Experimental and Clinical Psychopharmacology
2011, Vol. 19, No. 1, 53–63

1064-1297/11/$12.00 DOI: 10.1037/a0022212

Stress, Habits, and Drug Addiction: A Psychoneuroendocrinological Perspective

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It is well known that stress is a significant risk factor for the development of drug addiction and addiction relapse. Remarkably, the cognitive processes involved in the effects of stress on addictive behavior remain poorly understood. Here it is proposed that stress-induced changes in the neural circuits controlling instrumental action provide a potential mechanism by which stress affects the development of addiction and relapse vulnerability. Instrumental action can be controlled by two anatomically distinct systems: a goal-directed system that involves learning of action-outcome associations, and a habit system that learns stimulus–response associations. The transition from initial voluntary drug use to subsequent involuntary, compulsive drug use represents a switch from goal-directed to habitual control of action. Recent evidence indicates that this switch from goal-directed to habit action can be prompted by stress and stress hormones. We argue (i) that acute stressors reinstate habitual responding to drug-related cues and thus trigger relapse to addictive behavior, and (ii) that prolonged or repeated stress may accelerate the transition from voluntary to involuntary drug use and thus promote the development of addiction. The suggested mechanism encompasses cognitive processes that may contribute to the effects of stress on addictive behavior and could have important implications for the treatment of addiction and the prevention of relapse.

Keywords: stress, glucocorticoids, memory systems, instrumental learning, addiction

Drug addiction (or substance dependence) is a major burden to the individual who is addicted, to those around them, as well as to the society as a whole. It is increasingly seen as a chronic, often relapsing brain disease that is mainly characterized by compulsive drug seeking and use with impairments in social and occupational functioning (American Psychiatric Association, 1994).

Although no single factor can predict whether or not a person will become addicted to a drug and many factors such as availability, genetics, personality, social environment, or life events may contribute to addiction vulnerability, there is strong evidence that stress is an important risk factor for the development of addiction and relapse (Brewer, Catalano, Haggerty, Gainey, & Fleming, 1998; Koob & LeMoal, 2001; Piazza & LeMoal, 1998; Sinha, 2001, 2008), in particular to psychostimulants (for opiates and alcohol addiction these effects are less clear, see Lu, Shepard, Hall, & Shaham, 2003). A stressor is a real or interpreted threat to the physiological or psychological integrity of the individual (McEwen, 2000). It triggers behavioral and emotional responses and leads to numerous physiological changes.

Many brain systems, including the central dopaminergic and noradrenergic systems, are directly activated by stress. Moreover, stress leads to the activation of the rapidly acting sympathetic nervous system and the slower hypothalamus-pituitary-adrenal (HPA) axis. Sympathetic nervous system responses include the release of adrenaline and noradrenaline from the adrenal medulla, which cause, for example, increases in heart rate, enhanced blood flow to skeletal muscles or dilation of the pupils and thus prepare the organism for a "fight-or-flight" response. Furthermore, sympathetic activation can indirectly (via the vagal nerve, solitary tract nucleus, and locus coeruleus) lead to release of noradrenaline in the brain. The HPA axis is activated by the release of corticotrophin releasing factor (CRF) from the hypothalamus. CRF causes in the anterior pituitary the production of adrenocorticotropic hormone which stimulates the biosynthesis and secretion of glucocorticoids (mainly cortisol in humans and corticosterone in rodents) in the adrenal cortex. Glucocorticoids bind to glucocorticoid and mineralocorticoid receptors and exert various effects in the brain and in the peripheral

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This work was supported by a grant of the Deutsche Forschungsgemeinschaft (DFG) to Lars Schwabe and Oliver T. Wolf (SCHW1357/2–1).

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nervous system. In addition to glucocorticoids and catecholamines like adrenaline and noradrenaline, numerous other neutrotransmitters, neuropeptides and hormones are released during stress, such as vasopressin, substance P, neuropeptide Y, glutamate, or acetylcholine. Altogether, these stress-induced changes facilitate the individual's ability to face the imminent threat and are generally adaptive. However, if the stress responses are excessive or prolonged, they may promote pathologies, such as addiction (de Kloet, Joels, & Holsboer, 2005; McEwen, 1998).

