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Opponent Process Model and Psychostimulant Addiction

GEORGE F. KOOB, S. BARAK CAINE, LOREN PARSONS, ATHINA MARKOU AND FRIEDBERT WEISS

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KOOB, G. F., S. B. CAINE, L. PARSONS, A. MARKOU AND F. WEISS. *Opponent process model and psychostimulant addiction.* PHARMACOL BIOCHEM BEHAV **57**(3) 513–521, 1997.—There are many sources of reinforcement in the spectrum of cocaine dependence that contribute to the compulsive cocaine self-administration or loss of control of cocaine intake that constitutes the core of modern definitions of dependence. The development of withdrawal has long been considered an integral part of drug addiction but has lost its impact in the theorization of drug dependence because of new emphasis on the neurobiological substrates for the positive-reinforcing properties of drugs. The present treatise reviews the neurobiological substrates for the acute positive reinforcing effects of cocaine and what is beginning to be known about the neurobiological substrates of cocaine withdrawal. The concept of motivational or affective withdrawal is reintroduced, which reemphasizes opponent process theory *as a model* for the motivational effects of cocaine dependence. The same neural substrates hypothesized to be involved in the acute reinforcing properties of drugs (basal forebrain regions of nucleus accumbens and amygdala) are hypothesized to be altered during chronic drug treatment to produce the negative motivational states characterizing drug withdrawal. Within these brain regions, both the neurochemical system(s) on which the drug has its primary actions and other neurochemical systems may undergo adaptations to chronic presence of the drug. An understanding of the adaptations of the motivational systems of the brain accompanying cocaine dependence leads to important predictions not only about the etiology, treatment, and prevention of cocaine addiction but also about the vulnerability of these motivational systems in non-drug-induced psychopathology. © 1997 Elsevier Science Inc.

Opponent process Drug dependence Psychostimulants Drug withdrawal

COCAINE abuse and cocaine dependence continue to be a major part of the overall worldwide problem of drug abuse. In the United States, heavy cocaine use (past 30-day prevalence rates) is approximately 1.5 million in 1995, and there are still approximately 400,000 (1995 figures) crack cocaine users reporting frequent use of cocaine (41). The cost to society is significant in terms of human suffering, crime, and social ills. These statistics emphasize the need for an understanding of the actual mechanisms of dependence, with the hope that an understanding of such mechanisms will lead to new and innovative methods for treatment and prevention.

Drug addiction or substance dependence is usually defined as a compulsion to take a drug coupled with loss of control over drug intake. This loss of control can take many forms, including inability to regulate drug intake, inability to continue drug abstinence, and taking more drug than was intended (3). An important issue for research is how this loss of control develops and what processes contribute to its development. Tolerance and withdrawal, adaptive processes that are hypothesized to be the body's attempt to counter the acute effects of the drug, are key elements in a neuroadaptive view of drug dependence. Such conceptualizations have been explored at all levels of drug dependence research, from the behavioral to the molecular (14,23,28,55).

At the behavioral level, a motivational hypothesis called opponent process theory has particular relevance to dependence phenomena (55,56). Recently, attempts have been made to explore the neurobiological bases for opponent motivational processes by using behavioral models to measure the motivational effects of drug reward and withdrawal in animals. The hypothesis is that the neuroadaptive changes responsible for changes in motivation associated with dependence may be the key to the understanding of dependence (61):

> In terms of the pain–pleasure principle, is the speed-freak impelled to self-inject methamphetamine in closely spaced doses and to relapse in the Haight–Ashbury environment after crashing there because of the memories of the highs produced by the first dose or of the lows that followed? Similar questions may be asked about cocaine self-administration and marihuana

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smoking. However, answers to these questions in terms of the pain–pleasure principle will not be meaningful; rather, the answers should be sought in terms of the biochemical–neurophysiological mechanisms that are involved in the development of successive counter-adaptations to the initial receptor actions of such drugs and in reinforcement.

OPPONENT PROCESS THEORY

Opponent process theory (56) postulates that many affective states, pleasant or aversive, are automatically opposed by centrally mediated mechanisms that reduce the intensity of these states. It is hypothesized that positive reinforcers such as drugs engage positive hedonic processes that are opposed by negative hedonic processes. The positive hedonic processes are hypothesized to be simple and stable and to follow administration of the drug closely in time. In contrast, the negative hedonic processes are of longer latency, slow to build up strength, and slow to decay. Within this framework, the intense pleasure of the cocaine "rush" or "high" is presumed to reflect a positive hedonic process, and the negative mood state associated with the drug wearing off or abstinence following a binge is presumed to reflect the opponent negative hedonic process (28,55). These opponent processes have also been hypothesized to contribute to the development of tolerance (52), and compensatory responses have been observed in some opiate analgesia studies that would explain tolerance (53).

