Stress, Glucocorticoids, and Mesencephalic Dopaminergic Neurons: A Pathophysiological Chain Determining Vulnerability to Psychostimulant Abuse

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INTRODUCTION: VULNERABILITY TO DRUGS AND DRUG ABUSE

It is common knowledge that enormous individual differences exist in drug intake by humans (De Wit et al. 1986). A large number of people have tried drugs at least once, but for most of them drug use experiences are restricted to a single or a few incidents. Among those who persist in taking drugs, drug use can remain an occasional behavior limited, for example, to weekends or parties. Only some 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 drug abuse may be explained from two very different points of view. The first is a drug-centered vision of addiction that sees drug abuse as the consequence of the modifications induced in the brain by repeated drug intake. Through the development of tolerance, sensitization, and conditioning, repeated exposure to the drug induces drug dependence—the real cause of abuse. In this viewpoint, vulnerable individuals are those who have greater chances to be, and actually are, the most exposed to the drug because of the environment that surrounds them (peer and/or social pressure are the most often cited causes). The second view may be considered an individual-centered theory of addiction that regards drug abuse as the consequence of a peculiar, pathological reaction to the drug. From this perspective, vulnerable individuals are those who, because of a specific functional

state of the biological substrates that interact with the drug, can experience such a peculiar drug effect.

Understanding the role of the drug and the role of the individual in determining drug abuse is fundamental to defining the goals of addiction therapies. If a drug-centered vision can fully explain drug abuse, then addiction should be considered a neurotoxic disease and the treatment should be achieved by combining two strategies. The first is to suppress the drug's availability, and the second is to reverse the biological effects of repeated drug intake. Conversely, if drug abuse originates from the interaction of the drug with a peculiar individual substrate, the treatment approach should not differ from that of other behavioral pathologies. A therapy should be developed to counteract the biological peculiarity that makes some subjects respond to the drug in a pathological way.

An Experimental Approach to Individual Vulnerability to Drugs

The ideal experiment designed to understand the role of individual biological features in determining vulnerability to drug abuse must fulfill one essential requirement: All subjects should have equal access to the drug under identical environmental conditions. This condition is almost impossible to realize in human studies, but it can be easily achieved in experimental research in animals. Animal research may actually contrib-ute to the understanding of drug abuse because animals self-administer, either intravenously (IV) or orally (Pickens and Harris 1968; Schuster and Thompson 1969; Weeks 1962), almost all the drugs abused by humans (Yokel 1987).

In stable laboratory conditions individual differences in the propensity to develop drug intake are easily evidenced in rodents (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 IV self-administration (Piazza et al. 1989, 1990b, 1991b, 1993b). Propensity to develop psychostimulant self-administration not only exists, but can also be predicted by the individual behavioral re-sponse to stressful situations such as exposure to a novel environment (Piazza et al. 1989, 1990b, 1991b). 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-adminis-tration can be illustrated by dividing animals into subgroups on the

basis of their locomotor responses to novelty (Piazza et al. 1989,-1990b,1991b). 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 group median. When HR and LR animals are tested for IV self-administration of amphetamine (between 10 and 30 micrograms per injection (µg/inj)), HRs will acquire self-administration whereas LRs will not (Piazza et al. 1989, 1990b, 1991b). Similar results have been obtained when HRs and LRs are tested for self-administration of cocaine (100µg/inj) (Piazza et al., unpublished data).

Differences in psychostimulant 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. 1990b, 1991b, 1993b). This result suggests that LRs are not insensitive to the reinforcing effects of the drugs at the dose used, but that psychostimu-lants have a higher efficacy as reinforcers in HRs.

HR and LR rats also differ in other psychostimulant-induced behaviors. HRs show a higher sensitivity to the psychomotor effects of amphetamine and cocaine, displaying a higher locomotor response to systemic and intra-accumbens injection of these drugs (Exner and Clark 1993; Hooks et al. 1991, 1992a, 1992b, 1992c; Piazza et al. 1989, 1991b). HRs also seem more prone to develop conditioning of the motor effects of amphet-amine. Following low doses of amphetamine (0.5 milligrams per kilogram (mg/kg)), conditioning of amphetamine-induced locomotion is developed by HRs but not by LRs (Jodogne et al. 1994).

HRs and LRs also differ in amphetamine-induced sensitization, though contrasting results have been found. Some authors have shown that sensitization is exclusively developed by HRs (Hooks et al. 1992c), whereas in other laboratories (Exner and Clark 1993; Piazza et al. 1989) sensitization appears more prevalent in LRs. In these experiments, after sensitization LRs no longer differed from HRs in amphetamine-induced locomotion and self-administration (Exner and Clark 1993; Piazza et al. 1989). Variation in sensitization of HR and LR animals under 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 sensiti-zation in HRs is under the control of the environmental cues associated with the effect of the drug, whereas sensitization is not under such 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; when the influence of conditioning is minimized, sensitization may appear exclusively in LRs.

Animal research has shown that vulnerability to develop drug abuse may depend on preexisting individual differences, and propensity to develop self-administration can vary among individuals having equal access to the drug under identical laboratory conditions. This propensity can also be predicted in rodents by unconditioned spontaneous behaviors such as locomotor response to novelty. Prediction of drug intake by independent behavioral measures is an important finding for three reasons. First, it identifies that individual differences in drug intake are not due to uncon-trolled experimental errors. Second, it supports the hypothesis that indi-vidual differences in drug intake result from differences in the biological substrates interacting with the drug. Third, it provides an essential tool for the study of the biological basis of individual vulnerability to drugs. Indeed, the comparison of vulnerable and resistant subjects after repeated testing for self-administration or other drug-mediated responses would not allow differentiation between drug-induced and preexisting differences.

