

## REVIEW ARTICLE

## Interaction between glucocorticoid hormones, stress and psychostimulant drugs\*

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## Abstract

In this review we summarize data obtained from animal studies showing that glucocorticoid hormones have a facilitatory role on behavioural responses to psychostimulant drugs such as locomotor activity, self-administration and relapse. These behavioural effects of glucocorticoids involve an action on the meso-accumbens dopamine system, one of the major systems mediating the addictive properties of drugs of abuse. The effects of glucocorticoids in the nucleus accumbens are site-specific; these hormones modify dopamine transmission in only the shell of this nucleus without modifying it in the core. Studies with corticosteroid receptor antagonists suggest that the dopaminergic effects of these hormones depend mostly on glucocorticoid, not on mineralocorticoid receptors. These data suggest that an increase in glucocorticoid hormones, through an action on mesolimbic dopamine neurons, could increase vulnerability to drug abuse. We also discuss the implications of this finding with respect to the physiological role of glucocorticoids. It is proposed that an increase in glucocorticoids, by activating the reward pathway, could counteract the aversive effects of stress. During chronic stress, repeated increases in glucocorticoids and dopamine would result in sensitization of the reward system. This sensitized state, which can persist after the end of the stress, would render the subject more responsive to drugs of abuse and consequently more vulnerable to the development of addiction.

## Introduction

Glucocorticoid hormones (cortisol in humans and corticosterone in rodents) are the final step of the activation of the hypothalamic–pituitary–adrenal (HPA) axis, one of the major systems implicated in responding to environmental challenges (McEwen *et al.*, 1986; de Kloet *et al.*, 1998; de Kloet, 2000). In humans, as well as in animals, glucocorticoid hormones are characterized by a circadian cycle (Akana *et al.*, 1986). Hormone levels are low during the inactivity period (dark phase in humans and light phase in rodents) and increase progressively to reach a peak during the first hours of the active phase. The secretion of glucocorticoids also increases in response to stressful stimuli and this increase is considered one of the principal adaptive responses to stress (Münck *et al.*, 1984). Glucocorticoids exert their effects via two types of intracellular corticosteroid receptors: Type I or mineralocorticoid receptors (MR) and type II or glucocorticoid receptors (GR). In the brain, MRs are principally located in the septo-hippocampal system, whereas GRs have a more widespread distribution. MRs have high affinity for corticosterone and are saturated by low basal levels of the hormone; GRs have low affinity for the hormone, and they are activated by high corticosterone levels such as those during the circadian peak or after stress (Joels & de Kloet, 1994).

This review will analyse the interactions between glucocorticoid hormones, stress and the behavioural effects of psychostimulant drugs. This interaction will first be analysed in basal conditions and then in stress conditions. We will then describe possible mechanisms of glucocorticoid action and, in particular, the involvement of the dopamine system. Finally, we will try to address the question of the possible physiological meaning of the interaction between glucocorticoid hormones and drugs of abuse.

## Influence of glucocorticoids on the behavioural effects of psychostimulant drugs

We will analyse the influence of manipulation of glucocorticoid levels on psychostimulant-induced locomotor activation, self-administration and relapse.

*Locomotor response to psychostimulants*

Studies on the influence of corticosterone on drug-induced locomotor activity have consistently shown a facilitatory effect of this hormone. For example, suppression of glucocorticoids by adrenalectomy reduces the psychomotor stimulant effects of cocaine (Marinelli *et al.*, 1994, 1997a) and amphetamine (Cador *et al.*, 1993; Mormede *et al.*, 1994). Adrenalectomy produces a vertical downward shift in the dose–response function of psychostimulants, and decreases the maximal locomotor response to these drugs by  $\approx 50\%$ . This decrease in drug effects is reversed dose-dependently by corticosterone administration (Cador *et al.*, 1993; Marinelli *et al.*, 1997a). The response to cocaine is fully restored when basal concentrations of corticosterone are reached (Marinelli *et al.*, 1994, 1997a). This

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decrease in drug effects following adrenalectomy has been confirmed using pharmacological manipulations which reduce corticosterone levels as well as by blocking brain corticosteroid receptors (Marinelli *et al.*, 1997a, 1997b).

