Behavioral and Biological Factors Associated With Individual Vulnerability to Psychostimulant Abuse

Pier Vincenzo Piazza, Véronique Deroche, Françoise Rougé- Pont, and Michel Le Moal

INDIVIDUAL VULNERABILITY TO ADDICTION

It is common knowledge that enormous individual differences in drug intake exist in humans (de Wit et al. 1986). A large number of people have tried drugs at least once, but for most of them drug use consists in single or few nonrenewed experiences. Among people that persist in taking drugs, drug use can remain an occasional behavior that is limited, for example, to weekends or parties. Finally, only some subjects among drug users develop drug abuse, i.e., a compulsive drug use that becomes the principal goal-directed behavior of the subject (O'Brien et al. 1986). The origin of the peculiar vulnerability to develop drug abuse observed in some individuals is one of the principal questions to be answered about addiction.

Individual differences in the vulnerability to develop a drug habit may be explained using two very different points of view. The first is a drug-centered vision of addiction. It consists in saying that: "Drug abuse is the consequence of the modifications induced in the brain by repeated drug intake. Repeated exposure to the drug, through the development of tolerance, sensitization and conditioning, induces drug dependence, which is the real cause of abuse. In this case vulnerable individuals are the ones who, because of the environment that surrounds them (peer and/or social pressure are the most cited causes), have greater chances to be, and actually are, the most exposed to the drug." The second vision may be considered as an individual-centered theory of addiction. It consists in saying that: "Drug abuse is the consequence of a peculiar, pathological reaction to the drug. In this case vulnerable individuals are the ones who, because of a specific functional state of the biological substrates that interact with the drug, can experience such a peculiar drug effect."

An individual-centered theory of addiction can be developed around two different ideas. First, it could be said that individual vulnerability

to drugs is a drug-specific phenomenon. In this case, drug-vulnerable subjects would differ from drug-resistant ones for drug-induced behaviors, but would not show any other behavioral perturbation. The second point of view would lead to consider vulnerability to drugs as a symptom of a larger behavioral disorder. One idea that may be developed on this line would be, for example, to consider drug abuse as one of the possible behavioral expression of an addictive personality. This would imply that subjects who are vulnerable to drugs may also be vulnerable to develop other addictive behaviors, such as bulimia, sensation-seeking, or pathological gambling. Indeed a certain comorbidity between drug abuse and other addictive behaviors, such as sensation-seeking, has been found in humans (Zuckerman 1984).

Understanding the part played by the drug and the one played by the individual in determining drug abuse is a fundamental step in defining the goals of addiction therapies. If a drug-centered vision can fully explain drug abuse, then addiction should be considered as a neurotoxic disease. In this case the treatment of this condition should be achieved by two combined strategies. The first is to suppress drug availability. The second is to try to reverse the biological effects of repeated drug intake. On the contrary, if drug abuse originates from the interaction of the drug with a peculiar individual substrate, the approach to drug abuse should not differ from that of other behavioral pathologies. In other words also for addiction, it would be necessary to develop a real therapy that counteracts the biological peculiarity that makes some subjects respond in a pathological way to the drug. This disease concept of drug abuse is strengthened even more if it could be proven that compulsive drug intake is a symptom of a larger addiction disorder. In this case, suppression of drug availability would really appear as a poor measure.

AN EXPERIMENTAL APPROACH TO INDIVIDUAL VULNERABILITY TO ADDICTION

The study of the origins of individual vulnerability to drugs needs the fulfillment of two essential experimental conditions. First, all the subjects should have equal access to the drug under identical environmental circumstances. Second, the behavioral and biological features of the subject should be characterized before the exposure to the drug. Only the satisfying of these two conditions will allow evaluation of the weight of exposure to the drug and of preexisting individual differences in determining vulnerability to drug abuse. These experimental requirements are almost impossible to realize in

human studies, but they can be easily achieved by experimental research on animals. Indeed, in stable laboratory conditions, animals self-administer, either intravenously or orally (Pickens and Harris 1968; Schuster and Thompson 1969; Weeks 1962), almost all the drugs abused by humans (Yokel 1987).

Individual Differences in Drug Self-Administration

Individual differences in the propensity to develop drug intake are easily evidenced in the laboratory rat (Deminière et al. 1989). For example, when low doses of psychostimulant drugs are used, and the behavior is studied in the acquisition phase, only some laboratory rats acquire intravenous (IV) self-administration (Piazza et al. 1989, 1990*b*, 1991*b*, 1993*b*). Propensity to develop psychostimulant self-administration not only exists, but can also be predicted by the behavioral reactivity of an individual to stressful situations, such as the exposure to a novel environment (Piazza et al. 1989, 1990*b*, 1991*b*). Indeed, a positive correlation exists between locomotor response to novelty and the amount of amphetamine taken during the first days of testing for IV self-administration.

Individual differences in the propensity to develop drug self-administration can be represented by dividing animals into subgroups on the basis of their locomotor response to novelty (figure 1, top panel) (Piazza et al. 1989, 1990*b*, 1991*b*). The first subgroup, the high responders (HRs), contains all the animals with an activity score above the median of the entire group. The second subgroup, the low responders (LRs), contains all the rats with an activity score below the median of the whole group. When HR and LR animals are tested for IV self-administration of amphetamine (between 10 and 30 g/ inj), HRs will acquire self-administration whereas LRs will not (figure 2, right panel) (Piazza et al. 1989, 1990*b*, 1991*b*). Similar results have been obtained when HRs and LRs are tested for self-administration of cocaine (100 g/ inj) (Piazza et al., unpublished results). Differences in psycho-stimulant self-administration between HRs and LRs do not simply reflect differences in threshold sensitivity to the reinforcing effects of this class of drugs. In fact, during the first days of testing for self-administration, both groups self-administer amphetamine or cocaine at similar rates. However, this behavior rapidly extinguishes in LRs whereas it is stabilized and maintained in HRs (Piazza et al. 1990*b*, 1991*b*, 1993*b*). This result suggests that LRs are not insensitive to the reinforcing effects of the drugs at the dose used, but that psychostimulants have a stronger

