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Stress, alcohol and drug interaction: an update of human research

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Abstract

A challenging question that continues unanswered in the field of addiction is why some individuals are more vulnerable to substance use disorders than others. Numerous risk factors for alcohol and other drugs of abuse, including exposure to various forms of stress, have been identified in clinical studies. However, the neurobiological mechanisms that underlie this relationship remain unclear. Critical neurotransmitters, hormones and neurobiological sites have been recognized, which may provide the substrates that convey individual differences in vulnerability to addiction. With the advent of more sophisticated measures of brain function in humans, such as functional imaging technology, the mechanisms and neural pathways involved in the interactions between drugs of abuse, the mesocorticolimbic dopamine system and stress systems are beginning to be characterized.

This review provides a neuroadaptive perspective regarding the role of the hormonal and brain stress systems in drug addiction with a focus on the changes that occur during the transition from occasional drug use to drug dependence. We also review factors that contribute to different levels of hormonal/brain stress activation, which has implications for understanding individual vulnerability to drug dependence. Ultimately, these efforts may improve our chances of designing treatment strategies that target addiction at the core of the disorder.

Keywords

Addiction; alcoholism; dopamine; glucocorticoids; reward system; stress

INTRODUCTION

Addiction to alcohol and other drugs of abuse is a complex phenomenon influenced by genetic and environmental determinants (Kendler 2001). There is growing preclinical and clinical literature describing that various forms of stress are involved in escalating alcohol and drug use during the transition from episodic drug exposure to the addicted state. Preclinical studies have shown that stress and glucocorticoids increase drug use during the acquisition phase of self-administration (Goeders & Guerin 1996b; Lynch *et al.* 1999; Goeders 2002; Vengeliene *et al.* 2003; Koob & Kreek 2007). In humans, various forms of stress may precede the development of substance use disorders (Richman, Flaherty & Rospenda 1996; Jose *et al.* 2000; Rospenda *et al.* 2000).

Although the processes underlying this relationship remain inconclusive, preclinical evidence suggests that early in the development of drug use, both stress- and drug-induced activation of the hypothalamic–pituitary–adrenal (HPA) axis allows glucocorticoids to sensitize the reward

pathways (Rouge-Pont *et al.* 1995, 1998; Tidey & Miczek 1997; Piazza & Le Moal 1998). Therefore, it is possible that individual differences in HPA axis activity—with high and low cortisol states—underlie some of the individual mechanistic differences in vulnerability to addiction.

As the individual transitions from occasional drug use to drug dependence, the detrimental effects of stress and glucocorticoids ultimately lead to brain reward dysfunction and drug use escalation. During the addicted state, high levels of glucocorticoids and stress peptides associated with addiction create an internal form of stress characterized by anxiety-like behaviors (Koob & Kreek 2007). This negative affect state further escalates drug consumption. In preclinical models of reinstatement, various forms of stress precipitate relapse to drug use (Shaham & Stewart 1995; Erb, Shaham & Stewart 1996; Ahmed & Koob 1997; Breese *et al.* 2005). Also, in abstinent alcoholics and drug-dependent persons, exposure to stress increases drug craving (Sinha *et al.* 2003; Fox *et al.* 2007) and precipitates relapse (Noone, Dua & Markham 1999; Breese *et al.* 2005; Sinha *et al.* 2006).

The purpose of this paper is to describe the literature supporting the relationship between various forms of stress and drug use disorders as it fits into this model of transition from reward sensitization (Robinson & Berridge 1993, 2003) to hedonic allostasis and negative affect development (Koob & Le Moal 1997; Koob *et al.* 2004; Koob & Kreek 2007).

PHYSIOLOGICAL STRESS RESPONSE SYSTEM AND ALLOSTATIC LOAD MODEL

Stress is generally defined as any stimulus that disrupts physiological homeostasis (Miller & O'Callaghan 2002). To return to homeostasis, mammals respond by activating adaptive mechanisms that include at least three components. First, activation of the HPA axis is initiated by the release of corticotrophin-releasing factor (CRF) from paraventricular neurons (PVN) within the hypothalamus. CRF subsequently stimulates the synthesis and release of adrenocorticotropin (ACTH) by the anterior pituitary, which in turn stimulates the synthesis and release of glucocorticoids (specifically corticosterone in rodents and cortisol in humans) by the adrenal cortex. Second, stress activates the sympathetic adrenomedullary system resulting in the release of norepinephrine and epinephrine (Sterling & Eyer 1988). Third, stress increases the expression of CRF in extra-hypothalamic sites, including the amygdala, which plays a crucial role in inducing anxiety and other stress behaviors. The hypothalamus and the limbic system, particularly the hippocampus and amygdala, are intimately involved in the stress response (Cook 2002; McBride 2002; Koob 2003; Pandey 2003; Robison *et al.* 2004).

Homeostatic regulation reflects stability within a narrow range, and deviations from homeostasis trigger a restorative response to correct the changes. With repeated stress, the organism may not be able to return to normal homeostasis but instead adapts through a process known as allostasis (Sterling & Eyer 1988). An allostatic state can be defined as a state of chronic deviation of the regulatory systems from their normal (homeostatic) state of operation with establishment of a new set point. For the stress response this can mean the acquisition of higher diurnal cortisol levels. From the drug addiction perspective, allostasis is the process of maintaining apparent reward function stability through changes in reward and stress system neurocircuitry that are maladaptive.

When burdened by cumulative stress, the allostatic load (i.e. hypothetical measure of cumulative stress) of an organism increases, resulting in wear and tear on the organism from excessive exposure to the catabolic properties of glucocorticoids, stress peptides and pro-inflammatory cytokines (McEwen & Stellar 1993). For example, chronic HPA axis dysregulation is associated with the development of mood and anxiety disorders, such as

depression (Sapolsky 2000; Gold & Chrousos 2002; Sherwood Brown, Varghese & McEwen 2004). Moreover, excess cortisol exposure is related to a variety of medical conditions, including hypertension, atherosclerosis, obesity, insulin resistance, dyslipidemia, bone demineralization and impaired immunity (McEwen 1998; Tsigos & Chrousos 2002). In addition, the allostatic load is a persistent state of stress, which allows environmental events that would normally elicit drug-seeking behavior to have even more impact (Koob & Kreek 2007).

Importantly, diverse stress definitions have been proposed in the past without final agreement (Levine & Ursin 1991). Therefore, it remains a non-specific term and must always be qualified. While all forms of stress alter homeostasis in some manner, various forms of stress have different effects on physiological processes. Thus, it is crucial to always specify the type and duration of stress that an organism is subjected to. Moreover, physiological and behavioral responses to various forms of stress vary between individuals, and it has been shown that individual variation in responses to stress are influenced by the interaction of environmental and genetic factors (Federenko *et al.* 2004). Indeed, prenatal and early life stress can have effects on the HPA axis that predispose individuals to illness in later life (Meaney, Brake & Gratton 2002; Maccari *et al.* 2003). This programming effect is in part influenced by epigenetic mechanisms that can play a role in the development of substance use disorders (Weaver, Cervoni & Champagne 2004).

THEORIES AND PHASES OF ADDICTION

A variety of theories have been proposed to explain mechanisms involved in the addiction process. To conceptualize how various forms of stress play a role in the development of drug dependence, we have combined two models of drug addiction: incentive sensitization and hedonic allostasis (Vanderschuren & Everitt 2005). In the incentive sensitization model (Robinson & Berridge 1993, 2003) an exaggerated motivation for drugs of abuse results when factors associated with casual drug use sensitize the mesolimbic reward system. This neural system plays a prominent role in attributing incentive salience to stimuli, i.e. the way in which stimuli are perceived as attractive, and causes compulsive motivation or 'wanting' to take addictive drugs. This theory helps explain how initial experimentation with drugs of abuse in an occasional user can escalate to repeated drug administration as sensitization of the reward system increases salience of the drug. The motivational force at this stage is primarily hedonic pleasure. With chronic use, motivation for drug seeking can change as a result of a process referred to as hedonic allostasis. In the hedonic allostasis model (Koob & Le Moal 1997; Koob *et al.* 2004), chronic drug exposure results in downregulation of positive reward circuits and the subsequent recruitment of stress factors that create negative affect characterized by withdrawal symptoms, dysphoria and anxiety. Replacing hedonic pleasure, negative affect now becomes the dominant force driving compulsive drug use. Various forms of stress can impact this transition from incentive sensitization to hedonic allostasis.