It is important to note that although psychostimulants increase corticosterone secretion (for review see Mello & Mendelson, 1997), this increase does not seem to be involved in drug-induced locomotor activation; animals that cannot secrete corticosterone in response to drug challenges (i.e. adrenalectomized animals with corticosterone replacement treatments reproducing basal levels of the hormone) show similar effects of cocaine as do control animals (Marinelli *et al.*, 1994, 1997a). This finding is consistent with the observation that there is no correlation between drug-induced locomotion and drug-induced corticosterone increase (Spangler *et al.*, 1997; Schmidt *et al.*, 1999).

Finally, it is also noteworthy to specify that the reduction in drug effects induced by a decrease in glucocorticoids is not due to possible differences in the bioavailability of cocaine; cerebral concentrations of cocaine are not decreased in animals whose corticosterone secretion was suppressed (Marinelli *et al.*, 1997a; b).

Repeated injections of psychostimulants produce an increase in their psychomotor effects, which is referred to as behavioural sensitization (for review, see Robinson & Becker, 1986). Although suppression of glucocorticoids reduces the acute locomotor response to psychostimulants, its effect on sensitization is more controversial. Following adrenalectomy, both a decrease (Rivet *et al.*, 1989) and no effects (Badiani *et al.*, 1995) on amphetamine sensitization have been reported. Regarding cocaine sensitization, adrenalectomy does not prevent expression of behavioural sensitization tested at late withdrawal times, but it can prevent the development of cocaine-induced sensitization if it is performed prior to a sensitization regimen (Prasad *et al.*, 1996; Przegalinski *et al.*, 2000). Other studies have shown that blockade of GRs after a sensitization regimen prevents the expression of psychostimulant sensitization (De Vries *et al.*, 1996). These results illustrate the controversial role of glucocorticoids on drug-induced sensitization. It is possible that some of these discrepancies can be explained by the type of study/analysis used to determine sensitization. Within-group comparisons reveal that adrenalectomy does not reduce sensitization, i.e. it does not block the increase in drug effects observed over repeated injections. Between-group comparisons show that, despite sensitization, adrenalectomized animals have a lower locomotor response to a challenge injection of psychostimulants than do control animals.

#### *Self-administration of psychostimulants*

Several studies in rodents have shown that suppression or reduction of circulating corticosterone decreases the reinforcing effects of psychostimulants as measured by self-administration. For example, adrenalectomy abolishes acquisition of cocaine self-administration over a wide range of cocaine doses (Goeders & Guerin, 1996a, 1996b), an effect that is reversed by corticosterone replacement. Dose–response studies have shown that adrenalectomy induces a vertical downward shift of the dose–response curve to cocaine (Deroche *et al.*, 1997) during the maintenance phase. Thus, no matter what the dose is, drug intake is always lower in adrenalectomized animals than in controls, suggesting that reducing circulating levels of glucocorticoids decreases the reinforcing efficacy of cocaine (for a detailed analysis on the implication of vertical shifts in self-administration dose–response functions, see Piazza *et al.*, 2000). This reduction in the drug effect is reversed dose-dependently by exogenous administration of corticosterone and the response to cocaine is fully restored when stress levels of corticosterone are

reached (Deroche *et al.*, 1997). Blockade of corticosterone secretion by metyrapone also reduces self-administration of cocaine, both in the acquisition and maintenance phase (Goeders & Guerin, 1996a, 1996b). Another corticosterone synthesis inhibitor, ketoconazole, has similar effects and reduces acquisition of self-administration when it decreases circulating levels of glucocorticoids (Goeders *et al.*, 1998). These effects are not due to nonspecific decreases in motor behaviour or motivation, as these treatments do not modify seeking behaviour in food-related tasks (Piazza *et al.*, 1994).

Although high levels of corticosterone are necessary to maintain self-administration behaviour, drug-induced increases in hormone levels are not critical. Thus, self-administration of psychostimulants can dramatically increase glucocorticoid secretion (Baumann *et al.*, 1995; Broadbear *et al.*, 1999a, 1999b; Galici *et al.*, 2000; Mantsch *et al.*, 2000; Goeders, 2002), but blocking this drug-induced increase in hormone levels does not modify responding for cocaine (Deroche *et al.*, 1997; Broadbear *et al.*, 1999c). In addition, animals can reliably self-administer cocaine at doses that do not increase hormone levels (Broadbear *et al.*, 1999b), further supporting the notion that drug-induced glucocorticoid secretion is not essential to maintain self-administration behaviour.