reinforcing effect in HRs than in LRs. This hypothesis is supported

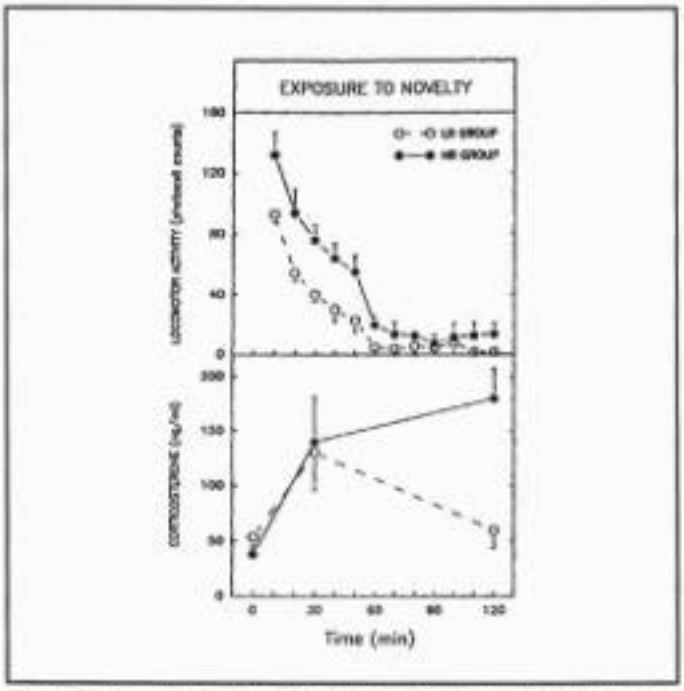

FIGURE 1. *Behavioral (upper) and hormonal (lower) responses to novelty of rats in the HR and LR groups. The two groups differed in total locomotor activity in the novel environment. Plasma corticosterone in the two groups varied differently over time.*

by recent results obtained in the authors' laboratory (Deroche et al., unpublished results) testing cocaine self-administration in HRs and LRs over a large range of doses (1, 0.5, 0.25, 0.125, 0.062, 0.031, and 0.016 mg/kg/inj). When the training dose was 1 mg/kg/inj, both LRs and HRs developed drug self-administration and showed the classical bell-shaped dose-response curve. However, for all the doses tested, the rate of responding was higher in HRs than in LRs. Similar results were found when the dose was maintained constant (1 mg/kg/inj), and the rate of responding was analyzed as a function of the ratio, i.e., the rate was higher in HRs than in LRs over a large number of ratios.

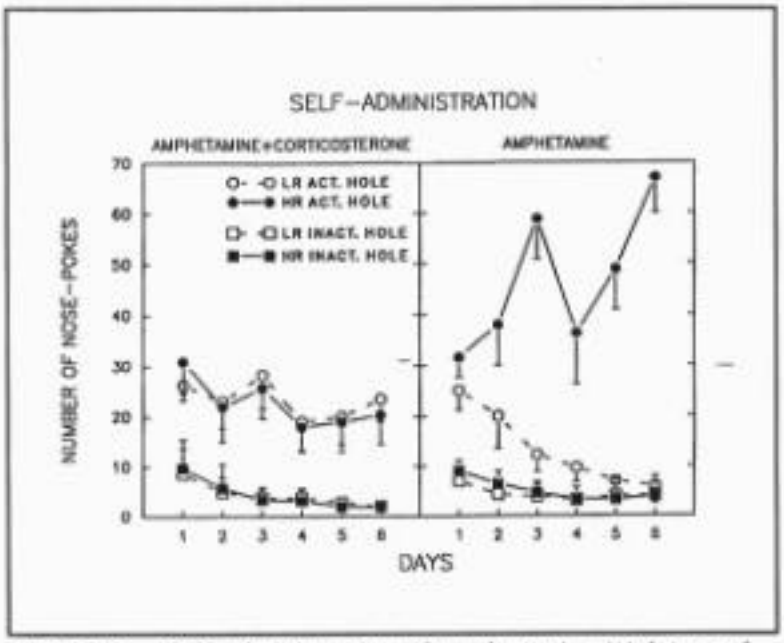

FIGURE 2. *Self-administration of amphetamine (right) or of amphetamine+corticosterone (left) in HR and LR animals. LR animals acquired self-administration of amphetamine when also administered corticosterone but progressively stopped to self-administer amphetamine alone. HR rats self-administered amphetamine in both cases. Self-administration is indicated by a higher number of nosepokes in the hole eliciting drug injections (act. hole) as compared to those in the control hole (inact. hole).*

Individual Differences in Drug-Mediated Behaviors

HR and LR rats also differ for other psychostimulant-induced behaviors. HRs show a higher sensitivity to the psychomotor effects of ampheta-mine and cocaine, displaying a higher locomotor response to systemic and intra-accumbens injection of these drugs (Exner and Clark 1993; Hooks et al. 1991, 1992*a*, 1992*b*, 1992*c;* Piazza et al. 1989, 1991*b*). HRs also seem more sensitive to develop conditioning of the motor effects of amphetamine. For low doses of amphetamine (0.5 mg/kg)

conditioning of amphetamine-induced locomotion was developed by HRs but not by LRs (Jodogne et al. 1994).

HRs and LRs also differ for amphetamine-induced sensitization, though contrasting results have been found on this issue. Some authors have shown that sensitization is exclusively developed by HRs (Hooks et al. 1992*c*), whereas in other laboratories (Exner and Clark 1993; Piazza et al. 1989) sensitization appears prevalently in LRs. In these experiments, after sensitization LRs no longer differed from HRs for amphetamine-induced locomotion and self-administration (Exner and Clark 1993; Piazza et al. 1989). Differences in sensitization of HR and LR animals in different experimental conditions may be explained by uncontrolled differences in the establishment of a stimulus-control of sensitization (Stewart and Badiani 1993). Thus, it has been shown that the expression of sensitization in HRs is under the control of the environmental cues that have been associated with the effect of the drug, whereas sensitization is not under such a control in LRs (Jodogne et al. 1994). In other words, in conditions that facilitate a stimulus-control of sensitization, HRs should show a higher sensitization than LRs, whereas when the influence of conditioning is minimized, sensitization may exclusively appear in LRs.

Individual Differences in Novelty- and Food-Directed Behaviors

HR and LR rats not only differ for drug self-administration, but also for their seeking for novel and stressful situations (Dellu et al. 1993). As said before, HRs show a higher locomotor response to a forced exposure to novelty than LRs. HR animals also show a high preference for novelty when given the choice between a familiar and a novel environment. Furthermore, when the two groups of animals are placed in a novel environment containing two compartments, a closed, dark one and a white, open, illuminated one, HRs explore the illuminated compartment sooner and more extensively than LRs (figure 3). In rodents, the light compartment is considered to be the more stressful situation. These behavioral features of HRs resemble the sensation-seeking traits observed in humans and defined as ". . . the need for varied, novel and complex sensations and experiences and the willingness to take physical and social risks for the sake of such experiences" (Zuckerman 1984).