Drug addiction has been conceptualized as a disorder that progresses through three phases: (1) preoccupation/anticipation; (2) binge/intoxication; and (3) withdrawal/negative affect (Koob & Le Moal 1997). First, the preoccupation phase is characterized by exaggerated motivation for drugs associated with a sensitized mesolimbic dopamine system. Thus, incentive sensitization may play an important role in the early phase of addiction (Robinson & Berridge 1993, 2003). In animal models used to study the development of drug dependence, this phase is referred to as the acquisition phase. Second, during the binge and intoxication phase, there is a downregulation of positive reward pathways (e.g. an increase in brain reward thresholds) (Koob & Kreek 2007). This is equivalent to the maintenance phase in animal models. When the drug user transitions to drug addict, a third phase emerges—withdrawal/negative affect—dominated by negative affect, further escalating craving and use of the addictive substance.

The equivalent phase in animal models can be created by drug withdrawal followed by drug deprivation and reinstatement. Dysfunction of brain reward systems after escalated drug intake supports a hedonic allostasis view of addiction, suggesting it may come into play during later stages of the addiction process (Koob & Kreek 2007).

DRUG USE ASSOCIATED WITH INCENTIVE SENSITIZATION

The mesocorticolimbic dopamine system and reward

The mesocorticolimbic dopaminergic system functions as a reward and reinforcement pathway providing salience to internal and external stimuli (Berridge 2007). The major components of this system are the ventral tegmental area (VTA) and the basal forebrain, composed of the nucleus accumbens (NAc), amygdala, olfactory tubercle, and frontal and limbic cortices. The integrity of the mesocorticolimbic dopaminergic system is crucial to maintaining a healthy response to stimuli and governs our attention and intentions related to a particular stimulus. The cell bodies of the dopaminergic neurons are located in the VTA, which extend axonal projections to areas in the basal forebrain, including the NAc and the prefrontal cortex. In addition, there are many neural systems that interact with the VTA and the basal fore-brain, including those involving γ -aminobutyric acid (GABA), endogenous opioids, glutamate and serotonin (Koob 1992; Leshner & Koob 1999). The NAc appears to be the primary zone assigning importance to the drug exposure experience. Two regions are recognized in the NAc: the core and the shell. The shell is strongly connected to areas of the brain associated with the VTA and the lateral hypothalamus.

Alcohol and other drugs of abuse have both positive and negative reinforcing properties. The positive reinforcing properties of drugs of abuse are linked to the hedonic aspects of drug intoxication. Considerable evidence suggests that these positive reinforcing effects act through signal transduction systems involving mesocorticolimbic dopaminergic neurons. In rodents, the rewarding effects of most drugs of abuse have been associated with increased synaptic dopamine (DA) in the NAc (Di Chiara & Imperato 1988; Tupala & Tiihonen 2004). There is evidence that this effect also occurs in humans. For instance, during casual use, alcohol, psychostimulants and opioids all increase synaptic DA accumulation as measured by positron emission tomography (PET) imaging within this important brain region and thereby provide salience to their signal (Volkow *et al.* 1999; Drevets *et al.* 2001; Leyton *et al.* 2002; Martinez *et al.* 2003; Oswald *et al.* 2005; Yoder, Kareken & Seyoum 2005). Different drugs of abuse may interact with the mesolimbic dopaminergic system in different ways. For example, stimulants, such as amphetamine and cocaine, activate DA activity in the dopaminergic synapse (Wise 1984). Opiates have been shown to activate mu- and possibly delta-receptors in the VTA and NAc and counteract the inhibition by GABAergic neurons on the firing of dopaminergic neurons (Johnson & North 1992; Wise 1998). Ethanol increases DA neuron activity by direct excitation of dopaminergic VTA neurons (Brodie, Pesold & Appel 1999; Appel *et al.* 2003), and it also appears to facilitate DA release by increasing opioidergic activity, therefore disinhibiting dopaminergic neurons (Benjamin, Grant & Pohorecky 1993; Gonzales & Weiss 1998; Cowen & Lawrence 1999).

Preclinical studies of the interaction of stress, glucocorticoids and mesocorticolimbic system function

Accumulating literature indicates the close interactions between HPA axis activity and the mesocorticolimbic dopaminergic system. Preclinical studies have shown that glucocorticoids alter mesolimbic dopamine signaling, thus amplifying the positive reinforcing effects of alcohol and other drugs of abuse. This sensitization of the reward system would render the subject more responsive to drugs of abuse and, consequently, more vulnerable to the development of addiction (Marinelli & Piazza 2002).

More direct evidence of the interaction between glucocorticoids and dopamine comes from studies showing that suppression of glucocorticoids by adrenalectomy reduces extracellular concentration of dopamine in the NAc, both in basal conditions and in response to psychostimulants or stress (Piazza *et al.* 1996a; Barrot *et al.* 2000). Interestingly, reduction in serum corticosterone following adrenalectomy selectively decreases DA levels in the shell of the NAc, without modifying those observed in the core of the NAc (Barrot *et al.* 2000). The decrease in dopamine observed in the shell is also translated postsynaptically, as evidenced by a decrease in Fos expression, an index of cellular activation that depends on dopamine D1 receptor activation (Barrot *et al.* 2000). Studies using glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) antagonists have shown that the effects of corticosterone on DA concentrations in the shell of the NAc involve activation of the GR, but not the MR (Marinelli & Piazza 2002).

Several studies have demonstrated that stress-induced corticosterone secretion also increases DA levels in the NAc. For example, using microdialysis techniques, investigators have shown that different stress paradigms increase mesocorticolimbic dopaminergic activity (Rouge-Pont *et al.* 1995, 1998; Tidey & Miczek 1997; Piazza & Le Moal 1998). In addition, blockade of stress-induced corticosterone secretion by either adrenalectomy or metyrapone treatment prevents the increase in NAc DA induced by stress (Rouge-Pont *et al.* 1995, 1998). However, some studies do not support these findings (Imperato *et al.* 1991; Reid *et al.* 1998), and found that adrenalectomy does not prevent the increase in NAc DA induced by repeated stress (Imperato *et al.* 1991).

Studies on DA levels following administration of corticosterone are controversial. Some investigators reported that acute administration of stress-like levels of corticosterone increases NAc dopamine in conditions in which the dopamine system is activated, such as during the dark phase, food intake or in animals with higher dopamine tone (Piazza *et al.* 1996b). However, another study showed that chronic hypercortisolism inhibits DA synthesis and turnover in the NAc (Pacak *et al.* 2002), suggesting a biphasic effect of glucocorticoids on mesolimbic dopamine. Thus, it appears that the presence of a normal range in glucocorticoid concentration is necessary for optimal mesolimbic dopaminergic transmission.

Interestingly, findings suggest that CRF and glucocorticoids enhance glutamatergic activity in the VTA, where cell bodies whose axons extend to the NAc are located, resulting in an increase in DA release in the NAc. Specifically, it has been shown that stress and corticosterone, as well as cocaine, amphetamine, morphine, nicotine and ethanol, sensitize VTA dopamine neurons to glutamatergic input (Overton *et al.* 1996; Saal *et al.* 2003). Such sensitization can also be induced by local application of CRF itself (Ungless *et al.* 2003). In addition, it has been shown that forced swim stress releases CRF in the VTA, which induces glutamate release, and activates dopaminergic neurons (Wang *et al.* 2005). The relationship between glutamatergic activity and mesolimbic DA release has also been observed in humans (Smith *et al.* 1998).

Preclinical studies of stress, glucocorticoids and drug self-administration

Psychostimulants in rodents—In animal models, during the acquisition of drug-taking behavior, an animal comes into contact with a drug and its rewarding properties for the first time (Goeders 2002). Various stressors, which increase serum glucocorticoid levels by activation of the HPA axis, have been shown to alter the acquisition of drug taking in rats. For example, the acquisition of psychostimulants (e.g. cocaine and amphetamine) and opiate self-administration is enhanced in rats exposed to tail pinch (Piazza *et al.* 1990), social defeat (Haney *et al.* 1995; Tidey & Miczek 1997), neonatal isolation (Kosten, Miserendino & Kehoe 2000), electric footshocks (Shaham & Stewart 1994), novelty stress (Piazza *et al.* 1991) and immobilization (Shaham 1993). In addition, exposure to electric foot-shock has been shown to increase the subsequent reinforcing efficacy of heroin (Shaham & Stewart 1994). Also, in

a classic experiment, Goeders & Guerin (1994) observed that during the acquisition phase, rats exposed to uncontrollable footshock stress were more sensitive to low doses of cocaine than rats exposed to controllable shock stress or that were not shocked.

