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REVIEW

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How does stress increase risk of drug abuse and relapse?

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Abstract *Rationale:* The notion that stress leads to drug abuse in vulnerable individuals and relapse in addicts is not new. Most major theories of addiction postulate that stress plays an important role in increasing drug use and relapse. Several animal studies and some human laboratory studies have shown that stress exposure enhances drug self-administration. Although clinical observations suggest that exposure to stress increases drug use, and are associated with craving and relapse in addicts, human research in this area is largely correlational and at times contradictory. *Objective:* Given the growing preclinical evidence that supports the key role of stress in substance abuse, careful examination of this research area in humans is warranted. This paper examines empirical evidence on how stress may increase the vulnerability to drug abuse, and explores whether chronic drug abuse alters the stress response and coping in addicts, thereby increasing the likelihood of drug seeking and relapse. Unanswered questions on the association between stress and substance abuse in humans are identified. *Conclusion:* Preclinical research has shown that stress, in addition to drug itself, plays a key role in perpetuating drug abuse and relapse. However, the mechanisms underlying this association in humans remain unclear. A greater understanding of how stress may perpetuate drug abuse will likely have a significant impact on both prevention and treatment development in the field of addiction.

Keywords Stress · Drug abuse · Relapse · Drug craving · Human studies

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Introduction

Several models of addiction have proposed that stress increases risk of drug abuse and relapse. However, the mechanisms by which stress exposure may enhance drug use and increase relapse risk remain elusive. There has been a dramatic increase in research to understand neural circuits associated with stress and those underlying addictive behaviors. While this paper focuses primarily on the evidence that links stress and drug abuse in humans, it draws from the broader animal and human literature to support the proposed hypotheses. The first part of the paper reviews (1) the definition of the term "stress" and its current conceptualization; (2) the evidence for a positive association between chronic and acute stress and increased drug use; and (3) the mechanisms that link brain stress circuits to an increased vulnerability for the development of substance use disorders. The second part examines recent studies on neuroadaptations in brain stress and reward circuits due to chronic drug abuse. Whether such changes in brain reward and stress systems alter the ability of addicts to cope with stress, particularly with respect to perpetuation of addictive behaviors and relapse is explored.

Stress: definition and current conceptualization

The term *stress* is frequently defined as a process involving perception, interpretation, response and adaptation to harmful, threatening, or challenging events (Lazarus and Folkman 1984). This conceptualization permits separate consideration of (1) events that cause stress (stressors or stressful life events); (2) cognitive and affective processes evaluating the event and available coping resources (appraisal); (3) biological responses and adaptation needed to cope with the stressor; and (4) behavioral and cognitive response to the stressful event (coping). Each of these components is associated with specific and overlapping neural systems that interact in a complex and intricate manner to coordinate the experience and response

to stress. A brief and simplified overview of these components is provided below.

Events that induce a stress response usually produce one or more conditioned or unconditioned emotional reactions, such as fear, anxiety, anger, excitement, pleasure and sadness. These reactions depend on the specific features of the situation, an appraisal of the event and available coping resources, and the prior emotional state of the individual. Perception of threat or challenge relies on the brain information processing circuits, such as the primary sensory projections and sensory association cortices, that are involved in perceiving external environmental stimuli as well as internally generated cognitive and affective stimuli (McEwen and Stellar 1993). Appraisal of the event relies on input from the sensory nervous system circuits, in the thalamus, insula and sensory association areas. In addition, the limbic-affective processing circuits including amygdala interactions with sub-cortical and prefrontal cortical areas, particularly the orbitofrontal and medial pre-frontal cortices, contribute to determine the meaning and significance of events. Furthermore, direct input from the thalamus and frontal regions to the amygdala and the limbic-affective processing circuits is thought to function as an early warning system that leads to rapid global avoidance and defense responses important for the survival of the organism (Gaffan et al. 1993; Lovallo 1997). These circuits also interact with the biological adaptive systems to produce stress-induced neuro-endocrine responses. Their interconnections with nucleus accumbens structures and the prefrontal cortex play a key role in approach and avoidance response selection and the mediation of goal directed behaviors, functions that are important in cognitive and behavioral coping (Gaffan et al. 1993; Robbins and Everitt 1996; Lovallo 1997). While there have been major advances in understanding this circuitry as it pertains to conditioned fear responding (LeDoux 2000), its potential role in setting the level of risk of drug abuse and relapse has yet to be understood. The latter sections of this paper will focus on the effects of stress and drug-associated stimuli on activation of the above circuits.

A substantial literature has focused on biological adaptation mechanisms associated with stress. The two main components of the brain stress circuitry involved in adaptation are corticotrophin releasing factor (CRF) released from the paraventricular nucleus (PVN) of the hypothalamus and noradrenergic activation initiated in the brain stem (locus coeruleus). These components are activated by the cognitive and affective processing circuits involved in perceiving/appraising the stressor, leading to a cascade of central and peripheral events. Activation of the hypothalamic-pituitary-adrenal axis (HPA) axis and the limbs of the autonomic nervous system result in a series of peripheral events that have a significant impact on behavioral and physiological adaptation (Lopez et al. 1999). In addition, co-release of mesolimbic dopamine, brain catecholamines in other limbic forebrain regions and endogenous opiates contribute to enhance adaptation to stressful events. Furthermore, the serotonin, acetylcholine and GABA systems are also involved in modulating brain CRF and noradrenergic circuits (Arborelius et al. 1999).

Facing danger, threat or a challenging event motivates individuals to adapt or reduce stress by use of coping strategies. In general, three classes of coping are identified: (1) "problem-focused" coping involve cognitive and behavioral strategies, such as cognitive restructuring, planning and preparation for recurrence of the event, consideration of alternate options, and behavioral coping involving direct action aimed at altering the source of stress or one's relationship to it; (2) "emotion-focused" coping is the management of one's emotional distress associated with the stressful event rather than the cause of the stress; and (3) finally, avoidance coping is aimed at avoiding any acknowledgement that the event has occurred or giving up the attempt to do anything about the event (Lazarus 1966; Lazarus and Folkman 1984; Carver et al. 1989). New approaches view coping in the self-regulation context with the function of attaining a goal or regaining a desired state/homeostasis (Carver and Scheier 1999). Given that difficulties in maintaining homeostasis have been conceptualized as central to addiction (Koob and Le Moal 1997), a closer look at stress-related coping and its neural representations is presented in the last section of the paper.