HR and LR rats also differ for their reactivity to other reinforcing stimuli such as food. In particular, HRs show a higher speed of eating than LRs (Piazza et al., unpublished results). Speed of eating was evaluated as the

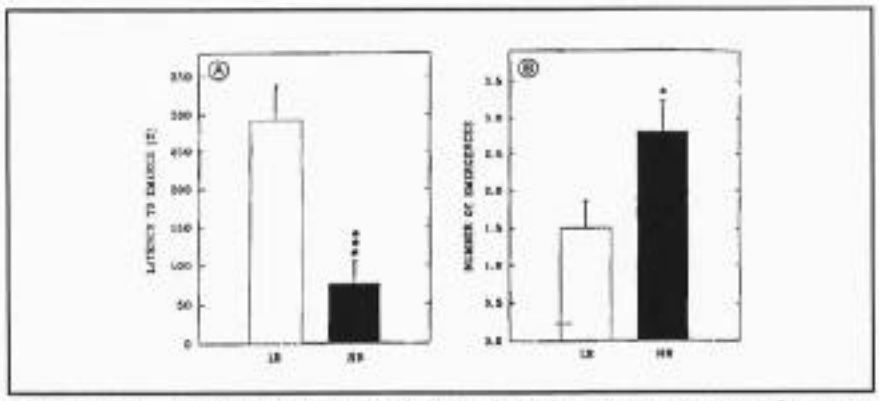

FIGURE 3. *Exploration in the light and dark emergence test. Latency to emerge (A) and number of emergences (B) from the dark compartment to the brightly illuminated one in HR and LR rats. The bars represent means±SEM of the first 5 min of a 10-min session.*** = $p < 0.001$, * = $p < 0.01$.*

time spent by mildly food-restricted rats (90 percent of their body weight) to consume a calibrated pellet (1 g) having a banana flavor (Whishaw et al. 1992). This measure showed large individual differences that were very constant for each individual both within and between sessions. The mean time required to eat one pellet in HRs was around 39.3Å1.6 whereas in LRs the amount of time was 50.4Å2.1 ($p < 0.01$). Higher speed of eating in HRs may be considered as an index of a higher sensitivity to the reinforcing effects of food in HR animals and may also be an index of compulsive behavior.

Higher sensitivity in HRs to food reinforcement is supported by another set of experiments that evaluated the behavioral response of HR and LR rats to the withdrawal of a reinforcing stimulus. Withdrawal of a reinforcer generates a peculiar class of behaviors defined as adjunctive (Falk 1961). These behaviors have the characteristic of not being *regulatory*, in other words, they are dissociate by the original physio-logical goal. Adjunctive behaviors are also characterized by large individual differences in the propensity to develop these behaviors. For example, certain food-restricted rats submitted to an intermittent schedule of food delivery (one 25 mg food pellet every minute) develop, during the interpellet interval, a nonregulatory drinking, and intake, in only 30 minutes, an amount of water that can be the double of the quantity normally drunk in 24 hours (Falk 1961). This behavior-defined, schedule-induced polydipsia (SIP) has been interpreted as an index of the frustration of the subject to the withdrawal of the reinforcement (Falk 1961). HRs have been found to acquire SIP (figure 4) more readily than LRs in the

authors' laboratory (Piazza et al. 1993*b*) and in other laboratories (Hooks et al. 1994).

Differences between HRs and LRs in preparatory behaviors also suggest that food can strengthen behavior more efficiently in HR than in LR rats. Preparatory behaviors are defined as those behaviors that normally precede and lead to consummatory responses (Jones and Robbins 1992). For example, food-restricted rats that are food deprived and are fed each day in a distinct environment develop a conditioned anticipatory locomotor activity. This activity develops after several pairings (around 10) of food presentation with the given environment. Both HRs and LRs developed conditioned locomotor activity, but this behavior appeared more readily and at a higher rate in HRs than in LRs (Hooks et al. 1994).

In conclusion, animal research has shown that vulnerability to develop drug intake may depend on preexisting individual differences. Propensity to develop drug self-administration can vary among individuals having equal access to the drug in identical laboratory conditions and can be predicted by an unconditioned spontaneous behavior, such as a high locomotor reactivity to novelty. Furthermore, vulnerability to develop drug abuse is associated with higher seeking for novel and stressful stimuli, behaviors that resemble those that characterize the sensation-seeking trait in humans. Animals showing a higher sensitivity to the reinforcing effects of psychostimulant also show a higher sensitivity to the reinforcing properties of other reinforcers such as food. These results support an individual-centered theory of addiction and suggest that drug abuse is just one of the possible behavioral expressions of an addictive personality.

FACTORS DETERMINING INDIVIDUAL VULNERABILITY TO ADDICTION

Research on the origins of individual vulnerability to addiction have focused on the specific role played by mesencephalic dopaminergic neurons, stress and glucocorticoids, as well as on the interactions between these three factors. In particular, it has been hypothesized