This could explain the apparent discrepancies between studies on rats, showing that blockade of corticosterone secretion reduces psychostimulant self-administration, and those on humans or on nonhuman primates, showing that blockade glucocorticoid secretion has no effects on cocaine self-administration (Broadbear *et al.*, 1999c), or on the subjective effects of cocaine (Ward *et al.*, 1998, 1999). Indeed, in rodent studies, treatments that reduce drug responding always reduce glucocorticoid levels to values that are below those seen in controls; instead, in primate studies, glucocorticoid levels never descend below those seen in controls; the pharmacological treatments only prevent drug-induced increases in hormone levels which, as shown above, are not important in self-administration. In another study, ketoconazole, which should decrease glucocorticoid levels, was found to increase cocaine use in methadone-maintained addicts (Kosten *et al.*, 2002). However, in this study, ketoconazole was administered with hydrocortisone (to prevent adrenal insufficiency and to suppress the morning increase in adrenocorticotrophic hormone). As a consequence, the pharmacological treatment did not decrease glucocorticoid levels, but actually increased them. This study actually confirms that, both in rodents and in primates, glucocorticoids facilitate psychostimulant self-administration. These are important considerations suggesting that differences in glucocorticoid levels across experiments might be perceived erroneously as interspecies differences in the role of glucocorticoids in psychostimulant reinforcement.

#### *Relapse in psychostimulant self-administration*

Relapse behaviour is generally studied following an extinction period from drug self-administration. Different priming factors like exposure to the drug or drug-associated cues can induce the reinstatement of drug-seeking behaviour (Stewart, 2000; Shalev *et al.*, 2002a). Although corticosterone plays a facilitatory role on many behavioural responses to psychostimulants, its role in relapse is a little more controversial. Suppression of glucocorticoids does not seem to have important effects on relapse induced by drug priming. Thus, cocaine-induced reinstatement of cocaine self-administration is only minimally decreased by adrenalectomy (Erb *et al.*, 1998) and is not modified by ketoconazole, which reduces circulating levels of corticosterone (Mantsch & Goeders, 1999b). Instead, corticosterone could play a significant role in cue-induced reinstatement of drug seeking. Thus, treatment with ketoconazole prevents reinstatement of

cocaine-seeking behaviour produced by contingent exposure to a light and tone previously paired with cocaine during self-administration (Goeders & Clampitt, 2002; Goeders, 2002). Furthermore, as we will see in the next section, corticosterone also plays an important role in stress-induced reinstatement.

### Involvement of glucocorticoids in stress-induced sensitization to the behavioural effects of psychostimulant drugs

#### *Locomotor response to psychostimulants*

Stressful conditions have been shown to increase the psychomotor stimulant effects of psychostimulant drugs (for review see Kalivas & Stewart, 1991), a phenomenon often referred to as stress-induced sensitization. Several studies have shown that these effects of stress depend on the increase in corticosterone levels induced by the stressor; treatments that block stress-induced corticosterone secretion, but maintain basal levels of the hormone, have been shown to inhibit stress-induced sensitization. For example, adrenalectomy associated with replacement of basal levels of glucocorticoids (via subcutaneous corticosterone pellets) prevents the increase in locomotor response to amphetamine observed after several types of stresses including food restriction, social isolation, restraint stress or exposure to a variety of different daily stressors (Deroche *et al.*, 1992a, 1993a, 1994; Prasad *et al.*, 1998). These findings are confirmed by the observation that pharmacological blockade of stress levels of corticosterone (with acute or repeated metyrapone treatment) also decreases sensitization to the psychomotor effects of cocaine or amphetamine (Rouge-Pont *et al.*, 1995; Marinelli *et al.*, 1996; Reid *et al.*, 1998). Finally, repeated administration of corticosterone at doses producing blood levels of the hormone that are similar to those observed in stressful conditions also increases (similarly to stress) the psychomotor effects of amphetamine (Deroche *et al.*, 1992b).

It is noteworthy that these glucocorticoid treatments were performed repeatedly, and not acutely. It is therefore possible that a long-term exposure to high levels of corticosterone may be necessary for stress-induced sensitization to develop.