In clarifying the term stress and its components, it is important to note that while stress is often associated with negative affect and distress, it includes states that may be perceived as pleasant and exciting (Selye 1976). For example, mild, brief or controllable challenge states perceived as pleasant and exciting also activate brain stress circuits, and are key to biological and cognitive adaptation (Hennessey and Levine 1979). However, the more severe the stress, e.g. states associated with increased intensity of affect, and greater the uncontrollability and unpredictability, the greater the magnitude of the stress response (Frankenhauser 1980; Lovallo 1997). Thus, the dimensions of intensity, controllability and predictability may be important in understanding the role of stress in increasing drug abuse and relapse.

Stress and increased vulnerability to drug abuse

Theoretical models linking stress to drug abuse

Most major theories of addiction postulate that acute and chronic stress play an important role in the motivation to abuse addictive substances (Tomkins 1966; Russell and Mehrabian 1975; Leventhal and Cleary 1980; Shiffman 1982; Marlatt and Gordon 1985; Wills and Shiffman 1985; Koob and Le Moal 1997). For example, the stress-coping model of addiction proposes that use of addictive substances serves to both reduce negative affect and increase positive affect, thereby reinforcing drug taking as an effective, albeit maladaptive, coping strategy (Shiffman 1982; Wills and Shiffman 1985). Marlatt's relapse prevention model (Marlatt and Gordon 1985) states

that in addition to other bio-psychosocial risk factors such as parental substance use, peer pressure, and positive expectancies over the potential benefits of using substances, individuals with poor coping resources are at increased risk for problematic use of addictive substances. The popular tension reduction (Conger 1956; Sher and Levenson 1982) and self-medication hypotheses (Khantzian 1985) have proposed that people use drugs to enhance mood and alleviate emotional distress. These models postulate that the motivation to enhance mood is great in acute and chronic stress states. Initially a drug may be used to modulate tension or distress; subsequently, with repeated success, it may become a more ubiquitous response for both stress relief and mood enhancement.

The above models suggest that both negative reinforcement/relief from stress or positive reinforcement/mood enhancement can increase the vulnerability to drug abuse. Based on preclinical findings, Koob and Le Moal (1997) have proposed a model that links the negative and positive reinforcement aspects. They postulate that stress leads to state-related changes in brain reward circuits resulting in a greater sensitivity to the reinforcing properties of drugs, and thereby increasing the motivation to use drugs compulsively. Thus, stress may act to "prime" brain reward systems, thereby enhancing the reinforcing efficacy of drugs, particularly in those vulnerable to drug abuse (Piazza and Le Moal 1998). While this model provides one explanation for how the transition from experimental drug use to chronic, regular use may occur, it remains untested and requires further empirical support.

Adverse life events, chronic distress and increased vulnerability to drug use

Evidence from animal studies suggest that specific types of stressful experiences in early life may increase the vulnerability to drug use. Experimental manipulations such as social separation or isolation in early life, in contrast to group housing, are known to increase self-administration of morphine and cocaine (Adler et al. 1975; Kostowski et al. 1977; Alexander et al. 1978; Schenk et al. 1987). In a systematic series of studies, Higley and colleagues (1991, 1993) studied alcohol consumption behavior in rhesus monkeys reared by mothers (normal condition) or by peers (stressed condition) for the first 6 months of their life. As adults, peer-reared monkeys consumed significantly more amounts of alcohol than mother-reared monkeys. Furthermore, when stress was increased in the adult monkeys by social separation, mother-reared monkeys increased their levels of alcohol consumption to that of peer-reared monkeys, while peer-reared monkeys maintained their level of alcohol consumption. These studies suggest that stress in early and adult life both appear to increase self-administration of alcohol. Recent work by Kosten and colleagues (2000) showing that neonatal isolation in adult rats enhances acquisition of cocaine self-administration are consistent with the above findings as well.

Other research has found that chronically stressed infant monkeys have increased levels of CRF in the cerebrospinal fluid (CSF). Such hypersensitivty of the CRF-HPA system has been linked to chronic distress states such as anxiety and mood disorders (Coplan et al. 1996; Arborelius et al. 1999). Sapolsky and colleagues (1997) reported that chronic social stress associated with social subordination in wild baboons is associated with hypercortisolism, a state commonly found among individuals with depressive symptoms and affective disorders. In a series of studies, Meaney and colleagues found long-lasting changes in the CRF-HPA stress response in animals exposed to a variety of early life environmental manipulations (Meaney et al. 1993; Plotsky and Meaney 1993). These changes included increased sensitivity to stressors and an altered HPA and behavioral stress response throughout development and adult life (Meaney et al. 1993). Elevated cortisol levels in primates stressed early in life has been associated with excessive self-administration of alcohol in these primates as adults (Higley et al. 1993; Fahlke et al. 2000). Furthermore, rats with high reactivity to novel situations, as measured by high circulating cortisol levels, are at increased vulnerability to self-administration of psycho-stimulants, such as amphetamines (Piazza et al. 1989; Piazza and Le Moal 1996). Therefore, differences in response to stressful events and previous experience of stressful events appear to predispose animals to an increased vulnerability to self-administer addictive substances. Furthermore, one aspect of the vulnerability may be linked to a hyper-responsivity of the CRF-HPA system to stress.

Several human studies have reported a positive association between adverse life events, chronic distress and increased drug abuse. Individuals with early physical and sexual abuse histories are at risk to abuse substances and report an earlier age of onset of substance abuse (Dembo et al. 1988; Harrison et al. 1997; Widom et al. 1999). Prospective studies in adolescents show that higher levels of stress and maladaptive coping, along with low parental support, predict escalation of nicotine, alcohol and marijuana use (Kaplan et al. 1986; Newcomb and Bentler 1988; Kaplan and Johnson 1992; Wills et al. 1996). Alcohol consumption is positively associated with stress levels, lack of social support and avoidance coping (Aro 1981; Cronkite and Moos 1984; DeFrank et al. 1987; Chassin et al. 1988; Pohorecky 1991). Furthermore, drinking and drug use as a coping response to stress is positively associated with dependence symptoms and compulsive drug use, while drug use for social and enhancement reasons is not associated with problematic levels of use (Cooper et al. 1992; Laurent et al. 1997). However, some studies do report a lack of association between occupational stress, anxiety states and alcohol consumption in social drinkers and college students (Conway et al. 1981; Schwartz et al. 1982; Rohsenow 1982; Allan and Cooke 1985; Stone et al. 1985).

