholamines epinephrine, norepinephrine, and dopamine; increased heart rate, blood pressure, and respiration; dilation of the pupils; increased blood flow to the skeletal muscles; and an increase in blood glucose) is part of the stress response and also occurs in response to some drugs (e.g., caffeine, cocaine, amphetamines, nicotine) that sometimes are called sympathomimetics, central nervous system (CNS) stimulants, or just stimulants. Interestingly, catecholamines (especially dopamine) are involved in drug reward in the ventral tegmental area (VTA) of the brain, an area that has been implicated as central to drug addiction.

The ANS response also includes alterations in activity of the parasympathetic nervous system, which acts to calm the body by decreasing heart rate, blood pressure, and respiration, constricting the pupils, and dilating the blood vessels. Drugs known as CNS depressants (e.g., alcohol, opiates [such as heroin], benzodiazepines, and barbiturates) mimic the actions of the parasympathetic system. Nicotine, a sympathomimetic, has CNS depressant as well as CNS stimulant actions that make it unique among recreational drugs. In addition to the ANS response during stress, there also is activation of the hypothalamus–pituitary–adrenal (HPA) axis. Activation of the HPA axis causes corticotropin-releasing factor (CRF) to be released from the hypothalamus in the brain, adrenocorticotropin (ACTH) from the pituitary in the brain, and cortisol from the adrenal cortex of the adrenal glands.

Table 22.1 ■ Drugs of Emphasis in This Chapter

	Legal substances	Illegal Substances	
Stimulants	Caffeine	Cocaine	Nicotine
Depressants	Alcohol	Heroin	("paradoxical drug")

that sit atop the kidneys. This hormonal system operates as a negative feedback system with the SNS to maintain homeostasis in the body when a stressor occurs. These systems underlie protective psychological and biological responses to acute stress, but can become deleterious and life-threatening when prolonged or severe. The fact that recreational drugs also alter ANS activation is relevant to the stress–drug use relationship. The effect on the ANS can be the mechanism for detrimental effects, but it also is often the reason the drug is used in the first place. For example, individuals use caffeine, a stimulant, to wake up; it increases heart rate and blood pressure, but too much caffeine can lead to heart arrhythmias.

The endogenous opioid peptide (EOP) system also is involved in the body's stress response and actions of many recreational drugs, including opioid and non-opioid drugs. EOPs are responsible for analgesic actions by blunting distress (the affective component of pain) without dulling the sensation. Opioids diminish stress-induced neuroendocrine and autonomic responses and stimulate EOP effector systems in the nonstressed state. Moreover, opioids play a role in the stress response by attenuating the emotion and affect associated with stress and by causing mild euphoria and a sense of well-being (see Drolet et al., 2001, for a complete review).

It also is relevant to the stress–drug use relationship to consider the effects of stress on performance and on emotional reactions. Yerkes and Dodson (1908) proposed that there is an inverse-U shaped relationship between arousal and performance, such that low levels of arousal are associated with low levels of performance, moderate levels of arousal produce high levels of performance, and high levels of arousal produce low performance. This function was based on studies in mice examining effects of electric shock (to manipulate arousal) on performance (i.e., movement to a white box to avoid further electric shock) similar to a passive avoidance task. Yerkes and Dodson found that the number of trials to choose the white box was related to the amount of electrical stimulation by an inverted-U function (see Figure 22.1).

Although Yerkes and Dodson are credited with this "law" of psychology, it actually is remarkably similar to Wundt's inverted-U hedonic curve (Berlyne, 1971) that relates arousal and hedonic tone (or perceived pleasure). Hebb (1955) interpreted the Yerkes-Dodson curve as a relationship between arousal and "cue function." In other words, as arousal increases, stimulus–response (S-R) connections are strengthened and then gradually weaken. Whether arousal (including arousal caused

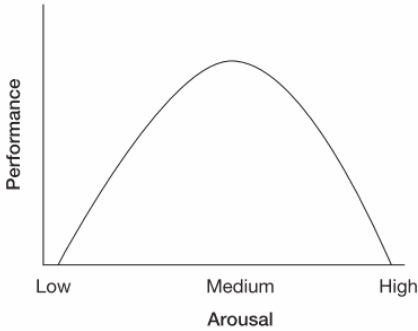


Figure 22.1 ■ Yerkes-Dodson curve.

by stress) results in an inverted-U in S-R connection, hedonic response, performance, or a combination of these effects remains unclear, but the so-called Yerkes-Dodson Law may help to account for the stress–substance use relationship and may help to resolve the puzzle of why self-administration of CNS stimulants and depressants increases under stress. More specifically, stimulants may be used under mild arousal to push us up the ascending limb of the Yerkes-Dodson curve, whereas depressants may be used under high arousal conditions to push us back from the descending limb of this function. Nicotine self-administration may be especially common during stress because it seems to jazz people up when they are down but calm them down when they are overaroused.

There also appear to be individual differences in the stress response. There are correlational reports that females show a predisposition toward emotion-based disease (e.g., depression; Becker et al., 2007). Women also self-report that they experience more stress (e.g., Greenglass & Noguchi, 1996). In addition to these reports, Taylor and colleagues (2000) argue that women may differ from men in stress responses with more oxytocin release in females rather than testosterone or other androgen release in males (see Taylor et al., 2000, and chapter 8). The authors contend that there is more of a social affiliation response in females to stressors ("tend and befriend"), rather than the classic "fight or flight" identified by W. B. Cannon (1935), which may be a more common stress response in males. These possible sex differences in stress responses also should be considered along with sex differences in drug use and drug effects. For example, alcohol dependence is more common among males (*DSM-IV-TR*, 2001). There also are sex differences in other drugs of abuse, including nicotine. In the United States, men are more likely to smoke cigarettes (23.9%) than women (18.0%), and men smoke more cigarettes than do women. In developing countries, men smoke dramatically more than do women (Centers for Disease Control [CDC], 2007). If we can better understand individual differences in the stress response, then this knowledge may have clinical utility in treating substance abuse and other mental health disorders.