Given that stress makes animals more vulnerable to psychostimulant self-administration, investigators also tested if this process may be mediated by corticosterone (cortisol in humans), which is secreted as the final step of HPA axis activation. Interestingly, increased low dose cocaine self-administration was observed to be positively correlated with footshock-induced increases in plasma corticosterone in rats. Moreover, self-administration did not occur unless plasma corticosterone levels were increased above a specific threshold (Goeders & Guerin 1996b; Goeders 2002). Likewise, pretreatment with corticosterone facilitates the acquisition of cocaine self-administration in rats (Mantsch, Saphier & Goeders 1998). Moreover, corticosterone administration has also been shown to facilitate psychomotor stimulant effects of cocaine and morphine (Marinelli *et al.* 1994).

In a related experiment, these same investigators observed that adrenalectomized rats, which eliminated the final step in HPA axis activation, did not self-administer cocaine at any dose tested (Goeders & Guerin 1996a). The reduction in self-administration was dose-dependently reversed by exogenous administration of corticosterone (Deroche *et al.* 1997). In another series of experiments, the blockade of the synthesis of corticosterone with keto-conazole reduced low-dose cocaine self-administration during acquisition (Goeders, Peltier & Guerin 1998). In addition, pretreatment with metyrapone, which blocks the synthesis of corticosterone, resulted in dose-related decreases in ongoing cocaine self-administration (Goeders & Guerin 1996a).

In an escalation model for cocaine self-administration associated with increased reward thresholds, Koob & Kreek (2007) reported a positive correlation between pre-session corticosterone levels and the amount of cocaine self-administered. Plasma corticosterone levels before self-administration predicted cocaine self-administration, but the relationship was only observed at a low dose of cocaine (0.25 mg/kg) (Mantsch *et al.* 2001). These findings are in agreement with those of Goeders and colleagues, indicating that individual differences in cocaine self-administration during the acquisition period are relevant only at low doses of cocaine.

Also, during acquisition, cocaine self-administration induces activation of the HPA axis leading to increased levels of plasma corticosterone in rodents. The cocaine-induced increases in plasma corticosterone ultimately result from the effects of the drug on CRF secretion from the hypothalamus (Sarnyai, Shaham & Heinrichs 2001). Thus, low-dose psychostimulant effects may be related to initial vulnerability to drug use, and activation of the HPA axis may contribute to such vulnerability.

Glucocorticoids act on the mammalian brain through two main receptors, the MR and GR, and each activates a different set of transcription factors. To further investigate the role of GR in psychostimulant self-administration, selective inactivation of the GR gene in the brains of mice utilizing the Cre/LoxP system has been evaluated. Mice with the targeted disruption of the GR showed reduced self-administration of cocaine and suppressed psychomotor sensitization compared with wild-type mice (Deroche-Gamonet *et al.* 2003). Furthermore, administration of the GR antagonist mifepristone reduced the motivation to self-administer cocaine (Deroche-Gamonet *et al.* 2003). Similarly, St-Hilaire and colleagues observed a blunted locomotor effect following the first cocaine administration using a different GR transgenic model which partially blocks GR expression (St-Hilaire *et al.* 2003). However, Steckler and Holsboer as well as Cyr and colleagues found that mice with a reduction of GR mRNA in the brain showed increased amphetamine-induced locomotor activity and increased concentrations of striatal dopamine (Cyr *et al.* 2001; Steckler & Holsboer 2001).

Thus, mediated through the GR, stress modulates low-dose cocaine self-administration during acquisition. Therefore, it has been speculated that exposure to a stressor increases the vulnerability to drug taking via a process analogous to sensitization, whereby repeated but intermittent injections of cocaine increases the behavioral and neurochemical responses to subsequent exposure to the drug (Piazza & Le Moal 1998). Interestingly, exposure to stressors or injections of corticosterone can also result in sensitization to the behavioral and neurochemical responses to cocaine, and these effects are attenuated in rats with their adrenal glands removed or when corticosterone synthesis is inhibited. Although exposure to the stressor itself may be aversive in many cases, the net result is reflected as an increased sensitivity to the drug. This suggests that if certain individuals are more sensitive to stress or if they find themselves in an environment where they do not feel that they have adequate control over this stress, then these individuals may be more likely to engage in substance abuse.

Alcohol in rodents—Acute alcohol administration, similar to psychostimulants, activates the HPA axis by inducing the release of CRF from the hypothalamus in rodents (Lee *et al.* 2004). Nevertheless, studies examining the effects of stress and glucocorticoids during the acquisition phase of alcohol drinking have not been as thorough as those described for psychostimulants. In non-alcohol dependent rodents, studies examining the effects of various forms of stress on ethanol consumption have produced less consistent results than alcohol deprivation models. In addition, the observed stress-induced increases in alcohol consumption are, in general, not robust. Despite these caveats, restraint stress was shown to significantly increase alcohol consumption in non-alcohol dependent Wistar rats (Lynch *et al.* 1999). Notably, the effects of the restraint stress on alcohol self-administration persisted after the stress schedule was terminated (Lynch *et al.* 1999). In another study, footshock stress was shown to increase ethanol consumption in several different lines of rodents: (1) unselected Wistar rats; (2) ethanol-preferring; (3) high-ethanol-drinking; and (4) Alko alcohol rats (Vengeliene *et al.* 2003). Interestingly, in the same study, a different stressor-swim stress caused an increase in ethanol consumption only in the unselected Wistar rats but not in the other lines (Vengeliene *et al.* 2003). However, another group reported that chronic, unpredictable restraint stress reduced voluntary ethanol drinking during the application of stress in rats with a genetic predisposition toward high alcohol intake (Chester *et al.* 2004). Also, Wand and colleagues (unpublished) have shown that restraint stress increases alcohol consumption in non-alcohol-dependent 129SVEV mice but not in C57BL/6 mice. The results of these studies suggest that in rodents, the effect of stress on voluntary alcohol consumption is influenced by the type of stress and the genetic background of the animal.

A role of GRs in modulating voluntary ethanol consumption has been suggested by the observation that alcohol consumption, during limited access conditions, was reduced by acute administration of the GR antagonist mifepristone (Koenig & Olive 2004).

Non-human primate—Studies with non-human primates generally corroborate findings from the rodent studies described earlier and suggest that exposure to stress early in life leads to increased drug self-administration. Experiments using rhesus monkeys observed that monkeys that were reared without adults (e.g. peer-rearing condition) during the first six months of their life consumed more alcohol than monkeys reared by their mothers (Higley *et al.* 1991). Interestingly, when stress was increased by social separation, monkeys that were reared by their mothers increased their alcohol consumption to a level comparable to that seen in the peer-reared monkeys (Higley *et al.* 1991).

Evidence in rhesus monkeys also suggests that altered HPA axis responses are related to the risk of addiction. Investigators observed that peer-reared monkeys experience chronically elevated blood cortisol levels and chronic anxiety (e.g. internal stress state) compared with mother-reared monkeys. Interestingly, Higley *et al.* (1991) found that independent of rearing

conditions, individual differences in alcohol consumption correlated with cortisol measures and level of anxiety. In addition, these same investigators reported that plasma cortisol response to social separation stress during infancy predicted adult alcohol drinking behavior several years later. Specifically, monkeys that responded to separation with high cortisol levels drank more alcohol as adults than monkeys with low cortisol responses to the separation challenge (Fahlke *et al.* 2000). These findings highlight the potentially important interaction of anxiety, cortisol and alcohol consumption in primates with a high phylogenetic likeness to humans.

Relationship between stress and vulnerability to addiction in humans

There is a growing clinical literature describing the link between stress and addiction in humans. It has been shown that exposure to stressful events early in life or to chronic internal and external stressors may increase vulnerability to addiction.

Similar to the primate models described above, several clinical studies have shown that adverse childhood experiences such as emotional, physical and sexual abuse are associated with increased risk for addiction, as well as with initiation of substance abuse at an early age (Dembo *et al.* 1988; Harrison, Fulkerson & Beebe 1997; Widom, Weiler & Cottler 1999). Interestingly, a longitudinal study showed that significant maternal anxiety in late pregnancy was associated with higher basal cortisol levels in the children of age 10 years, suggesting that prenatal anxiety might have lasting effects on HPA axis functioning in the child and might constitute a mechanism for an increased vulnerability to psychopathology in children and adolescents (O'Connor *et al.* 2005).