#### *Self-administration of psychostimulants*

Stress also increases psychostimulant self-administration (for review see Piazza & Le Moal, 1998). As in the case of locomotor activity, the increase in self-administration induced by stress also depends on stress-induced corticosterone secretion. To our knowledge, these effects have only been examined following treatment with ketoconazole, a corticosterone synthesis inhibitor. Repeated ketoconazole treatment reduces both the rate of acquisition of cocaine self-administration and the percentage of rats meeting acquisition criterion following food restriction stress (Campbell & Carroll, 2001). The effects of corticosterone reduction are not due to nonspecific changes in motivation or motor behaviour, because operant responding for food is not decreased in groups whose corticosterone levels have been modified (Micco *et al.*, 1979; Piazza *et al.*, 1994).

Two studies have also examined the consequences of administering high (stress levels) of corticosterone. These studies show that repeated administration of such high doses of glucocorticoids increases drug self-administration, and reproduces the increase in drug responding seen during stressful situations. For example, rats receiving repeated injections of corticosterone intraperitoneally acquire cocaine self-administration at a lower dose than do vehicle-treated controls (Mantsch *et al.*, 1998). An intravenous injection of

corticosterone prior to a self-administration session can also increase drug responding in animals that would not readily acquire cocaine self-administration (Piazza *et al.*, 1991).

Again, as in the case of locomotor activity, it is important to note that most studies on self-administration have reported increases in drug responding following repeated or prolonged exposure to stress levels of glucocorticoids (Goeders & Guerin, 1996b; Deroche *et al.*, 1997; Mantsch *et al.*, 1998; although see Piazza *et al.*, 1991). It is therefore possible that long-term exposure to high levels of these hormones is necessary for the stress-induced increase in drug effects to develop, while an acute increase might not be sufficient. This could explain the apparent discrepancies with studies performed in humans, where changes in the subjective responses to amphetamine were not observed after a single exposure to high levels of glucocorticoids (Wachtel *et al.*, 2001).

#### *Relapse in psychostimulant self-administration*

Following extinction training, reinstatement of drug-seeking behaviour can be elicited by exposure to different stressors such as foot shock or food restriction (Erb *et al.*, 1996; Shaham *et al.*, 2000; Shalev *et al.*, 2000; Stewart, 2000). Regarding foot-shock stress, it was shown that basal levels of corticosterone are necessary for foot shock to induce cocaine seeking, but that stress-induced increase in corticosterone does not play an important role on this type of reinstatement. Thus, adrenalectomy decreases foot-shock-induced reinstatement, but basal levels of corticosterone are sufficient to reverse this effect (Erb *et al.*, 1998). Similarly, in a different study, treatment with ketoconazole has been shown to decrease foot-shock-induced reinstatement while only partially decreasing stress-induced corticosterone secretion (Mantsch & Goeders, 1999a). Studies on foot-shock-induced reinstatement show that this behaviour is blocked by administration of corticotropin-releasing hormone (CRH) antagonists (Erb *et al.*, 1998; Shaham *et al.*, 1998) or alpha-2 adrenergic receptor agonists (Erb *et al.*, 2000), suggesting that extra-hypothalamic CRH and the central noradrenergic system are the important players in this type of relapse. More recently an implication of corticosterone in stress-induced reinstatement has been shown using a different stressor (food restriction). Adrenalectomy prevents food-restriction-induced reinstatement of cocaine-seeking behaviour. These effects are not reversed by restoring basal levels of the hormone but only by achieving higher levels, suggesting that more elevated levels of corticosterone might be necessary for food restriction to produce reinstatement of drug-seeking behaviour (Shalev *et al.*, 2002b). Overall, these results suggest that corticosterone plays an important role in relapse to drug-seeking behaviour induced by stress. However, it is possible that different stressors require different threshold doses of corticosterone to produce reinstatement.

The implication of stress levels of corticosterone in drug-seeking behaviour has also been assessed in studies using different relapse paradigms. This work shows that intravenous injections of corticosterone can precipitate reinstatement of drug-seeking behaviour following extinction training. This effect is dose-dependent, and the highest effect is observed for doses of corticosterone that are similar to those observed during stress (Deroche *et al.*, 1997). In another study it has been shown that, after acquisition and stabilization of cocaine self-administration, food-restricted animals treated with metyrapone during withdrawal and then re-exposed to drug self-administration show decreased drug taking during the latter phase (Piazza *et al.*, 1994). This suggests that corticosterone facilitates relapse to drug taking in animals undergoing food-restriction stress.