WHAT IS SUBSTANCE USE?

This chapter is focused on specific recreational drug use, which also may involve drugs acting as reinforcers, addictive substances, and abused substances. Drug use refers to the self-administration of at least one non-prescribed drug. Drug reinforcement is the capacity of the drug to maintain self-administration (O'Brien, 2006). Drug addiction or drug dependence occurs when there is highly controlled or compulsive drug use. Addictive behaviors often involve stereotypic patterns of use, use despite harmful effects, relapse following abstinence, and recurrent drug cravings. Furthermore, dependence-producing drugs often produce tolerance (i.e., drugs have weakening effects with repeated administration or greater amounts of drug are required to have similar effects), physical dependence, pleasant or euphoric affect, and withdrawal effects after cessation (United States Department of Health and Human Services [USDHHS], 1998). Drugs vary in their addiction potential based on properties of the drug itself, individual biological and psychological differences, and interactions with environmental variables. Drugs with potent reinforcing properties are more likely to lead to substance abuse or dependence. Withdrawal refers to the development of a substance-specific syndrome that interferes with functioning and is the result of cessation or reduction in substance use that has been heavy and prolonged. Substance abuse is commonly based on the definition in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition ([DSM-IV]; American Psychiatric Association, 1994), which includes symptoms such as recurrent use in situations where it presents a physical danger, failure to meet obligations at work or school, or recurrent social or interpersonal problems caused by effects of the drug. According to the National Institute on Drug Abuse's (NIDA, 2007) Web site:

Addiction is a chronic, often relapsing brain disease that causes compulsive drug seeking and use despite harmful consequences to the individual that is addicted and to those around them. Drug addiction is a brain disease because the abuse of drugs leads to changes in the structure and function of the brain.

Many variables affect drug onset, continued use, abuse, or addiction. Relevant drug variables include availability, cost, potency, mode or route of administration, and speed of onset. Relevant person variables include hereditary tolerance, drug metabolism, psychiatric symptoms, prior experiences/expectations, and propensity for risk-taking behavior. Environmental variables include the social setting (e.g., a bar vs. the office), community attitudes, availability of other reinforcers, employment or educational opportunities, and conditioned stimuli (environmental cues become associated with drugs after repeated use in the same environment; O'Brien, 2006).

SUBSTANCES OF FOCUS

Drugs of abuse and recreational drugs are often categorized by pharmacological groups: CNS stimulants; CNS depressants; psychedelics (e.g., marijuana, peyote, lysergic acid diethylamide [LSD], phencyclidine [PCP]); and inhalants. Drugs of abuse also can be categorized as licit (e.g., nicotine, caffeine, alcohol, and over-the-counter drugs) or illicit (e.g., cocaine, heroin). Each of these categories is large and the effects of stress on each of them could be a chapter in itself. Therefore, this chapter focuses on the most widely used licit stimulant (caffeine), illicit stimulant (cocaine), licit depressant (alcohol), illicit depressant (heroin), and a paradoxical drug that has stimulant and depressant actions (nicotine).

Nicotine

Nicotine is a tertiary amine made up of pyridine and pyrrolidine rings and is the pharmacologic agent of addiction in tobacco. Nicotine is an oily liquid that forms salts with acids. It occurs naturally in the tobacco plant, with a high concentration in the leaves. In humans, nicotine is administered most often via smoking (through cigarettes, cigars, pipes, or hookah). Nicotine also can be administered orally through chewing and smokeless tobacco, transdermally via nicotine patch, or by aerosol inhalation. It has a relatively short half-life (about 2 hours in humans), which helps to explain why addicted smokers self-administer nicotine so often (USDHHS, 1998).

Nicotine acts at nicotinic acetylcholine receptors (nAChRs) in the brain and nervous system to stimulate dopaminergic, glutamatergic, and cholinergic nerve terminals. Stimulation of nAChRs in the VTA of the brain enhances dopamine release in the nucleus accumbens (NAcc), which is thought to play a key role in the reinforcing effects of many drugs (Feldman et al., 1997).

Approximately 20% of adults in the United States smoke tobacco cigarettes (CDC, 2007). Smoking rates have decreased in recent years in the United States but are increasing in developing nations. In the United States, it is estimated that roughly 4,000 youth try smoking every day and that about 2,000 become regular smokers (World Health Organization, 2006). The health hazards associated with tobacco smoking are well documented and profound. Worldwide, someone dies every 8 s from tobacco use and it is the single most preventable cause of death. Health hazards include cardiovascular diseases, pulmonary damage, and a variety of cancers (CDC, 2006). Potential cardiovascular outcomes include myocardial infarction, sudden cardiac death, peripheral vascular disease, atherosclerosis, and hypertension. Pulmonary changes include lung damage, decreased pulmonary function, histologic abnormalities, and chronic obstructive pulmonary disease. Cancers occur everywhere that carcinogens in tobacco reach in the body, including the lung, larynx, oral cavity, esophagus, urinary bladder,

kidney, and pancreas. Despite these well-publicized health hazards, people continue to use tobacco products largely because of the highly addictive actions of nicotine and other psychobiological effects that people enjoy.

Nicotine stimulates the SNS and, therefore, increases heart rate and respiration. In small to moderate doses it causes release of catecholamines from isolated organs; large doses prevent catecholamine release from the adrenal medulla. Nicotine also can induce vomiting by stimulating emetic chemoreceptors and cause an alert EEG pattern (low voltage, fast activity), decrease skeletal muscle tone, decrease amplitude in EMG, decrease deep-tendon reflexes, and increase plasma levels of growth hormone, cortisol, and glycerol (Jaffe, 1980). Nicotine increases plasma glucose levels and circulation levels of endogenous opioids, and acts to decrease body weight (Glauser, Glauser, Reidenberg, Rusy, & Tallarida, 1970; Grunberg, 1982; Pomerleau, 1981; Wack & Rodin, 1982; USDHHS, 1998).