ACUTE REWARDING EFFECTS OF COCAINE: NEUROBIOLOGICAL SUBSTRATES

Identification of neurobiological substrates for neuroadaptive processes hypothesized to occur as part of an opponent process requires basic knowledge of the initial response that becomes compromised to elicit the opponent process. In the case of cocaine, this would be the acute hedonic response. In fact, much is known about the acute rewarding effects of cocaine as measured in animal studies. Acute administration of cocaine or amphetamine lowers thresholds for rewarding brain stimulation (32), an effect hypothesized to reflect an activation of brain reward systems (57) (see Fig. 1).

Animals will readily self-administer cocaine (46), and studies of intravenous self-administration of drugs have strongly

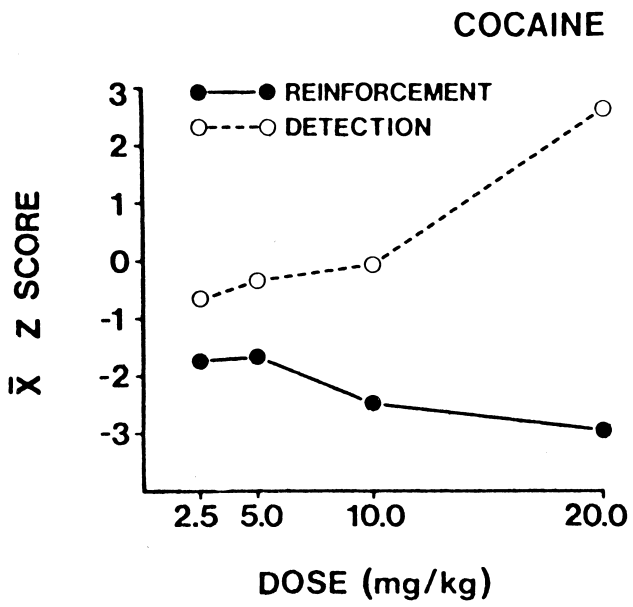

FIG. 1. Effects of cocaine on brain stimulation reward thresholds and brain stimulation detection thresholds. For detection threshold measures, the initial noncontingent stimulus varied in intensity (at subreward levels), and the second or response-contingent stimulus was held constant at a rewarding intensity (above threshold) to maintain responding. Each point is the mean z score ± SEM, which is based on the difference between the means for each animal of the thresholds after administration of vehicle and drug, divided by the standard deviation of all thresholds after vehicle administration. A z score of 2 indicates a significant deviation from vehicle treatment sessions. These results show that acute administration of cocaine can lower brain stimulation reward thresholds (e.g., facilitate central reward). The cocaine treatment does not affect the ability of the rat to make a discrimination because detection of a nonrewarding stimulus is not altered (detection threshold). (Error bars not shown indicate SEM less than the diameter of the symbols in this illustration.) [Taken with permission from Kornetsky and Bain (31).]