Factors Determining Individual Vulnerability to Psychostimulants

Research on the origins of individual vulnerability to drugs has principally focused on psychostimulant drugs. However, individual differences in the vulnerability to self-administer opioids have also been reported (Glick et al. 1992) and may correlate with differences in vulner-ability to psychostimulants (Deroche et al. 1993b). In particular, the specific roles of mesencephalic dopaminergic neurons, stress, glucocorti-coids, and the interactions between these three factors have been exten-sively studied in determining vulnerability to cocaine and amphetamine. The observed effects of these three factors upon vulnerability to psycho-stimulant use are briefly reviewed below.

Mesolimbic Dopaminergic Neurons. These neurons, and in particular an increase in the activity of their projection to the nucleus accumbens, may be a crucial factor in determining a greater vulnerability to the reinforcing effects of psychostimulants. Indeed,

the reinforcing properties of this class of drugs seem to be mediated by the psychostimulant-induced increase in extra-cellular concentration of dopamine (DA) in the nucleus accumbens (Koob and Bloom 1988; LeMoal and Simon 1991). Specific neurochemical lesions of the dopaminergic projection to the nucleus accumbens decrease or are extinguished depending on the self-administered dose of IV psycho-stimulants (Roberts et al. 1977, 1980, 1982). Furthermore, animals will self-administer psychostimulants directly into the nucleus accumbens (Hoebel et al. 1983). 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-hydroxy-N,N-di-n-propyl-2-aminotetralin (7-OHDPAT), a dopaminergic agonist showing the highest affinity for dopamine type 3 (D3) receptors, is more potent than agonists with a higher affinity for D1 or D2 dopaminergic receptors (Caine and Koob 1993). D3 receptors are localized primarily in the nucleus accumbens, whereas D1 and D2 receptors have a widespread distribution throughout the brain (Sokoloff et al. 1990).

Stressful Situations. Stressful situations affect the activity of mesencephalic dopaminergic neurons, which in turn modify behavioral response to stress. Three main interactions between stress and DA can be identified. First, following the pioneer work of Thierry and coworkers (1976), it is now widely accepted that acute exposure to most 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 psychostimulants (Kalivas and Stewart 1991; Robinson and Becker 1986; Robinson and Berridge 1993). Third, behaviors that are specifically elicited by situations that may be interpreted as stressful depend on the activity of mesencephalic dopaminergic neurons. For example, the polydipsia (Falk 1961) displayed by food-deprived rats on a fixed interval of food reinforcement schedule (schedule-induced polydipsia) or the compulsive eating induced in satiated rats by a mild pinching of the tail (Antelman et al. 1976) are decreased by neurochemical lesions of dopaminergic mesencephalic neurons (Antelman et al. 1975; Robbins and Koob 1980).

Glucocorticoids. Glucocorticoids may be one of the factors that mediate the increase in stress-induced dopaminergic activity. 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. 1983, 1985). Third, suppression of corticosterone secretion suppresses DA-dependent behavioral responses to stress such as schedule-induced polydipsia (Levine and Levine 1989) or wheel running (Lin et al. 1988).

Working Hypothesis. On the basis of these observations it has been hypothesized (Piazza et al. 1991a) that stress, glucocorticoids, and dopaminergic neurons may be organized in a pathophysiological chain that determines vulnerability to develop drug abuse. In order to develop this hypothesis, the authors first review the relationship that exists between each of these factors and the propensity to develop IV self-administration of psychostimulants. Then the possible interactions in a pathophysiological chain are examined.

Dopaminergic Neurons and Vulnerability to Psychostimulants

Comparisons between HRs and LRs have shown that a higher vulnerability to develop drug self-administration is associated with a higher dopaminergic activity in the nucleus accumbens. Postmortem studies have shown that animals vulnerable to develop IV self-administration of psychostimulants (HRs) have a higher 3,4-dihydroxyphenylacetic acid (DOPAC)/DA ratio in the nucleus accumbens compared with more resistant subjects (LRs). The DOPAC/DA ratio, which is considered an indirect index of the release of DA, is higher in HRs than in LRs both under basal conditions and after exposure to novelty (Piazza et al. 1991c). Microdialysis studies have confirmed and extended these results. Quanti-tative microdialysis has shown that, in basal conditions, extracellular concentrations of DA in HR rats are three times higher than that observed in LRs (Hooks et al. 1992a). Furthermore, the percentage increase in extracellular concentrations of DA in response to stress (Rougé-Pont et al. 1993) or to the intraperitoneal (IP) administration of cocaine (Hooks et al. 1991) is also greater in HRs than in LRs.

Greater dopaminergic activity in the nucleus accumbens is not simply associated with a higher propensity to develop amphetamine self-administration; a causal relationship may also exist between these two

variables. Very different experimental manipulations, such as 6-hydroxydopamine (6-OHDA) lesion of the amygdala (Deminière et al. 1988) or electrolytic lesion of the raphe (Simon et al. 1980), that have a common ability to increase dopaminergic activity in the nucleus accum-bens (Hervé et al. 1981; Simon et al. 1988) also increase propensity to acquire amphetamine self-administration.

The possible origins of the hyperactivity of the dopaminergic projection to the accumbens in vulnerable subjects is certainly a very important question. One of the possible causes, a hyperactive hypothalamic-pituitary-adrenal (HPA) axis, is analyzed in detail in the following paragraphs. However, another possible cause that should not be disregarded is the low dopaminergic activity in the prefrontal cortex which characterizes HR rats (Piazza et al. 1991c). This factor may be relevant because dopaminergic activity in the prefrontal cortex exercises inhibitory control on the activity of the dopaminergic projections in the nucleus accumbens (Louilot et al. 1989). Furthermore, lesions of the dopaminergic terminal fields in the prefrontal cortex increase the propensity to self-administer cocaine (Schenk et al. 1991).

Thus, results obtained with multiple approaches converge in suggesting that increased dopaminergic activity in the nucleus accumbens may increase the vulnerability of an individual to develop psychostimulant self-administration.