Many theories have been proposed to account for the influence of stress on drug addiction, most of which focus on stress-induced changes in the motivation to take the drug, in the brain reward circuits, or in the efficacy of the drug (Koob & LeMoal, 1997; Piazza & LeMoal, 1998; Sinha, 2001). Surprisingly little, however, is known about how stress facilitates drug addiction at the cognitive level. In the present article, we argue that stress leads—in addition to its effects on motivation, reward systems and drug efficacy—to an excessive engagement of habit processes in instrumental action and that this may contribute to the development of and relapse to addictive behavior. We first show that instrumental action can be controlled by goal-directed or habitual systems and that the transition from drug abuse to drug addiction can be conceptualized as a switch from goal-directed to habitual and ultimately compulsive action. We argue that acute stress prompts this switch and may by this means increase the risk of relapse to addictive behavior. Finally, we suggest that an aberrant recruitment of habit processes may also contribute to the enhanced risk of developing drug addiction following periods of prolonged stress.

Goal-Directed Versus Habitual Control of Instrumental Behavior

Instrumental behavior, that is, behavior that is directed at obtaining rewards or pleasant states and at avoiding punishments or unpleasant states, can be controlled by two distinct systems, operating in tandem: (i) a goal-directed system that involves learning the association between a certain action and the incentive value of the action outcome (action-outcome learning) and (ii) a habit system that involves learning the association between stimuli (or contexts) and responses (stimulus-response learning), without a link to the outcome that the behavior engendered (Dickinson, 1985). During initial learning, instrumental actions are goal-directed; they are guided by the current incentive value of the outcome in conjunction with knowledge of the causal relationship between the action and the outcome. As learning proceeds, however, actions become more and more habitual, so they are automatically evoked by triggering stimuli independently of the current value of the outcome used to establish the behavior in the first place (Adams, 1982; Balleine & Dickinson, 1991).

Goal-directed and habitual actions can be elegantly separated in an outcome devaluation paradigm (Adams & Dickinson, 1981). In typical devaluation experiments, subjects are initially trained to perform a certain action to gain a particular reward, for example, a particular food. Subsequently, this outcome is devalued, for example, by feeding subjects to satiety with that specific food. Finally, the effects of this outcome devaluation are assessed in an extinction test. Goal-directed behavior is indicated by a decrease in responding to the action that is associated with the now devalued outcome. If instrumental behavior, however, is insensitive to the changes in the value of the action goal it would be considered habitual. It is critical that this test is conducted in extinction, that is, in the absence of the outcome, so that the now-devalued outcome cannot have a directed effect on responding.

Rodent studies that used such a devaluation paradigm provide evidence that goal-directed and habitual actions are supported by distinct neural networks. Lesions of the medial prefrontal cortex, the mediodorsal thalamus or the dorsomedial striatum render rats' instrumental behavior independent of the value of the action goal, that is, habitual (Balleine & Dickinson, 1998; Corbit, Muir, & Balleine, 2003; Yin, Ostlund, Knowlton, & Balleine, 2005). Conversely, lesions of the dorsolateral striatum block the formation of habits, even after extended training (Yin, Knowlton, & Balleine, 2004; Yin et al., 2005). In line with this dissociation, recent neuroimaging studies in humans implicated the prefrontal (orbitofrontal) cortex in goal-directed actions and the dorsolateral striatum in habitual actions (Tricomi, Balleine, & O'Doherty, 2009; Valentin, Dickinson, & O'Doherty, 2007; see Figure 1). F1

Goal-Directed Versus Habitual Action: Relevance for Drug Addiction

The choice to try a drug for the first time is mainly voluntary. Reinforcing actions of the drug consolidate this behavior and increase the likelihood of repeated drug-taking. After continued repetition of drug-taking, the drug user may lose the ability to control the use of the drug and there is a compulsive, often overwhelming involuntary aspect of continuing drug use (O'Brien & McLellan, 1996). In terms of the above described systems of instrumental action, this transition from voluntary drug use to involuntary drug ad-

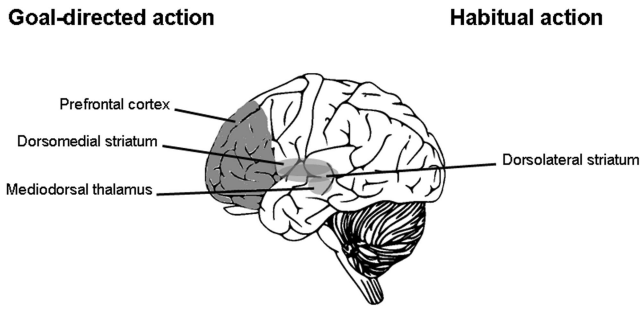

Figure 1. Brain areas implicated in goal-directed and habitual control of action. Goal-directed action is linked to the prefrontal cortex, the dorsomedial striatum and the mediodorsal thalamus, whereas habitual action is supported by the dorsolateral striatum.