Exposure to other forms of external stress may also precede the development of drug use disorders. For example, being separated or divorced and being unemployed have been associated with increased alcohol use (Jose *et al.* 2000). Also, workplace harassment experiences, abusive work relationships and other workplace stressors increase the risk of alcohol use disorders (Richman *et al.* 1996; Rospenda *et al.* 2000). In addition, laboratory interactions have demonstrated that acute stress exposure can increase alcohol self-administration. Using child confederates trained to act normal or simulate behavior disorders such as attention-deficit hyperactivity disorder, Pelham *et al.* (1997) found that parents exposed to the confederates with behavior disorders subsequently consumed more of their preferred alcohol beverage than parents exposed to the normal confederates.

Studies have also shown that internal stress states (e.g. anxiety) may precede alcohol and drug use. In a recent study, a large European population ($n = 7076$) was examined retrospectively and prospectively to study the nature of the relationship between comorbid alcohol dependence and anxiety disorders, a form of chronic stress. Investigators observed that alcohol dependence was associated with very high rates of lifetime anxiety, and anxiety disorders were found to precede the development of alcohol dependence (Marquenie *et al.* 2007). Another large-scale, international study also suggested that the presence of an anxiety disorder may predispose to the development of substance use disorders. The International Consortium in Psychiatric Epidemiology (Merikangas *et al.* 1998) reported findings of patterns of comorbidity between substance use and psychiatric disorders in six study sites in Europe and North America. Across sites, 45% of subjects with drug dependence also met criteria for an anxiety disorder. Of relevance, in contrast to mood disorders, which were typically found to develop after the onset of drug use disorders, the onset of anxiety disorders preceded drug use disorders at nearly all levels of severity of substance use disorders. This raises the possibility of a causal link between anxiety, a form of chronic stress, and vulnerability to development of substance use disorders. Furthermore, an additional study examined the relationship between social phobia—an anxiety disorder—and alcohol use in 300 hospitalized alcoholics. The study confirmed the high prevalence of anxiety disorders, particularly social phobia, among alcoholics. In addition, it also suggested that social phobia precedes alcohol dependence (Terra *et al.* 2006).

Another group of individuals who appear to be at greater risk for substance abuse are combat veterans, especially those suffering from combat-related post-traumatic stress disorder (PTSD), and there is growing recognition of the co-occurrence of PTSD and substance abuse among individuals (Donovan, Padin-Rivera & Kowaliw 2001). Prevalence estimates suggest the rate of PTSD among substance abusers is between 40% and 60%, whereas the rates of substance abuse among persons with PTSD may be as high as 60–80% (Keane *et al.* 1988; Kofoed, Friedman & Peck 1993). Also, veterans with PTSD typically report a higher lifetime use of alcohol, cocaine and heroin than veterans screening negative for PTSD (Saxon *et al.* 2001). However, despite the well-documented relationship between PTSD and substance abuse, the causal nature of this relationship is not completely settled. One model suggests that substance abuse predisposes individuals to PTSD (North *et al.* 2002). A second model posits that substance abuse drugs are used to self-medicate PTSD (Jacobsen *et al.* 2001). A third model suggests that the co-occurrence is due to shared genetic vulnerability.

Relationship between stress, cortisol and mesocorticolimbic dopamine in human studies

Based on the preclinical literature, it appears that glucocorticoids can alter drug reward during the early stage of drug use. If the preclinical literature generalizes to the human condition, then glucocorticoids associated with initial stress, alcohol or psychostimulant use may also sensitize mesolimbic reward pathways in humans.

Observations originally made in rodent models have been translated to the human condition with the use of PET imaging. PET is a nuclear medicine imaging technique that produces a three-dimensional image or map of functional processes in the body. For example, the changes of regional blood flow in various anatomic structures can be visualized and relatively quantified with PET imaging. Also, several radiotracers (i.e. radioligands) have been developed for PET imaging that are ligands for specific receptor subtypes (e.g. dopamine receptors D1, D2), reuptake transporters or enzyme substrates. Competition between endogenous transmitters and radioligands for binding to their receptors is the principle underlying this technique: changes in transmitter synaptic concentration translate in changes in transmitter receptor occupancy that can be detected as changes in the binding potential (BP) of the radioligand.

To investigate striatal DA function non-invasively in humans, PET imaging with [^{11}C] raclopride, a radioligand that competes with endogenous DA for occupancy of the D2/D3 receptors, has been used. The technique allows the comparison of the BP between study groups and the measurement of changes in BP in response to the administration of drugs that modify the concentrations of synaptic DA in human subjects (i.e. amphetamine, methylphenidate, cocaine, alcohol). [^{11}C] raclopride BP represents a ratio between the concentration of binding sites (B_{max}) and the affinity of [^{11}C] raclopride for D2/D3 receptors (K_d). The percent change in BP from baseline (i.e. the placebo scan) to the drug scan is used to estimate DA release as $[(BP_{\text{placebo}} - BP_{\text{drug}})/BP_{\text{placebo}}] \times 100$, with lower BP values during the drug scan indicating greater levels of endogenous synaptic DA. Although the term ‘dopamine release’ is generally used in the literature as a expedient manner of describing drug-induced changes in [^{11}C] raclopride BP and DA receptor occupancy, the increases in dopamine concentrations that occur after drug administration probably result from several different mechanisms of action, including dopamine reuptake blockade, reverse transport of dopamine through the dopamine transporter and possible actions on endogenous opioid systems. Therefore, it is important to understand that these caveats apply to the interpretation of these studies (Laruelle 2000).

A substantial body of evidence has accumulated in humans indicating that drugs of abuse alter mesolimbic DA activity and that mesolimbic dopaminergic responses are correlated with positive subjective effects for the drug triggering DA release. Specifically, PET imaging has demonstrated that alcohol promotes DA release in the brain, with a preferential effect in the ventral striatum (Boileau *et al.* 2003). Also, it has been shown that methylphenidate-induced

levels of released DA correlate with intensity of the 'high' drug effects (Volkow *et al.* 1999). Moreover, greater amphetamine-induced ventral striatal DA release has been associated with higher ratings of positive subjective responses, including drug liking, desire, good effect, high, rush (Oswald *et al.* 2005), euphoria (Drevets *et al.* 2001; Martinez *et al.* 2003) and drug wanting (Leyton *et al.* 2002).

The relationship among stress-induced cortisol, mesolimbic dopaminergic activity and drug liking has also been examined using PET technology. In response to a psychosocial stressor involving a mental arithmetic task, ventral striatal DA release has been shown to be increased in individuals who reported low early life maternal care. In addition, in the same study, the amount of DA released was proportional to the cortisol response to the stressor (Pruessner *et al.* 2004). In a series of studies using PET imaging, Wand and colleagues examined the relationship among cortisol, DA responses to amphetamine and drug liking in a healthy group of college students without a history of alcohol use disorders, drug use or psychiatric illness. In a first study, they observed that amphetamine-induced ventral striatal DA release correlated with amphetamine-induced cortisol secretion as well as with positive subjective responses to amphetamine (Oswald *et al.* 2005). However, the study did not clarify whether cortisol responses to a psychosocial stressor would also be associated with DA responses to amphetamine administered during a separate session. Therefore, in a second study, these investigators examined whether cortisol responses to a psychosocial stressor, the Trier Social Stress Test (TSST), were associated with DA or subjective responses to amphetamine (Wand *et al.* 2007). The TSST, as described in detail in a subsequent section in this paper, is a well-validated procedure that has been widely used to evoke the stress response in a human laboratory setting (Kirschbaum, Pirke & Hellhammer 1993a). Interestingly, Wand and colleagues observed that baseline and stress-induced cortisol levels were positively correlated with DA release in the ventral striatum, which contains the NAc, and other striatal regions (Fig. 1). In addition, stress-induced cortisol levels were positively associated with the positive subjective effects of amphetamine. As the study design allowed for stress-induced cortisol levels to be obtained for up to a month prior to or after the PET procedures, the results suggest that the observed relationships between cortisol and DA release are not based solely on acute mechanisms. These observations imply that in healthy, young adults without significant exposure to alcohol or drugs, high cortisol secretors are high DA releasers and experience greater subjective effects from psychostimulants than low cortisol/DA secretors. In agreement with preclinical findings, the fact that both baseline and stress-induced cortisol levels correlated with DA release suggests that ambient cortisol concentrations over time may influence or sensitize mesolimbic DA transmission.