Repeated administration of nicotine is accompanied by tolerance, dependence, and withdrawal following abstinence. Withdrawal from nicotine includes nausea, headache, constipation, irritability, insomnia, inability to concentrate, decrease heart rate and blood pressure, and weight gain. These effects can last for weeks with the most intense symptoms occurring in the first few days after cessation.

Alcohol

Ethanol, more commonly known as alcohol, is a two-carbon alcohol ($\text{CH}_3\text{CH}_2\text{OH}$) and a CNS depressant. More than 90% of American adults report experience with alcohol and approximately 70% report some level of current use. The lifetime prevalence of alcohol abuse and dependence (alcoholism) in the United States is 5% to 10% for men and 3% to 5% for women (O'Brien, 2006). Alcohol is administered orally through beverages such as beer, wine, or liquor. The alcohol content of beverages typically ranges from 4% to 6% for beer, 10% to 15% for wine, and 40% or higher for distilled spirits.

Alcohol is a general CNS depressant and causes decreased heart rate and blood pressure and vasodilation. It enhances cutaneous and gastric blood flow, which results in a feeling of warmth. Alcohol also can stimulate the release of adrenocortical hormones and lead to an increase in the urinary excretion of epinephrine and norepinephrine.

Prolonged alcohol use can result in the disruption of sleep patterns including EEG and evoked cortical responses, increases in hepatic microsomal enzyme activity, fatty liver, cirrhosis of the liver, damage to the cardiac and skeletal muscle, and cerebral atrophy. Repeated administration can result in tolerance and/or dependence. Withdrawal symptoms of prolonged alcohol use include tremulousness, nausea, weakness, anxiety, sweating, cramps, vomiting, hyperreflexia, hallucinations, and

possibly grand mal seizures. Attention and motor reflex disruptions caused by moderate to high levels of alcohol intake contribute to alcohol-related traffic and other accidents.

Amphetamines, Cocaine, and Caffeine

Amphetamines are racemic β -phenylisopropylamines. Examples of amphetamines include methamphetamine, dextroamphetamine (Dexedrine), and methylenedioxymethamphetamine (also known as Ecstasy). Depending on the specific amphetamine, methods of administration can include oral, intravenous, or intranasal (snorting/sniffing). Amphetamines stimulate the CNS and increase synaptic levels of norepinephrine and dopamine. They increase blood pressure, cause a reflexive decrease in heart rate, relax bronchial smooth muscle, and decrease gastrointestinal motility. Amphetamines have a host of behavioral effects including sleeplessness, decreased appetite, elevated mood, and increased alertness. Some amphetamine use can result in a sense of physical strength, energy, and mental capacity.

There are additional effects associated with excessive amphetamine use including anxiety, irritability, loquaciousness, and drowsiness. Acute intoxication may result in dizziness, tremor, irritability, confusion, tachycardia, headache, hallucination, chest pain, heart palpitations, hypertension, sweating, cardiac arrhythmias, and even death. Toxic symptoms may include bruxism, touching and picking at the face and extremities, and paranoia.

Cocaine also stimulates the CNS. It occurs in an alkaloid form that lends itself to smoking and a hydrochloride potassium form that is used for nasal or intravenous use. Cocaine has a shorter half-life than many other stimulants.

It is estimated that more than 23 million Americans have used cocaine at some point, but the number of current users has declined markedly since the 1980s. The breakdown in numbers and type of use is estimated to be 8.6 million occasional users, 5.8 million regular users, and 3.6 million chronic cocaine users. Cocaine stimulates the CNS, blocks the initiation or conduction of nerve impulses, and potentiates the response of sympathetically innervated organs to norepinephrine. Cocaine leads to increased dopamine concentrations in the brain by blocking dopamine reuptake at presynaptic sites.

Health hazards of cocaine include irritability, loss of appetite, paranoia, and lethal effects. Tolerance develops to repeated cocaine administration. Withdrawal symptoms include craving for the drug, prolonged sleep, general fatigue, lassitude, hyperphagia, and possibly depression (Jaffe, 1980; Johanson, 1986).

Caffeine is the most commonly used CNS stimulant. It is a plant alkaloid closely related to the methylated xanthines, theophylline, and theobromine. Caffeine usually

is self-administered orally in beverages, such as coffee and soft drinks, or in foods including chocolate.

It is estimated that 80% of Americans are coffee drinkers (64% daily drinkers). Caffeine is a direct stimulant of the CNS that increases respiration, stimulates voluntary muscles, decreases fatigue, increases alertness, and serves as a mild diuretic. Caffeine is not generally considered by the public to be a dangerous drug, but that is because doses usually are quite low. In extremely high doses, caffeine's effects can be similar to amphetamines and cocaine. Like other stimulants, it can be addictive. Yet estimates of caffeine addiction prevalence are not well researched. One telephone survey did find that 30% of individual who used caffeine met *DSM-IV-TR* criteria for caffeine dependence (Griffiths, Juliano, & Chausmer, 2003). Of individuals who meet *DSM-IV* criteria for caffeine dependence, 10% to 55% of them show clinically significant impairments during withdrawal (Juliano & Griffiths, 2004). In large doses, caffeine also can lead to arrhythmias or mental changes (e.g., irritability). Withdrawal symptoms include headaches, fatigue, lethargy, and depression (*DSM-IV-TR*, 2001).