diction may be seen as a transition from prefrontal cortex-dependent goal-directed to dorsolateral striatum-dependent habitual action (Everitt, Dickinson, & Robbins, 2001; Everitt & Robbins, 2005; Robbins & Everitt, 1999). The view that drug addiction reflects a maladaptive recruitment of habit processes is supported by several lines of evidence.

First, by signaling reward prediction errors, dopamine, the neurotransmitter that has been closely linked to drug addiction (Koob & LeMoal, 2005), may act as a teaching signal for striatal habit learning (Schultz & Dickinson, 2000). Dopamine is involved in the development of habits and facilitates the consolidation of habit learning (Packard & McGaugh, 1996; Packard & White, 1989). Lesions to the striatal dopamine system prevent habit formation (Faure, Haberland, Condé, & El Massioui, 2005). Moreover, drug-related cues elicit dopamine release in the dorsal striatum (Ito, Dalley, Robbins, & Everitt, 2002) and infusions of a dopamine antagonist into the dorsal striatum reduce drug seeking (Vanderschuren, Di Ciano, & Everitt, 2005). Although dopamine mediates the reinforcing effects of drugs, it is also of note here that dopamine function is disrupted in individuals with addiction, as indicated by decreases in dopamine release and dopamine receptors in the striatum (Volkow, Fowler, Wang, & Swanson, 2004).

Second, compulsive drug use in the face of aversive consequences is the hallmark of drug addiction (American Psychiatric Association, 1994). It is characterized by inflexible behavior that may become independent from the subjective value of the drug (Robinson & Berridge, 1993). Habits are operationally defined as behavior that continues although the incentive value of the goal has been reduced in a devaluation procedure. Once developed, habits are remarkably persistent. For instance, after overtraining, they are resistant to the imposition of an omission schedule, in which a previously rewarded action needs to be suppressed to earn a reward (Dickinson, Squire, Varga, & Smith, 1998; Yin, Knowlton, & Balleine, 2006). It is interesting that there is evidence from studies on cocaine and alcohol self-administration suggesting that habitual responding—expressed as insensitivity to devaluation by gastric malaise—develops unusually rapid for drugs (Dickinson, Wood, & Smith, 2002; Miles, Everitt, & Dickinson, 2003). However, habitual action itself does not cover all compulsive aspects of drug seeking (Everitt & Robbins, 2005). Some additional factors, such as sensitization or negative reinforcement through opponent motivational processes (Koob & LeMoal, 2001), appear to be necessary.

Third, relapse to drug addiction can be triggered by stimuli that were associated with the drug, even without the pleasurable anticipation associated with earlier drug experiences (Robbins & Everitt, 1999). Moreover, there is evidence that those individuals that have a predisposition to attend to drug-related cues show a higher risk for relapse (Robinson & Berridge, 2003). The power of such drug-related stimuli indicates that strong stimulus response (habit) associations have been established. It is important that drugs themselves lead to neuroadaptations that facilitate the development of habits (Robinson & Berridge, 1993). For instance, exposure to drugs may alter dopaminergic neurotransmission and thereby enhance the acquisition of drug-taking habits (Pierre & Vezina, 1998).

Finally, the transition from goal-directed drug use to compulsive drug addiction may also depend on deficits in the goal-directed system. Lesions of the prefrontal cortex lead to enhanced acquisition of drug self-administration (Weissenborn, Robbins, & Everitt, 1997). Although there are alternative explanations for this effect such as alterations in reward processing, this effect could be related to impairments in cognitive control processes (Dalley, Cardinal, & Robbins, 2004). In line with this view, neuroimaging and neuropsychological studies in humans indicate that drug users are impaired in inhibitory control tasks and in decision making (Bolla et al., 2003; Hester & Garavan, 2004; Rogers et al., 1999). Moreover, chronic drug administration results in prefrontal cortex damage in rats (Robinson & Kolb, 1999). Similarly, neuroimaging studies in humans revealed a hypoactive prefrontal cortex and reduced levels of dopamine D2 receptor availability which was associated with lower blood glucose metabolism, a marker of brain function, in drug abusers (Volkow et al., 2001; Volkow & Fowler, 2000). Post mortem analyses found significant changes in the neurochemistry of the prefrontal cortex following chronic drug abuse (Wilson et al., 1992).

