[11:20～12:00]

THE IMPACT OF STRESS ON ADDICTION

Nick E. Goeders, Ph.D.
Departments of Pharmacology & Therapeutics and Psychiatry
LSU Health Sciences Center
Shreveport, LA USA

Corresponding Author:
Nick E. Goeders, Ph.D.
Department of Pharmacology & Therapeutics
LSU Health Sciences Center
PO Box 33932
1501 Kings Highway
Shreveport, LA 71130-3932
USA

Telephone: 318-675-7863
FAX: 318-675-7857

E-mail: NGOEDE@LSUHSC.EDU

Abstract

This paper will review data obtained primarily from our preclinical investigations that show that exposure to stress has a significant impact on drug taking. Stress increases reward associated with psychomotor stimulants, possibly through a process similar to sensitization, and a growing clinical literature indicates that there is also a link between substance abuse and stress in human addicts. 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 drug self-administration is that drug delivery and its subsequent effects on the 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, however, 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. 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. Of primary importance is to reduce the impact of cocaine-associated environmental stimuli on the HPA axis so that they no longer function as triggers for relapse.

Key Words: HPA axis, reward, self-administration, stress, relapse

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 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.

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; Tidy 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 non-contingent ("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 (non-contingent 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 be-

lieved 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, pre-treatment 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.

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 reviews on the reinstatement of extinguished drug seeking have been published (Stewart, 2000; Weiss *et al.*, 2001, See, 2002; Shaham *et al.*, 2003), including reviews on the specific 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. 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 intermit-

tent 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).

We have investigated 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 non-contingent 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). 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).

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). 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 40-60% (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; Goeders, 2002). Accordingly, one might expect that augmenting HPA axis activity would increase the aversive effects of the drug and reduce the motivation for it. However, an important 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 *et al.*, 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. Of primary importance is to reduce the impact of cocaine-associated environmental stimuli on the HPA axis so that they no longer function as triggers for relapse.

Acknowledgments: This work was supported by USPHS grants DA06013 and DA13463 from the National Institute on Drug Abuse.

References

Ball, S. A., Carroll, K. M. and Rounsaville, B. J. (1994). Sensation seeking, substance abuse, and psychopathology in treatment-seeking and community cocaine abusers. *J. Consult. Clin. Psychol.* **62**, 1053-1057.

Bardo, M. T., Donohew, R. L. and Harrington, N. G. (1996). Psychobiology of novelty seeking and drug seeking behavior. *Behav. Brain Res.* **77**, 23-43.

Brady, K. T. and Sonne, S. C. (1999). The role of stress in alcohol use, alcoholism treatment, and relapse. *Alcohol Res. Health* **23**, 263-271.

Campbell, U. C. and Carroll, M. E. (2001). Effects of ketoconazole on the acquisition of intravenous cocaine self-administration under different feeding conditions in rats. *Psychopharmacology* **154**, 311-318.

Carton, S., Jouvent, R. and Widlocher, D. (1994). Sensation seeking, nicotine dependence, and smoking motivation in female and male smokers. *Addict. Behav.* **19**, 219-227.

Clampitt, D. M., Peltier, R. L. and Goeders, N.E. (2001). The effects of alprazolam on the ability of conditioned cues to reinstate extinguished cocaine-seeking behavior in rats. *Drug Alcohol Dependence* **63**, Suppl. 1, S28.

de Wit, H. (1996). Priming effects with drugs and other reinforcers. *Exp. Clin. Psychopharmacol.* **4**, 5-10.

Dellu, F., Piazza, P. V., Mayo, W., Le Moal, M. and Simon, H. (1996). Novelty-seeking in rats-biobehavioral characteristics and possible relationship with the sensation-seeking trait in man. *Neuropsychobiology* **34**,136-145.

Donovan, B., Padin-Rivera, E. and Kowaliw, S. (2001). "Transcend": initial outcomes from a posttraumatic stress disorder/substance abuse treatment program. *J. Trauma Stress* **14**, 757-772.