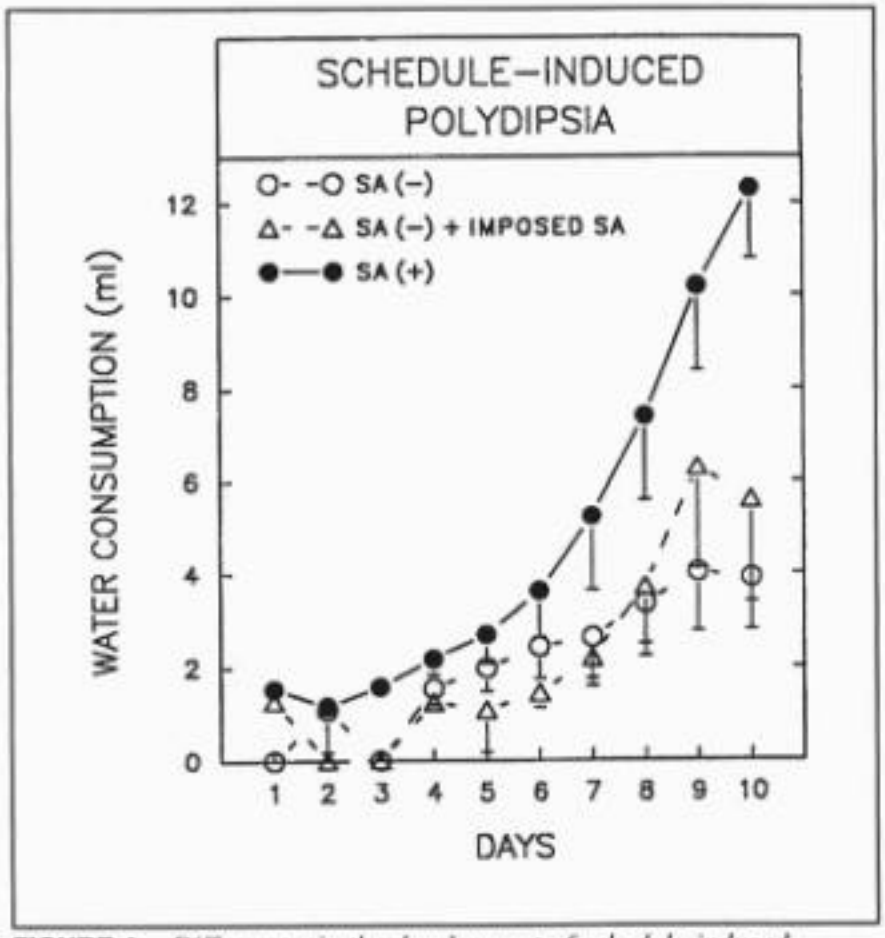

FIGURE 4. *Differences in the development of schedule-induced polydipsia (SIP) between animals predisposed and resistant to develop amphetamine self-administration. SA(+) rats correspond to HRs and SA(-) animals correspond to LRs. Animals have been tested for amphetamine self-administration (10 μg/inj) first and for SIP afterward. Animals that did not develop amphetamine self-administration and that showed a low locomotor response to novelty [SA(-)] did not develop SIP. On the contrary, animals that showed a higher locomotor response to novelty and developed self-administration [SA(+)] also developed SIP. Differences in SIP did not depend on differences in drug exposure since SA(-) rats that received, by means of imposed administrations, the same amount of amphetamine as SA(+) rats did not develop SIP.*

(Piazza et al. 1991*a*) that stress, glucocorticoids, and dopaminergic neurons may be organized in a pathophysiological chain that determines vulnerability to develop addiction. In order to develop this hypothesis, this section will review the relationship that exists between each of these factors and the propensity to develop IV self-administration of psycho-stimulants. Then, in the next section, their possible interactions in a pathophysiological chain will be taken into account.

Dopaminergic Neurons and Vulnerability to Psychostimulants

Mesolimbic dopaminergic neurons, and in particular an increase in the activity of their projection to the nucleus accumbens, may be a crucial factor in determining a higher vulnerability to the reinforcing effects of psychostimulants. Indeed, the reinforcing properties of this class of drugs seem to be mediated by the increased extracellular concentration of dopamine in the nucleus accumbens that they induce (Koob and Bloom 1988; Le Moal and Simon 1991). First, specific neurochemical lesions of the dopaminergic projection to the nucleus accumbens decrease or extinguish, depending on the dose of drug, IV self- administration of psychostimulants (Roberts and Koob 1982; Roberts et al. 1977, 1980). Second, animals will self-administer psychostimulants directly into the nucleus accumbens (Hoebel et al. 1983). Third, specific agonists or antagonists of dopaminergic receptors may respectively increase or decrease the reinforcing properties of psychostimulants (Davis and Smith 1977; Risner and Jones 1976; Roberts and Vickers 1984, 1987). In this respect 7-OH-DPAT, a dopaminergic agonist showing the highest affinity for D_3 dopaminergic receptors, is more potent than agonists with a higher affinity for D_1 or D_2 dopaminergic receptors (Caine and Koob 1993). D_3 receptors are prevalently localized in the nucleus accumbens, whereas D_1 and D_2 receptors have a widespread distribution throughout the brain (Sokoloff et al. 1990).

Individual differences studies support the idea that a higher vulnerability to develop drug self-administration is associated with a higher dopaminergic activity in the nucleus accumbens. Postmortem investigations have shown that animals vulnerable to develop IV self-administration of psychostimulants (HRs) have a higher DOPAC/DA ratio in the nucleus accumbens compared to more resistant subjects (LRs). The DOPAC/DA ratio, which is considered an indirect index of the release of dopamine, is higher in HRs than in LRs both in basal conditions and after exposure to novelty (Piazza et al. 1991*c*). Microdialysis studies have confirmed and extended these results.

Quantitative microdialysis has shown that, in basal conditions, extracellular concentrations of dopamine in HR rats are three times higher than those observed in LRs (Hooks et al. 1992). Furthermore, the percentage increase in extracellular concentrations of dopamine in response to stress (figure 5) (Rougé-Pont et al. 1993) or to the intraperitoneal administration of cocaine (Hooks et al. 1991) is also higher in HRs than in LRs.

A higher dopaminergic activity in the nucleus accumbens is not simply associated with a higher propensity to develop amphetamine self-administration; a causal relationship seems also to exist between these two variables. Very different experimental manipulations, such as
6-OHDA lesion of the amygdala (Deminière et al. 1988) or electrolytic lesion of the raphe (Simon et al. 1980), which have the common property to increase dopaminergic activity in the nucleus accumbens (Hervé et al. 1981; Simon et al. 1988), also increase propensity to acquire amphetamine self-administration.

In conclusion, results obtained with multiple approaches converge in suggesting that a higher dopaminergic activity in the nucleus accumbens may be a condition increasing the vulnerability of an individual to develop psychostimulant self-administration.

Stress and Vulnerability to Psychostimulants

Stressful situations largely interact with the activity of mesencephalic dopaminergic neurons. Two main interactions between stress and dopamine can be singled out. First, following the pioneer work of Thierry and coworkers (1976), it is now widely accepted that acute exposure to most of the situations that are considered experimental models of stress increases the activity of mesencephalic dopaminergic neurons. Second, repeated exposure to stress induces a long-term sensitization of the response of mesencephalic dopaminergic neurons to subsequent activation, and in particular a sensitization of their response to drugs of abuse (Kalivas and Stewart 1991; Robinson and Becker 1986; Robinson and Berridge 1993).