Stress and Vulnerability to Psychostimulants

An increase in vulnerability to psychostimulants can be induced by several conditions considered as models of stress. The first evidence of the strong control that stressors exercise on psychostimulant self-adminis-tration is probably that from Carroll and coworkers (1979), showing that food restriction increases the efficacy of psychostimulants to act as rein-forcers in a self-administration test. 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 subjected to situations that seem relevant from an ethological point of view, for instance social isolation (Deroche et al. 1994; Schenk et al. 1987), social aggression (Haney et al., unpublished results; Miczek et al. 1994), and fixed social hierarchy in highly competitive colonies (Maccari et al. 1991). Furthermore, more artificial and physical stressors such as tail-pinch (Piazza et al. 1990a) or electric foot-shock

(Goeders and Guerin 1994), also increase propensity to develop psychostimulant self-administration.

Very early experiences such as prenatal stress can also increase vulnera-bility to psychostimulants (Deminière et al. 1992). An increase in the propensity to develop amphetamine self-administration has been observed in adult rats (4 months old) whose mothers had been submitted to a re-straint 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 spon-taneously vulnerable subjects. Similar to the comparison between HRs and LRs, prenatally stressed rats show a greater locomotor response to novelty and amphetamine as compared with controls (Deminière et al. 1992).

Two recent papers by Shaham and Stewart (1994, 1995) increased the knowledge of the influences of stress on drug self-administration. These authors clearly point out that the effects of stress are not limited to a faster acquisition of self-administration; they also relate to a higher seeking for the drug that can be seen in stressed subjects and in other experimental conditions. These authors found that, over a large range of doses, the breaking point for heroin self-administration is consistently higher in stressed than in control rats (Shaham and Stewart 1994). Furthermore, in rats in which responding for the drug has been extinguished by a long period of extinction, a single stressful experience can induce a relapse in responding for the drug (Shaham and Stewart 1995). Shaham and Stewart (1994) also raised some interesting methodological considera-tions: Although stressed and control rats differ in their breaking points in a progressive ratio schedule, they are almost identical for the rate of self-administration when a fixed ratio (FR) schedule is used. This result indi-cates that when a low fixed ratio is used, measurement of the rate of re-sponding as a function of dose may not reveal differences in vulnerability to the reinforcing properties of drugs.

These results obtained with multiple approaches agree in suggesting thatstressful experiences, either very early in life or during adulthood, may increase the vulnerability of an individual to develop drug self-administration.

Glucocorticoids and Vulnerability to Psychostimulants

Corticosterone, the main glucocorticoid in the rat, seems to have a large influence on the vulnerability to psychostimulants. This hormone facilitates psychomotor and reinforcing effects of amphetamine and/or cocaine, and individual differences in stress-induced corticosterone secretion correlate with individual differences in vulnerability to drugs.

Psychomotor Effects. Psychomotor effects of cocaine depend on basal corticosterone secretion. Suppression of endogenous glucocorticoids by adrenalectomy reduces the locomotor response to cocaine by approxi-mately 50 percent, and a corticosterone replacement treatment, which reinstates diurnal basal levels of the hormone, totally suppresses the effects of adrenalectomy (Marinelli et al. 1994). Suppression of gluco-corticoid secretion similarly reduces the locomotor response to an intra-accumbens injection of cocaine (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-acumbens injection of psychostimulants depends on DA (Delfs et al. 1990; Kelly and Iversen 1976).

Reinforcing Effects. Reinforcing effects of psychostimulants are also increased by corticosterone. Administration of corticosterone induces the acquisition and maintenance of amphetamine self-administration in LR rats that do not acquire this behavior otherwise (Piazza et al. 1991b). Furthermore, in HR rats, 8 days of treatment with metyrapone (the inhibitor of corticosterone synthesis) reduced the intake of cocaine by approximately 50 percent during a testing for relapse (Piazza et al. 1994). More precisely, in this study animals were permitted to acquire and stabilize cocaine self-administration (100 µg/inj) over 10 days. They were then submitted to a drug-free period of 4 days followed by 8 days ofmetyrapone treatment (100 mg/kg twice a day). After this 12-day period (4 days drug free followed by 8 days of metyrapone), the testing for relapse started. Animals had access to cocaine for 5 days during the metyrapone treatment. Metyrapone treatment seemed devoid of major nonspecific motor effects because it did not modify exploratory and food-directed behaviors (Piazza et al. 1994).

Individual Differences. Individual differences in corticosterone secretion can predict vulnerability to drug intake. HR rats have a

longer lasting corticosterone secretion in response to different stressors such as exposure to a novel environment and restraint (Piazza et al. 1991b). Furthermore, the levels of corticosterone 2 hours after exposure to stress are positively correlated with the intake of amphetamine during self-administration (Piazza et al. 1991b). The higher locomotor response to novelty observed in HRs also depends on corticosterone. Suppression of individual differences in stress-induced corticosterone secretion, by fixing corticosterone levels in the range of basal diurnal levels, induces a decrease in HRs' locomotor response to novelty to levels that do not differ from LRs (Piazza et al., unpublished results). Thus, an increase in cortico-sterone secretion may be a factor in increasing individual vulnerability to psychostimulant drugs.

Interactions Between Stress, Corticosterone, and DA 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-adminis-tration. The following paragraphs discuss whether these three factors may be organized in a pathophysiological chain determining vulnerability to drugs. The possible dependence of the effects of one factor upon the activation of the others is considered, including whether stress-induced sensitization of drug effects depends on changes in the reactivity of dopaminergic neurons or stress-induced corticosterone secretion. The authors also discuss whether an increase in corticosterone levels can increase the activity of mesencephalic dopaminergic neurons and the role played by stress-induced corticosterone secretion on the dopaminergic effects of stress.

Stress, Dopamine, and Vulnerability to Psychostimulants

The first step in the study of the possible relevance of the interactions between stress, corticosterone, and DA in determining vulnerability to drugs is to ask if the stress-induced increase in vulnerability to psycho-stimulants may be mediated by an increase in the activity of dopami-nergic neurons.

A large body of evidence indicates that stress-induced sensitization of the behavioral effects of drugs may be mediated by an increase of the response of mesencephalic dopaminergic neurons to the drug. Reviewing this litera-ture it is not the purpose of the present synthesis; the reader is referred to several very good reviews on this subject

(Kalivas and Stewart 1991; Robinson and Becker 1986; Robinson and Berridge 1993; Stewart and Badiani 1993).