In addition to these drug intake-related adaptations in the prefrontal cortex, neuroadaptations associated with chronic drug use can also be found in the dorsal striatum. While neuroadaptations in the ventral striatum after regular drug intake are well-known (for reviews see Everitt & Robbins, 2005; Koob & LeMoal, 2001), there are also changes in the dorsal striatum. For example, repeated drug use increased dopamine transmission in the caudate-putamen (Cadoni & di Chiara, 1999). Furthermore, the augmented release of dopamine in the caudate nucleus after chronic drug use was accompanied by an increase in stereotyped behavior (Patrick, Thompson, Walker, & Patrick, 1991). Taken together, these findings suggest impaired prefrontal cortex functioning and rather enhanced dorsal striatum functioning after repeated drug intake.

Acute Stress, Habit Behavior, and the Relapse to Drug Addiction

Although it is not clear from the above mentioned findings whether the use of drugs leads to changes in the neural circuits underlying goal-directed and habitual action or whether there is a comorbidity of drug-taking with a genetic or developmental predisposition to habitual responding (Robbins & Everitt, 1999), they show that the shift from goal-directed to habitual control of action is most likely involved in the transition from drug use to drug addiction and in the high prevalence of relapse to drug use. Does stress, as a major risk factor for drug addiction and relapse, affect the shift from goal-directed to habit behavior?

It is by now well documented that stress and stress hormones influence cognitive functions, in particular learning and memory processes (de Quervain, Aerni, Schelling, & Roozendaal, 2009; Joels, Pu, Wiegert, Oitzl, & Krugers, 2006; Roozendaal, McEwen, & Chattarji, 2009; Schwabe,

Wolf, & Oitzl, 2010; Wolf, 2008). The nature of the stress effect on memory depends on the timing of the stress exposure. Stress within the context of a learning experience enhances memory, whereas stress impairs memory when it is experienced out of the learning context (Joels et al., 2006). In addition to these enhancements and impairments of (hippocampus-dependent) memory performance, stress may also affect the contribution of multiple memory systems to behavior (Schwabe, Wolf, et al., 2010). In a dual-solution task that can be solved by hippocampus-dependent spatial ("cognitive") and neostriatum dependent stimulus-response ("habit") memory, acute stress before learning favors "habit" over "cognitive" memory (Kim, Lee, Han, & Packard, 2001; Schwabe et al., 2007). Glucocorticoids operate as switch between memory systems (Schwabe, Oitzl, Richter, & Schächinger, 2009; Schwabe, Schächinger, de Kloet, & Oitzl, 2010). For instance, pharmacological blockade of the mineralocorticoid receptor prevents the switch from "cognitive" to "habit" memory (Schwabe, Schächinger et al., 2010). The prefrontal cortex is highly stress sensitive. It expresses mineralocorticoid receptors and glucocorticoid receptors, the two receptor types that mediate glucocorticoid actions in the brain, at very high density (de Kloet et al., 2005) and stress or stress hormones impair neuroplasticity in the prefrontal cortex (Diamond, Campbell, Park, Halonen, & Zoladz, 2007). Furthermore, cognitive control processes that are mediated by the prefrontal cortex are impaired by stress (Lyons, Lopez, Yang, & Schatzberg, 2000; Scholz et al., 2009). The neostriatum expresses mineralocorticoid and glucocorticoid receptors to a lower extent (de Kloet et al., 2005) and less is known about stress effects on striatal behavior. Yet, there is recent evidence that stress hormones facilitate striatum-dependent memory processes (Quirarte et al., 2009). In the light of these findings, it is tempting to hypothesize that stress may modulate instrumental action in favor of the dorsolateral striatum-based habit system and at the expense of the prefrontal cortex-based goal-directed system.