An increase in vulnerability to psychostimulants can be induced by several conditions considered as models of stress. The first report that points out the strong control that stressors exercise on psychostimulant self-administration is probably the one of Carroll and coworkers,

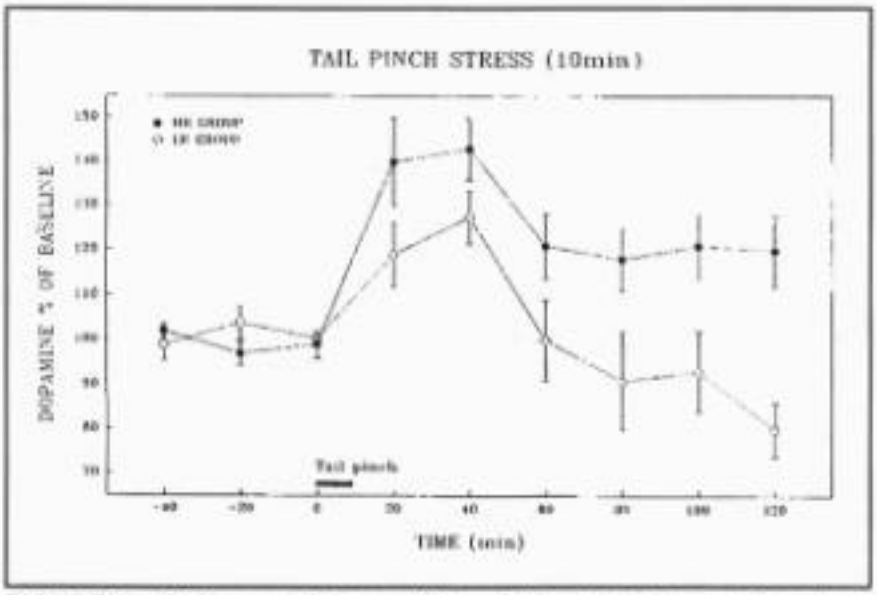

FIGURE 5. *Differences between HR and LR rats in stress-induced increase in extracellular concentrations of dopamine in the nucleus accumbens. Tail-pinch (10 min) was used as stressor. HR rats showed a higher and longer increase in extracellular concentrations of dopamine in response to stress than LRs.*

showing that food restriction increases the efficacy of psychostimulants to act as reinforcers in a self-administration test (Carroll et al. 1979). Subsequent research has shown that a large variety of stressful conditions, occurring during adult life, can increase propensity to self-administer drugs in rodents. For example, a faster acquisition of psychostimulant self-administration has been found in rats submitted to situations that seem relevant from an ethological point of view, such as: (1) social isolation (Deroche et al. 1994; Schenk et al. 1987); (2) social aggression (Haney et al., unpublished results; Miczek et al. 1994); and (3) fixed social hierarchy in high competition colonies (Maccari et al. 1991). Furthermore, more artificial and physical stressors, such as tail-pinch (Piazza et al. 1990*a*) or electric footshock (Goeders and Guerin 1994) also increase propensity to develop psychostimulant self-administration.

Very early experiences, such as prenatal stress, can also increase vulnerability to psychostimulants (Deminière et al. 1992). An increase in the propensity to develop amphetamine self-administration (figure 6, right panel) has been observed in adult rats (4 months old) whose mothers had been submitted to a restraint procedure (half an hour twice a day) during the third and fourth week

of gestation. Prenatal stress not only increases amphetamine self-administration but also the unconditioned behaviors that characterize spontaneously vulnerable subjects. Similarly to the comparison between HRs and LRs, prenatally stressed rats show a higher locomotor response to novelty and amphetamine (figure 6, left panel) as compared to controls (Deminière et al. 1992).

In conclusion, results obtained with multiple approaches converge in suggesting that stressful experiences, very early in life or during adulthood, may be a condition that increases the vulnerability of an individual to develop drug self-administration.

Glucocorticoids and Vulnerability to Psychostimulants

Several observations suggest that glucocorticoids may be one of the factors that mediate vulnerability to addiction. First, glucocorticoid secretion by the adrenal gland is one of the principal biological responses to stress (Selye 1950), and an increase in corticosterone secretion is observed in all those situations that increase the activity of dopaminergic neurons (Bohus et al. 1982; Dantzer and Mormède 1983; Knych and Eisenberg 1979; Sachser 1986). Second, mesencephalic dopaminergic neurons contain corticosteroid receptors (Härfstrand et al. 1986), and glucocorticoids can modify the metabolic activity of aminergic neurons (Rothschild et al. 1985). Third, suppression of corticosterone secretion suppresses dopamine-dependent behaviors, such as schedule-induced polydipsia (Levine and Levine 1989) or wheel running (Lin et al. 1988). Corticosterone, the main glucocorticoid in the rat, seems to be strictly related to individual vulnerability to psychostimulants. As will be analyzed in the next paragraphs: (I) individual differences in cortico-sterone levels are correlated with propensity to develop drug intake (Piazza et al. 1991*b*); (ii) this hormone increases sensitivity to the psychomotor and reinforcing effects of psychostimulants (Marinelli et al. 1994; Piazza et al. 1991*b*); and (iii) corticosterone has proper interactions with reward processes since it can act as a positive reinforcer (Deroche et al. 1993*b*; Piazza et al. 1993*a*).

Individual differences in stress-induced corticosterone secretion are correlated with drug intake during amphetamine self-administration.

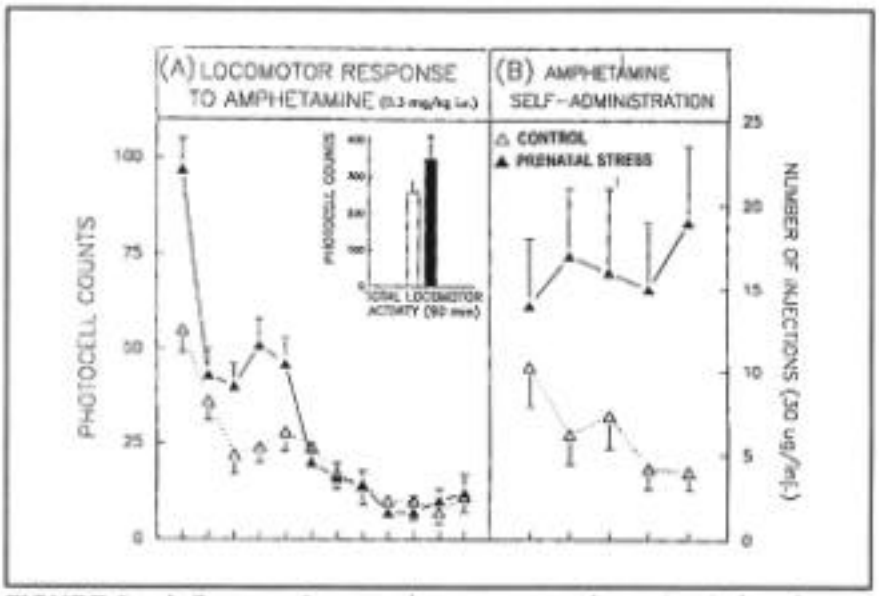

FIGURE 6. *Influence of prenatal stress on amphetamine-induced locomotion (0.3 mg/kg IV) (A) and self-administration (30 µg/inj) (B). Prenatal stress significantly increased both the locomotor response to an IV injection of amphetamine and the intake of this drug over the 5 days of testing for self-administration.*