Briefly, it is well known that stress activates dopaminergic activity and that repeated stress induces a long-lasting increase in the dopaminergic response to psychostimulants. A criticism to these observations may be that, although stressors increase the activity of dopaminergic neurons, many other neuronal systems are also activated and modified and could mediate the increase in vulnerability to drugs induced by stressors. For this reason, it was important to examine if a stimulation more selective than stress that also activates the dopaminergic neurons may similarly increase vulnerability to psychostimulants. For this purpose, the effects of repeated tail-pinch were compared with those of repeated amphetamine injections. Indeed, repeated stress and repeated amphetamine injections seem to have comparable effects on the activity of dopaminergic neurons (Antelman et al. 1980). It was found that the two treatments had compar-able effects and increased both amphetamine-induced locomotion and self-administration in a similar way (Piazza et al. 1990a).

An increase in the activity of mesencephalic dopaminergic neurons thus may be the neural mechanism through which stressful experiences enhance vulnerability to drugs.

Stress, Corticosterone, and Vulnerability to Psychostimulants

Stress-induced sensitization of the behavioral effects of psychostimulants depends on corticosterone. Three lines of observations support this state-ment. First, blockade of stress-induced corticosterone secretion totally suppresses the increase in the locomotor response to amphetamine induced by different stressful experiences such us repeated restraint (Deroche et al. 1992a) or food restriction (Deroche et al. 1993a). Second, repeated injections of corticosterone, at doses that increase the levels of the hor-mone to the range induced by stress, induce sensitization of the loco-motor response to amphetamine (Deroche et al. 1992b). Third, animals made vulnerable to drugs by previous stressful experiences present an enhanced corticosterone secretion. For example, rats submitted to pre-natal stress (Maccari et al., in press), repeated tail pinch (Piazza et al. 1991b), 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.

Stress-induced corticosterone secretion seems to control both the development and the expression of stress-induced sensitization to the behavioral effects of psychostimulants. Thus, metyrapone treatment suppresses food restriction-induced sensitization of the locomotor effects of cocaine when administration is started before the beginning of the food restriction or when administration is started 8 days later (i.e., when the sensitization is already established) (Rougé-Pont et al. 1994). 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 composed of stress, cortico-sterone, and DA implies that glucocorticoids can control the activity of mesencephalic dopaminergic neurons. Although postmortem studies indicate that synthetic glucocorticoids such as dexamethasone can control the metabolism of catecholaminergic neurons, more recent in vivo inves-tigations have provided contrasting results. For example, Imperato and coworkers (1989, 1991) have shown, by means of microdialysis, that although corticosterone can induce a moderate increase in extracellular DA concentrations, such an effect is only obtained with doses that induce plasmatic levels of the hormone that are above the physiological range. In contrast, Mittleman and coworkers (1992), using in vivo voltammetry, have shown an important increase in extracellular DA concentrations following an injection of corticosterone that should maintain the levels of the hormone in the physiological range.

Variability of results in dopaminergic effects of glucocorticoids may be explained by possible state-dependent effects of these hormones. This hypothesis is supported by three observations. First, the effect of cortico-sterone on membrane potentials is dependent on background neuronal activity (Joels and De Kloet 1992). For example, the effects of cortico-sterone on hippocampal CA1 cells are evident only if these neurons are in a depolarized state, whereas glucocorticoids are without effect in resting conditions. Second, behavioral effects of glucocorticoids can differ in different periods of the circadian cycle (Kumar and Leibowitz 1988; Temple and Leibowitz 1989). In adrenalectomized rats, central or systemic corticosterone administration is able to induce intense eating during the first hours of the dark period, but has poor or no effects during the light phase or at the end of the dark period. Third, neurochemical effects of

glucocorticoids may vary among individuals. Rats with a higher predisposition to develop amphetamine self-administration (HRs) are four times more sensitive to the behavioral effects of corticosterone than resistant subjects (LRs) (Piazza et al. 1993a).

Results recently obtained in the authors' laboratory support state-dependent effects of glucocorticoids on the activity of dopaminergic neurons (Piazza et al. 1993c). The administration of corticosterone, at doses that induce an increase in the levels of the hormone similar to those induced by stress, increases extracellular DA levels in the nucleus accum-bens. However, the intensity of the dopaminergic effects of corticoste-rone is influenced by the contingent situation and individual differences. First, the effects of the hormone are influenced by the dark/light cycle, being significant only when the hormone is administered in the dark phase, which corresponds to the period of activity in rodents. Second, in the dark period, the effects of corticosterone on DA are greater (around 80 percent increase) when the hormone is administered contingent to eating than when it is administered in basal conditions (around 20 percent increase). Third, dopaminergic effects of corticosterone vary profoundly among individuals. HR animals, compared with LRs, show a greater increase in extracellular DA concentrations in response to the same dose of corticosterone.

The effects of corticosterone on DA may be proportional to the level of dopaminergic activity at the moment when corticosterone levels rise. Several observations support this hypothesis. First, in the rat, the meta-bolic activity of dopaminergic neurons is greater during the dark period than in the light one (Paulson and Robinson 1994). Second, eating is a behavioral activity that induces an increase in dopaminergic activity (Hoebel et al. 1989). Third, the effects of corticosterone on DA are amplified in animals (such as HRs) that have a higher level of dopami-nergic activity in the nucleus accumbens (Piazza et al. 1991c; Hooks et al. 1991, 1992a).

Corticosterone can thus stimulate the activity of mesencephalic dopaminergic neurons. These effects are greater in animals that are vulnerable to develop psychostimulant self-administration. This interaction between corticosterone and DA is compatible with the hypothesis that these two factors may interact in determining vulnerability to psychostimulants.

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 is dependent on stress-induced corticoste-rone 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.