Opioids and Heroin

"Opioid" refers to all compounds related to opium (exogenous and endogenous). Opiates refer to drugs that affect opioid systems in the body. Opium is a drug derived from the juice of the opium poppy that contains more than 20 distinct alkaloids. Opioid drugs (or opiates) act on the endogenous opioid system, which is made up of three classes of opioids: enkephalins, endorphins, and dynorphins. Each opioid class has a different role but they share the common amino-terminal sequence of Tyr-Gly-Gly-Phe-(Met or Leu). Opioid drugs also are called narcotics (based on the word "narcosis" or sleep). They are commonly used to treat pain (e.g., morphine) but also are common drugs of abuse (e.g., heroin, which is diacetylmorphine). Routes of administration are oral or via intravenous administration. Approximately 1% to 2% of individuals in the United States have used heroin (Gutstein & Akil, 2001). Opiates prescribed for pain are the most commonly abused prescription drugs.

Opiates have significant effects on the CNS and the bowel. They also have analgesic, euphoric, sedative, and addictive effects. Respiratory depression and decreased blood pressure, emesis, warm flushing of the skin, and sensation in the lower abdomen may occur. Other effects include decreased intestinal contractions, delayed gastric emptying, decreased gastric contractile activity, restriction of the pupils, changes in temperature, and inhibition of norepinephrine release from sympathetic neurons.

Chronic administration of opiates results in an eventual decrease in glucocorticoid secretion. Morphine also increases levels of ACTH and decreases hypothalamic levels of norepinephrine. Tolerance develops to the

analgesic, sedative, emetic, and euphoric effects of opiates. There appears to be little tolerance for the gastrointestinal effects that cause constipation. Acute administration of heroin can be dangerous because of its depressant effect on respiration and blood pressure.

Withdrawal occurs after cessation from chronic use and can include CNS hyperexcitability, nausea, cramps, lacrimation, rhinorrhea, yawning, sweating, tremors, and increased respiration, dilated pupils, anorexia, gooseflesh, restlessness, irritability, insomnia, tremor, weakness, increased heart rate, increased blood pressure, and diarrhea.

THE RELATIONSHIP BETWEEN STRESS AND DRUG USE

Now that stress and several recreational drugs have been briefly discussed, we turn to the relationship between stress and each of the drugs highlighted above. The relevant information is summarized and, where available, specific explanations for the individual drug relationships with stress are provided.

Stress and Nicotine

Stress is associated with the initiation and maintenance of tobacco use (Kassel, Stroud, & Patronis, 2003). Cigarette smokers report that they smoke more when they are stressed, angry, anxious, or sad (McKennell, 1970; Russell, Peto, & Patel, 1974; Shiffman, 1993). Smoking increases after adverse childhood experiences (Anda et al., 1999), negative life events (Koval & Pederson, 1999), acute and chronic stressors (Koval, Pederson, Mills, McGrady, & Carvajal, 2000), and perceived stress (Dugan, Lloyd, & Lucas, 1999). Some research suggests that this relationship may be more pronounced in cases of social stress based on gender (Byrne & Mazanov, 1999) or race (Biafora, Warheit, Vega, & Gil, 1994). Smokers commonly report that smoking reduces anxiety (Frith, 1971; Leventhal & Cleary, 1980) and alleviates negative moods (Brandon & Baker, 1991; Copeland, Brandon, & Quinn, 1995). Many smokers report that they lapsed or relapsed to smoking while experiencing stress or negative affect (Borland, 1990; Cummings, Jaen, & Giovino, 1985; Shiffman, 1982; Swan et al., 1988). Yet smokers also report more stress than nonsmokers (e.g., Jorm et al., 1999; Naquin & Gilbert, 1996; Vollrath, 1998).

Nicotine (in tobacco) is usually classified as a stimulant because it often increases CNS arousal and acts to stimulate the SNS. So, the relationship between stress and smoking/nicotine is a bit more difficult to understand and nicotine is, therefore, considered to be a paradoxical drug (because it acts as a stimulant, yet it also is reported to induce a calming effect). In the laboratory, stress increases smoking intensity (e.g., Pomerleau & Pomerleau, 1987), amount smoked (Epstein & Collins,

1977; Rose, Behm, & Levin, 1993; Schachter, Silverstein, et al., 1977; Schachter, Kozłowski, & Silverstein, 1977), and desire to smoke (Perkins & Grobe, 1992). Whether smoking actually reduces stress or whether abstinence from smoking increases stress (so that smoking only reduces stress by contrast) is not clear (Grunberg & Kozłowski, 1986; Schachter, Kozłowski, et al., 1977; Schachter, Silverstein, et al., 1977).

Stress and Alcohol

Many people report that they drink alcohol in response to stress (Pohorecky, 1991). Alcohol use has been associated with a wide range of stressors, including exposure to traumatic stress (e.g., Donovan, Padin-Rivera, & Koaliw, 2001), unhappy marriages, and dissatisfaction with employment (Jose, van Oers, van de Mheen, Garretsen, & Mackenbach, 2000). Alcohol also is used to cope with tension associated with stress in the environment (Tyseen, Vaglum, Aasland, Gronvold, & Ekeberg, 1998) or to relieve symptoms of anxiety, irritability, and depression in individuals with post-traumatic stress disorder (PTSD; Volpicelli, Balarman, Hahn, Wallace, & Bux, 1999). Furthermore, stress may exert its greatest influence in precipitating the initial consumption of alcohol after a period of abstinence (Brown, Vik, Patterson, Grant, & Schuckit, 1995). Rats exposed to stress increase alcohol self-administration (Higley, Hasert, Suomi, & Linnoila, 1991; Hilakivi-Clarke & Lister, 1992; Volpicelli, 1987). The fact that alcohol is a CNS depressant makes sense as an account for the stress–alcohol relationship. Yet there also is evidence that drinking alcohol produces physiological stress (Meaney et al., 1995; Rivier, Imaki, & Vale, 1990; Tsigos & Chrousos, 1995; Waltman, Blevins, Boyd, & Wand, 1993), which clouds an otherwise clear picture. There also may be individual differences underlying whether one drinks in response to stress. Some factors that potentially mediate the stress–alcohol use relationship are genetic determinants of drinking in response to stress, expectations regarding the effect of alcohol on stress, type of stressor, sense of control over the stress, and the range of available responses for coping with stress (e.g., Clarke et al., 2008; Jennison, 1992; Pohorecky, 1991; Sadava & Pak, 1993; Volpicelli, 1987).