Prevalence of anxiety and mood disorders and behavioral conduct problems in adolescents is associated with an increased frequency and regular use of substances such as alcohol, nicotine and marijuana (King et al. 1996; Rohde et al. 1996; Kandel et al. 1997, Riggs et al. 1999; Rao et al. 1999). Psychiatric and substance use disorders are highly co-morbid in adults as well, with lifetime prevalence rates above 50% for co-occurrence of any psychiatric disorder with substance abuse (Regier et al. 1990; Kessler et al. 1994, 1996). Increased frequency of substance abuse is more likely to follow the occurrence of behavior problems and psychiatric disorders (Kessler et al. 1996; Rohde et al. 1996; Riggs et al. 1999). It has been postulated that psychiatric disorders such as anxiety and affective disorders are manifestations of chronic stress states that are associated with dysregulated brain stress circuits (Plotsky et al. 1995; Arborelius et al. 1999). It is possible that such neuroadaptations in brain stress circuits may lead to a greater sensitivity to the reinforcing properties of drugs in those vulnerable to drug abuse, thereby increasing the frequency of drug use in these individuals. Consistent with this hypothesis, Covington and Miczek (2001) have reported that chronic exposure to social defeat stress in laboratory animals increased cocaine self-administration during cocaine binge episodes.

Acute behavioral stress increases drug use and drug seeking

Exposure to acute behavioral stress facilitates self-administration of amphetamines (Piazza et al. 1990; Piazza and Le Moal 1996), morphine (Alexander et al. 1978; Hadaway et al. 1979; Shaham and Stewart 1994) and cocaine (Ramsey and Van Ree 1993; Goeders and Guerin 1994; Haney et al. 1995; Miczek and Mutschler 1996). In contrast to these facilitative effects of stress on drug self-administration, research on the effects of stress on alcohol consumption have been inconsistent. For example, alcohol consumption in response to stress has been found to increase (Anisman and Waller 1974; Volpicelli and Ulm 1990), decrease (van Erp and Miczek 2001) or not change (Myers and Holman 1967; Fidler and Lolordo 1996). These differences in findings have been attributed to several factors such as pre-stress alcohol consumption levels, timing and exposure to stress and differences in type of stress manipulation (Wolfgramm 1990; Wolfgramm and Heyne 1991; Pohorecky et al. 1995; van Erp and Miczek 2001). However, using the stress-reinstatement paradigm, several studies have demonstrated that exposure to brief foot-shock stress reinstated drug seeking behavior after extinction trials in animals dependent on heroin, cocaine, alcohol and nicotine (Shaham and Stewart 1995; Erb et al. 1996; Ahmed and Koob 1997; Le et al. 1998; Mantsch and Goeders 1998; Shaham et al. 1998; Buczek et al. 1999). Therefore, while the facilitative effects of stress on stimulant and heroin self-administration are well demonstrated, the effects of stress on alcohol consumption appear to be suppressive. Nonetheless, the stress-reinstatement studies have consistently shown that foot-shock stress increases drug-seeking behavior in dependent animals. It may well be that the mechanisms that underlie the facilitative effects of stress on stimulant self-administration and the suppressive effects of stress on alcohol self-administration are different from those that underlie stress-induced reinstatement of drug seeking behavior.

Early evidence from human laboratory studies also found increased drug taking after stress as opposed to non-stress situations. In social drinkers, exposure to stressors such as fear of interpersonal evaluation, anger due to provocation by a confederate and failure feedback on exposure to insolvable problems, led to increased alcohol consumption as compared to drinking behavior in non-stressful situations (Higgins and Marlatt 1975; Marlatt et al. 1975; Hull and Young 1983). Other research has shown that parents exposed to child confederates exhibiting deviant externalizing behaviors, as compared to normal behaviors, consume significantly more alcohol (Lang et al. 1989; Pelham et al. 1997). Alcoholics, as compared to non-alcoholics, are also known to increase alcohol intake in response to stressful situations (Miller et al. 1974), and in smokers, smoking increases after exposure to high anxiety as compared to low anxiety provoking situations (Pomerleau and Pomerleau 1987). These findings indicate that in social drinkers, smokers and alcoholics, stress exposure enhances drug self-administration.

In light of these findings, preclinical studies have examined specific aspects of the stress response that facilitate drug self-administration. Activation of brain stress circuits (i.e. CRF activation and subsequent increases in adrenocorticotrophic hormone (ACTH) and cortisol (glucocorticoids), catecholamines co-released with CRF and opioid release) is known to increase dopaminergic neurotransmission in mesolimbic regions (Thierry et al. 1976; Dunn 1988; Kalivas and Duffy 1989; Prasad et al. 1995; Piazza and Le Moal 1996). The mesocorticolimbic dopaminergic system is believed to make up the brain reward pathways, and increased dopaminergic transmission in these pathways is critical for the reinforcing properties of abusive drugs (Roberts et al. 1980; Taylor and Robbins 1984; Di Chiara and Imperato 1988; Koob and Le Moal 1997). Thus, stress co-activates brain stress circuits and the putative reward circuitry simultaneously, thereby providing a common neural substrate by which stress may enhance the drug taking experience and increase self-administration.

Stress-induced increases in cortisol levels have also been associated with enhanced self-administration of psycho-stimulants such as cocaine and amphetamines (Piazza et al. 1990; Goeders and Guerin 1996; Piazza and Le Moal 1996; Mantsch et al. 1998) and alcohol (Fahlke et al. 2000). Elimination of the cortisol response by adrenalectomy, by treatment with metyrapone, a cortisol synthesis blocker, or by ketoconazole, a glucocorti-