## Methodological considerations

While most studies examining the effects of adrenalectomy on the behavioural responses to drugs are consistent, some studies have not observed decreased drug effects following ablation of the adrenal glands. For example, as mentioned previously, adrenalectomy does not decrease sensitization to the locomotor effects of cocaine when it is performed after a sensitizing paradigm (Prasad *et al.*, 1996; Przegalinski *et al.*, 2000). In addition, adrenalectomy does not reduce cocaine facilitation of brain stimulation (Abrahamsen & Carr, 1997; Carr & Abrahamsen, 1998) or drug-induced reinstatement of seeking behaviour (for review, see Erb *et al.*, 1998). The nature of this discrepancy is unclear. However, it is important to point out that corticosterone levels at the time of adrenalectomy (i.e. circulating levels of corticosterone at the time when the adrenal glands are removed) could play a fundamental role in determining whether adrenalectomy will or will not reduce drug effects. Thus, it has been shown (Ratka *et al.*, 1988; Marinelli *et al.*, 1997a) that adrenalectomy has no effects on the locomotor response to cocaine or on the analgesic effects of morphine if it is performed when corticosterone levels are elevated, such as during the dark phase, following stress, following an injection of corticosterone, or when animals are anaesthetized with pentobarbital (because of the longer induction of anaesthesia with barbiturates, adrenals are removed several minutes after animals have been removed from the colony room, a time long enough for corticosterone levels to rise). Adrenalectomy seems most efficient in reducing drug effects when levels of the hormone are low, i.e. when it is performed rapidly, under inhalant anaesthetics (Ratka *et al.*, 1988; Marinelli *et al.*, 1997a). Although the mechanisms underlying this state-dependent effect of adrenalectomy are not known, it is likely that this effect could explain, at least in part, the discrepancies in the literature. For example, it is possible that high levels of corticosterone after withdrawal from drug self-administration could prevent the effects of adrenalectomy on drug-induced reinstatement of seeking behaviour, or that removing the adrenal glands during a drug sensitizing paradigm (when levels of the hormone are elevated) could also prevent the locomotor-suppressing effects of adrenalectomy.

Finally, a note of caution should be added concerning the use of corticosterone synthesis inhibitors such as metyrapone or ketoconazole. Although it has been shown that metyrapone does not decrease the response to cocaine by affecting cocaine metabolism (Marinelli *et al.*, 1997b), these pharmacological agents could have other nonspecific effects. In fact, not only do they modify glucocorticoid secretion but they also modify the biosynthesis of other steroids, as well as neurotransmitter and neurosteroid levels (Couch *et al.*, 1987; Jain *et al.*, 1993; Rupprecht *et al.*, 1998; Khisti *et al.*, 2000). Consequently, the use of these drugs should be viewed critically, and should only be used to support studies using surgical blockade of glucocorticoids or corticosteroid receptor antagonists.

## The mesolimbic dopamine system: a possible substrate mediating the effects of glucocorticoids on drug responses

The dopaminergic projection from the midbrain to the nucleus accumbens (NAc) is considered one of the major systems implicated in drug addiction (for review see Robinson & Berridge, 1993; Robbins & Everitt, 1996; Wise, 1998; Di Chiara *et al.*, 1999; Koob & Le Moal, 2001).

The first evidence of a dopaminergic involvement in the interaction between glucocorticoids and psychostimulants probably comes from

studies investigating the behavioural effects of centrally injected psychostimulants. The locomotor response induced by the injection of psychostimulants in the NAc is dopamine-dependent (Vezina & Stewart, 1984; Delfs *et al.*, 1990), and it has been shown that this response is decreased by suppressing corticosterone and re-established by restoring basal levels of the hormone (Marinelli *et al.*, 1994). This response is also modulated by glucocorticoids in stress conditions. In food-restricted animals, blockade of stress-induced increase in corticosterone (by adrenalectomy and replacement of basal levels of corticosterone) prevents the stress-induced increase in locomotor activity following intra-NAc amphetamine. These effects are reversed by reproducing stress levels of the hormone (Deroche *et al.*, 1995).