A positive correlation exists between corticosterone levels after 2 hours of exposure to stress and the intake of amphetamine over the first days of testing in self-administration (Piazza et al. 1991*b*), though no correlation has been found between drug intake and basal diurnal level of cortico-sterone or corticosterone levels 30 minutes after stress. The relationship between corticosterone levels and vulnerability to drugs is exemplified by the comparison of HR and LR rats (figure 1, bottom panel). In response to the exposure to a novel environment, HRs show a longer stress-induced corticosterone secretion than LRs. Differences in corticosterone secretion between HR and LR animals do not depend on their difference in novelty-induced locomotion, instead the opposite seems to be true. First, HR and LR rats still differ in stress-induced corticosterone secretion when the stress used (restraint) prevented the expression of locomotion. Second, suppression of individual differences in stress-induced corticosterone secretion, by fixing corticosterone levels in the range of basal diurnal levels, induces a decrease in the locomotor response to novelty of HRs that no longer differ from LRs (Piazza et al., unpublished results).

Psychomotor effects of cocaine depends on basal corticosterone secretion. Suppression of endogenous glucocorticoids by adrenalectomy reduces of around 50 percent the locomotor response to cocaine, and a cortico-sterone replacement treatment, which reinstates diurnal basal levels of the hormone, totally suppresses the effects of adrenalectomy (Marinelli et al. 1994). Suppression of glucocorticoid secretion similarly reduces the locomotor response to an intra-accumbens injection of cocaine (figure 7) (Marinelli et al. 1994). This result indicates that modulation of sensitivity to cocaine by glucocorticoids involves changes of the mesencephalic dopaminergic transmission in reactivity to the drug. Thus, the locomotor response to the intra-accumbens injection of psychostimulants depends on dopamine (Delfs et al. 1990; Kelly and Iversen 1976).

Reinforcing effects of psychostimulants are also increased by cortico-sterone. Administration of corticosterone induces the acquisition and maintenance of amphetamine self-administration in LR rats, which do not acquire this behavior otherwise (figure 2, left panel) (Piazza et al. 1991*b*). Furthermore, in HR rats, 8 days of treatment with the inhibitor of corticosterone synthesis metyrapone, reduces of about 50 percent the intake of cocaine during a test for relapse (figure 8) (Piazza et al. 1994). More precisely, for this study animals were left to acquire and stabilize cocaine self-administration (100 g/ inj) for 10 days. They were then submitted to a drug-free period of 4 days followed by 8 days of metyrapone treatment (100 mg/kg twice a day). After this period (12 days of cocaine withdrawal of which the last 8 under metyrapone) the testing for relapse started. Animals again had access to cocaine for 5 days and the metyrapone treatment was continued. Metyrapone treatment seemed devoid of major nonspecific motor effects, because it did not modify exploratory and food-directed behaviors (Piazza et al. 1994).

Reinforcing effects of corticosterone have been evidenced using IV self-administration (Piazza et al. 1993*a*). Naive rats tested for corticosterone self-administration will self-administer the hormone (figure 9) showing a dose response curve that resembles that of other reinforcing drugs. Thus, a decrease in the number of injections per session is obtained by increasing the dose per infusion. This is considered to be the animal's attempt to obtain an optimal level of reinforcement. The doses of

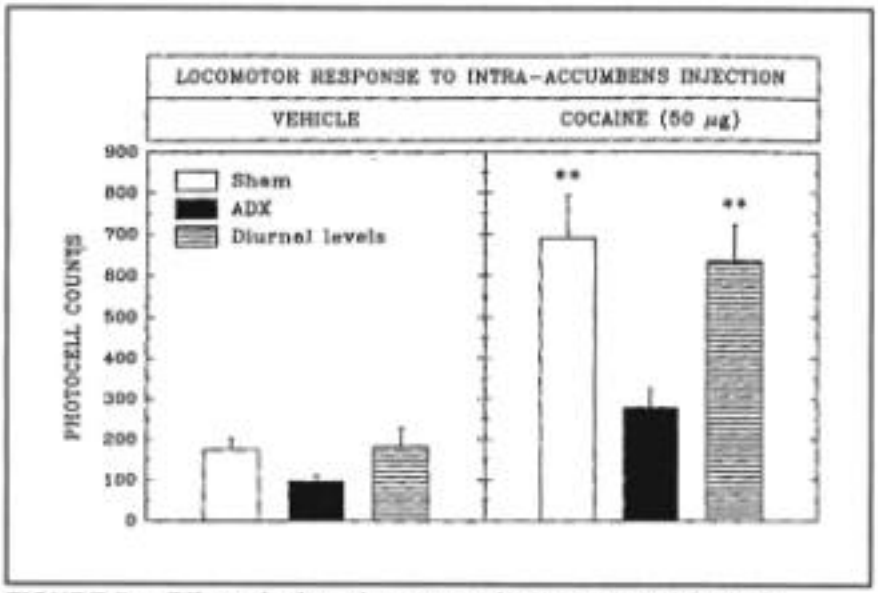

FIGURE 7. *Effect of adrenalectomy and restoration of diurnal corticosterone levels on the locomotor response to intra-accumbens vehicle and cocaine. Groups did not differ in the locomotor response to vehicle. Suppression of corticosterone levels by adrenalectomy (ADX group) reduced the locomotor response to cocaine and the reinstatement of basal diurnal levels of corticosterone reversed this effect. Thus, ADX animals exhibited lower activity scores than both sham (** $p < 0.01$) and diurnal levels (** $p < 0.01$) groups, and the latter two groups did not differ.*

corticosterone that the animals try to maintain constant correspond to plasma levels of corticosterone that are comparable to those induced by stress (around 40 g/100 mL). Positive reinforcing effects could thus be part of the physiological role of corticosterone secretion during stress. Individual differences for self-administration of corticosterone are also observed. HRs rats are four time more sensitive to the reinforcing effects of corticosterone than are the LRs (Piazza et al. 1993*a*).