Dopaminergic response to stress is decreased in subjects in which stress-induced corticosterone secretion is suppressed (Rougé-Pont et al., unpub-lished results). The increase in extracellular DA concentrations in the nucleus accumbens induced by 10 minutes of tail pinch is less in subjects in which corticosterone levels have been fixed in the basal range by adrenalectomy (ADX) associated with 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 DA is similar to that of controls if ADX + pellet rats receive, concomitantly with the stress, an IP injection of corticosterone (3 mg/kg). The injection of corticosterone at this dose increases the hormone levels to the range of those observed during stress (Rougé-Pont et al., unpublished results).

Stress-induced corticosterone secretion has different effects on the dopami-nergic response to stress by HR and LR rats (Piazza et al. 1993c). Thus, blockade of stress-induced corticosterone secretion does not modify the dopaminergic response to stress in animals resistant to developing psycho-stimulant self-administration (LRs). In contrast, the enhanced dopami-nergic response to stress that characterizes vulnerable subjects (HRs) is suppressed by blockade of stress-induced corticosterone secretion. In other words, after an adrenalectomy associated with the implantation of a cortico-sterone pellet, HR rats show an identical dopaminergic response to stress as LRs; this response, in turn, is not modified by manipulation of corticoste-rone secretion.

Thus, stress-induced corticosterone secretion may be one of the biological mechanisms by which life experiences increase the activity of dopami-nergic neurons. This last observation supports the hypothesis that stress, corticosterone, and mesencephalic

dopaminergic neurons may be organized in a pathophysiological chain determining vulnerability to psychostimulant abuse.

CONCLUSIONS

The results outlined in this chapter permit one to draw three principal conclusions. First, the development of psychostimulant abuse it is not the simple consequence of the proper effects of these substances, but the result of their interaction with specific individual substrates. Thus, differences in the propensity to develop psychostimulant intake are evidenced in animals having 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.

Second, stress, corticosterone, and mesencephalic dopaminergic neurons may be organized in a pathophysiological chain determining vulnerability to psychostimulants. More precisely, an increased corticosterone secre-tion, spontaneously present in certain individuals or induced by stress in others, could increase the activity of mesencephalic dopaminergic neurons and thereby enhance the probability (i.e., predispose) that psychostimu-lant administration will result in its abuse.

Third, the possibility of modulating the behavioral and dopaminergic re-sponses to psychostimulants by pharmacological manipulations of cortico-sterone secretion may open new therapeutic strategies for drug abuse.

REFERENCES

Antelman, S.M.; Eichler, A.J.; Black, C.A.; and Kocan, D. Interchangeability of stress and amphetamine in sensitization. Science 207:329-331, 1980.

Antelman, S.M.; Rowland, N.E.; and Fisher, A.E. Stimulation bound ingestive behavior: A view from the tail. Physiol Behav 17:743-748, 1976.

Antelman, S.M.; Szechtman, H.; Chin, P.; and Fisher, A.E. Tail pinch induced eating, gnawing and licking behavior in rats: Dependence on the nigrostriatal dopamine system. Brain Res 99:319-337, 1975.

Bohus, B.; De Kloet, E.R.; and Veldhuis, H.D. Adrenal steroids and behavioural adaptation: Relationship to brain corticoid receptors. In:-Ganten, D., and Pfaff, D., eds. Adrenal Actions on Brain. New York: Springer-Verlag, 1982. pp. 108-148.

Caine, S.B., and Koob, G.F. Modulation of self-administration in the rat through D-3 dopamine receptors. Science 260:1814-1816, 1993.

Carroll, M.E.; France, C.P.; and Meisch, R.A. Food deprivation increases oral and intravenous drug intake in rats. Science 205:319-321, 1979.

Dantzer, R., and Mormède, P. Stress in farm animals: A need for reevaluation. J Anim Sci 56:6-18, 1983.

Davis, W.M., and Smith, S.G. Catecholaminergic mechanisms of reinforcement: Direct assessment by drug self-administration. Life Sci 20:483-492, 1977.

De Wit, H.; Uhlenhuth, E.H.; and Johanson, C.E. Individual differences in the reinforcing and subjective effects of amphetamine and diazepam. Drug Alcohol Depend 16:341-360, 1986.

Delfs, J.M.; Schreiber, L.; and Kelly, A.E. Microinjection of cocaine in the nucleus accumbens elicts locomotor activation in the rat. JNeurosci 10:303-310, 1990.

Deminière, J.M.; Le Moal, M.; and Simon, H. Catecholamine neuronal systems and (+)-amphetamine administration in the rat. In: Sandler,M., ed. Progress in Catecholamine Research. 6th ed. New York: Alan R. Liss, Inc., 1988. pp. 489-494.

Deminière, J.M.; Piazza, P.V.; Guegan, G.; Abrous, N.; Maccari, S.; LeMoal, M.; and Simon, H. Increased locomotor response to novelty and propensity to intravenous amphetamine self-administration in adult offspring of stressed mothers. Brain Res 586:135-139, 1992.

Deminière, J.M.; Piazza, P.V.; Le Moal, M.; and Simon, H. Experimental approach to individual vulnerability to psychostimulant addiction. Neurosci Biobehav Rev 13:141-147, 1989.

Deroche, V.; Piazza, P.V.; Casolini, P.; Le Moal, M.; and Simon, H. Sensitization to the psychomotor effects of amphetamine and morphine induced by food restriction depends on corticosterone secretion. Brain Res 611:352-356, 1993a.

Deroche, V.; Piazza, P.V.; Casolini, P.; Maccari, S.; Le Moal, M.; and Simon, H. Stress-induced sensitization to amphetamine and morphine psychomotor effects depend on stress-induced corticosterone secretion. Brain Res 598:343-348, 1992a.

Deroche, V.; Piazza, P.V.; Le Moal, M.; and Simon, H. Individual differences in the psychomotor effects of morphine are predicted by reactivity to novelty and influenced by corticosterone secretion. Brain Res 623:341-344, 1993b.