Taken together, the preclinical and clinical evidence suggests an important role for stress and the subsequent activation of the HPA axis in the vulnerability to drug taking. Numerous studies suggest that stress and stress-related hormones can modulate the activity of the brain reward pathway and thus may account for individual vulnerability toward the reinforcing effects of drugs of abuse.

Aberrant cortisol dynamics and vulnerability for addiction in human studies

Given the evidence that suggests a relationship between stress and the development of drug addiction, it is plausible that individual differences in HPA axis activity—with high and low cortisol states—could contribute to explaining the observed differences in vulnerability to addiction. Thus, elucidating the sources of the marked interindividual variability in HPA axis dynamics might assist in identifying subgroups with enhanced or decreased vulnerability for alcohol and drug use disorders.

A. Stress induction paradigms: psychosocial stress—Several stress induction paradigms have been extensively used to provoke activation of the stress response in a human laboratory setting. These comprise: (1) physical stressors, including pain-induction procedures (e.g. cold pressor test) (Bullinger *et al.* 1984; Edelson & Robertson 1986), and strenuous physical exercise (e.g. bicycle ergometry) (Kirschbaum, Strasburger & Langkrar 1993b; Kirschbaum, Scherer & Strasburger 1994); (2) pharmacological challenges, such as administration of naloxone hydrochloride, naltrexone (Wand *et al.* 1998, 1999b, 2001; Wand, Mangold & Ali 1999a; Hernandez-Avila *et al.* 2002; King, Bernardy & Hauner 2003; Adinoff *et al.* 2005b) and corticotrophin-releasing hormone (Kirschbaum *et al.* 1993b, 1994; Adinoff *et al.* 2005b); and (3) psychosocial stressors, including social interaction tasks (Stroud, Salovey & Epel 2002), guided imagery procedures (Sinha *et al.* 2003) and the TSST, which consists of public speaking and mental arithmetic exercises (Kirschbaum, Wust & Hellhammer 1992; Kirschbaum *et al.* 1993a, 1995a,b; Uhart *et al.* 2006). Application of these procedures has identified factors that influence the large interindividual variance in the glucocorticoid response to stress.

The TSST is a well-validated procedure that has been widely used to evoke the stress response in human laboratory settings, and at least 120 articles have been published using this paradigm (Kirschbaum *et al.* 1993a). During the TSST, individuals listen to audio-taped instructions for 5 minutes. Then they are given 10 minutes to mentally prepare for their performance task, 5 minutes to complete a public speaking task, and finally another 5 minutes to complete a mental arithmetic task. Cortisol responses to this stress procedure have been demonstrated to be stable over time, even when repeated three times over a 3-month interval (Schommer, Hellhammer & Kirschbaum 2003). Although there is some cortisol habituation between sessions, high cortisol responders remain high cortisol responders and vice versa for low cortisol responders. Therefore, response to the TSST could predict future and past cortisol responses to psychosocial stress over a significant time period.

Individual differences in stress reactivity are regulated by the interaction of environmental and genetic determinants. Moderate to high heritability has been shown for stress-induced activation of the HPA axis (Federenko *et al.* 2004). Specifically, a twin study observed modest heritability in cortisol responses following a first exposure to the TSST ($h^2 < 0.33$) and that heritability estimates increased following two additional repetitions of the stressor ($h^2 > 0.97$) (Federenko *et al.* 2004). Our group and others have evaluated the influence of family history of alcoholism and genetic variants on cortisol dynamics in response to the TSST.

B. Hormonal responses to stress and family history of alcoholism—A positive family history for alcoholism is recognized as a major risk factor for the development of alcohol dependence (Cotton 1979; Goodwin 1984). As previously described in this paper, evidence suggests that stress-related vulnerability for alcoholism and other drugs of abuse may be due, in part, to a dysregulated stress response by the HPA axis (Rouge-Pont *et al.* 1995, 1998; Tidey & Miczek 1997; Piazza & Le Moal 1998). Therefore, it is possible that individual differences in HPA axis activation create a vulnerable substrate for alcohol dependence, even before heavy drinking begins. In this case, aberrant cortisol dynamics would be identified in individuals at increased risk for alcoholism. To test this hypothesis, investigators have conducted studies using a family history of alcoholism-related design. In these studies, the offspring of alcohol-dependent (family history-positive, FHP) persons were compared with the offspring of non-alcohol-dependent (family history-negative, FHN) persons before either group developed heavy alcohol consumption (Schuckit 1994).

Using this research design, HPA axis responses following an ethanol challenge have been shown to predict future development of alcoholism (Schuckit & Smith 1996). Furthermore, Wand and colleagues, and subsequently other investigators, observed that stimulation of the

HPA axis by administration of the opioid receptor antagonists naloxone hydrochloride and naltrexone resulted in higher ACTH or cortisol response in FHP than FHN individuals (Wand *et al.* 1998, 1999a, Wand *et al.* b, 2001; Hernandez-Avila *et al.* 2002; King *et al.* 2003).

More recently, a number of studies have specifically examined the influence of family history of alcoholism on the HPA axis hormonal responses to psychosocial stress. In these studies, Caucasian FHP subjects demonstrated higher cortisol responses to a psychosocial challenge compared with Caucasian FHN subjects (Fig. 2) (Zimmermann *et al.* 2004; Uhart *et al.* 2006). However, such differences in cortisol responses to stress have not always been observed (Dai, Thavundayil & Gianoulakis 2002; Sorocco *et al.* 2006).

Thus, the differences observed in these studies suggest that individuals at increased risk for alcoholism have altered HPA axis dynamics, which possibly predates alcohol use disorders. The ability to develop markers to predict the future development of addiction to alcohol and other drugs of abuse could lead to early interventions that target high-risk subjects.

C. Genetic polymorphisms associated with HPA axis variability—A significant part of the variance in the glucocorticoid response to stress is influenced by genetic factors. Studies of the heritability of basal HPA axis activity consistently suggest a moderate genetic load (Wust *et al.* 2000). For instance, a recent review of five comparable twin studies reported a heritability of 62% for basal cortisol (Bartels *et al.* 2003). Also, moderate to high heritability has been shown for stress-induced activation of the HPA axis. In fact, it has been shown that heritability of cortisol responses to stress may be as high as 97% (Federenko *et al.* 2004). Such moderate to high heritability has motivated a search for genetic variants governing HPA axis dynamics. However, thus far, few studies have specifically examined the influence of genetic variants on the HPA axis hormonal response to stress.

The magnitude of CRF release following stress is an important determinant of the magnitude of the subsequent release of ACTH and cortisol. Hypothalamic CRF neurons are modulated by glucocorticoid feedback (De Kloet *et al.* 1998) and by neuronal pathways, including the GABAergic and β -endorphin inhibitory systems (Jessop 1999), and stimulatory serotonergic and norepinephrine fibers (Contesse *et al.* 2000; Isogawa *et al.* 2000). Therefore, candidate genes within these systems have been selected to evaluate modulation of the stress response by genetic variants.

GABA: The neurotransmitter GABA, which is the main inhibitory neurotransmitter in the mammalian central nervous system (CNS), inhibits the HPA axis through its actions on GABA receptors expressed by CRF neurons within the PVN of the hypothalamus (Jessop 1999). Furthermore, GABA inhibits the locus ceruleus–norepinephrine system, which constitutes a central sympathetic system (Tsigos & Chrousos 2002). The actions of GABA are mediated by receptors belonging to two major classes, termed GABA_A and GABA_B (Chu *et al.* 1990). GABA_A receptors are the most widely expressed in the CNS and are coupled with chloride channels. At least 18 distinct GABA_A receptor subunits have been identified, and most of their corresponding genes are organized into clusters localized in chromosomes 4p, 5q and 15q (<https://www.ncbi.nlm.nih.gov/>). Based on their amino acid sequence homologies they are divided into seven classes, and some have multiple isoforms (Mehta & Ticku 1999). Functional GABA_A receptors are formed by the assembly of five subunit proteins, including two α , two β and either γ , δ , ϵ , ω or π subunits (Chang *et al.* 1996; Tretter *et al.* 1997).