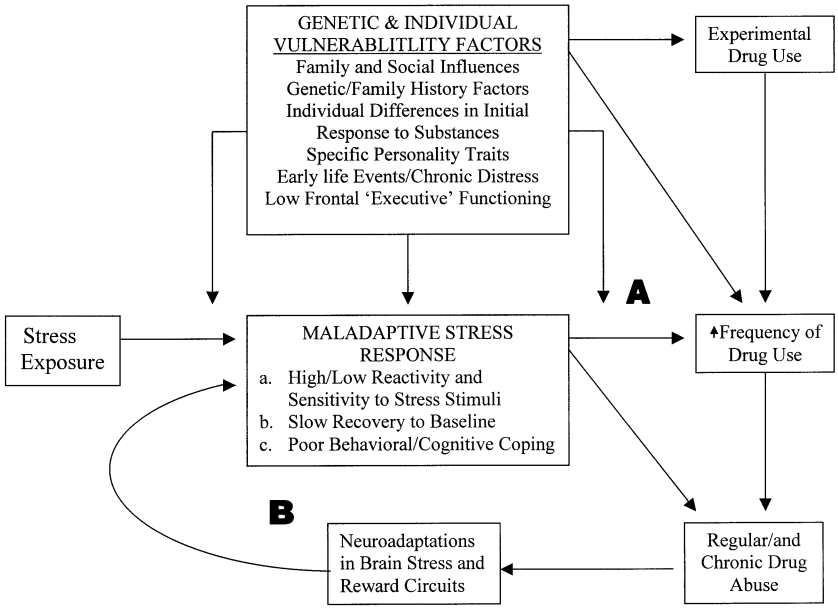

Fig. 1 A schematic diagram of how stress may increase the risk of drug abuse (**A**), and how alterations in brain stress and reward circuits due to chronic drug abuse results in maladaptive stress responses (**B**) is presented. **A** While experimental drug use is associated with family and social influences and individual differences in initial response to substances, a maladaptive stress response is shown to mediate the increased frequency of drug use to regular and abusive levels in vulnerable individuals who are exposed to stress. Specific aspects of the maladaptive stress response include high or low reactivity and sensitivity to stress stimuli, a slow recovery to baseline after stress exposure and poor behavioral and cognitive coping. Such maladaptive stress responding is postulated to express genetic and individual vulnerabilities with an increase in the frequency and regular use of abusive substances. **B** This aspect of the model is discussed in the second section of the paper and highlights neuroadaptations occurring in stress and reward circuits as a result of chronic drug abuse. These neuroadaptations are shown to promote maladaptive stress responding during stress, thereby resulting in increased drug use behavior in dependent individuals

coid receptor antagonist, decreases stress-induced reinstatement of stimulant self-administration (Goeders and Guerin 1996; Piazza and Le Moal 1996; Mantsch and Goeders 1999), and alcohol consumption in high alcohol-preferring rats (Fahlke et al. 1994, 2000). Thus, a hyper-responsive HPA axis leading to increased circulating cortisol and its stimulation of dopaminergic transmission in mesolimbic pathways appears to enhance drug self-administration (Piazza and Le Moal 1996; Goeders 1997). To the extent that depression and anxiety are chronic stress states associated with hypercortisolism (Plotsky et al. 1995; Arborelius et al. 1999), higher levels of circulating cortisol may mediate increased drug self-administration in individuals with such psychopathology who also have a vulnerability to drug abuse.

However, there is evidence to suggest that increased brain CRF and noradrenergic activation, and not elevated circulating cortisol levels, mediates stress-induced drug seeking and relapse (Shaham et al. 1997, 1998; Erb et al. 1998; Stewart 2000). A hypo-responsive HPA axis with low levels of cortisol has also been associated with enhanced drug self-administration (Deroche et al. 1997; Kosten et al. 2000). The latter findings are consistent with human studies showing lower cortisol response to stress in individuals with behavioral conduct problems, externalizing symptoms and antisocial personality (Virkkunen 1985; Tennes et al. 1986; King et al. 1990; Vanyukov et al. 1993; Moss et al. 1995). Lower stress-related cortisol levels are also associated with subsequent increased frequency of drug use in adolescent boys (Moss et al. 1999).

These somewhat disparate findings may be understood in terms of different HPA dysregulation profiles in subgroups with varying psychopathological phenotypes. Altered cortisol levels have been linked to many psychiatric syndromes, including affective disorders and post-traumatic stress disorder (PTSD), as well as in individuals with externalizing pathologies such as conduct problems, children with aggressivity and impulsivity, and in substance abusers with antisocial personality disorder. Clearly, both hyper-responsive and hypo-responsive cortisol levels are indicative of a dysregulated HPA response to stress (termed as maladaptive stress response in Fig. 1) and may be viewed as markers for increased vulnerability to drug self-administration. However, the specific mechanism that links stress to increased drug self-administration may involve brain CRF and NE circuits, which have not been specifically manipulated in humans.

Figure 1 presents a flowchart to illustrate the role of stress exposure in development of drug abuse (A), and the reciprocal relationship between chronic drug abuse, stress response and continued drug use (B, described in the next section). A number of vulnerability factors are known to increase the risk of drug abuse. These include genetic/family influences, parental psychopathology and drug abuse, early adverse life events, personality characteristics such as sensation seeking, chronic stress states,

decreased executive frontal functioning, and initial sensitivity to the rewarding effects of abusive drugs (Kandel et al. 1978; Tarter 1985; Monti et al. 1989; Sher et al. 1991; Kaplan and Johnson 1992; Wills et al. 1994; Gilbert 1995; Giancola et al. 1996; Schuckit 1996; Kandel et al. 1997; Gilbert et al. 1999). The role of these vulnerability factors in the development of drug abuse is highlighted in Fig. 1. Several of these vulnerability factors, particularly early life experiences, chronic affective distress, specific personality traits, decreased executive frontal functioning contribute to the individual differences in the stress response. The model in Fig. 1 suggests that stress exposure in the presence of these vulnerability factors results in a maladaptive stress response that increases the risk of drug abuse. The specific mechanism by which the "maladaptive stress responding" increases this risk appears to involve dysregulation in brain stress circuits, particularly the CRF and NE systems, and their interactions with the mesocorticolimbic reward pathways. This model would predict that enhancing "adaptive" stress responding would reduce stress vulnerability and the risk of drug abuse. Indeed, the stress-buffering effects of parental and social support on substance use in children have been documented (Wills et al. 1996). The positive effects of strategies such as enhancing adaptive coping skills and improved mood regulation in reducing the risk of drug abuse in vulnerable children has also been demonstrated (Catalano et al. 1990; Hawkins et al. 1992).

Research gaps and future directions

Despite some inconsistent findings, a growing body of research points to a positive association between stress and drug self-administration. Specific aspects of brain stress circuits are associated with stress-related enhancement of drug self-administration and drug seeking. However, human studies that examine the psychobiological aspects of the stress response and its association to drug taking in vulnerable individuals have been lacking. Several key questions remain unanswered. For example, does acute stress induction or chronic stress states such as anxiety and depression lead to increased drug use in vulnerable individuals? If so, how does acute or chronic stress differ in its effects on drug taking? Do anxiety and depressive states alter the reinforcing properties of addictive substances? In addition, research on the question of what specific psychological (e.g. appraisal and coping related factors) and neurobiological (e.g. increased levels of circulating cortisol) aspects of stress are associated with drug self-administration in humans is of significance. Studies examining whether drug ingestion significantly alters subjective and neurobiological aspects of the stress response, which may in turn be associated with an increased motivation to use and abuse substances are important in understanding the function and purpose of stress-related drug use.