Franques, P., Auriacombe, M., Piquemal, E., Verger, M., Brisseau-Gimenez, S., Grabot, D. and Tignol, J. (2003). Sensation seeking as a common factor in opioid dependent subjects and high risk sport practicing subjects. A cross sectional study. *Drug Alcohol Depend.* **69**, 121-126.

Gelkopf, M., Levitt, S. and Bleich, A. (2002). An integration of three approaches to addiction and methadone maintenance treatment: the self-medication hypothesis, the disease model and social criticism. *Isr. J. Psychiatry Relat. Sci.* **39**, 140-151.

Gerber, G. J. and Stretch, R. (1975). Drug-induced reinstatement of extinguished self-administration behavior in monkeys. *Pharmacol. Biochem. Behav.* **3**, 1055-1061.

Goeders, N. E. and Clampitt, D. M. (2002). Potential role for the HPA axis in the conditioned reinforcer-induced reinstatement of extinguished cocaine seeking in rats. *Psychopharmacology* **161**, 222-232.

Goeders, N. E. and Guerin, G. F. (1994). Non-contingent electric footshock facilitates the acquisition of intravenous cocaine self-administration in rats. *Psychopharmacology* **114**, 63-70.

Goeders, N. E. and Guerin, G. F. (1996a). Role for corticosterone in intravenous cocaine self-administration in rats. *Neuroendocrinology* **64**, 337-348.

Goeders, N. E. and Guerin, G. F. (1996b). Effects of surgical and pharmacological adrenalectomy on the initiation and maintenance of intravenous cocaine self-administration in rats. *Brain Res.* **722**, 145-152.

Goeders, N. E. and Guerin, G. F. (1999). Pretreatment with corticosterone or dexamethasone fails to affect ongoing cocaine self-administration in rats. *Neuroscience Abstr.* **25**, 1872.

Goeders, N. E. (1997). A neuroendocrine role in cocaine reinforcement. *Psychoneuroendocrinology* **22**, 237-259.

Goeders, N. E. (2002). Stress and cocaine addiction. *J. Pharmacol. Exp. Ther.* **301**, 785-789.

Haney, M., Maccari, S., Le Moal, M., Simon, H. and Piazza, P. V. (1995). Social stress increases the acquisition of cocaine self-administration in male and female rats. *Brain Res.* **698**, 46-52.

Henry, C., Bellivier, F., Sorbara, F., Tangwongchai, S., Lacoste, J., Faure-Chaigneau, M. and Leboyer, M. (2001). Bipolar sensation seeking is associated with a propensity to abuse rather than to temperamental characteristics. *Eur. Psychiatry* **16**, 289-292.

Kabbaj, M., Norton, C. S., Kollack-Walker, S., Watson, S. J., Robinson, T. E. and Akil, H. (2001). Social defeat alters the acquisition of cocaine self-administration in rats: role of individual differences in cocaine-taking behavior. *Psychopharmacology* **158**, 382-387.

Khantzian, E. J. (1985). The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. *Am. J. Psychiatry* **142**, 1259-1264.

Kosten, T. A., Miserendino, M. J. and Kehoe, P. (2000). Enhanced acquisition of cocaine self-administration in adult rats with neonatal isolation stress experience. *Brain Res.* **875**, 44-50.

Lamon, B. C. and Alonzo, A. (1997). Stress among males recovering from substance abuse. *Addict. Behav.* **22**, 195-205.

Levine, S. (2000). Influence of psychological variables on the activity of the hypothalamic-pituitary adrenal axis. *Eur. J. Pharmacol.* **405**, 149-160.

Liu, X. and Weiss, F. (2002). Additive effect of stress and drug cues on reinstatement of ethanol seeking: exacerbation by history of dependence and role of concurrent activation of corticotropin-releasing factor and opioid mechanisms. *J. Neurosci.* **22**, 7856-7861.