More direct evidence of the interaction between glucocorticoid and dopamine comes from studies analysing extracellular concentrations of dopamine using *in vivo* microdialysis and expression of Fos-related proteins. Suppression of glucocorticoids by adrenalectomy reduces extracellular concentrations of dopamine in the NAc, both in basal conditions and in response to psychostimulants (Piazza *et al.*, 1996a; Barrot *et al.*, 2000). These effects are corticosterone-dependent as they are reversed by corticosterone replacement. Interestingly, glucocorticoids have a specificity of action in the NAc. Thus, adrenalectomy selectively and dramatically (> 50%) decreases dopamine in the shell of the NAc, without modifying dopamine concentrations in the core (Barrot *et al.*, 2000). The reduction in NAc shell dopamine following adrenalectomy has been observed for basal levels of dopamine, as well as for dopamine increases following cocaine or stress (Barrot *et al.*, 2000). Detailed studies on the role of MRs and GRs in these effects have revealed a role for GRs. Thus, administration of an MR antagonist does not modify extracellular levels of dopamine, whereas administration of GR receptor antagonists dose-dependently decreases basal levels of dopamine in the shell of the NAc (Marinelli *et al.*, 1998). These effects are very similar to those produced by adrenalectomy (50% decrease in basal levels of dopamine).

The selective decrease in dopamine levels in the NAc shell following glucocorticoid suppression is also translated postsynaptically. Thus, in adrenalectomized animals, Fos expression, an index of cellular activation which largely depends on dopamine D1 receptor activation (Graybiel *et al.*, 1990), is also decreased in the shell of the NAc after administration of cocaine. No changes are observed in the core (Barrot *et al.*, 2000). Adrenalectomized and sham controls show similar Fos activation in the shell in response to D1 receptor agonists, suggesting that postsynaptic D1 receptors are functionally unaltered in this structure.

Studies on the effects of stress-induced corticosterone secretion on NAc dopamine are more controversial. Using *in vivo* microdialysis, Imperato and co-workers (Imperato *et al.*, 1989, 1991) found that adrenalectomy does not prevent the increase in NAc dopamine induced by repeated stress, and Reid *et al.* (1998) reported that blockade of stress levels of corticosterone by treatment with metyrapone enhances amphetamine-induced dopamine release. In contrast, we found, using acute or chronic stress, that blockade of stress-induced corticosterone secretion by either adrenalectomy or metyrapone treatment prevents the increase in NAc dopamine induced by stress (Rouge-Pont *et al.*, 1995, 1998). It is possible that the location of the microdialysis probe (core vs. shell), which was not clearly determined in these studies, could explain these discrepancies.

Studies on dopamine levels following administration of corticosterone are also controversial. Using *in vivo* microdialysis, Imperato and co-workers (Imperato *et al.*, 1989, 1991) reported that

corticosterone administration produces a modest increase in NAc dopamine, but these effects are only obtained with concentrations of corticosterone that are well above the physiological range observed during stress. Mittleman *et al.* (1992) found, however, that dopamine release as measured with voltammetry is increased following administration of stress-like levels of corticosterone.

The variability in the effects of glucocorticoids on NAc dopamine may be explained by possible state-dependent effects of these hormones. It has been shown that corticosterone administration increases NAc dopamine if it is administered during the dark phase, but not during the light phase, and these effects are greater in the dark phase if the hormone is administered just prior to eating (Piazza *et al.*, 1996b). In addition, after administration of corticosterone, there is a greater increase in NAc dopamine in rats that spontaneously have a higher dopamine tone than in those with lower dopaminergic activity (Rouge-Pont *et al.*, 1998). In other words, it appears that corticosterone can only increase NAc dopamine if the hormone is administered in conditions in which the dopamine system is activated, such as during the dark phase (Paulson & Robinson, 1994), during food intake (Hoebel *et al.*, 1989) or in animals with a spontaneously increased dopaminergic tone (Rouge-Pont *et al.*, 1993). These data are consistent with the observation that corticosterone only modulates impulse activity of midbrain dopamine cells when these cells are stimulated by application of glutamate (Overton *et al.*, 1996; Cho & Little, 1999).