This hypothesis is supported by recent studies from our lab. Stress before training in an instrumental learning task rendered the behavior of healthy human participants insensitive to the devaluation of the action goal (Schwabe & Wolf, 2009). In other words: stress before learning made participants' behavior habitual. It is interesting that the persistence of the instrumental responding was accompanied by reduced explicit knowledge of action-outcome associations. This finding underlines the habitual character of instrumental behavior after stress. While these findings demonstrate that stress modulates goal-directed versus habitual systems in instrumental action, they did not address which processes were affected by stress. Because stress preceded both instrumental learning and the extinction test after outcome devaluation, it could have affected either the acquisition or the performance of the action. Recent evidence shows that stress induces habitual responding even without any effect on instrumental learning (Schwabe & Wolf, 2010). Acute stress shortly before extinction testing (i.e., after learning and outcome devaluation) abolished individuals' sensitivity to outcome devaluation. These data indicate that stress affects mainly the expression of goal-directed versus habitual action, that acute stress may facilitate the reactivation of previously over learned, automatic behavior.

This effect of stress on instrumental action can be mimicked by the simultaneous administration of cortisol and the α2-adrenoceptor antagonist yohimbine, which increases noradrenaline levels in the brain (Schwabe, Tegenthoff, Höffken, & Wolf, 2010). However, neither cortisol nor yohimbine alone altered instrumental responding suggesting that glucocorticoids and noradrenaline may act in concert to shift instrumental action from goal-directed to habitual control. Habit formation may also be facilitated by dopaminergic sensitization, for example, after amphetamine exposure (Nelson & Killcross, 2006). Given that stress and glucocorticoids increase dopaminergic transmission (Piazza et al., 1996), it might be that such a dopamine mechanism mediates the effects of stress and stress hormones on instrumental action.

This stress (hormone)-induced switch to habit action may provide a mechanism by which acute stressors increase the risk of relapse. Drug users cite stress or negative mood as a major reason for relapse to drug use (Brandon, 1994; Kosten, Rounsaville, & Kleber, 1986; McKay, Rutherford, Alterman, Cacciola, & Kaplan, 1995) and a meta-analysis identified high stress as an important predictor of relapse (Brewer et al., 1998). Corroborating these human data, rodent studies showed that stress may elicit reinstatement of drug-seeking after extinction, a frequently used animal model of relapse to drug abuse (Shaham, Erb, & Stewart, 2000). For example, acute footshock stress reinstates drug-seeking behavior in drug-free rats (Ahmed & Koob, 1997; Erb, Shaham, & Stewart, 1996). Glucocorticoids seem to play no important role in these effects. Although there is evidence that the administration of a corticosterone synthesis inhibitor may abolish the effect of stress on the reinstatement of drug-seeking (Mantsch & Goeders, 1999), other studies argue against a role of corticosterone in the stress-induced reinstatement of drug seeking (Erb, Shaham, & Stewart, 1998; for a review see Shalev, Erb, & Shaham, 2010). Instead, it has been demonstrated that the stress-induced reinstatement is mediated by extrahypothalamic CRF (Erb, Salmaso, Rodaros, & Stewart, 2001; Shaham et al., 1997). Moreover, there is evidence for an involvement of brain noradrenaline circuits in the stress-induced reinstatement of drug-seeking behavior, which can be blocked by centrally acting α2-adrenergic agonists (Shaham, Highfield, Delfs, Leung, & Stewart, 2000).

As argued above, acute stress or stress hormone exposure may disrupt the neural systems underlying goal-directed behavior and promote the reactivation of previously over learned, automatic behavior (habits). During the development of addiction, drug-related habits and rituals are built up; strong stimulus–response associations are established (Carter & Tiffany, 1999). At the same time, prefrontal cortex functioning is significantly reduced (Bechara et al., 2001; Goldstein & Volkow, 2002). To overcome addiction, willpower and cognitive control processes are crucial (Bechara, 2005), that is, an enhancement of the goal-di-

rected system. After acute stress, however, this goal-directed control is disrupted and the habit system takes over control again. In consequence of that, the responsivity to drug-related cues increases significantly and so does the risk to relapse (see Figure 2). In line with the argument that the stress-induced relapse may be related to a reactivation of the habit system, both the stress-induced reinstatement of drug-taking and the stress-induced switch from goal-directed to habitual control of action involve the activation of the noradrenergic system (Schwabe, Tegenthoff, et al., 2010; Shaham, Highfield, et al., 2000). Further support for the view that stress disrupts the goal-directed system and may thus contribute to stress-induced relapse comes from studies on the effects of stress and stress hormones on cognitive processes in addicted individuals. For example, it has been demonstrated that addicts are impaired in impulse control during early abstinence (Fox, Hong, & Sinha, 2008), which is often very stressful (Sinha, 2008). Moreover, there is evidence that elevated cortisol levels in abstinent addicts may reduce explicit memory and executive functions that could be recruited to inhibit incorrect responses (Fox, Jackson, & Sinha, 2009). Remarkably, these memory impairments—but not distress measures—predicted subsequent relapse (Fox et al., 2009). At a neural level, abstinent addicts showed reduced activity in frontal areas but increased activity in the dorsal striatum during stress-induced craving (Sinha et al., 2005) which suggests opposite activation patterns in the neural structures that are associated with goal-directed and habit action, respectively. It is interesting that the activation in the caudate nucleus but not the activity in frontal regions was associated with stress-induced craving.