In conclusion, results obtained with multiple approaches converge in suggesting that an increase in corticosterone secretion may be a condition increasing the vulnerability of an individual to psychostimulant drugs. Furthermore, this hormone not only interacts with the reinforcing properties of other stimuli but also has proper positive reinforcing

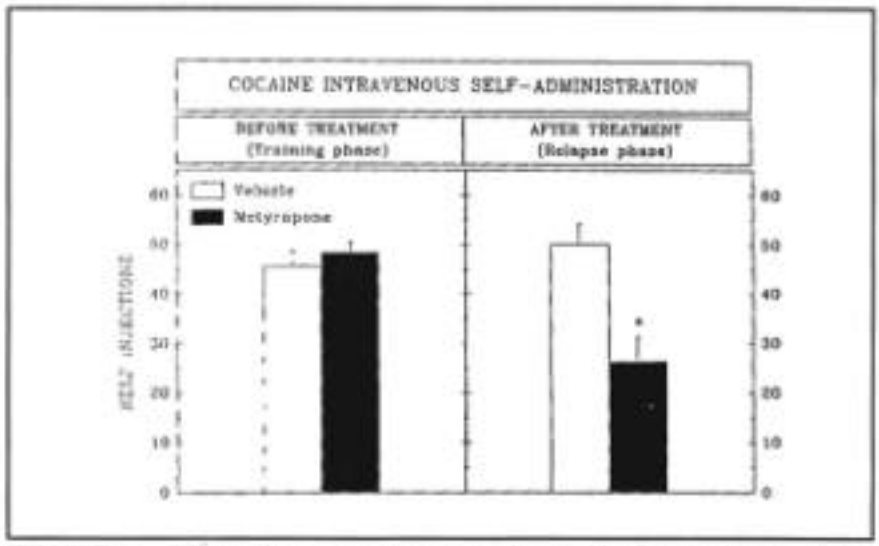

FIGURE 8. *Effect of metyrapone on cocaine self-administration. Bars represent the mean±SEM of the number of injections over the last 5 days of testing in the training phase and the first 5 days of testing in the relapse phase. The two phases were separated by 5 days of acute withdrawal and 8 days of metyrapone treatment (100 mg/kg SC twice a day). Animals in the control (N = 6) and metyrapone (N = 5) group did not differ for cocaine intake before treatment (training phase). In contrast, after treatment (relapse phase) cocaine intake was significantly reduced in animals receiving metyrapone. During the relapse phase the metyrapone treatment was continued.*

effects. These results throw light on the possible role of stress-induced corticosterone secretion in adaptation. Glucocorticoids are thought to prevent an overreaction of physiological mechanisms designed to protect the organism from the effects of stressors. This protective role of glucocorticoids in adaptation to stress is generally attributed to the peripheral action of the hormones and the central effects are rather overlooked. The positive reinforcing effects of glucocorticoids could extend the protection to the central nervous system, helping the individual to defend himself from the highly aversive effects of stress, thereby enabling him to better cope with the stress. However, a particularly high sensitivity to the reinforcing effects of corticosterone, such as that shown by HRs, may have adaptive side effects. Higher

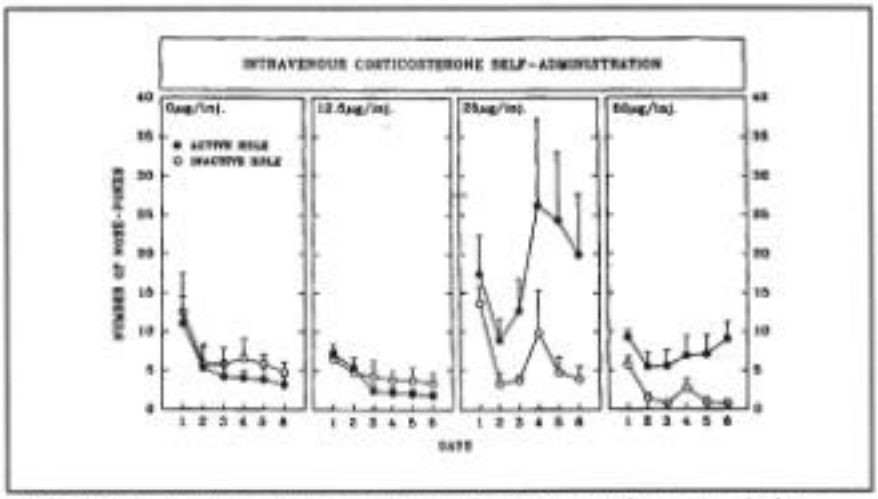

FIGURE 9. *Number of nosepokes in the active and inactive holes during 6 days of testing for corticosterone IV self-administration. Corticosterone-induced self-administration at doses of 25 and 50 µg/inj is indicated by the higher number of nosepokes in the hole eliciting corticosterone injections (active) compared to the control hole (inactive).*

sensitivity to corticosterone may underlie the propensity to seek novel and intense experiences, as well as the higher predisposition to drug abuse shown by individuals with sensation-seeking personality traits.

INTERACTIONS BETWEEN STRESS, CORTICOSTERONE, AND DOPAMINE IN DETERMINING INDIVIDUAL VULNERABILITY TO PSYCHOSTIMULANTS

The data outlined in the previous paragraphs show that stress, cortico-sterone, and dopaminergic activity by themselves can influence the propensity of an individual to develop psychostimulant self-administration. It will be now analyzed if these three factors can be organized in a pathophysiological chain determining vulnerability to addiction. For this purpose, the authors will take into account, step by step, the possible dependence of the effects of one factor upon the activation of the others. More precisely, the first paragraph will analyze if stress-induced sensitization of drug effects depends on stress-induced corticosterone secretion; the second paragraph will analyze if an increase in corticosterone levels can increase the activity of mesencephalic dopaminergic neurons; and the third and

last paragraph will take into account the role played by stress-induced corticosterone secretion on the dopaminergic effects of stress.

Stress, Corticosterone, and Vulnerability to Psychostimulants

Stress-induced sensitization of the behavioral effects of psychostimulants depends on corticosterone. Three lines of observations support this statement. First, blockade of stress-induced corticosterone secretion totally suppresses the increase in the locomotor response to amphetamine induced by different stressful experiences, such as repeated restraint (Deroche et al. 1992*a*) or food restriction (Deroche et al. 1993*a*). Second, repeated injections of corticosterone, at doses that raise the levels of the hormone in the range of those produced by stress, induce sensitization of the locomotor response to amphetamine (Deroche et al. 1992*b*). Third, animals made vulnerable to drugs by previous stressful experiences present an enhanced corticosterone secretion. For example, rats submitted to prenatal stress (Maccari et al. 1995), repeated tail-pinch (Piazza et al. 1991*b*), social aggression (Haney et al., unpublished results; Miczek et al. 1994), or fixed social hierarchy (Maccari et al. 1991), show both a higher propensity to develop amphetamine self-administration and a longer stress-induced corticosterone secretion.