Given that the GABA system is a plausible candidate for modulating the stress response, Uhart *et al.* (2004) examined the association of the 1521T>C single nucleotide polymorphism (SNP) [rs 3219151 (<http://www.ncbi.nlm.nih.gov/>)] located in the 3' untranslated region of the GABA_A α 6 receptor subunit gene (*GABRA6*) with the hormonal and autonomic responses to

psychosocial stress. In this study, subjects homozygous for the C allele had blunted ACTH, cortisol and diastolic blood pressure responses compared to subjects heterozygous or homozygous for the T allele (Fig. 3). Also, subjects homozygous for the C allele had lower scores on the personality factor of extraversion (Uhart *et al.* 2004). Similarly, another study showed higher postprandial salivary cortisol in homozygotes for the T allele compared with heterozygotes (Rosmond, Bouchard & Bjorntorp 2002). These findings may not be the result of the 1521T>C SNP itself. Instead, this proposed polymorphism, which is located in a cluster in chromosome 5q35 with three other GABA subunit genes, may be a marker for a haplotype that influences *GABRA6* function or expression. Interestingly, this SNP, as well as haplotypes throughout the *GABRA6* gene, has also been associated with alcohol dependence in several case-control samples (Loh *et al.* 1999; Sander *et al.* 1999; Radcliff *et al.* 2005). Together, these findings provide a good basis for further examination of the contribution of variation in the genes encoding GABA-related proteins to differences in the stress response.

The μ -Opioid Receptor Gene (MOR): Given the important role of the endogenous opioid system in addiction and stress, there has been great interest in identifying genes related to this neurotransmitter system that may contribute to genetic vulnerability to alcohol and other drugs of abuse. Much of the attention has been focused on the μ -opioid receptor gene. Investigators have identified numerous polymorphisms in the μ -opioid receptor gene, such as the 118A>G SNP in exon 1. This SNP has a minor allele frequency as high as 48.9% within racial groups [rs1799971 (<http://www.hapmap.org/>)] and causes an asparagine-to-aspartate exchange at protein position 40 of the extracellular N-terminal portion of the receptor. The minor (G) allele of this SNP was originally associated with increased binding affinity to β -endorphin (Bond *et al.* 1998). More recently, research has suggested that the G allele is associated with lower production of μ -opioid receptor mRNA and protein (Zhang *et al.* 2005). It is still uncertain, however, whether the 118A>G SNP is truly a functional polymorphism (Bond *et al.* 1998; Beyer *et al.* 2004; Zhang *et al.* 2005).

There have been several studies highlighting the pharmacogenetic significance of the 118A>G MOR polymorphism. For instance, it has been demonstrated that persons expressing the minor allele (G) of the 118A>G MOR polymorphism have an exaggerated cortisol response to naloxone, a non-selective opioid antagonist, when compared with subjects expressing only the major allele (Wand *et al.* 2002; Hernandez-Avila *et al.* 2003; Chong *et al.* 2006). Also, it may be of clinical relevance that one study has demonstrated that 12 weeks of naltrexone treatment led to significantly lower relapse rates in alcohol-dependent persons with the 118G allele, who also took longer to resume drinking than did individuals with only the 118A allele (Oslin *et al.* 2003).

The influence of the 118A>G MOR polymorphism on the HPA axis response to stress has also been examined and suggests that the 118A>G MOR SNP exerts not only a pharmacogenetic effect on naloxone-induced activation of the HPA axis but also an effect on HPA axis activation by stress. Hypothalamic CRF neurons are directly and indirectly inhibited by β -endorphin-producing neurons via the MOR (Johnson & North 1992). Given that the minor (G) allele of this SNP was associated with increased binding affinity to β -endorphin, it would theoretically increase the inhibitory tone on CRF neurons (Bond *et al.* 1998). Thus, the two alleles might be expected to show differences in HPA axis stress reactivity. Indeed, subjects expressing the G allele of the SNP have been shown to have a blunted cortisol response to psychosocial stress compared with subjects expressing only the major allele (Fig. 4) (Chong *et al.* 2006). There is supporting evidence from rhesus monkeys that have a functional polymorphism analogous to 118A>G; the variant allele is associated with lower basal and ACTH-stimulated plasma cortisol levels (Miller *et al.* 2004).

GR: Cortisol participates in its own production through sensitive negative feedback loops at the hippocampal, hypothalamic and pituitary levels (De Kloet *et al.* 1998). The GR mediates many of the effects of glucocorticoids on target tissues by directly binding to hormone-responsive elements within DNA regions or by interacting with other transcription factors resulting in a modulation of gene transcription (Charmandari *et al.* 2003). A cell's response to glucocorticoids is predominantly determined by both the steroid level it is exposed to and by its glucocorticoid sensitivity, i.e. the efficiency of GR-mediated signal transduction (Bamberger, Schulte & Chrousos 1996). Thus, genetic variation in the GR gene that affect a cell's sensitivity to glucocorticoids might contribute to the large individual variability of HPA axis activity (DeRijk & de Kloet 2005).

The GR gene structure is complex with several copies of exon 1, each with its own promoter, and alternative splicing resulting in cell-specific GR expression (Breslin *et al.* 1997; DeRijk & de Kloet 2005). Several polymorphisms within the GR gene have been reported to be associated with glucocorticoid sensitivity (Huizenga *et al.* 1998; van Rossum *et al.* 2002; Stevens *et al.* 2004). However, only a few have been shown to influence cortisol responses to stress, including the N363S variant, an A to G substitution at nucleotide position 1220 in exon 2 which results in an asparagine to serine amino acid change in codon 363 (Koper *et al.* 1997) and a common *BclI* restriction fragment length polymorphism located in intron 2 (Murray *et al.* 1987; van Rossum *et al.* 2003). Following an acute psychosocial stress, Wust *et al.* (2004) observed that healthy men who were 363S carriers had increased salivary cortisol response compared with subjects with the wild-type GR genotype, whereas the *BclI* genotype GG was associated with an attenuated cortisol response. In the same study, investigators did not observe differences in cortisol response between the *BclI* genotype groups, whereas in response to a different stimulus—a standardized lunch—Rosmond *et al.* (2000) reported elevated cortisol responses in *BclI* GG subjects compared with CC subjects. Of note, the exact mechanisms through which these polymorphisms exert their effects are presently unknown (de Lange *et al.* 1997; Huizenga *et al.* 1998; van Rossum *et al.* 2003).

In summary, the role of genetic factors in addiction has witnessed significant growth in recent years, and we highlighted here findings that bear directly on systems involved in stress and addiction, such as the HPA axis. There are promising lines of research to identify specific functional polymorphisms implicated in regulating the stress response and reinforcement-related neurobiological functions. Future research should determine the extent to which these polymorphisms may inform the development of new intervention strategies.

DRUG USE ASSOCIATED WITH HEDONIC ALLOSTASIS

The preclinical and clinical evidence described in previous sections of this paper suggests that stress and the associated glucocorticoids 'sensitize' the mesocorticolimbic reward pathway during the acquisition/preoccupation phase of addiction. The amplified dopamine signal may enhance the reinforcement of the drug experience, thereby contributing to vulnerability to transitioning from casual drug use to abuse. However, it has also been shown that excessive or prolonged stress can result in allostatic changes that induce the opposite effect—reward dysfunction. The allostatic changes are evidenced as a decrease in mesolimbic dopamine signal in response to drugs and recruitment of enhanced expression of CRF leading to a state of negative affect characterized by anxiety and craving.

Repeated exposure to addictive drugs, chronic stress and brain reward dysfunction

As previously described, during casual use, alcohol and psychostimulants increase mesolimbic DA accumulation, enhancing drug reward. However, it has been hypothesized that during the transition from recreational drug use to drug dependence, there is a parallel impairment in the

reward pathway that results in decreased DA accumulation (Schultz, Dayan & Montague 1997) and that stress and glucocorticoids may be involved in this process.

Lending evidence to this hypothesis, multiple animal studies have shown that acute administration of alcohol and other drugs of abuse increases mesolimbic DA accumulation (Di Chiara *et al.* 2004). However, repeated cocaine and ethanol administration followed by abstinence has been shown to cause a lowering in the basal and stimulated dopamine signal in several studies (Parsons, Smith & Justice 1991; Diana *et al.* 1993; Weiss *et al.* 1996; Zhang *et al.* 2003; Mateo *et al.* 2005). Similar to these observations, PET human studies have shown downregulation of the mesolimbic dopamine system in alcohol-dependent persons and in chronic users of cocaine and methamphetamine (Volkow, Fowler & Wang 2003). Also, rodent studies demonstrated that the transition from acquisition to maintenance of cocaine use is accompanied by brain reward dysfunction, characterized by progressive elevation in brain reward thresholds and correlating with a decrease in dopamine signal (Koob & Kreek 2007).