Mantsch, J. R., Goeders, N. E. (1999). Ketoconazole blocks the stressor-induced reinstatement of cocaine-seeking behavior in rats: relationship to the discriminative stimulus effects of cocaine. *Psychopharmacology* **142**, 399-407.

Mantsch, J. R., Saphier, D. and Goeders, N. E. (1998). Corticosterone facilitates the acquisition of cocaine self-administration in rats: opposite effects of the glucocorticoid receptor agonist, dexamethasone. *J. Pharmacol. Exp. Ther.* **287**, 72-80.

Martin, C. A., Kelly, T. H., Rayens, M. K., Brogli, B. R., Brenzel, A., Smith, W. J. and Omar, H. A. (2002). Sensation seeking, puberty, and nicotine, alcohol, and marijuana use in adolescence. *J. Am. Acad. Child Adolesc. Psychiatry* **41**, 1495-1502.

Mathieu-Kia, A. M., Kellogg, S. H., Butelman, E. R. and Kreek, M. J. (2002). Nicotine addiction: insights from recent animal studies. *Psychopharmacology* **162**, 102-118.

McBride, W. J., Le, A. D. and Noronha, A. (2002). Central nervous system mechanisms in alcohol relapse. *Alcohol Clin. Exp. Res.* **26**, 280-286.

McKay, J. R., Rutherford, M. J., Alterman, A. I., Cacciola, J. S. and Kaplan, M. R. (1995). An examination of the cocaine relapse process. *Drug Alcohol Depend.* **38**, 35-43.

Meil, W. M. and See, R. E. (1996). Conditioned cued recovery of responding following prolonged withdrawal from self-administered cocaine in rats: an animal model of relapse. *Behavioural Pharmacol.* 7, 754-763.

Patkar, A. A., Berrettini, W. H., Hoehe, M., Thornton, C. C., Gottheil, E., Hill, K. and Weinstein, S. P. (2002). Serotonin transporter polymorphisms and measures of impulsivity, aggression, and sensation seeking among African-American cocaine-dependent individuals. *Psychiatry Res.* **110**, 103-115.

Pedersen, W., Clausen, S. E. and Lavik, N. J. (1989). Patterns of drug use and sensation-seeking among adolescents in Norway. *Acta. Psychiatr. Scand.* **79**, 386-390.

Piazza, P. V. and Le Moal, M. (1998). The role of stress in drug self-administration. *Trends Pharmacol. Sci.* **19**, 67-74.

Piazza, P. V., Deminiere, J. M., le Moal, M. and Simon, H. (1990). Stress- and pharmacologically-induced behavioral sensitization increases vulnerability to acquisition of amphetamine self-administration. *Brain Res.* **514**, 22-26.

Sarnyai, Z., Shaham, Y. and Heinrichs, S. C. (2001). The role of corticotropin-releasing factor in drug addiction. *Pharmacol. Rev.* **53**, 209-243.

Scourfield, J., Stevens, D. E. and Merikangas, K. R. (1996). Substance abuse, comorbidity, and sensation seeking: gender differences. *Compr. Psychiatry* **37**, 384-392.

See, R. E. (2002). Neural substrates of conditioned-cued relapse to drug-seeking behavior. *Pharmacol. Biochem. Behav.* **71**, 517-529.

Shaham, Y. and Stewart, J. (1994). Exposure to mild stress enhances the reinforcing efficacy of intravenous heroin self-administration in rats. *Psychopharmacology* **114**, 523-527.

Shaham Y, Erb S, Stewart J. (2000). Stress-induced relapse to heroin and cocaine seeking in rats: a review. *Brain Res Rev.* **33**, 13-33.

Shaham, Y., Shalev, U., Lu, L., De Wit, H. and Stewart, J. (2003). The reinstatement model of drug relapse: history, methodology and major findings. *Psychopharmacology* **168**, 3–20.

Shalev, U., Grimm, J. W. and Shaham, Y. (2002). Neurobiology of relapse to heroin and cocaine seeking: a review. *Pharmacol. Rev.* **54**, 1-42.