Stress and Cocaine

Cocaine use increases during stress in humans and animals (e.g., Goeders, 1997; Kreek & Koob, 1998) even though cocaine, a sympathomimetic, clearly stimulates many of the same neurochemical and hormonal systems activated by stress exposure (e.g., CRF, ACTH). Cocaine can even produce anxiety and panic in humans and anxiogenic responses in animals through its effects on CRF release (Goeders, 1997, 2002). Cocaine stimulates parts of the mesolimbic area of the brain (the area involved in

feeling pleasure), which may help to explain the stress–cocaine relationship (Kreek & Koob, 1998). In humans, individuals with a history of cocaine use reported more cocaine craving and negative affect in response to stress and drug cue imagery but not with neutral-relaxing imagery (Sinha, Fuse, Aubin, & O'Malley, 2000). In a sample of individuals who were dependent on cocaine, individuals who were more sensitive to daily hassles used more cocaine (Waldrop et al., 2007). Stress and cocaine also interact to affect reward during various phases of cocaine self-administration and withdrawal. During acquisition of cocaine self-administration, rats exposed to physical or social stress increase cocaine intake (Goeders, 2002). During reinstatement (a preclinical method that is widely regarded as an animal model for the propensity to relapse drug use) and relapse, stress also is associated with cocaine intake.

Stress and Caffeine

There is little empirical research directly relevant to effects of stress on caffeine consumption. One study did find that 41% of habitual coffee drinkers self-reported that they increase consumption under stress and faced with a lab test in which stress was perceived they did increase their coffee consumption (Ratliff-Crain, 1991). There is a wealth of literature on how caffeine affects the stress response (e.g., Goldstein, Kaizer, & Whitby, 1969). If caffeine use is altered during times of stress, then there would be at least two possible explanations. First, caffeine use may increase because caffeine is a mild CNS stimulant that decreases feelings of fatigue (Patat et al., 2000). Given that stress can result in less sleep, caffeine may alleviate this negative effect of stress. A second, alternative explanation is that caffeine use decreases in response to stress because caffeine consumption also can result in increased anxiety ratings in nonclinical populations (Chait, 1992; Goldstein et al., 1969) and individuals with high baseline measures of anxiety are less likely to choose caffeine over placebo in a blind choice procedure (Evans & Griffiths, 1992; Griffiths & Woodson, 1988). The stress–caffeine use/effect relationship appears to be more complex than a simple, linear function or a single underlying mechanism of action.

Stress and Opiates (e.g., Heroin)

There is a strong relationship between stress and heroin use, particularly with regard to heroin reinstatement (e.g., Bossert, Ghitza, Lu, Epstein, & Shaham, 2005; Shaham, Shalev, Lu, De Wit, & Stewart, 2003; Shalev, Grimm, & Shaham, 2002). Stress is one of the best predictors of relapse in individuals addicted to opiates (Brewer, Catalano, Haggerty, Gainey, & Fleming, 1998). Also, stress increases rat self-administration of morphine (Shaham, Alvares, Nespor, & Grunberg, 1992; Shaham, Klein, Alvares, & Grunberg, 1993; Shaham & Stewart,

1994). Because endogenous opioids and exogenous opiates inhibit the stress cycle and produce feelings of well-being and euphoria, it could be that heroin and other opiates (e.g., morphine) blunt the stress response and experience of stress (Kreek & Koob, 1998).

EXPLANATIONS FOR THE RELATIONSHIP BETWEEN STRESS AND DRUG USE

It is clear that stress and recreational drug use are related, but why? This section describes explanations that have been offered and also proposes new ones. We categorize these explanations into four broad groups that we believe are most likely to help explain the stress–drug use relationship: (1) self-medication hypotheses, (2) withdrawal hypotheses, (3) pharmacodynamic hypotheses, and (4) positive feedback loop hypotheses.

SELF-MEDICATION HYPOTHESES

Self-medication is a popular explanation for why there is a stress–drug use relationship. Simply put, individuals use a given drug under stress to reduce stress. Actually, even this “simple” explanation is a large bin with several different possible mechanisms. For example, the drug may actually decrease the body’s stress response; the drug may maintain performance (either behavioral or cognitive performance) during stress but not actually decrease stress; or the drug may distract the user from a stressor or stress response. The drug also may act indirectly to help buffer stress. Each of these self-medication hypotheses is discussed below.

Drugs Decrease Stress

Self-administration of CNS depressants, especially under stress, is consistent with this particular self-medication hypothesis. Stress is arousing. CNS depressants reduce arousal. Therefore, CNS depressants are taken during stress to reduce it and the more stress, the more CNS depressants are taken. With regard to the recreational drugs discussed in this chapter, this explanation works for alcohol, opiates, and possibly nicotine (because of its “paradoxical” actions).

Another source of evidence for this hypothesis comes from the relationship between drug use and depression. It has been suggested that recreational drug use and dependence involve self-medication to reverse neurotransmitter abnormalities associated with depression (e.g., Khantzian, 1997; Koob & LeMoal, 2008; Markou, Kosten, & Koob, 1998). To the extent that depression is a stressful state, this hypothesis about depression and drug use might be generalized to stress and drug use. Even if the depression argument cannot be generalized to stress in the broad sense, it does offer the possibility

that drugs other than CNS depressants per se may act to mediate a stressful state (via normalization of neurotransmitter levels).