There is also little information on whether prior exposure to licit and illicit drugs modifies the association between stress and drug self-administration. There are still unanswered questions on whether the association between stress and increased drug use varies by type and severity of stressful events. Information is lacking on the specific aspects of stress-related coping that are linked to abusing drugs, and those that are protective in the link between stress and drug abuse. Such information may have significant implications for the development of effective prevention and treatment strategies. Finally, research on the relationship between stress-related variables and vulnerability factors may be of significance in assessing the separate and combined contributions of stress exposure and individual vulnerability factors in the development of addiction.

Chronic drug abuse, stress reactivity and vulnerability to relapse

Most commonly abused drugs such as alcohol, nicotine, cocaine, amphetamines, opiates and marijuana that stimulate brain reward pathways (mesocorticolimbic dopaminergic systems) also activate brain stress systems (Cobb and Van Thiel 1982; Cinciripini et al. 1989; Robinson and Berridge 1993; Baumann et al. 1995; Heesch et al. 1995; Kreek and Koob 1998). As stated earlier, activation of brain stress circuits increases dopaminergic neurotransmission in brain reward pathways (Thierry et al. 1976; Dunn 1988; Kalivas and Duffy 1989; Prasad et al. 1995; Piazza and Le Moal 1996; Goeders 1997). Given that the neural circuitry in brain stress and reward pathways overlap considerably, this section examines whether neuroadaptations in these circuits increases the vulnerability to stress and relapse to drugs.

It is well known that chronic abuse of addictive substances results in hallmark symptoms of dependence, namely, compulsive drug use, tolerance and withdrawal. States of tolerance and withdrawal are associated with alterations in brain stress circuits, namely the CRF-HPA and noradrenergic systems. For example, during active drug use, alcoholics, chronic smokers and cocaine addicts show hypercortisolism (Wilkins et al. 1982; Wand and Dobs 1991; Mello and Mendelson 1997), whereas opiate addicts show reduced plasma levels of ACTH and cortisol (Ho et al. 1977; Facchinetti et al. 1985). Acute withdrawal states are associated with increases in CRF levels in CSF, plasma ACTH, cortisol, norepinephrine (NE) and epinephrine (EPI) levels (Adinoff et al. 1990, 1991; Vescovi et al. 1992; Ehrenreich et al. 1997; Tsuda et al. 1996; Koob and Le Moal 1997; Mello and Mendelson 1997; Kreek and Koob 1998). Early abstinence states are associated with a blunted ACTH response to hCRF in alcoholics, while hyper-responsivity of HPA hormones in response to metyrapone have been reported in opiate and cocaine addicts (Kreek 1997; Schluger et al. 1998). An abnormal noradrenergic response to yohimbine challenge in early abstinence from cocaine has also been observed (McDougle et al. 1994). Furthermore, neurochemical tolerance in the HPA re-

sponse to cocaine, alcohol, nicotine and opiates with chronic abuse has been reported (Eisenman et al. 1969; Delitala et al. 1983; Friedman et al. 1987; Mendelson et al. 1998). These findings suggest that active drug use, acute and protracted withdrawal and tolerance symptoms are associated with alterations in brain stress circuits.

Neuroadaptations in the mesolimbic dopaminergic system as a result of chronic drug abuse have also been documented. Both stress and psychostimulants increase dopaminergic transmission in the nucleus accumbens and other regions of the mesolimbic reward pathways (Thierry et al. 1976; Roberts et al. 1980; Taylor and Robbins 1984; Di Chiara and Imperato 1988; Dunn 1988; Kalivas and Duffy 1989; Piazza and Le Moal 1996). Reduced dopamine transmission in the nucleus accumbens during acute withdrawal from opiates, cocaine, alcohol, marijuana and nicotine has been reported (Acquas et al. 1991; Diana et al. 1993, 1998; Kuhar and Pilotte 1996; Hildebrand et al. 1998). On the other hand, "sensitization" or enhanced behavioral and neurochemical response to drugs and to stress has been noted subsequent to acute withdrawal in dependent animals. This process of sensitization has been associated with long-term changes in dopamine release and transduction in specific areas of the mesocorticolimbic dopamine system (Robinson and Berridge 1993, 2000; Nestler et al. 1993; White et al. 1995; Pierce and Kalivas 1997). An intriguing aspect of sensitization is that exposure to drugs and to stress in addicted animals produces a sensitized behavioral and pharmacological response to the drug (Robinson and Berridge 1993; Kalivas et al. 1998). For example, augmentation of dopamine transmission in the nucleus accumbens and reduced dopamine release in the prefrontal cortex has been reported with cocaine and with stress exposure, in animals pretreated with daily cocaine (Sorg and Kalivas 1993; Hooks et al. 1994; Sorg et al. 1997). These long-term changes in brain reward pathways as a result of chronic drug abuse have been hypothesized to play a key role in craving, drug-seeking behavior and relapse (Robinson and Berridge 1993, 2000; Kalivas et al. 1998). The section below on drug craving will examine this aspect in greater detail.

Brain imaging studies have reported short and long-term changes in the dopaminergic system in humans. Reduced glucose metabolism especially in frontal regions during both acute and protracted withdrawal (up to 3–4 months) from cocaine has been observed (Volkow et al. 1990, 1991, 1992). Alcoholics and cocaine abusers show a significant reduction in dopamine D_2 receptors as compared to healthy controls, particularly in frontal-striatal regions (Volkow et al. 1993, 1996, 1997). Some evidence also suggests increased density of dopamine transporter binding sites in the striatum with chronic cocaine abuse (Malison et al. 1998; Staley et al. 1994; Little et al. 1999), a finding that has been replicated in rhesus monkeys chronically exposed to cocaine (Letchworth et al. 2001). Thus, these data point to alterations in frontal and striatal regions of the dopaminergic pathways, that exist past acute withdrawal, and may be associated with cognitive, affective and behavioral symptoms during protracted withdrawal and relapse (Porrino and Lyons 2000; Volkow and Fowler 2000).