In conclusion, these observations suggest that stress-induced corticosterone secretion may be one of the hormonal mechanisms by which stressful experiences enhance vulnerability to drugs.

Corticosterone and Dopamine

The existence of a pathophysiological chain made by stress, corticosterone, and dopamine implies that glucocorticoids can control the activity of mesencephalic dopaminergic neurons. A set of results recently obtained in the authors' laboratory suggest that glucocorticoids have state-dependent effects on the activity of dopaminergic neurons (Piazza et al., in press). The administration of corticosterone, at doses that induce an increase in the levels of the hormone similar to those induced by stress, increases extracellular levels of dopamine in the nucleus accumbens, but only when the hormone is administered in the dark phase (around 20 percent increase), which corresponds to the period of activity in rodents. Administration of corticosterone during the light period is without effects. Furthermore, in the dark period, the effects of corticosterone on dopamine are higher when the hormone is administered contingently to eating (around 80 percent increase) than when it is

administered in basal conditions. State-dependent effects of glucocorticoids on dopamine are in agreement with previous literature data. First, the effect of corticosterone on membrane potentials is dependent on background neuronal activity (Joels and De Kloet 1992). Second, behavioral effects of glucocorticoids can be different in different periods of the circadian cycle (Kumar and Leibowitz 1988; Temple and Leibowitz 1989), being higher during the dark phase as compared to the light one.

Individual differences also exist in the dopaminergic effects of cortico-sterone. Similarly to what is observed for the reinforcing effects of corticosterone (Piazza et al. 1993*a*), HR animals are more sensitive than LRs to the dopaminergic effects of this hormone. Thus, in response to the administration of the same dose of corticosterone, HRs show an increase in extracellular concentrations of dopamine in the nucleus accumbens that is double the one of LRs. The higher sensitivity to the dopaminergic effects of corticosterone may be the neurobiological substrate of the higher sensitivity to the reinforcing effects of corticosterone observed in HRs.

In conclusion, corticosterone can stimulate the activity of mesencephalic dopaminergic neurons, and these effects are higher in animals that are vulnerable to develop psychostimulant and corticosterone self-administration. This interaction between corticosterone and dopamine is compatible with the hypothesis that these two factors may interact in determining vulnerability to addiction.

Stress, Corticosterone, and Dopamine

In the previous paragraph it has been shown that stress-induced increase in vulnerability to drugs could be mediated by an increase in the activity of dopaminergic neurons and depend on stress-induced corticosterone secretion. This hormone, in turn, can stimulate the activity of the mesencephalic dopaminergic transmission. In order to complete the picture of the interactions between stress, corticosterone, and dopamine, the dependence of the dopaminergic effects of stress on corticosterone should be analyzed.

The dopaminergic response to stress is decreased in subjects in which stress-induced corticosterone secretion is suppressed (Rougé-Pont et al., unpublished results). The increase in extracellular concentrations of dopamine in the nucleus accumbens induced by 10 minutes of tail-pinch is lower in subjects in which corticosterone levels have been

fixed in the range of basal ones by an adrenalectomy associated with a corticosterone pellet implantation (ADX+pellet). Such corticosterone pellets release a stable amount of corticosterone in the range of basal physiological levels (Meyer et al. 1979). In contrast, stress-induced increase in accumbens dopamine is similar to the one of controls if ADX+pellet rats receive, concomitantly with the stress, an intraperitoneal injection of cortico-sterone (3 mg/kg). The injection of corticosterone at this dose raises the levels of the hormone in the range of those observed during stress (Rougé-Pont et al., unpublished results).

Stress-induced corticosterone secretion has different effects on the dopaminergic response to stress of HR and LR rats (Piazza et al., in press). Thus, blockade of stress-induced corticosterone secretion does not modify the dopaminergic response to stress in animals resistant to develop psychostimulant self-administration (LRs). In contrast, the enhanced dopaminergic response to stress that characterizes vulnerable subjects (HRs) is suppressed by blockade of stress-induced cortico-sterone secretion. In other words, after an adrenalectomy associated with an implantation of a corticosterone pellet, HR rats show an identical dopaminergic response to stress as that of LRs that, in turn, are not modified by this manipulation of corticosterone secretion.

In conclusion, stress-induced corticosterone secretion may be one of the biological mechanisms by which life experiences increase the activity of dopaminergic neurons. This last observation supports the hypothesis that stress, corticosterone, and mesencephalic dopaminergic neurons may be organized in a pathophysiological chain determining vulnerability to addiction.

CONCLUSIONS

The results that have been outlined in the previous paragraphs offer two principal considerations: First, the development of psychostimulant abuse does not seem to be the simple consequence of the proper effects of these substances, but rather the result of their interaction with specific individual substrates. Differences in the propensity to develop psychostimulant intake can be evidenced in animals that have equal access to the drug in stable laboratory conditions. Such individual differences do not arise from uncontrolled experimental errors, since they can be predicted by unconditioned spontaneous behaviors. Furthermore, in animals, vulnerability to take

drugs is associated with a higher propensity to seek other reinforcing stimuli such as novelty or food. The latter results suggest that drug abuse may be the symptom of a more general behavioral disorder, which underlies different addictive behaviors. Second, stress, corticosterone, and mesencephalic dopaminergic neurons may be organized in a pathophysiological chain determining vulnerability to addiction. More precisely, an increased corticosterone secretion, spontaneously present in certain individuals or induced by stress in others could, by increasing the activity of mesencephalic dopaminergic neurons, determine a predisposed state that enhances the probability that the encounter with rewarding or novel stimuli can result in their abuse. The possibility to modulate the behavioral and dopaminergic responses to psychostimulants by pharmacological manipulations of corticosterone secretion, suggests that manipulations of this endocrine system may constitute the ground for new therapeutic strategies of drug abuse.

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AUTHORS

Pier Vincenzo Piazza
Chargé de Recherche INSERM

Véronique Deroche
Chargé de Recherche INSERM

Françoise Rougé-Pont
Ingegneur de Recherche INSERM

Michel Le Moal
Professeur Institut Universitaire de France

Psychobiologie des Comportements Adaptatifs
INSERM U259
Université de Bordeaux II
Domaine de Carreire
Rue Camille Saint-Saëns
33077 Bordeaux Cedex
FRANCE

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