Drugs Help to Maintain Performance

Drug use might increase as a method of self-medication to help maintain performance while stressed (e.g., increase attention, decrease distraction, and maintain energy level). Many students and professionals use stimulants (including caffeine, cocaine, amphetamines, and the paradoxical nicotine) during stressful periods that demand long hours of work in order to stay awake and to perform (University of Michigan Health System, 2008). This particular explanation, therefore, can account for the stress–CNS stimulant relationship, but not for the stress–CNS depressant relationship.

Drugs Affect Attention

Another variant of self-medication emphasizes cognitive mechanisms (rather than cognitive performance). People may use drugs under stress to increase attention, to focus or “narrow” attention, or to reduce the interference of distracters (e.g., Kassel, 1997; Kassel & Shiffman, 1997). These attention effects can then serve indirectly to reduce anxiety or negative affect that is associated with the stressor. This particular explanation is consistent with that fact that shifts in attention for drug-related stimuli are implicated in drug addiction (e.g., Field, 2005). Attentional bias for drug-related stimuli (defined a phenomenon whereby attentional channeling is directed toward a drug despite an individual’s efforts to ignore them it; Williams, Mathews, & MacLeod, 1996) predicts relapse to cigarette smoking (Waters et al., 2003) and to alcohol use (Cox, Hogan, Kristian, & Race, 2002) in individuals attempting to quit. Manipulating attentional bias for alcohol-related stimuli causes participants trained to attend to alcohol-related stimuli to experience increased craving for alcohol and to consume more alcohol than participants trained to attend away from alcohol-related stimuli (Field & Eastwood, 2005).

Also relevant to this discussion is Franken’s (2003) hypothesis that dopamine mediates attentional bias and Oswald et al.’s (2005) report regarding interrelationships among cortisol levels, subjective responses to amphetamines, and dopamine (DA) release. Attentional bias for drug-related stimuli increases motivation to consume drugs. Drug use may increase under stress because stress-induced dopamine release increases attentional bias for drug-related stimuli, which increases craving and leads to increased consumption. This version of the self-medication hypothesis is relevant to any drug that alters dopamine release, which includes most, if not all, recreational drugs and even some prescription drugs.

Drug Use Increases Social Support

A different explanation that can be viewed as a self-medication hypothesis is that stress increases drug use because drug use increases social interactions that act to buffer stress. For example, smoking is frequently used as a social tool (e.g., Russell et al., 1974). Kassel et al. (2003) suggested that cigarette smoking decreases negative affect by promoting social interactions. Social support decreases stress responses in humans (Kirschbaum, Klauer, Filipp, & Hellhammer, 1995) and animals (e.g., Westenbroek et al., 2003) and thereby acts to “buffer” stress (Cohen & Wills, 1985). Therefore, to the extent that drug use involves increased social interaction, the drug use may act indirectly to buffer stress. This explanation could be applied to any of the drugs, regardless of pharmacological class, if their use involves increased social interaction.

Drugs Might Alter Extinction Learning

Another variation of the self-medication explanation is that drug use decreases stress by enhancing extinction learning which in turn diminishes memories for negative events. Davis, Walker, and Myers (2003) have suggested that extinction learning is disrupted in PTSD, thereby enhancing memories associated with traumatic events (or decreasing the naturally protective process of extinguishing unpleasant memories). Furthermore, they suggest that receptor activation of the neurotransmitter N-methyl-D-aspartate (NMDA) in the amygdala is critical for the extinction of fear and other negative emotions. Extinction is a conditioning phenomenon that occurs when presentation of a conditioned stimulus ceases to elicit the conditioned response and is a component of treatment for conditioned fear disorders, such as phobias and PTSD. It appears that NMDA is critical for learning new associations in extinction. So if drugs augment the release of NMDA, then drug use may serve to reduce stress by increasing the learning of new stimulus-response contingencies. This novel idea fits under the self-medication category but involves neurobiological and cognitive mechanisms. If, indeed, drugs discussed in this chapter act on NMDA (as many do), then they may act via this extinction learning mechanism.

WITHDRAWAL HYPOTHESES

Another, quite different set of explanations for the stress–drug use relationship focuses on withdrawal symptoms associated with abstinence from previously self-administered drugs. This set of explanations is not as straightforward as the self-medication hypotheses, and it too has several variations.

Pharmacokinetic Explanations

Stress may alter the pharmacokinetics (i.e., the distribution, absorption, metabolism, or elimination) of drugs in

the body in ways that increase the self-administration of the drugs. For example, Schachter, Kozlowski, et al. (1977) argued that stress acidifies the urine, thereby increasing the elimination of unmetabolized nicotine from the body, resulting in increased cigarette smoking to replenish the lost nicotine to avoid the unpleasant state of nicotine withdrawal. According to this stress–drug use explanation, cigarette smoking does not relieve stress in general. Instead, stress precipitates increased smoking withdrawal and smoking increases to offset this exacerbated unpleasant state. Smokers perceive that smoking relieved stress but, instead, stress exaggerated and hastened nicotine withdrawal. Although increased smoking alleviates the stress-potential withdrawal, it does not reduce stress compared with a “baseline stress” state. This negative reinforcement explanation for why smoking increases under stress was based on the physical chemistry and pharmacokinetics of nicotine (Beckett, Rowland, & Triggs, 1965; Beckett & Triggs, 1966; Grunberg, Morse, & Barrett, 1983). It also could be applied to opiates, cocaine, and perhaps caffeine (based on physical chemistry and responses to pH alterations) but is unlikely to explain the alcohol–stress relationship.

Psychological Explanations

Alternatively, stress may precipitate drug self-administration because the experience of stress resembles the unpleasant state of withdrawal that accompanies abstinence from dependence-producing drugs. As a result, individuals misinterpret the experience of withdrawal as the experience of stress. This Cognitive Misattribution Model (Grunberg & Baum, 1985) suggests that drugs are taken to offset stress because the same drugs offset withdrawal. So, over time, the cognitive misattribution becomes a strongly learned response. This explanation is consistent with Pham’s (2007) report that individuals misattribute the valence of their incidental affective states, their arousal, and cognitive appraisal components. Incidental emotional arousal can be misinterpreted as an integral affective response to a target stimulus (e.g., Dutton & Aron, 1974). Classical and operant learning processes are likely to be involved in and reinforce the misattribution.