Psychobiological changes during early abstinence from drugs

Increases in irritability, anxiety, emotional distress, sleep problems, dysphoria, aggressive behaviors and drug craving are common during early abstinence from alcohol, cocaine, opiates, nicotine and marijuana (1992; American Psychiatric Association 1994; Kouri et al. 1999). Recent conceptualizations of drug dependence emphasize the establishment of a "negative affect" or psychologically distressed state during abstinence in addicts, potentially associated with neuroadaptive changes in brain stress and reward circuits (Koob and Le Moal 1997; Kreek and Koob 1998; Volkow and Fowler 2000). Severity of the above abstinence symptoms are known to predict treatment outcome and relapse among smokers, cocaine addicts, heroin dependent individuals and alcoholics (McLellan et al. 1983; Carroll et al. 1993; Doherty et al. 1995; Tennant et al. 1991; Mulvaney et al. 1999). In general, findings indicate that the greater the dependence and abstinence severity, greater the susceptibility to relapse and poor treatment outcome. However, few studies have systematically examined frequency and severity of abstinence symptoms and specific neurobiological changes in the above-mentioned systems. Recent exceptions include Elman et al.'s (1999) findings showing a positive association between increased ACTH and cortisol levels and depressive symptoms during cocaine crash in cocaine addicts, and Frederick et al.'s (1998) findings on the association between cortisol levels and nicotine withdrawal-related distress.

While some evidence suggests that alcoholics and opiate addicts report significantly greater stressful life events than healthy controls (Kosten et al. 1983, 1986), few studies have examined how drug dependent individuals respond to stress and whether drug abuse results in an altered stress response. Studies with smokers indicate a blunted cortisol response in response to the stress of public speaking and mental arithmetic as compared to non-smokers, but such blunting is not present in response to exercise or hCRF challenge (Kirschbaum et al. 1993; Roy et al. 1994). Similarly, a blunted cortisol response to public speaking stress has also been reported in alcoholics and those addicted to both cocaine and alcohol, as compared to healthy controls (Errico et al. 1993; Lovallo et al. 2000). Kirschbaum et al.'s findings indicating intact pituitary-adrenal response to exercise and hCRF challenge but not with psychological stress suggests that supra-pituitary stress circuits may be responsible for the blunted stress-related cortisol changes. CRF-containing neurons from the basal forebrain and the amygdala are known to project into the para-ventricular nucleus (PVN) (Gallagher et al. 1987; Petrusz and Merchenthaler 1992) and amygdaloid lesions are known

to result in stress-related changes in HPA activation (Blanchard and Blanchard 1972). Because the basal forebrain and amygdala are also key areas in the mesolimbic circuitry, neuroadaptations resulting from chronic drug abuse in these regions could result in altered stress-induced cortisol responsiveness in addicts. However, altered perception and appraisal of standard laboratory stressors in these samples of addicts cannot be ruled out as an explanation for the blunted cortisol response as well. Clearly, evaluation of the stress response with different types of stress at varying intensities and periods of exposure, especially as they pertain to drug craving and relapse needs specific attention in future studies.

Effects of stress on drug craving

Drug craving or "wanting" for drug is a prominent feature in clinical conceptualizations of addiction, and one that may be important in maintenance of addictive behaviors (Dackis and Gold 1985; Tiffany 1990). Robinson and Berridge (1993, 2000) postulated that sensitization processes resulting from neuroadaptations in brain reward pathways due to chronic drug abuse underlie the excessive "wanting" or drug seeking behavior in addicted animals. They suggest that these neuroadaptations lead to an increase in the incentive salience of drugs such that exposure to drugs and drug-associated stimuli results in an excessive "wanting" or craving that may increase the susceptibility to relapse. To the extent that subjective craving in addicts and drug-seeking behavior in animals represents a measure of "wanting", recent research has focused on examining neural substrates underlying these states.

Environmental stimuli previously associated with drug use, or internal cues such as stress responses, negative affect and withdrawal-related states associated with drug abuse, can function as conditioned stimuli capable of eliciting craving (Stewart et al. 1984; Rohsenow et al. 1991; Childress et al. 1993). Foltin and Haney (2000) demonstrated that classical conditioning is one mechanism by which neutral environmental cues paired with cocaine smoking in cocaine abusers acquires emergent stimulus effects in contrast to stimuli paired with placebo cocaine. These findings validate a host of human laboratory studies documenting that exposure to external drug-related cues, such as drug paraphernalia or in vivo exposure to drug itself, results in increased drug craving and physiological reactivity (Carter and Tiffany 1999). Exposure to negative affect, stress or withdrawal-related distress has also been associated with increases in drug craving and physiological reactivity (Childress et al. 1994; Cooney et al. 1997; Sinha et al. 1999a, 2000a). Although external cues produce craving and reactivity in the laboratory, presence of negative affect, stress, and abstinence symptomatology have been predictive of relapse (Killen et al. 1997; Doherty et al. 1996; Cooney et al. 1997). Preclinical studies have also found that stress exposure, in addition to drug itself, is a potent stimulus in reinstating drug-seeking behavior in dependent animals (Stewart 2000).

We examined drug craving and reactivity in cocaine abusers who were exposed to previous stressful and non-stressful drug cue situations, using personalized imagery procedures as the induction method (Miller et al. 1987; McNeil et al. 1993; Sinha et al. 1992; Sinha and Parsons 1996; Sinha 2001). Our initial findings indicated that stress imagery elicited multiple emotions of fear, sadness and anger in cocaine dependent individuals as compared to the stress of public speaking, which elicited increases in fear but no anger and sadness. In addition, stress imagery produced significant increases in cocaine craving while public speaking did not (Sinha et al. 1999a). Significant increases in heart rate, salivary cortisol levels, drug craving and subjective anxiety were also observed with exposure to stress and non-stress drug cues as compared to neutral-relaxing cues (Sinha et al. 2000a). Given that drug use often occurs in the context of stressful events in addicts, and the reactivity associated with the stress response may resemble a withdrawal/abstinence-like internal state, previous stress situations may be considered drug-associated conditioned cues, and the findings may be explained in terms of conditioned drug effects. On the other hand, the data also suggest that the stress imagery exposure produced a more intense emotional experience as compared to standard public speaking stress, and increased reactivity may have been a result of the intensity of the emotional experience. Indeed, intensity of conditioned stimuli is important for the activation of amygdala circuits in conditioned emotional responding (LeDoux 2000).

Preclinical studies examining neural substrates that mediate conditioned drug effects have shown that nucleus accumbens and the amygdala, key structures in the mesolimbic dopamine pathways and in brain stress circuits, are involved in both conditioned reward and punishment (Taylor and Robbins 1984; Killcross et al. 1997). For example, increased drug seeking behavior in response to presentation of drug cues results in increased dopamine levels in the nucleus accumbens (Katner et al. 1996; Parkinson et al. 1999, 2000; Hutcheson et al. 2000; Weiss et al. 2000). Furthermore, stress-related stimuli such as foot-shock, restraint stress and anxiogenic drugs increase nucleus accumbens dopamine release (Imperato et al. 1992; McCullough and Salamone 1992; Kalivas and Duffy 1995). Thus, it has been suggested that dopamine release in the nucleus accumbens may mediate the conditioned reinforcement effects of both appetitive and aversive stimuli in their ability to produce drug seeking behavior (Salamone et al. 1997).