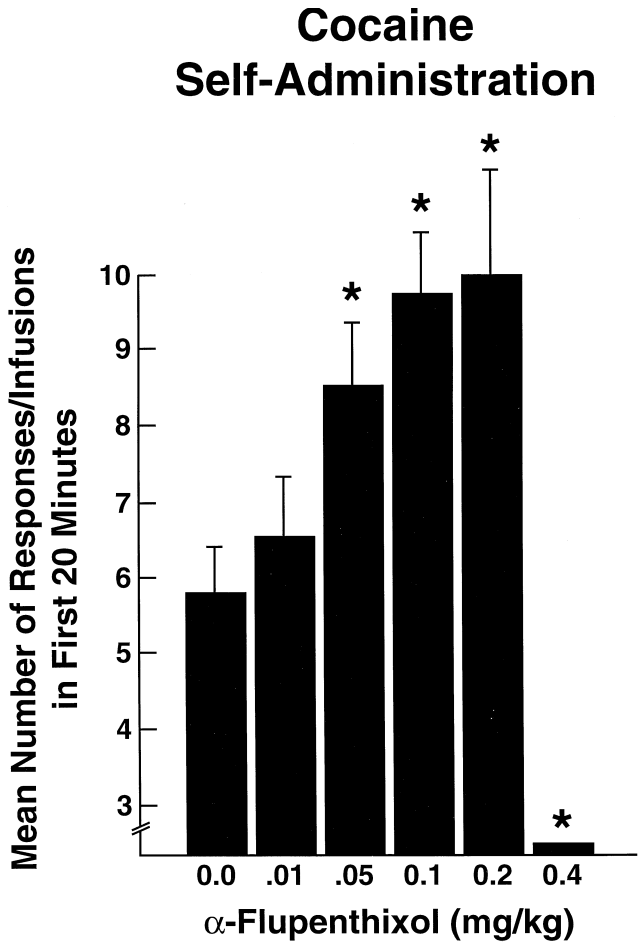

FIG. 2. Effects of pretreatment with the dopamine antagonist alpha-flupenthixol on cocaine self-administration in the rat. Alpha-flupenthixol, a long-acting, mixed D-1/D-2 antagonist, was injected 2.5 h before the session. The data represent the effects of alpha-flupenthixol on the loading dose (infusions in the first 20 min of the 3-h test sessions) in cocaine self-administering animals. Asterisks reflect differences between each treatment dose and the appropriate no-drug control ($p < 0.05$, Newman–Keuls test). [Taken with permission from Ettenberg et al. (19).]

implicated dopamine in the reinforcing effects of cocaine and amphetamines. Low doses of dopamine receptor antagonists, when injected systemically, reliably increase cocaine and amphetamine self-administration in rats (16,19,66) (see Fig. 2). The animals appear to compensate for decreases in the magnitude of reinforcement with an increase in cocaine self-administration (or a decrease in the interinjection interval), a response similar to that seen upon lowering the unit dose of cocaine. This suggests that a partial blockade of dopamine receptors produces a partial blockade of the reinforcing actions of cocaine, a hypothesis supported by recent studies showing a dopamine antagonist-induced shift to the right of the full dose–effect function for cocaine self-administration (5,12). Investigations of the effects of agonists and antagonists selective for different dopamine receptor subtypes have provided evidence for a role of D-1 (10,30,51), D-2 (5,51,64), and D-3 (9,12) receptors in cocaine self-administration.

ROLE OF THE DOPAMINE D-1 RECEPTOR SUBTYPE IN THE REINFORCING ACTIONS OF COCAINE

Previous work has established that the reinforcing properties of cocaine in nondependent rats may involve neural circuitry that includes dopamine receptors in the region of the nucleus accumbens (10,26,35). D-1 dopamine receptors have been implicated in the reinforcing actions of cocaine based on both selective antagonist and agonist studies (5,11,24,25,30), and several brain locations and several of the specific dopamine receptor subtypes may be involved in this reinforcing action. D-1 antagonists either increase self-administration of cocaine doses on the descending limb of the U-shaped dose–effect function relating cocaine dose and number of infusions, or they shift the entire dose–effect function to the right (5,11,24, 25,30) (see Fig. 3). These effects are consistent with an attenuation of the reinforcing properties of cocaine and are similar to those seen with decreases in the unit dose of cocaine. In addition, low doses of the benzazepine dopamine D-1 antagonists selectively reduce cocaine self-administration without altering food intake under a multiple schedule for food and cocaine (5,10).

In addition, results following microinjection of the D-1 antagonist SCH 23390 show that the shell region of the nucleus accumbens and the central nucleus of the amygdala are particularly sensitive sites (8) (see Fig. 4). In this study, rats trained to self-administer cocaine intravenously and implanted with bilateral cannulas aimed at the shell of the nucleus accumbens, the central nucleus of the amygdala, and the caudate nucleus showed a site-related decrease in the interinjection interval during the first 20 min following injection of microgram amounts of SCH 23390. The most sensitive site was the shell of the nucleus accumbens, whereas microinjections in the caudate nucleus had no effect during this time period. Interestingly, there was a moderate effect from microinjections into the central nucleus of the amygdala (8), and more recently injections into the bed nucleus of the stria terminalis have been shown to produce results similar to those observed in the amygdala (18).

ROLE OF THE DOPAMINE D-2 RECEPTOR SUBTYPE IN THE REINFORCING ACTIONS OF COCAINE

D-2 antagonists also increase self-administration of cocaine doses on the descending limb of the U-shaped dose–effect function relating cocaine dose and number of infusions and decrease cocaine self-administration in multiple schedule paradigms (5,6,24,30). However, response decrements in motor tasks appear to be more likely to be observed with D-2 antagonists (1). The effectiveness of D-2 antagonists in increasing the interinjection interval (30) and in shifting the dose–effect functions to the right appears to be limited, possibly because of the motor effects of these drugs (2,5). The basis for such differential effects may be the high density of D-2 receptors in the corpus striatum and the known motor function associated with this structure (2).