Another related psychological explanation based primarily on nicotine withdrawal research also might explain stress and drug use. When an individual addicted to nicotine abstains from drug use, a withdrawal syndrome of negative psychological symptoms results, including irritability and negative affect (Hughes, Higgins, & Hatsukami, 1990; Shiffman, 1979). Nicotine self-administration to offset this unpleasant withdrawal is an example of negative reinforcement. Parrott (1995) termed this phenomenon “nicotine withdrawal escape” and emphasized the reduction of negative affect. The notion of escape can be extended and applied to any drug that involves withdrawal states after cessation of repeated administration. People increase drug use to reduce negative psychological symptoms associated with withdrawal

from a drug. When stress increases negative affect, drug use would increase to “escape” the negative affect. This explanation, therefore, overlaps with the cognitive misattribution model and the self-medication hypotheses.

Neurobiological Explanations

Kreek and Koob (1998) offered a neurobiological explanation for the stress–drug use relationship that drew primarily from studies with cocaine and hypothesized a key role for the HPA axis and withdrawal. Recently, Koob’s research group has built upon this early explanation based on empirical work with nicotine. More specifically, George et al. (2007) reported that nicotine withdrawal recruits the CRF system and activates CRF(1) receptors, resulting in anxiety-like behaviors. This response is part of the HPA axis activity that is central to the stress response. Additional stressors during withdrawal may augment the CRF–CRF(1) system and exacerbate withdrawal. There also is evidence that brain stress/emotional systems are activated and provide an additional source of negative hedonic valence (i.e., unpleasant feeling) during withdrawal (Koob & LeMoal, 2006). Therefore, increased drug use under stress may modulate the HPA axis via the same mechanisms that are involved during withdrawal. This neurobiological explanation has some overlap with the self-medication hypotheses but the emphasis is on withdrawal. There also is some overlap with the psychological withdrawal hypotheses because of the hedonic component of this explanation. It would apply to any drug that involves the HPA-axis in withdrawal.

PHARMACODYNAMIC HYPOTHESES

There is some compelling evidence that stress itself may alter drug actions and thereby explain why drug use increases during stress. Pharmacodynamic explanations for the stress–drug use relationship hold that increased stress leads to increased drug response and increased reward, which in turn leads to increased drug taking. Either increases or decreases in sensitivity to drug actions during stress could lead to increased drug use during stress. There is evidence, for example, that corticosteroids increase actions of nicotine. Specifically, corticosteroid administration increases the development of sensitization to the locomotor-activating effects of nicotine (Caggiula et al., 1998). Such an effect could result in increased drug use under stress, but this mechanism has received little research attention. Conversely, it has been reported that adrenalectomy increases, and corticosterone administration decreases, some of the physiological and behavioral effects of nicotine (Caggiula et al., 1998).

Incentive Sensitization Theory

Incentive Sensitization focuses on how drug cues trigger excessive incentive motivation for drugs, leading

to compulsive drug seeking, drug taking, and relapse (Robinson & Berridge, 1993, 2000, 2003). Addictive drugs affect NAccs-related brain systems that mediate incentive salience. These neural circuits become sensitized to specific drug effects and drug-related stimuli with repeated exposure to the drugs. Perhaps, stress interacts with incentive sensitization. That is, stress associated with drug use may come to act as a conditioned stimulus for drug use. Over time, the stress cues may serve to increase sensitivity to the drug action and thereby increase the stress–drug use relationship. This mechanism might apply to all drugs that result in dopamine release because dopamine is a key neurotransmitter that often signals reward and is released in response to pleasurable activities (Bratcher, Farmer-Dougan, Dougan, Heidenreich, & Garris, 2005). Dopamine also may mediate a signal for reward opportunity (Schultz, 1998), or it may mediate activation of an organism toward a potential reward (Dommett et al. 2005; Horvitz, 2002; Robbins & Everitt, 1992; Salamone, Cousins, & Bucher, 1994; Salamone, Cousins, & Snyder, 1997; Stricker & Zigmond 1986). Dopamine might also mediate hedonia, pleasure, or reinforcement (Small, Jones-Gotman, & Dagher, 2003; Volkow et al., 1999; Wise, 1980). Finally, dopamine might mediate incentive salience or desire for the drug (Berridge, 2007). Research by Pecina, Berridge, Aldridge, and Zhuang (2003) suggests that dopamine mediates drug “wanting.” Because stress also increases dopamine release, stress might increase wanting and craving for drugs that also release dopamine.

Cross-Sensitization of Stress and Drugs

There also may be cross-sensitization of stress and drugs. Sensitization is the progressive augmentation of behavioral hyperactivity and neurobiological responses elicited by repeated intermittent administration of psychostimulant drugs (Kalivas & Stewart, 1991). Repeated intermittent administration of amphetamine, cocaine, morphine, and nicotine to rats augments the motor stimulant effects of these drugs (DiFranza & Wellman, 2007; Kalivas & Stewart, 1991). Because stress and drugs target similar pathways (i.e., dopaminergic pathways and the HPA axis), it is possible that prior exposure to stress may cross-sensitize pathways underlying reinforcement from nicotine (Kassel et al., 2003) and other drugs. Cross-sensitization between stress and the reinforcing actions of drugs may help to explain the relations between stress and drug use. Kassel et al. (2003) speculate that cross-sensitization might explain the role of stress in initiation, maintenance, and withdrawal from nicotine. Stress may act through cross-sensitization to increase the reinforcing effects of other drugs of abuse during the initiation, maintenance, and withdrawal stages of drug use and addiction, which would increase an individual’s vulnerability to use drugs during times of stress. This explanation may be applied to any drug use but it has not received empirical attention.