Interestingly, a number of studies suggest a biphasic effect of stress and glucocorticoids on mesolimbic dopamine accumulation. Thus, while mild or moderate stressors enhance DA and behavioral response to drugs (as described previously), intense stressors do not have this effect. For example, in rodents, reduced levels of mesolimbic dopamine are observed following high levels of glucocorticoid administration (Pacak *et al.* 2002), and chronic stress can reduce the dopamine output in response to cocaine administration (Gambarana *et al.* 1999). Moreover, in a recent human PET study, our group observed that individuals with no history of substance abuse who report high levels of life-events stress have blunted dopamine and pleasant responses to a single dose of intravenous amphetamine compared with persons reporting low life-events stress (Oswald *et al.* 2007). Thus, it could be speculated that glucocorticoids amplify mesolimbic dopamine accumulation in response to drug administration early on during drug exposure, but impair positive reward when chronic stress—with its accompanying state of hypercortisolism—begins to dampen the dopamine signal and recruits enhanced expression of CRF. Further studies are needed in this area to determine the role of glucocorticoids and stress in the transition from recreational drug use to drug dependence.

Recruitment of the CRF brain stress system and development of negative affect

In addition to downregulation of the mesolimbic reward signal during the transition from drug use to dependence, allostatic mechanisms also create a state of negative affect. Negative affect is described, in part, as a state of internal stress characterized by anxiety, dysphoria and intense drug craving. Therefore, individuals self-administer the drug to alleviate negative affect. As a result, the reduction of the negative affective state by drug use negatively reinforces drug-taking behavior, leading to further drug use. Thus, individuals who are dependent on alcohol and other drugs of abuse are subjected to internal stress in the form of negative affect and anxiety and, additionally, to the same types of external stress experienced daily by non-substance-abuse individuals.

The negative reinforcing effects of both drugs of abuse and stress are mediated, in part, by the extended amygdala, a brain region that is considered to be part of the limbic system and is located in the medial temporal lobes of the brain. The amygdala consists of several nuclei, each with distinct functional traits, including the basolateral complex, the centromedial nucleus and the cortical nucleus. The basolateral complex can be further subdivided into the lateral, the basal and the accessory basal nuclei. In addition, the extended amygdala receives limbic and olfactory afferents and projects fibers that innervate the hypothalamus and midbrain (Alheid *et al.* 1998).

Preclinical rodent models—Animal models of relapse, known as reinstatement procedures, have been used extensively to study the neurobiology and phenomenology of

relapse to drug use. The most conventional reinstatement procedures are based on the drug self-administration (SA) model, in which animals are trained to self-administer a given drug (e.g. Gerber & Stretch 1975; de Wit & Stewart 1981). Once stable self-administration is observed, the animals are subjected to repeated extinction, whereby responding is no longer reinforced by the delivery of the drug, or to a period of abstinence from drug availability. Once extinction has been successful or the period of abstinence has been reached, the animals are exposed to various events, such as a priming injection of the drug, presentation of a drug-paired cue or exposure to an environmental stressor, in an attempt to reinstate drug-seeking behavior. More recently, a reinstatement procedure was developed that is based on the conditioned place preference paradigm, to study the reinstatement of an extinguished preference for a previously drug-paired environment (e.g. Wang, Cen & Lu 2001; Lu *et al.* 2002; Mueller, Perdikaris & Stewart 2002). With both types of reinstatement procedures, various forms of stress have been found to trigger relapse to, or the reinstatement of, drug seeking after prolonged drug-free periods. For example, exposure to stress in the form of intermittent electric footshock has been reported to reinstate heroin (Shaham & Stewart 1995) and cocaine-seeking behavior in rats (Erb *et al.* 1996; Ahmed & Koob 1997). Also, exposure to intermittent footshock stress can reinstate extinguished responding for alcohol (Breese *et al.* 2005).

Several lines of evidence suggest that alterations in CRF systems may be involved in the development and reinstatement of dependence on drugs of abuse. In this regard, neuropharmacological studies reported that reinstatement of ethanol self-administration following alcohol withdrawal and protracted abstinence can be reduced dose-dependently by intracerebroventricular administration of the CRF-1 receptor antagonist D-Phe-CRF(12–41) in rats (Valdez *et al.* 2002). However, this effect was not reported in nondependent rats. In addition, D-Phe-CRF(12–41) has also been shown to decrease ethanol intake in C57BL/6 mice during withdrawal from intermittent ethanol exposure (Finn *et al.* 2007). Moreover, administration of other CRF-1 receptor antagonists, such as antalarmin, as well as MJL-1-109-2 and R121919, have also been shown to reduce excessive self-administration of ethanol in dependent rats during acute withdrawal (Funk *et al.* 2007). Also, antalarmin has been shown to block stress-induced reinstatement of alcohol seeking in Marchigian–Sardinian preferring rats (Hansson *et al.* 2006). Taken together, these results suggest that recruitment of CRF activity during the development of ethanol dependence induces motivated ethanol-seeking behaviors that persist into protracted abstinence.

CRF has been suggested to play a role in the anxiogenic effects of stressful stimuli and contribute to the negative affective state that is associated with drug withdrawal. Lending support to this hypothesis, microdialysis studies have measured increased extracellular levels of CRF in the central amygdala during acute ethanol withdrawal as well as during the administration of exogenous forms of stress (e.g. restraint stress) in rats (Merlo Pich *et al.* 1995). In agreement with this finding, the CRF-1 receptor antagonist antalarmin have been shown to inhibit fear conditioning (Deak *et al.* 1999) and inhibit CRF-induced anxiety-like behaviors (Zorrilla *et al.* 2002). Also, the CRF-1 receptor antagonist D-Phe-CRF(12–41) has been shown to attenuate the increased behavioral responsiveness to stress associated with ethanol abstinence (Valdez *et al.* 2003). Thus, it is likely that mediated through the increases in CRF, chronic alcohol can lead to an increased responsiveness to stress, which in turn can lead to enhanced negative affect. This enhanced negative affect provides a motivational basis for the negative reinforcing properties of ethanol (Valdez & Koob 2004).

Substantial evidence also suggests a role of CRF in psychostimulant as well as opiate self-administration and withdrawal. A number of studies have shown that CRF mRNA and CRF-like immunoreactivity are altered in the rat amygdala during self-administration and withdrawal from cocaine and morphine (Zorrilla, Valdez & Weiss 2001; Maj *et al.* 2003; Erb, Funk & Le 2005). Also, increased CRF in rat amygdala was observed using microdialysis

techniques during cocaine withdrawal in self-administering rats (Richter & Weiss 1999). Adding further evidence, central injection of CRF has been shown to reinstate cocaine seeking in rats (Erb *et al.* 2006) and, conversely, pretreatment with the CRF-1 receptor antagonist CP-154 526 has been reported to significantly attenuate cocaine self-administration (Goeders & Guerin 2000), as well as re-instatement of methamphetamine (Moffett & Goeders 2007) and morphine-seeking (Wang *et al.* 2006) behaviors. Furthermore, injection of the CRF-1 receptor antagonist D-Phe-CRF(12–41) into the bed nucleus of the stria terminalis attenuates stress-induced reinstatement of cocaine seeking (Erb & Stewart 1999).

Although a detailed description is beyond the scope of this paper, in addition to CRF, several other stress peptides and neurotransmitters associated with the extended amygdala appear to be involved in the development of negative affect and anxiety. The GABAergic system in the central amygdala has also been implicated in regulating alcohol intake (Hyytia & Koob 1995). It has been shown that ethanol enhancement of GABAergic synaptic transmission in the central amygdala seems to be mediated via CRF1 receptors, thus suggesting a mechanism underlying involvement of CRF in ethanol's behavioral and motivational effects (Nie *et al.* 2004). Several lines of evidence suggest that neuropeptide Y (NPY) expression in the amygdala is also involved in modulating anxiety and alcohol consumption (Valdez & Koob 2004). The NPY gene expression is in part regulated by the cyclic adenosine monophosphate/protein kinase A (cAMP/PKA) pathway and cAMP response element-binding protein (CREB) expression (Pandey *et al.* 1999, 2004). Interestingly, it has been suggested that decreased CREB function in the central amygdala could be associated with maintaining high anxiety levels and alcohol-drinking behaviors of alcohol-preferring rats (Pandey *et al.* 2005). A role for cocaine and amphetamine-regulated transcript (CART), an endogenous peptide that functions as a brain/gut neurotransmitter, has also been suggested (Jaworski & Jones 2006).