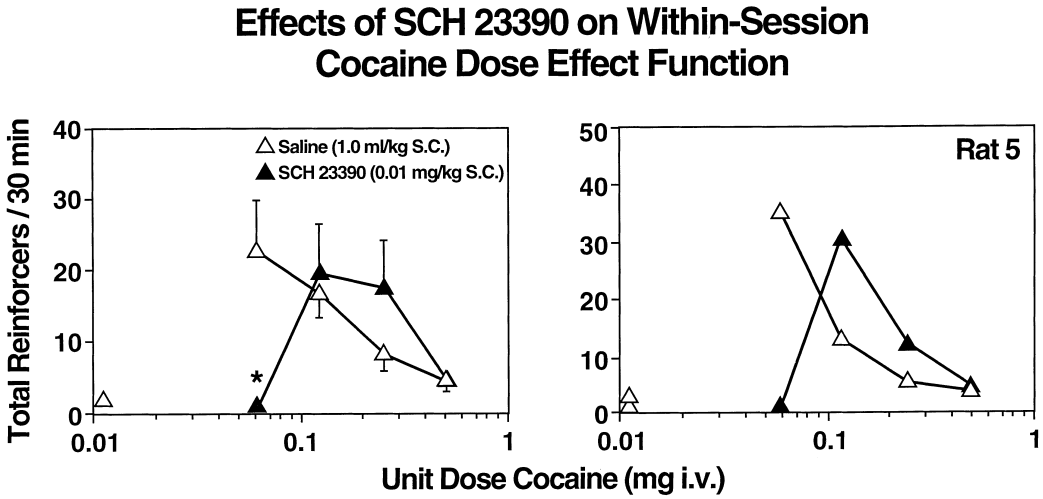

FIG. 3. Effects of pretreatment with the selective D-1 dopamine antagonist SCH 23390 on the cocaine self-administration dose–effect function relating dose of cocaine to the number of infusions. The left panel shows the effects of pretreatment with SCH 23390 (0.01 mg/kg SC) on the cocaine (0.06–0.5 mg) self-administration dose–effect function measured using the within-session dose–effect paradigm (n = 4). The right panel is the same as the left but for an individual rat. An individual rat is shown to emphasize that individual animals typically showed a shift to the right of the dose–effect function, but individual variability often masks such effects when presented as mean data. [Taken with permission from Caine and Koob (12).]

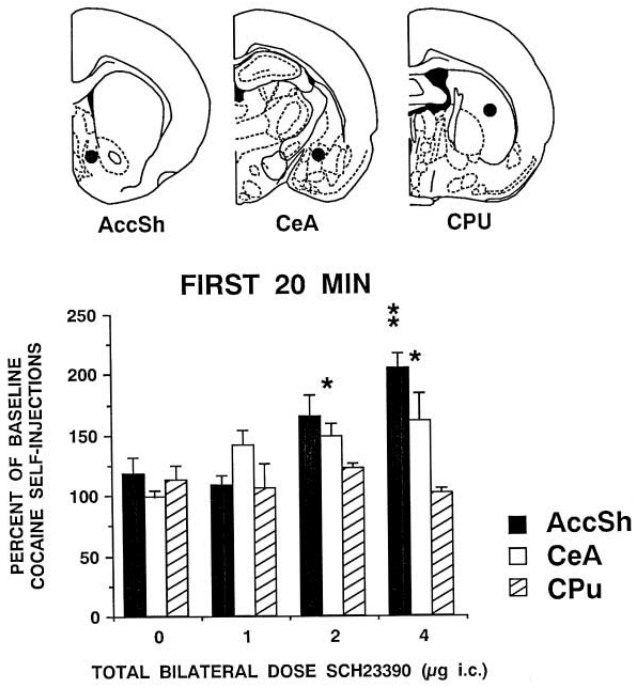

FIG. 4. Effects of the dopamine D-1 selective antagonist SCH 23390 on cocaine self-administration when directly injected into the shell of the nucleus accumbens, the amygdala, and the caudate nucleus of the rat. Doses of 0, 0.5, 1.0, 2.0, and 4.0 mg total dose were microinjected into the accumbens shell (AccSh), central amygdala (CeA), and dorsal striatum (CPu) in separate groups of rats. Values are group means and standard errors (n = 6/brain region). Data represent the first 20 min following injections. Three-hour totals showed no significant differences between the groups but an overall main effect of injection. Asterisks indicate significant differences from vehicle injection ($p < 0.05$, Newman–Keuls test). [Taken with permission from Caine et al. (8).]