Deroche, V.; Piazza, P.V.; Le Moal, M.; and Simon, H. Social isolation-induced enhancement to the psychomotor effects of morphine depends on corticosterone secretion. Brain Res 640:136-139, 1994.

Deroche, V.; Piazza, P.V.; Maccari, S.; Le Moal, M.; and Simon, H. Repeated corticosterone administration sensitizes the locomotor response to amphetamine. Brain Res 584:309-313, 1992b.

Donovan, D.M. Assessment of addictive behaviors. Implications of an emerging biopsychosocial model. In: Donovan, D.M., and Marlatt,-

G.A., eds. Assessment of Addictive Behaviors. London: Hutchinson, 1988. pp. 3-48.

Exner, E., and Clark, D. Behaviour in the novel environment predicts responsiveness to d-amphetamine in the rat: A multivariate approach. Behav Pharmacol 4:47-56, 1993.

Falk, J.L. Production of polydipsia in normal rats by an intermediate food schedule. Science 133:195-196, 1961.

Glick, S.D; Merski, C.; Steindorf, S.; Wang, S.; Keller, R.W.; and Carlson, J.N. Neurochemical predisposition to self-administer morphine in rats. Brain Res 578:215-220, 1992.

C Goeders, N.E., and Guerin, G.F. Non-contingent electric footshock facilitates the acquisition of intravenous cocaine self-administration in rats. Psychopharmacology 114:63-70, 1994.

Härfstrand, A.; Fuxe, K.; Cintra, A.; Agnati, L.F.; Zini, I.; Wilkström,A.C.; Okret, S.; Zhao-Ying, Y.; Goldstein, M.; Steinbusch, H.; Verhofstad,A.; and Gustafsson, J.A. Glucocorticoid receptor immunoreactivity in monoaminergic neurons in the rat brain. Proc Natl Acad Sci U S A 83:9779-9783, 1986.

Hervé, D.; Simon, H.; Blanc, G.; Le Moal, M.; Glowinski, J.; and Tassin,J.P. Opposite changes in dopamine utilization in the nucleus accumbens and the frontal cortex after electrolytic lesion of the median raphe in the rat. Brain Res 216:422-428, 1981.

Hoebel, G.B.; Monaco, P.A.; Hernandez, L.; Aulisi, E.F.; Stanley, G.B.; and Lenard, L. Self-injection of amphetamine directly into the brain. Psychopharmacology 81:158-163, 1983.

Hoebel, G.B.; Monaco, P.A.; Hernandez, L.; Schwartz, D.H.; Mark, G.P.; and Hunter, G.A. Microdialysis studies of brain norepinephrine, serotonin and dopamine release during ingestive behavior: Theoretical and clinical implications. Ann NY Acad Sci 575:171-193, 1989.

Hooks, M.S.; Colvin, A.C.; Juncos, J.L.; and Justice, J.B., Jr. Individual differences in basal and cocaine stimulated extracellular dopamine in the nucleus accumbens using quantitative microdialysis. Brain Res 587:306-312, 1992a.

Hooks, M.S.; Jones, G.H.; Lien, B.J.; and Justice, J.B., Jr. Sensitization and individual differences to IP amphetamine, cocaine or caffeine following repeated intracranial amphetamine infusions. Pharmacol Biochem Behav 43:815-823, 1992b.

Hooks, M.S.; Jones, G.H.; Neill, D.B.; and Justice, J.B., Jr. Individual differences in amphetamine sensitization: Dose-dependent effects. Pharmacol Biochem Behav 41:203-210, 1992c.

Hooks, M.S.; Jones, G.H.; Smith, A.D.; Neill, D.B.; and Justice, J.B., Jr. Response to novelty predicts the locomotor and nucleus accumbens dopamine response to cocaine. Synapse 91:21-128, 1991.

Imperato, A.; Puglisi-Allegra, S.; Casolini, P.; and Angelucci, L. Changes in brain dopamine and acetylcholine release during and following stress are independent of the pituitary-adrenocortical axis. Brain Res 538:111-117, 1991.

Imperato, A.; Puglisi-Allegra, S.; Casolini, P.; Zocchi, A.; and Angelucci,L. Stress-induced enhancement of dopamine and acetylcholine release in limbic structure role of corticosterone. Eur J Pharmacol 165:337-339, 1989.

Jodogne, C.; Marinelli, M.; Le Moal, M.; and Piazza, P.V. Animals predisposed to develop amphetamine self-administration show higher susceptibility to develop contextual conditioning of both amphetamine-induced hyperlocomotion and sensitization. Brain Res 657:236-244, 1994.

Joels, M., and De Kloet, E.R. Control of neuronal excitability by corticosteroid hormones. Trends Neurosci 15:25-30, 1992.

Kalivas, P.W., and Stewart, J. Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. Brain Res Rev 16:223-244, 1991.

Kelly, P.H., and Iversen, S.D. Selective 6-OHDA-induced destruction of mesolimbic dopaminergic neurons: Abolition of psychostimulant-induced locomotor activity in rats. Eur J Pharmacol 40:45-56, 1976.

Koob, G.F., and Bloom, F.E. Cellular and molecular basis of drug dependence. Science 242:715-723, 1988.

Knych, E.T., and Eisenberg, R.M. Effect of amphetamine on plasma corticosterone in conscious rat. Neuroendocrinology 29:110-118, 1979.

Kumar, B.A., and Leibowitz, S.F. Impact of acute corticosterone administration on feeding and macronutrient self-selection patterns. Am J Physiol 254:R222-R228, 1988.

Le Moal, M., and Simon, H. Mesocorticolimbic dopamine network: Functional and regulatory roles. Physiol Rev 71:155-234, 1991.

Levine, R., and Levine, S. Role of the pituitary-adrenal hormones in the acquisition of schedule-induced polydipsia. Behav Neurosci 103:621-637, 1989.

Lin, W.; Singer, G.; and Papasava, M. The role of adrenal corticosterone in schedule-induced wheel running. Pharmacol Biochem Behav 30:101-106, 1988.