Other evidence demonstrates the involvement of the amygdala in conditioned reinforcement effects of drug associated stimuli. Presentation of cocaine-related environmental cues increase expression of c-fos in the amygdala (Brown et al. 1992; Neiswander et al. 2000), while amygdala lesions disrupt conditioned place preference for cocaine (Brown and Fibiger 1993). Lesions of the basolateral nucleus of the amygdala have been found to im-

pair cue-mediated acquisition and reinstatement of drug seeking in rats (Whitelaw et al. 1996; Meil and See 1997). Most recently, See et al. (2001) reported that the conditioned reinstatement of drug seeking is dependent on dopamine D_1 receptors in the basolateral amygdala. Brain imaging studies with drug abusers have shown that exposure to drug cues known to increase craving resulted in activation of the amygdala and regions of the frontal cortex (Grant et al. 1996; Childress et al. 1999; Kilts et al. 2001). Amygdala nuclei are also essential in the acquisition of Pavlovian fear conditioning (LeDoux 2000), and stress exposure is known to increase dopamine release in the basolateral amygdala (Inglis and Moghaddam 1999). Pilot findings from a functional brain imaging study examining brain activation during stress and neutral imagery revealed increased medial temporal lobe (amygdala) and decreased frontal activation during stress imagery in cocaine dependent individuals as compared to controls (Sinha et al. 2000b). These data suggest that the amygdala which is anatomically linked to both the regions of the prefrontal cortex and the nucleus accumbens, and plays a key role in conditioned emotional responding and affective learning (Gaffan et al. 1993; Dias et al. 1996; LeDoux 2000), may be involved in mediating the effects of stress and drug cues on craving and drug-seeking behavior.

Stress-induced relapse

Using a unique animal model of relapse, several studies have shown that brief foot-shock stress reinstates drug-seeking behavior in drug-free, dependent rats (Shaham and Stewart 1995; Erb et al. 1996; Ahmed and Koob 1997; Le et al. 1998; Buczek et al. 1999; Mantsch and Goeders 1999). This stress-induced reinstatement of drug seeking can be blocked by CRF antagonists and is not affected by cortisol loss or suppression (Erb et al. 1998; Shaham et al. 1998). More recently, alpha$_2$-adrenergic agonists, such as clonidine, which inhibit NE activity centrally, have been found to reduce stress-induced relapse to drug seeking (Erb et al. 2000; Shaham et al. 2000). Together these data suggest that brain CRF and NE circuits are directly involved in stress-induced drug seeking in dependent animals. However, human studies that manipulate these systems to assess stress-induced craving or relapse in addicts have been lacking thus far.

Clinical samples of drug abusers and alcoholics often cite stress and negative affect as reasons for relapse to drug use (Ludwig et al. 1974; Littman et al. 1977; Marlatt and Gordon 1980, 1985; Bradley et al. 1989; Wallace 1989; McKay et al. 1995). Coping with stress is positively associated with relapse in people who are quitting smoking (Shiffman 1982; Brownell et al. 1986; Wevers 1988; Cohen and Lichtenstein 1990), in recovering alcoholics (Brown et al. 1990; Hodgkins et al. 1995), heroin addicts (Marlatt and Gordon 1980; Brewer et al. 1998) and in cocaine abusers (Sinha et al. 1999b). However, the mere occurrence of stressful life events is not predictive of relapse (Hall et al. 1990, 1991; Miller et al. 1996). Instead, patients resources for coping with stress, e.g. positive thinking and avoidance coping, have been predictive of relapse (Littman et al. 1984; Miller et al. 1996). Adolescent and adult drug abusers are known to predominantly use avoidant coping strategies (Cooper et al. 1988; Madden et al. 1995; Wills et al. 1995; Belding et al. 1996; Laurent et al. 1997). The notion that substance abusers have poor coping skills, and teaching addicts adaptive coping skills to deal with drug cues, craving and stress has led to the development and validation of coping skills-based cognitive behavioral interventions for addictive behaviors (Marlatt and Gordon 1985; Monti et al. 1989).

While there is significant support for coping skills and cognitive behavioral treatment in the addictions field (Hall et al. 1984; Monti et al. 1989; Carroll et al. 1994), large multi-site trials of alcoholism and cocaine dependence have not found it to be superior to standard drug counseling approaches (Project Match Collaborative Study Group 1997; Crits-Christoph et al. 1999). Furthermore, the hypothesis that coping skills and cognitive behavioral treatments would be particularly advantageous for substance abusers with greater psychiatric or abstinence severity, presumably those with greater deficits in coping, has not been supported in these trials (Project Match Collaborative Study Group 1997; Crits-Christoph et al. 1999). Contrary to expectations, smokers high in pretreatment distress and craving show better outcomes with social support treatments rather than coping skills interventions as compared to smokers with low distress and craving levels (Zelman et al. 1992; Hall et al. 1996). Thus, the above findings question the coping hypothesis and suggest that poor coping alone may not adequately explain relapse. Clinically, it is striking that substance abusers do not have trouble learning coping skills in treatment, but are unable to use them effectively in real-life situations. This raises the question as to whether stress exposure results in a dysregulated stress system that may in turn reduce access to adaptive coping. In other words, does chronic drug abuse alter the ability to adapt/cope with stress and increase the susceptibility to stress-induced relapse?