ROLE OF THE DOPAMINE D-3 RECEPTOR SUBTYPE IN THE REINFORCING ACTIONS OF COCAINE

The dopamine D-3 receptor has recently been cloned and is expressed mainly in limbic structures such as the nucleus accumbens (34,54). Within this nucleus, the D-3 receptor is expressed primarily in medium-sized neurons of the rostral pole and ventromedial shell subdivisions but not in the core region (17).

The D-3 receptor subtype has also recently been implicated in the reinforcing properties of cocaine and other psychostimulants. The D-3 receptor-preferring agonist 7-OH-DPAT enhances cocaine reinforcement (9,12). 7-OH-DPAT administered to rats in intravenous solution with cocaine increases the interinjection interval during cocaine self-administration and, when injected subcutaneously, shifts the dose–effect function for cocaine to the left (see Fig. 5). This D-3 agonist was also self-administered by the rats at higher doses than those that decreased cocaine self-administration.

The mechanism by which D-3 agents modulate psychostimulant reinforcement remains to be established, however. A recent series of experiments was designed to explore the relationship between the reinforcing actions of cocaine and specific elements of the mesolimbic dopamine system in the basal forebrain by combining drug self-administration techniques with in vivo neurochemical approaches. In these experiments, nucleus accumbens dopamine levels were monitored by in vivo microdialysis while rats self-administered a combination of cocaine and quinelorane, a selective D-3 receptor agonist. Cocaine self-administration significantly elevated dopamine levels in the nucleus accumbens, as is well documented (43,45), and the addition of quinelorane to the cocaine solution significantly reduced the amount of self-administered cocaine, as was observed above with 7-OH-DPAT. In this study, the quinelorane systematically increased the interinjection interval without altering the regular pattern of self-administration (42). However, the addition of quinelorane to the self-administered cocaine solution significantly attenuated the cocaine-induced increase in dialysate dopamine levels (42).

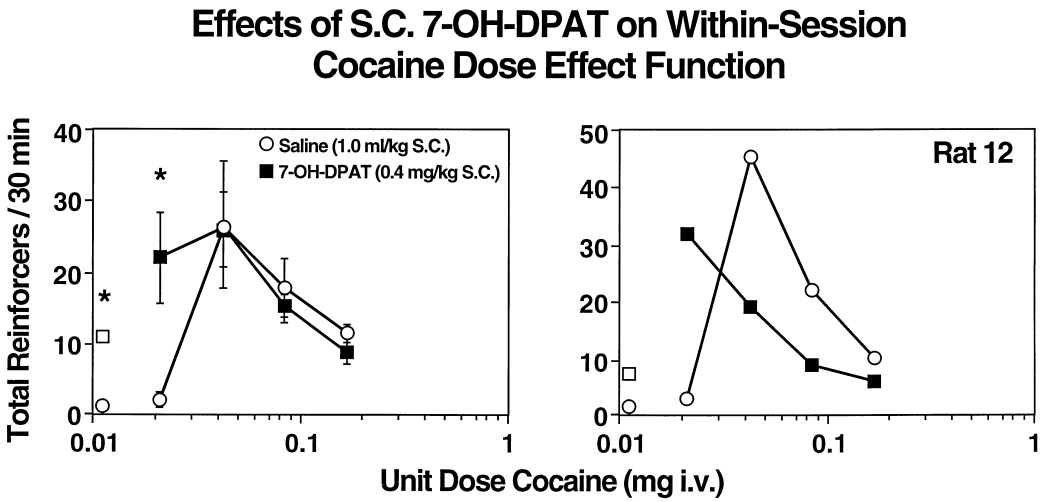

FIG. 5. Effects of the D-3 selective dopamine agonist 7-OH-DPAT on the cocaine self-administration dose–effect function relating dose of cocaine to the number of infusions. The left panel shows a group mean of seven rats; the right panel shows a single rat. An individual rat is shown to emphasize that individual animals typically showed a shift to the left of the dose–effect function, but individual variability often masks such effects when presented as mean data. The unit dose of cocaine was varied between test sessions. Small symbols adjacent to the vertical axis represent effect of saline substitution for cocaine. Asterisks indicate significant differences at that dose, simple main effects following a significant ANOVA interaction. Values represent means ± SEM. [Taken with permission from Caine and Koob (12).]