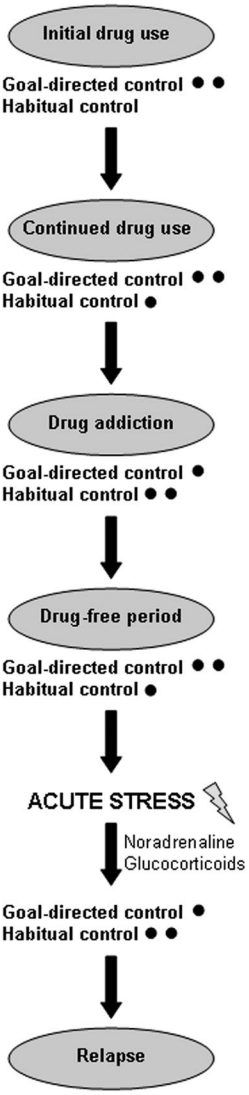

Figure 2. Acute stressors and relapse. The development of drug addiction involves a transition from goal-directed to habitual control of action. Acute stress may reinstate the habitual control of behavior after a drug-free period and may increase by this means the risk of relapse. The black dots indicate the strength of the goal-directed versus habitual control of action.

Noteworthy, the idea that stress facilitates the reinstatement of simple habits does not necessarily imply that the actions undertaken to get drugs are simple and reflexive (in fact, they are often complex). Rather, the exposure to a stressor appears to reactivate the salience, the motivational value of drug-related cues (Goddard & Leri, 2006); stress may even in the absence of drug-related cues promote drug craving (Sinha et al., 2009; for a review see Weiss, 2005).

At a neuroendocrinological level, many substances may contribute to these effects. Our data suggest an important role of glucocorticoids and noradrenaline (Schwabe et al., 2010). However, in addition to the HPA axis and sympathetic activation, several brain stress systems are most likely involved. In particular, extrahypothalamic CRF, one of the main stress-related systems associated with stress-induced reinstatement (Koob, 2008), may play a critical role.

It is important that many of the hormone, neurotransmitter, and peptide systems that are activated in response to stress are also stimulated by the intake of drugs such as cocaine, nicotine or alcohol (Mendelson et al., 2002; Mendelson et al., 2005; Wand & Dobs, 1991). The regular use of such drugs results in drug-specific adaptations in brain stress systems, the HPA axis, and the autonomic nervous system (for a review see Sinha, 2008). For instance, the chronic use of alcohol has been associated with alterations in heart rate, heart rate variability, and skin conductance (Bar et al., 2006; Thayer, Hall, Sollers, & Fischer, 2006). HPA axis hyperactivity has been reported in individuals addicted to psychostimulants (Schluger, Borg, Ho, & Kreek, 2001; Vestovi, Coiro, Volpi, & Passeri, 1992). These direct effects of drugs on stress response systems suggest that drug taking itself might potentiate the suggested effects of stress on instrumental action which in turn may lead to continued drug addiction or promote relapse.

Chronic Stress and Drug Addiction: Role of Habit Processes

Although acute stress may trigger the relapse to drug taking behavior and plays most likely a role in the vulner-