In conclusion, glucocorticoids, probably via GRs, modulate extracellular concentrations of dopamine in the NAc. These hormones specifically modulate dopamine transmission in the shell of the NAc, without influencing dopamine transmission in the core. In addition, the effects of glucocorticoids are state-dependent, and are greater when the dopamine system is activated. These observations suggest that glucocorticoid hormones could enhance drug responding by selectively facilitating dopamine transmission in the shell of the NAc.

### Why glucocorticoids interact with drugs of abuse

The data reviewed above indicate that glucocorticoid hormones have a profound influence on the behavioural effects of psychostimulant drugs. In particular, glucocorticoids seem to modify the motivation of the subject to self-administer drugs. Thus, after suppression or decrease of endogenous glucocorticoids, animals still self-administer psychostimulants, but the amount of work they are ready to provide is reduced. On the other hand, increased glucocorticoid secretion following stress enhances drug effects. In addition, these hormones exert a profound control over drug-induced dopamine release in the shell of the NAc, a brain region that seems involved in the extremely powerful incentive value of these drugs and in their capacity to induce addiction (Di Chiara *et al.*, 1999; Leshner & Koob, 1999; Zahm, 1999).

It is not known why glucocorticoids, which are secreted in response to stressful situations, could have such a role. These hormones are generally considered 'the' stress hormones and it is certainly true that their secretion constitutes one of the major responses to external challenges. However, this does not necessarily imply, as is generally believed, that glucocorticoids mediate the primary effects of stress, i.e. its aversive and avoidance-inducing properties. In fact, glucocorticoids might have the opposite effects. These hormones are more probably a component of the endogenous reward system whose primary role could be to 'energize' goal-directed behaviours. Activation of glucocorticoids during stress could

thus be a secondary compensatory response which would reduce the aversive effects of stress and thus increase coping capacities. In fact, glucocorticoids are not only activated by stress, but their secretion also precedes many goal-directed behaviours and in particular food seeking (for example, see Hoebel *et al.*, 1989; Salamone *et al.*, 1994; Westerink *et al.*, 1994; Wilson *et al.*, 1995; Taber & Fibiger, 1997; Bassareo & Di Chiara, 1999). Furthermore, glucocorticoids, in the range of concentrations induced by stress, have positive reinforcing effects and stimulate dopamine release (Piazza *et al.*, 1993; Deroche *et al.*, 1993b).

This hypothesis on the role of glucocorticoids in the central nervous system allows for the unification of the central and the peripheral function of these hormones. Indeed, it has already been hypothesized that the action of glucocorticoid hormones in the periphery is not part of the primary response to stress but a way for the organism to protect itself from the primary responses to stress (Munck *et al.*, 1984; Dallman *et al.*, 1989; Reul *et al.*, 1990). For example, glucocorticoids increase lipolysis and glyconeogenesis, which increase blood glucose levels and help the organism under stressful conditions by increasing the availability of energy substrates. Similarly, the immunosuppressive effects of glucocorticoids can reduce or prevent the potential adverse effects of over-activating the immune system and the inflammatory responses to external aggressions (for a more extensive review on this issue, see Munck *et al.*, 1984; Piazza & Le Moal, 1996).

In this context, the increase in vulnerability to psychostimulant drugs observed after repeated stress could be reinterpreted as the activation of a protective compensatory response during environmental challenges. During chronic stress the repeated increase in glucocorticoid hormones and dopamine would compensate for the aversive effects of acute stress, but could also result in sensitization of the reward system. This sensitized state, which can persist after the end of the stress, would render the subject more responsive to drugs of abuse and consequently more vulnerable to the development of addiction.

In conclusion, glucocorticoid hormones are an essential component of our capacity to endure stressful situations, probably by attenuating their aversive impact. The role of these hormones in drug abuse is probably related to the long-lasting sensitization they induce in the reward system when they are repeatedly activated during stress. Consequently, understanding the mechanisms that mediate such long-lasting effects of glucocorticoids could help to better explain addiction and to develop new treatments for this condition.

### Abbreviations

GR, glucocorticoid receptor; HPA, hypothalamic–pituitary–adrenal (axis); MR, mineralocorticoid receptor; NAc, nucleus accumbens.

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