Thus, peptides and neurotransmitters localized in the amygdala, including CRF, GABA and NPY, the CREB transcription factor, and possibly CART, constitute a complex system underlying stress-induced anxiety and drug intake. However, the influence of glucocorticoids on these systems remains unclear and needs further investigation.

Human studies—In agreement with the preclinical observations described above, clinical studies indicate that negative affective states play an important role in the maintenance of continuous craving and relapse for alcohol as well as other drugs of abuse. In this regard, it has been shown that the negative emotional aspects of alcohol withdrawal appear to be more involved in continued alcohol craving than physical withdrawal symptoms, which are not highly correlated with relapse in alcoholics. For example, in a study where less than 25% of alcoholic patients reported drinking to alleviate physical withdrawal symptoms, more than 80% of these same patients reported drinking due to feelings of anxiety or depressed mood (Hershon 1977). Lending further evidence, in another study, both male and female alcoholics reported negative emotional states as the most common reason for relapse (Annis, Sklar & Moser 1998).

Studies evaluating the role of CRF in addiction in humans have been largely limited to CRF challenge studies and measures of CRF in cerebrospinal fluid samples. However, the results suggest a potential activation of extrahypothalamic CRF during acute alcohol withdrawal as well as a dysregulation of the HPA axis during protracted abstinence (Wand 1993; Junghanns *et al.* 2003; Adinoff *et al.* 2005a). Specifically, it has been shown that actively drinking alcohol-dependent persons, as well as those individuals in acute withdrawal, usually generate high levels of cortisol, and on occasion develop features of hypercortisolism known as the pseudo-Cushing syndrome. Following resolution of withdrawal symptoms, most alcohol-dependent persons enter into a phase where they have an impaired ability to generate normal amounts of cortisol in response to pharmacological and psychological challenges (Wand 1993; Adinoff

et al. 2005a). In addition, studies have also reported elevated CRF levels in the cerebrospinal fluid of alcohol-dependent persons during withdrawal (Adinoff *et al.* 1996), and a study reported that low cortisol responses to stress in recently abstinent alcohol-dependent persons were associated with early relapse and may be causally related (Junghanns *et al.* 2003). A similar pattern of HPA axis activation followed by impairment has been observed following exposure to cocaine in clinical studies. Acute administration of cocaine activates the HPA axis, with increased levels of ACTH and cortisol, in cocaine abusers (Wilkins *et al.* 1992; Baumann *et al.* 1995). However, reduction of the cocaine-induced HPA axis stimulation seems to occur during chronic cocaine use (Mendelson *et al.* 1998).

It has been suggested that exposure to acute stress or to drug-related cues may increase craving and negative affect, possibly contributing to relapse to drug use. This drug use is reinforced by the reduction of craving and negative affect, increasing risk for reinstatement of regular drug-using behavior. Accordingly, it has been shown that alcoholics who are confronted with stressful circumstances following treatment are more likely to relapse than alcoholics not experiencing such stress (Noone *et al.* 1999). In addition, human laboratory studies have also shown that exposure to various forms of stress may precipitate relapse to drug use. In this regard, Sinha and colleagues have shown that exposure to stress imagery in treatment-engaged, abstinent alcoholic individuals produced significant increases in alcohol craving, anxiety and negative emotions (Fox *et al.* 2007). Moreover, an increased level of stress-induced alcohol craving is associated with alcohol relapse as measured by alcohol intake and number of days of drinking after treatment in a 90-day follow up (Breese *et al.* 2005). Similar observations were made in treatment-seeking cocaine-dependent individuals, in which exposure to stress increases drug craving, and greater stress-induced craving has been shown to be associated with a shorter time to cocaine relapse (Sinha *et al.* 2003, 2006). In addition, stress-induced levels of ACTH and cortisol predicted higher amounts of cocaine use per occasion in a 90-day follow-up (Sinha *et al.* 2006).

Interestingly, brain imaging studies have begun to identify neural correlates of stress- and drug cue-induced craving states. Findings indicate considerable overlap in neural circuits involved in processing stress and drug cues with activity in the corticostriatal limbic circuitry underlying both affective and reward processing (Sinha & Li 2007).

CONCLUSIONS

There is a complex and bidirectional relationship between stress and drug use disorders. Accumulating evidence establishes a link between internal and external forms of stress and vulnerability to drug addiction. Conversely, drug addiction leads to altered hormonal and brain stress systems and an internal state of stress, which can enhance drug use. The generalizations described in this review oversimplify a field that requires further investigation. However, several salient points can be made.

Both stress and drugs of abuse activate the HPA axis and extended amygdala. Preclinical and human studies have generally shown that specific forms of stress are associated with vulnerability to drug use disorders and can precipitate relapse. The effects of stress on drug use depend in part on the type, context and severity of the stressor, the genetic background of the drug taker and the interplay between the positive and negative reinforcing influences of the drug and the stressor. Stress-related effects on dopaminergic activity may be one mechanism underlying increased risk for addiction. Early in the development of drug use, both stress- and drug-induced activation of the HPA axis allows glucocorticoids to sensitize the reward pathways, although the exact effects on mesolimbic dopamine are still to be determined. Altered HPA axis stress response, which is influenced by a multitude of genetic and environmental factors, may also be a mechanism involved in increased risk for addiction.

Although most single genes and individual factors described in this review probably account for only a small proportion of the variability in cortisol responses to stress, even a small difference in cortisol responses could result in substantial divergence in lifetime cortisol exposure (McEwen 1998) and therefore influence risk for drug addiction.

As a person transitions from social drug use to drug dependence, the balance between the positive and negative reinforcing effects of the drug shifts. Although multiple brain regions are involved in this transition, the mesolimbic dopamine system, modulated by various forms of stress and glucocorticoids and the extended amygdala, through alterations in CRF, GABA, NPY and CREB, are likely to alter the reinforcing properties of both drugs of abuse and stress. When drug dependence is manifest, along with episodes of withdrawal, the neurochemical environment in the amygdala produces anxiogenic states by increasing expression of CRF and further activating the HPA axis. This neurochemical milieu creates craving and drug-seeking behaviors, which increase vulnerability of relapse to addiction.

Although research has progressed to explore the role and characteristics of the stress response in the context of risk for addiction, more work is still needed to understand the specific nature of how stress and the subsequent activation of the HPA axis impact addiction. An improved understanding of what biological mechanisms underlie stress-related disorders may be helpful in elucidating their pathogenesis, a step crucial in developing their prevention and treatment. Eventually, a combination of pharmacotherapies targeting the stress response systems such as HPA axis and other cognitive behavioral stress management techniques may lead to improved outcomes of addiction treatments.

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Figure 1.

Cortisol levels, summarized as area under the curve (AUC) and peak (PK), at baseline and following the Trier Social Stress Test (TSST) correlated with amphetamine-induced dopamine (DA) release in the left ventral striatum (LVS). The age and gender-adjusted associations between DA release and AUC and PK cortisol are presented in this figure. Reprinted by permission from Macmillan Publishers Ltd: Neuropsychopharmacology 32(11), copyright (2007)

Figure 2.

Plasma cortisol response to the Trier Social Stress Test (TSST) by family history of alcoholism. Values reflect means (SE). TSST box denotes TSST, which includes 5 minutes of instructions period, 10 minutes of preparation period, and 10 minutes of public speaking and mental arithmetic task. Caucasian family history-positive (FHP) subjects showed greater cortisol response to the TSST compared with family history-negative (FHN) subjects ($P = 0.039$). Reprinted by permission from Macmillan Publishers Ltd: Neuropsychopharmacology 31(10), copyright (2006)

Figure 3.

Plasma cortisol response to the Trier Social Stress Test (TSST) as a function of T1521C γ -aminobutyric acid alpha-6 receptor gene genotype. Healthy subjects homozygous for the C allele of this polymorphism show a blunted cortisol response to the TSST when compared with subjects expressing the T allele ($P = 0.010$). Data are presented as means (SE) change from baseline. Reprinted by permission from Macmillan Publishers Ltd: *Molecular Psychiatry* 9 (11), copyright (2004)

Figure 4.

Plasma cortisol response to the Trier Social Stress Test (TSST), as a function of A118G μ -opioid receptor gene genotype. Healthy subjects expressing the minor allele (G) of this polymorphism show a blunted cortisol response to the TSST when compared with subjects expressing only the major allele ($P = 0.044$). Values reflect means (SE) adjusted for gender, age, race, body mass index, level of education and baseline cortisol. Reprinted by permission from Macmillan Publishers Ltd: Neuropsychopharmacology 31(1), copyright (2006)