DRUG USE INCREASES STRESS

An entirely different type of explanation for the stress–drug use relationship is that drug use acts to increase stress, which serves as a positive feedback loop that then links with one or more of the mechanisms discussed above to increase drug use under stress. In other words, stress increases drug use (by one or more of the mechanisms discussed above), which increases stress, which increases drug use, and so on. There are at least two explanations that can be categorized under this broad interpretation.

Stress and Opponent Processes

Solomon and Corbit's (1973) Opponent Process Theory provided a two-process explanation for drug use. Initially, drug administration activates a "pleasant" dose-dependent A-process shortly after presentation of the drug, which correlates closely with the stimulus intensity, quality, and duration of the reinforcer, and involves tolerance. Activation of the A-process triggers the opponent B-process, which serves to bring the body back to homeostasis. Temporally, the B-process lags behind the A-process, especially upon first use, and lasts longer. The sum of the A and B processes creates the final subjective state experienced by the drug user. The B-process gets larger with repeated exposure and can become a conditioned response (Siegel, 1975). Over time, therefore, the drug response involves less drug "excitement" and increasing drug "withdrawal." The drug use, therefore, may be conceptualized as increasing a dysphoric, stress-like effect. So the drug use would come to induce stress even when it is a response to stress. Koob and Kreek (2007) provide a more detailed neurobiological explanation that applies the opponent process conceptualization to stress and drug use.

Allostasis Explanation

McEwen (1998) has proposed that allostasis, a change in homeostatic set point or ranges in response to stress, is the process of adaptation to acute stress and involves the output of stress hormones to restore homeostasis in the face of challenge. Allostasis comprises actions in the brain and throughout the body. The allostatic load is the detrimental toll taken on the body when it is forced to adapt to repeated adverse psychosocial or physical situations. Over time with continuous demand, the body's ability to make allostatic adaptations decreases, leading to breakdown and illness. Koob and LeMoal (2001) hypothesized that drug addiction is similar to the allostatic process. They suggested that repeated exposure to an addictive drug alters drug reward set point and reflects an allostasis. In addition, the stability to be maintained is reward function. Change in the mobilization of multiple neurotransmitters and hormonal systems

(including dopamine and EOPs) is needed to maintain normal reward function. Molecular or cellular changes occur within a given reward-circuit to accommodate overactivity of hedonic processing associated with addiction, resulting in a decrease in reward function. Neural circuitry changes act as opposing actions to limit reward function. Perhaps, stress further alters the drug reward set point through the effects of stress on dopamine release. Additional stressors during withdrawal may augment the CRF-CRF(1) system and exacerbate withdrawal. Koob and LeMoal (2001) address stress that originates from the drug cycle. But the effect of additional stressors could be to augment the "antireward system," causing the release of more CRF (and downstream, cortisol), which would in turn promote more drug administration, just as in the proposed stress application of the Opponent Process Theory. Koob and LeMoal (2001) apply and extend the Opponent Process Theory, arguing that the A process also involves incentive sensitization and that the B process acts as an antireward system. Stress may potentiate both arms of the opponent process. This explanation has not received direct empirical examination.

Stress Hypersensitivity

Another variation on the theme that drug use may increase stress suggests that drug users may be hypersensitive to stress. This hypersensitivity may occur because of drug use or because these hypersensitive individuals may have a genetic predisposition toward stress sensitivity (Kreek, 1984; Kreek & Koob, 1998; Schluger et al., 1998; Stocker, 1999).

SUMMARY AND AREAS FOR FUTURE RESEARCH

It is clear that there is a bidirectional relationship between stress and drug use. It also is clear that the stress–drug use relationship occurs for recreational (and likely for some prescription) drugs of different pharmacological classes. Therefore, considering traditional psychopharmacological mechanisms alone (e.g., CNS stimulation vs. CNS depression), it is unlikely that a single biological or psychobiological mechanism can explain the stress–drug use relationship. Several interesting explanations have been offered to explain the stress–drug use relationship. Each has tended to ignore alternatives. As a result, with each new explanation or variation on an old explanation, the list just gets longer and longer with little attempt to achieve some conceptual order or parsimony.

In this chapter, we offer a conceptual framework to classify various explanations into four major groups: (1) drug use decreases stress ("self-medication hypotheses"), (2) abstinence from drug use is altered by or resembles stress ("withdrawal hypotheses"), (3) stress alters drug actions ("pharmacodynamic hypotheses"), and (4) drug

use increases stress ("positive feedback loop hypotheses"). The self-medication hypotheses are more varied than may appear from the category label. They include direct and indirect, biological, psychological, and social mechanisms. The withdrawal hypotheses also are quite different from each other even though they all involve drug-induced withdrawal effects. The pharmacodynamic and positive-feedback loop hypotheses draw from ideas that were offered decades ago but do so in novel psychological ways.

Our own view is that several or all of these mechanisms are operating with regard to stress and drug use. Each explanation seems logical and has some theoretical or empirical support. However, most lack convincing, empirical examination and no research has pit one explanation against another in a "head-to-head" comparison. We hope that these stress-drug use explanations receive more research attention to determine which are most useful. We also hope that individual differences (including sex, age, genetic variations) are thoughtfully incorporated into these investigations. Furthermore, we believe that identification of the operating mechanisms will lead to novel treatments for drug abuse, including biological/pharmacological and psychological/social interventions. Better mechanism identification may even lead to novel stress management strategies. We began this chapter with the position that this topic is complex. We end this chapter with the conclusion that the explanations for the stress-drug use relationship are indeed complex but with the belief that conceptual progress is being made. No doubt this topic, and the advances in biotechnology that allow us to examine this topic, will keep many of us engaged for years to come.

NOTE

The opinions expressed in this chapter are the sole ones of the authors and are not to be construed as official or reflecting the views of the Uniformed Services University or the Department of Defense.

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