ability to initial drug use (Goeders & Guerin, 1994; Piazza, Deminiere, LeMoal, & Simon, 1990; for a review see Piazza & LeMoal, 1998), it appears rather unlikely that a single exposure to a stressor is sufficient to develop addiction. Repeated or prolonged periods of stress, however, may promote the development of addictive behavior (Sinha, 2008). Stress-related psychiatric disorders, such as anxiety, depression, and posttraumatic stress disorder, are associated with an increased risk of drug abuse and addiction (Brady & Sinha, 2005). Furthermore, individuals with early abuse histories or chronic levels of stress are at higher risk to abuse drugs (Widom, Weiler, & Cottler, 1999). Childhood physical abuse and high levels of stress (along with low coping skills) in adolescence are strong predictors of drug addiction in later life (Lo & Cheng, 2007; Wills, Vaccaro, McNamara, & Hirky, 1996). In rodents, repeated or prolonged exposure to stressors enhances self-administration of drugs and their acute behavioral effects (Boyce-Rustay, Cameron, & Holmes, 2007; Lu et al., 2003). The release of glucocorticoids, which is exaggerated following chronic stress, plays an important role in these effects. Inhibiting the release of glucocorticoids through removal of the adrenals or pharmacological suppression of the HPA axis blocks the stress-induced self-administration of cocaine in rats (Goeders & Guerin, 1996; Mantsch & Katz, 2007; Mantsch, Saphier, & Goeders, 1998). Moreover, stress reactivity is an important predisposition that predicts vulnerability to addiction (Kreek, Nielsen, Butelman, & LaForge, 2005). For instance, rats that show higher stress reactivity to a mild stressor are more likely to self-administer drugs (Piazza et al., 1991). It is interesting that rats that normally do not self-administer drugs do so after corticosterone administration (Piazza et al., 1991).

May the facilitating effects of chronic stress on the development of drug addiction be mediated by changes in the systems controlling instrumental behavior? It is well known that prolonged and repeated stress impairs neuroplasticity processes in the neural circuits supporting goal-directed behavior, in particular the prefrontal cortex (Diamond et al., 2007). Furthermore, chronic stress results in major dendritic reorganization in the prefrontal cortex (Radley et al., 2004); chronic treatment with glucocorticoids has similar effects (Wellman, 2001). At the behavioral level, chronic stress impairs prefrontal cortex-dependent memory processes (Mizoguchi et al., 2000). Moreover, chronic stress favors, both in humans and in rodents, the use of "habitual" stimulus-response memory over "cognitive" spatial memory (Schwabe, Dalm, Schachinger, & Oitzl, 2008). Direct evidence for an effect of chronic stress on goal-directed versus habitual control of instrumental action comes from a recent study in rats. Repeated exposure to physical and psychosocial stressors rendered rats' behavior in a devaluation paradigm and in a contingency degradation paradigm habitual (Dias-Ferreira et al., 2009). Most important, this study revealed the neural mechanism underlying the influence of chronic stress on instrumental behavior: Chronic stress caused opposing structural changes in the neural networks subserving goal-directed and habitual action, with atrophy of the prefrontal cortex and the dorsomedial striatum and hypertrophy of the dorsolateral striatum.

Given that drug addiction may be viewed as the endpoint of a number of transitions from initially goal-directed to habitual and finally compulsive action, the bias toward habitual responding after chronic stress may accelerate these transitions and thus increase the risk of developing drug addiction (see Figure 3). Support for this assumption comes from studies that emphasize the role of impulsivity, that is, a lack of goal-directed cognitive control, in the development of addiction. Reduced cognitive control may interact with overshooting stress reactivity to influence the progression from initial drug use to addiction (Kreek et al., 2005). Chronically increased glucocorticoid concentrations inhibit cognitive control processes (Lyons et al., 2000). Moreover, elevated glucocorticoid levels associated with prolonged stress increase the expression of CRF in limbic brain areas (Shepard, Schulkin, & Myers, 2006) and CRF injected directly in the striatum promotes responding to cues that were previously associated with a reward (Pecina, Schulkin, & Berridge, 2006). Future studies are needed to assess the relation between chronic stress, habit behavior and drug addiction more directly, for example, by measuring stress (hormone) levels and the sensitivity of instrumental action to drug revaluation in individuals that are in different stages of the addiction cycle.

Concluding Remarks

Stress increases the risk of developing drug addiction and may induce relapse to drug abuse. We propose that these effects are mediated by stress-induced changes in the systems that control instrumental action. Stress, whether acute or chronic, facilitates dorsolateral striatum-dependent habits, at the expense of prefrontal cortex-dependent goal-directed action (Dias-Ferreira et al., 2009; Schwabe & Wolf, 2009). We argue that easily accessible drug-taking habits