Shiffman, S., Wills, T. A. (1985). Coping and substance abuse. *Academic Press*, Orlando.

Sinha, R., Catapano, D., O'Malley, S. (1999). Stress-induced craving and stress response in cocaine dependent individuals. *Psychopharmacology* **142**, 343-351.

Sinha, R., Fuse, T., Aubin, L. R. and O'Malley, S.S. (2000). Psychological stress, drug-related cues and cocaine craving. *Psychopharmacology* **152**, 140-148.

Sinha, R. (2001). How does stress increase risk of drug abuse and relapse? *Psychopharmacology* **158**, 343-359.

Spealman, R. D., Barrett-Larimore, R. L., Rowlett, J. K., Platt, D. M. and Khroyan, T. V. (1999). Pharmacological and environmental determinants of relapse to cocaine-seeking behavior. *Pharmacol. Biochem. Behav.* **64**, 327-336.

Stanton, M. D. (1976). Drugs, Vietnam, and the Vietnam veteran: an overview. *Am. J. Drug Alcohol Abuse* **3**, 557-570.

Stewart, J. and de Wit, H. (1987). Reinstatement of drug-taking behavior as a method of assessing incentive motivational properties of drugs. In: Bozarth, M.A. (Ed) *Methods of Assessing the Reinforcing Properties of Abused Drugs*. New York, Springer, pp. 21-227.

Stewart, J. (2000). Pathways to relapse: the neurobiology of drug- and stress-induced relapse to drug-taking. *J. Psychiatry Neurosci.* **25**, 125-136.

Tidey, J. W. and Miczek, K. A. (1997). Acquisition of cocaine self-administration after social stress: role of accumbens dopamine. *Psychopharmacology* **130**, 203-212.

Turnbull, A. V. and Rivier, C. (1997). Corticotropin-releasing factor (CRF) and endocrine responses to stress: CRF receptors, binding protein, and related peptides. *Proc. Soc. Exp. Biol. Med.* **215**, 1-10.

Tyssen, R., Vaglum, P., Aasland, O. G., Gronvold, N. T. and Ekeberg, O. (1998). Use of alcohol to cope with tension, and its relation to gender, years in medical school and hazardous drinking: a study of two nation-wide Norwegian samples of medical students. *Addiction* **93**, 1341-1349.

Volpicelli, J., Balaraman, G., Hahn, J., Wallace, H. and Bux, D. (1999). The role of uncontrollable trauma in the development of PTSD and alcohol addiction. *Alcohol Res. Health* **23**, 256-262.

Wagner, M. K. (2001). Behavioral characteristics related to substance abuse and risk-taking, sensation-seeking, anxiety sensitivity, and self-reinforcement. *Addict. Behav.* **26**, 115-120.

Weiss, F., Ciccocioppo, R., Parsons, L. H., Katner, S., Liu, X., Zorrilla, E. P., Valdez, G. R., Ben-Shahar, O., Angeletti, S. and Richter, R. R. (2001). Compulsive drug-seeking behavior and relapse. Neuroadaptation, stress, and conditioning factors. *Ann. N. Y. Acad. Sci.* **937**, 1-26.

Will, M. J., Watkins, L. R. and Maier, S. F. (1998). Uncontrollable stress potentiates morphine's rewarding properties. *Pharmacol. Biochem. Behav.* **60**, 655-664.

Winhusen, T. and Somoza, E. (2001). The HPA axis in cocaine use: implications for pharmacotherapy. *J. Addict. Dis.* **20**, 105-119.

Woods, J. H., Winger, G. D. and France, C. P. (1986). Reinforcing and discriminative stimulus effects of cocaine: analysis of pharmacological mechanisms. In: *Cocaine: Clinical and Biobehavioral Aspects*, Fisher S, Raskin A and Uhlenhuth EH, Eds, Oxford University Press: New York, pp. 21-65.