An earlier body of social-cognitive research demonstrated that stress exposure interferes with cognitive performance, particularly in the ability to sustain attention and in inhibition of prepotent responding (Glass et al. 1969, 1971; Hockey 1970; Cohen 1980). Stress and negative affect states are known to increase impulsivity and decrease self-control (see Muraven and Baumeister 2000). Lesions of the prefrontal cortex result in impaired sustained attention and response inhibition (Perret 1974; Wilkins et al. 1987). Arnsten and Goldman-Rakic (1998) have shown that uncontrollable noise stress impairs prefrontal cognitive function in monkeys, which is modulated by prefrontal dopaminergic pathways. Chronic drug abuse, particularly of stimulants results in neuroadaptations in dopaminergic pathways involving the nucleus accumbens, caudate-putamen and prefrontal regions

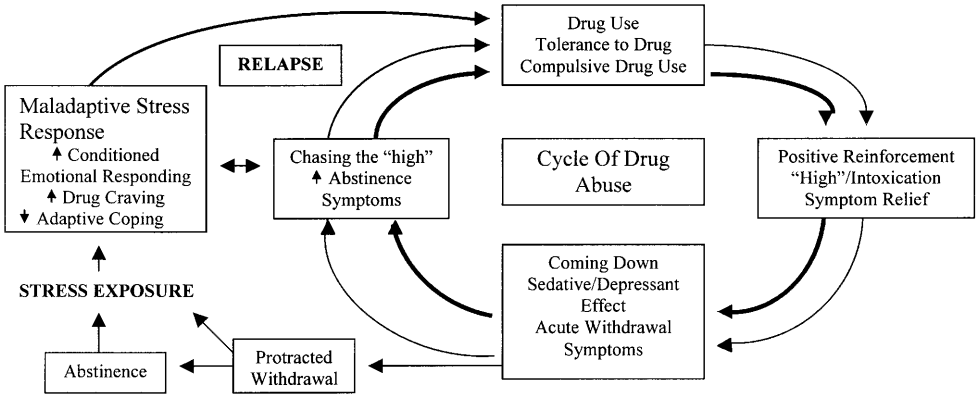

Fig. 2 The cycle of drug abuse illustrates how the transition to drug dependence occurs with drug use behaviors become increasingly under the control of conditioned drug effects. In this cycle, regular drug use leads to an initial positive state ("high"/euphoria) followed by sedative/depressant effects, which in turn results in drug seeking and continued drug use. With repeated chronic use, onset of tolerance and withdrawal symptoms emerge and increased drug use and loss of control over drug taking is observed. The occurrence of stressful situations during short and long-term abstinence is known to increase the risk of relapse. Based on evidence cited in the text, this model proposes that neuroadaptations in brain stress and reward circuits results in maladaptive stress responding in addicts, with increased conditioned emotional responding and drug craving, and decrements in adaptive coping, aspects that contribute to an increased risk of relapse. The possibility that the maladaptive stress responding state may be comparable to the drug abstinent state is also shown, with both states resulting in an increased likelihood of drug use

(Kalivas et al. 1998). Such neuroadaptations include increased dopamine transmission in the nucleus accumbens and reduction in dopamine release in the prefrontal cortex with cocaine or with stress in dependent animals (Sorg and Kalivas 1993; Kalivas et al. 1998; Prasad et al. 1999). Thus, it is possible that such neuroadaptations may disrupt functioning of cortico-striatal loops that serve cognitive and affective information processing during stress (Alexander et al. 1986; Robbins and Everitt 1996; Jentsch and Taylor 1999). To the extent that prefrontal circuits are involved in producing adaptive coping, such as problem solving, exercising restraint or response inhibition and behavioral flexibility during stress, the above findings suggest that stress reduces adaptive coping. Some earlier research has shown that stress prevents the acquisition or execution of coping responses in affectively vulnerable individuals (Rosen et al. 1982; Faust and Melamed 1984). Interestingly, a study in chronic smokers completing a coping skills intervention found that exposure to negative affect-related drug cue situations produced significantly lower confidence in the ability to resist smoking, less effective coping responses and lower likelihood of engaging in adaptive coping responses (Drobes et al. 1994). Whether stress-induced decrements in frontal cognitive function is a pre-existing condition in addicts, or a result of neuroadaptations in the above pathways due to chronic drug abuse has not been examined thus far. Systematic investigation of the effects of stress on production of adaptive coping may be an important component in understanding the mechanisms underlying relapse.

Figure 2 presents a model wherein the transition to drug dependence occurs when drug use behaviors become increasingly under the control of conditioned drug effects and dependence symptoms. Alterations in brain stress circuits particularly during early and short-term abstinence results in maladaptive stress responding with stress exposure. The model proposes that the maladaptive stress response, with enhanced conditioned emotional responding and drug craving as well as decreased adaptive coping, increases the risk of relapse. Thus, neuroadaptations in neural circuits that underlie affective, cognitive and behavioral responding during stress are identified as key mediators of relapse risk. Future research examining mechanisms underlying the above linkages will likely explain how stress increases relapse risk.

Research gaps and future directions

The second section of this paper examined the neural changes that occur in brain stress and reward circuits with chronic drug abuse, and explored whether these changes increase the vulnerability to stress and stress-induced relapse. Research has documented alterations in brain stress and reward circuits as a result of drug abuse, and preclinical research has shown that such changes may increase drug-seeking behavior. However, human studies examining neurobiological changes associated with stress during abstinence and its association to drug seeking and relapse has lagged behind. Several questions remain unanswered. For example, what aspects of brain stress and reward circuits are associated with abstinence symptoms? Do abstinence symptoms alter the ability to respond and cope with stress in addicts? Are there specific neural systems that are associated with adaptation and others associated with sensitization processes? If sensitization is one mechanism that increases drug seeking, there is a need to identify specific behavioral and neural measures that may accurately detect such an association in humans. What specific neurobiological changes occur with stress exposure in dependent individuals

and how do these changes modify their ability to perceive, respond and cope with stress? Which if any of such changes are associated with drug-seeking behavior? Does stress and/or abstinence symptoms impair production of adaptive coping in addicts? If so, what aspects of coping are modified in addicts? Systematic research on these questions will lead to a greater understanding of how stress is associated with relapse. Furthermore, such research may be significant in developing new treatment targets to reduce relapse both in the area of medication development as well as in developing behavioral treatments that specifically target the effects of stress on continued drug use and relapse in addicts.

Conclusion

This paper has examined how stress increases the propensity to self-administer drugs. Possible mechanisms that have been put forth to explain how stress may increase the vulnerability to chronic drug use were considered. In the larger context of genetic and vulnerability factors that have been found to increase the propensity to abuse substances, it is proposed that maladaptive stress responses mediate the expression of such vulnerabilities with stress exposure. The second part of the paper highlighted that the transition to addiction is accompanied by neuroadaptations in brain stress and reward circuits. These alterations produce biological, cognitive and behavioral changes that may last for varying lengths of time and contribute to perpetuation of addictive behaviors. Thus, the notion that such changes alter an addict's ability to cope with stress thereby increasing the risk of relapse is explored. While it is often assumed that addicts are predisposed to poor coping, the effects of drug abuse on stress response and coping has not been systematically examined. The question of whether stress exposure results in decrements in adaptive coping thereby increasing the risk of relapse is raised. Some areas of future research are identified to promote a better understanding of the mechanisms underlying the association between stress and drug abuse.

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