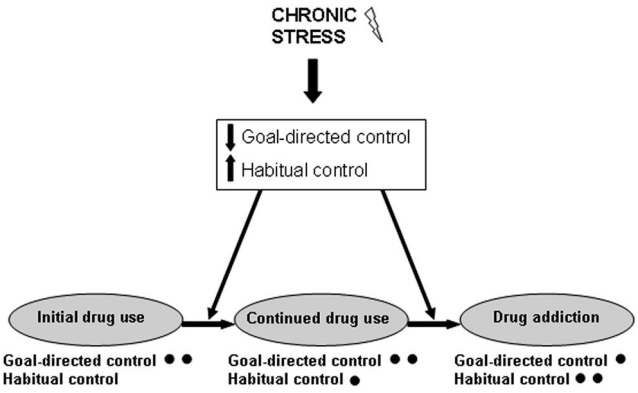

Figure 3. Chronic stress and addiction. Chronic stress shifts instrumental action from goal-directed to habitual control. This switch may accelerate the transition from voluntary to habitual and finally compulsive drug use that characterizes addiction. The black dots indicate the strength of the goal-directed versus habitual control of action.

can be reinstated by an acute stressor, thus increasing the risk of relapse to addictive behavior. Moreover, the aberrant recruitment of habit processes following prolonged or repeated stress may accelerate the transition from initially goal-directed and voluntary drug use to subsequently compulsive and involuntary drug-seeking and -taking. Considering the role of stress-induced alterations of instrumental behavior in the vulnerability to drug addiction and relapse might have important treatment implications. Cognitive–behavioral therapies of drug addiction (e.g., Carroll, 1998; Waldron & Kaminer, 2004) could address habits and rituals that are associated with drug-taking and help patients to develop strategies to counteract established drug-related habits. Training goal-directed action and decision-making might also strengthen the goal-directed system and hinder the switch toward the habit system. Such training could involve the explicit discussion of the action goals and their values, alternative ways to achieve these goals as well as consequences of drug-taking behavior that are contrary to the actual goals. To prevent relapse in the face of stress and craving, these strategies should be accompanied by elements that help the patients to build up motivation for abstinence, to identify and cope with high-risk situations for relapse, to manage stressful and painful feelings, and to improve the interpersonal functioning and social support (Carroll & Onken, 2005; Larimer, Palmer, & Marlatt, 1999). In addition to these psychotherapeutic approaches, the finding that concurrent glucocorticoid and noradrenergic activity is required to shift instrumental action from goal-directed to habitual control (Schwabe, Tegenthoff, et al., 2010) points to a potential use of glucocorticoid receptor antagonists or beta blockers, particularly in the prevention of relapse.

Some findings from animal studies might at first glance appear to be in conflict with our hypothesis. Inactivation of the medial prefrontal cortex - which promotes habit behavior - inhibits rather than potentiates the stress-induced reinstatement of drug seeking (Capriles, Rodaros, Sorge, & Stewart, 2003; Sanchez, Bailie, Wu, Li, & Sorg, 2003). Furthermore, the blockade of the substantia nigra (and by implication the nigrostriatal projection) does not affect the reinstatement of drug-seeking induced by stress (Wang et al., 2005). These findings, however, do not necessarily argue against the present hypothesis because both goal-directed and habitual behavior may be supported by a network of different neural structures. Goal-directed behavior may be supported by the prefrontal cortex, by the dorsomedial striatum and by the dorsomedial thalamus (Balleine & Dickinson, 1998; Corbit et al., 2003; Yin et al., 2005). Habit behavior may be subserved by the dorsolateral striatum and the infralimbic cortex (Killcross & Coutureau, 2003; Yin et al., 2004). Which of these structures are critical for the effects of acute or chronic stress on instrumental responding and whether there are compensatory mechanisms is not known.

Many other questions remain. Are interindividual differences in the bias toward more habit action after stress related to a differential vulnerability to addiction and relapse? Does the suggested stress-induced transition from goal-directed drug use to habitual and ultimately compulsive drug-taking depend on the intensity, duration or type of stress? May drugs and the withdrawal from drugs of abuse change the stress systems in a way that promotes habit responding and thus the relapse to drug-taking? Does the proposed habit mechanism apply equally for different types of drugs, such as opioids and psychostimulants? Are the known effects of adverse life events on the vulnerability to drug addiction mediated by changes in the reactivity of the stress systems or by structural changes in the neural circuits underlying goal-directed and habitual action? Answering these and other questions that can be derived from the hypothesis outlined here is a challenge for future research and might help to reduce the risk of addiction or relapse following stressful experiences.

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Received August 19, 2010
Revision received November 3, 2010
Accepted November 5, 2010 ■