Louilot, A.; Le Moal, M.; and Simon, H. Opposite influences of dopaminergic pathways to the prefrontal cortex or the septum on the dopaminergic transmission in the nucleus accumbens. An in vivo voltammetric study. Neuroscience 29:45-56, 1989.

Maccari, S.; Piazza, P.V.; Deminière, J.M.; Lemaire, V.; Mormède, P.; Simon, H.; Angelucci, L.; and Le Moal, M. Life events-induced decrease of type I corticosteroid receptors is associated with reduced corticosterone feedback and enhanced vulnerability to amphetamine self-administration. Brain Res 547:7-12, 1991.

Maccari, S.; Piazza, P.V.; Kabbaj, M.; Barbazanges, A.; Simon, H.; and LeMoal, M. Adoption reverses the long-term impairment in gluco-corticoid feedback induced by prenatal stress. J Neurosci, in press.

Marinelli, M.; Piazza, P.V.; Deroche, V.; Maccari, S.; Le Moal, M.; and Simon, H. Corticosterone circadian secretion differentially facilitates dopamine-mediated psychomotor effect of cocaine and morphine. JNeurosci 14:2724-2731, 1994.

Meyer, J.S.; Micco, D.J.; Stephensons, B.S.; Krey, L.C.; and McEwen,B.S. Subcutaneous implantation method for chronic glucocorticoid replacement therapy. Physiol Behav 22:867-870, 1979.

Miczek, K.A.; Vivian, J.A.; and Valentine, J.O. “Social Stress: Cocaine Reinforcing and Stimulus Effects.” Abstract presented at the annual meeting of the Society for Neuroscience, Miami Beach, FL, November 13-18, 1994.

Mittleman, G.M.; Blaha, C.D.; and Phillips, A.G. Pituitary-adrenal and dopaminergic modulation of schedule-induced polydipsia: Behavioral and neurochemical evidence. Behav Neurosci 106:402-408, 1992.

O'Brien, C.P.; Ehrman, R.N.; and Terns, J.N. Classical conditioning in human opioid dependence. In: Goldeberg, S.R., and Stolerman, I.P., eds. Behavioral Analysis of Drug Dependence. London: Academic Press, 1986. pp. 329.

Paulson, P.E., and Robinson, T.E. Relationship between circadian changes in spontaneous motor activity and dorsal versus ventral striatal dopamine neurotransmission as assessed with on-line microdialysis. Behav Neurosci 3:624-635, 1994.

Piazza, P.V.; Deminière, J.M.; Le Moal, M.; and Simon, H. Factors that predict individual vulnerability to amphetamine self-administration. Science 245:1511-1513, 1989.

Piazza, P.V.; Deminière, J.M.; Le Moal, M.; and Simon, H. Stress- and pharmacologically-induced behavioral sensitization increases vulnerability to acquisition of amphetamine self-administration. Brain Res 514:22-26, 1990a.

Piazza, P.V.; Deminière, J.M.; Maccari, S.; Mormède, P.; Le Moal, M.; and Simon, H. Individual reactivity to novelty predicts probability of amphetamine self-administration. Behav Pharmacol 1:339-345, 1990b.

Piazza, P.V.; Deminière, J.M.; Maccari, S.; Le Moal, M.; Mormède, P.; and Simon, H. Individual vulnerability to drug self-administration: Action of corticosterone on dopaminergic systems as a possible pathophysiological mechanism. In: Wilner, P., and Scheel-Kruger, J., eds. The Mesolimbic Dopamine System: From Motivation to Action. New York: Alan R. Liss, 1991a. pp. 473-495.

Piazza, P.V.; Deroche, V.; Deminière, J.M.; Le Moal, M.; and Simon, H. Reinforcing properties of corticosterone demonstrated by

intravenous self-administration. Possible biological basis of sensation-seeking. Proc Natl Acad Sci U S A 90:11738-11742, 1993a.

Piazza, P.V.; Maccari, S.; Deminière, J.M.; Le Moal, M.; Mormède, P.; and Simon, H. Corticosterone levels determine individual vulnerability to amphetamine self-administration. Proc Natl Acad Sci U S A 88:2088-2092, 1991b.

Piazza, P.V.; Marinelli, M.; Jodogne, C.; Deroche, V.; Rougé-Pont, F.; Maccari, S.; Le Moal, M.; and Simon, H. Inhibition of corticosterone synthesis by metyrapone decreases cocaine-induced locomotion and relapse of cocaine self-administration. Brain Res 658:259-264, 1994.

Piazza, P.V.; Mittleman, G.; Deminière, J.M.; Le Moal, M.; and Simon,H. Relationship between schedule-induced polydipsia and amphetamine intravenous self-administration. Individual differences and role of experience. Behav Brain Res 55:185-193, 1993b.

Piazza, P.V.; Rougé-Pont, F.; Deminière, J.M.; Kharouby, M.; Le-Moal,M.; and Simon, H. Dopaminergic activity is reduced in the prefrontal cortex and increased in the nucleus accumbens of rats predisposed to develop amphetamine self-administration. Brain Res 567:169-174, 1991c.

Piazza, P.V.; Rougé-Pont, F.; Deroche, V.; Kharouby, M.; Le Moal, M.; and Simon, H. "Corticosterone Sensitivity to Drugs of Abuse: Role of Dopamine Release." Abstract presented at the annual meeting of the Society for Neuroscience, Washington, DC, November 7-12, 1993c.

Pickens, R.; and Harris, W.C. Self-administration of d-amphetamine by rats. Psychopharmacologia (Berlin) 12:158-163, 1968.

Risner, M.E., and Jones, B.E. Role of noradrenergic and dopaminergic processes in amphetamine self-administration. Pharmacol Biochem Behav 5:477-482, 1976.

Robbins, T.W., and Koob, G.F. Selective disruption of displacement behavior by lesion of the mesolimbic DA system. Nature 285:409-412, 1980.

Roberts, D.C.S.; Corcoran, M.E.; and Fibiger, H.C. On the role of ascending catecholaminergic systems in intravenous self-administration of cocaine. Pharmacol Biochem Behav 6:615-620, 1977.

Roberts, D.C.S., and Koob, G.F. Disruption of cocaine self-administration following 6-hydroxydopamine lesions of the ventral tegmental area in rats. Pharmacol Biochem Behav 17:901-904, 1982.

Roberts, D.C.S.; Koob, G.F.; Klonoff, P.; and Fibiger, H.C. Extinction and recovery of cocaine self-administration following 6-hydroxy-dopamine lesions of the nucleus accumbens. Pharmacol Biochem Behav 12:781-787, 1980.

Roberts, D.C.S., and Vickers, G. Atypical neuroleptics increase self-administration of cocaine: An evaluation of a behavioral screen for antipsychotic activity. Psychopharmacology 82:135-139, 1984.

Roberts, D.C.S., and Vickers, G. The effect of haloperidol on cocaine self-administration is augmented with repeated administrations. Psychopharmacology 93:526-528, 1987.

Robinson, T.E., and Becker, J.B. Enduring changes in brain and behavior produced by chronic amphetamine administration: A review and evaluation of animal models of amphetamine psychosis. Brain Res Rev 11:157-198, 1986.

Robinson, T.E., and Berridge, K.C. The neural basis of drug craving: An incentive sensitization theory of addiction. Brain Res Rev 18:247-291, 1993.

Rothschild, A.J.; Langlais, P.J.; Schatzberg, A.F.; Miller, M.M.; Saloman, M.S.; Lerbinger, J.E.; Cole, J.O.; and Bird, E. The effect of a single acute dose of dexamethasone on monoamine and metabolite levels in the rat brain. Life Sci 36:2491-2505, 1985.

Rothchild, A.J.; Schatzberg, A.F.; Langlais, P.J.; Cole, J.O.; and Bird,E.D. "Dexamethasone Elevates Dopamine in Human Plasma and Rat Brain." Paper presented at the annual meeting of the American College of Neuropsychopharmacology, San Juan, Puerto Rico, December 1983.

Rougé-Pont, F.; Deroche, V.; Marinelli, M.; Kharouby, M.; Le Moal, M.; Simon, H.; and Piazza, P.V. “Glucocorticoids and Drugs of Abuse (IV): Influence of Stress-induced Corticosterone Secretion on Stress-induced Increase in Cocaine's Effects on Accumbens Dopamine.” Abstract presented at the annual meeting of the Society for Neuroscience, Miami Beach, FL, November 13-18, 1994.

Rougé-Pont, F.; Piazza, P.V.; Kharouby, M.; Le Moal, M.; and Simon, H. Higher and longer stress-induced increase in dopamine concentrations in the nucleus accumbens of animals predisposed to amphetamine self-administration. A microdialysis study. Brain Res 602:169-174, 1993.

Sachser, N. Short-term responses of plasma norepinephrine, epinephrine, glucocorticoid and testosterone titers to social and non-social stressors in male guinea pigs of different social status. Physiol Behav 39:11-20, 1986.

Schenk, S.; Horger, B.A.; Peltier, R.; and Shelton, K. Supersensitivity to the reinforcing effect of cocaine following 6-hydroxydopamine lesions to the median prefrontal cortex in rats. Brain Res 543:227-235, 1991.

Schenk, S.; Lacelle, G.; Gorman, K.; and Amit, Z. Cocaine self-adminis-ration in rats influenced by environmental conditions: Implications for the etiology of drug abuse. Neurosci Lett 81:227-231, 1987.

Schuster, C.R., and Thompson, T. Self-administration and behavioral dependence on drugs. Ann Rev Pharmacol 9:483-502, 1969.

Selye, H. Stress: The Physiology and the Pathology of Exposure to Stress. Montreal: Acta Medica Publication, 1950.

Shaham, Y., and Stewart, J. Exposure to mild stress enhances the reinforcing efficacy of intravenous heroin self-administration in rats. Psychopharmacology 114:523-527, 1994.

Shaham, Y., and Stewart, J. Stress reinstates heroin-seeking in drug-free animals: An effect mimicking heroin, not withdrawl. Psychopharmacology 116:334-341, 1995.

Simon, H.; Stinus, L.; and Le Moal, M. Effets de la lésion des noyaux du raphé sur l'auto-administration de d-amphétamine chez le rat: Augmentation considérable de l'appétence aux toxiques. CR Acad Sci (III) 290:225-258, 1980.

Simon, H.; Taghzouti, K.; Gozlan, H.; Studler, J.M.; Louilot, A.; Herve,D.; Glowinski, J.; Tassin, J.P.; and Le Moal, M. Lesion of dopaminergic terminals in the amygdala produces enhanced locomotor response to d-amphetamine and opposite changes in dopaminergic activity in prefrontal cortex and nucleus accumbens. Brain Res 447:335-340, 1988.

Sokoloff, P.; Giros, B.; Martres, M.P.; Bouthenet, M.L.; and Schwartz,J.C. Molecular cloning and characterization of a novel dopamine receptor (D3) as a target for neuroleptics. Nature 347:146-151, 1990.

Stewart, J., and Badiani, A. Tolerance and sensitization to the behavioral effects of drugs. Behav Pharmacol 4:289-312, 1993.

Temple, D.L., and Leibowitz, S.F. PVN steroid implants: Effects on feeding patterns and macronutrient selection. Brain Res Bull 23:553-560, 1989.

Thierry, A.M.; Tassin, J.P.; Blanc, G.; and Glowkinski, J. Selective activation of the mesocortical dopaminergic system by stress. Nature 263:242-244, 1976.

Weeks, J.R. Experimental morphine addiction: Method for automatic intravenous injections in unrestrained rats. Science 138:143-144, 1962.

Yokel, R.A. Intravenous self-administration: Response rates, the effects of pharmacological challenges, and drug preferences. In: Bozarth,M.A., ed. Methods of Assessing the Reinforcing Properties of Abused Drugs. New York: Springer-Verlag, 1987. pp. 1-34.

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