The changes in cocaine self-administration indicating that quinelorane increases the reinforcing effects of cocaine in the presence of reduced interstitial dopamine concentrations suggest that the effects of quinelorane are mediated postsynaptically. This hypothesis is supported by the finding that quinelorane alone was reliably self-administered when substituted for the cocaine/quinelorane solution, even though the neurochemical consequence of this self-administration is a further decrease in nucleus accumbens dopamine levels to below drug-free baseline concentrations. Also, it is unlikely that D-3 receptors work as direct terminal autoreceptors, because it has been demonstrated that there is a limited expression of D-3 receptors in dopamine-containing cells in the nucleus accumbens (17). One possibility is that the quinelorane-induced decrease in dopamine afflux in the present study reflects stimulation of long-loop feedback mechanisms that serve to decrease dopamine neuronal activity (7).

NEUROBIOLOGICAL CORRELATES OF OPPONENT PROCESSES: COCAINE WITHDRAWAL

Neuroadaptation has long been hypothesized to be the basis for drug tolerance and dependence (23), and a more recent formulation has argued that these neuroadaptations can be divided into both within-system and between-systems changes (28). In a within-system adaptation, the primary cellular response responsible for the acute hedonic effects of the drug would itself adapt to oppose and neutralize the drug's effects; persistence of the opposing effects after the drug disappears would produce the motivational withdrawal response. In a between-systems adaptation, cellular and molecular systems different from those responsible for the acute hedonic effects of the drug, triggered by the changes in the primary drug response neurons, would contribute to or produce the motivational effects of withdrawal after drug removal.

Cocaine withdrawal in humans in the outpatient setting is characterized by severe depressive symptoms combined with irritability, anxiety, and anhedonia lasting several hours to several days (i.e., the "crash") and may be one of the major motivating factors in the maintenance of the cocaine-dependence cycle (21). Inpatient studies have shown similar changes in mood and anxiety states, but they generally are much less severe (59).

Withdrawal signs associated with cessation of chronic drug administration are usually characterized by responses opposite the acute initial actions of the drug; however, few, if any, physical signs have ever been observed with cocaine and other indirect sympathomimetics. Also, while many of the overt *physical* signs associated with withdrawal from drugs such as alcohol and opiates can be easily quantified, *motivational* measures require more than simple observation in most cases. Nevertheless, motivational measures are extremely sensitive measures of drug withdrawal. Animal models for the motivational effects of drug withdrawal include: locomotor activity, operant schedules, place aversion to measure the aversive stimulus effects of withdrawal, intracranial self-stimulation (ICSS) behavior to assess changes in reward systems during the course of drug dependence, the elevated plus-maze to measure anxiogenic-like responses associated with withdrawal, and drug discrimination to characterize specific and nonspecific aspects of withdrawal (27). Several of these dependent variables have been used for psychostimulants to date: operant responding, locomotor activity, ICSS, and animal models of anxiety.

In animal studies, withdrawal has been studied using either repeated administration of cocaine over days and weeks or prolonged self-administration bouts (12–48 h). Withdrawal from prolonged self-administration of cocaine in rats results in a dose- and time-dependent increase in ICSS reward thresholds (37,43) (see Fig. 6), an effect that is opposite that of acute cocaine (38). In earlier studies, similar effects have been observed following withdrawal from chronic amphetamine administration (33). The increase in reward thresholds during cocaine withdrawal was reversed by treatment with the dopamine agonist bromocriptine (39) and attenuated by chronic treatment with the tricyclic antidepressant desmethylimipramine, with an injection regimen that produced a downregulation of beta-adrenergic receptors (36). Operant responding has also proved sensitive to cocaine withdrawal, with rats showing several days of suppressed operant responding following discontinuation of chronic cocaine injections (13).

Using in vivo microdialysis to assess extracellular dopamine levels in the nucleus accumbens before, during, and after a cocaine self-administration bout, extracellular dopamine levels in the nucleus accumbens were decreased 30–40% during cocaine withdrawal compared with presession levels (60). This dopamine decrease was correlated with the amount of cocaine consumed during the preceding binge and was maximal at the time points when maximal elevation in ICSS thresholds was observed (37). Similar decreases in basal extracellular dopamine

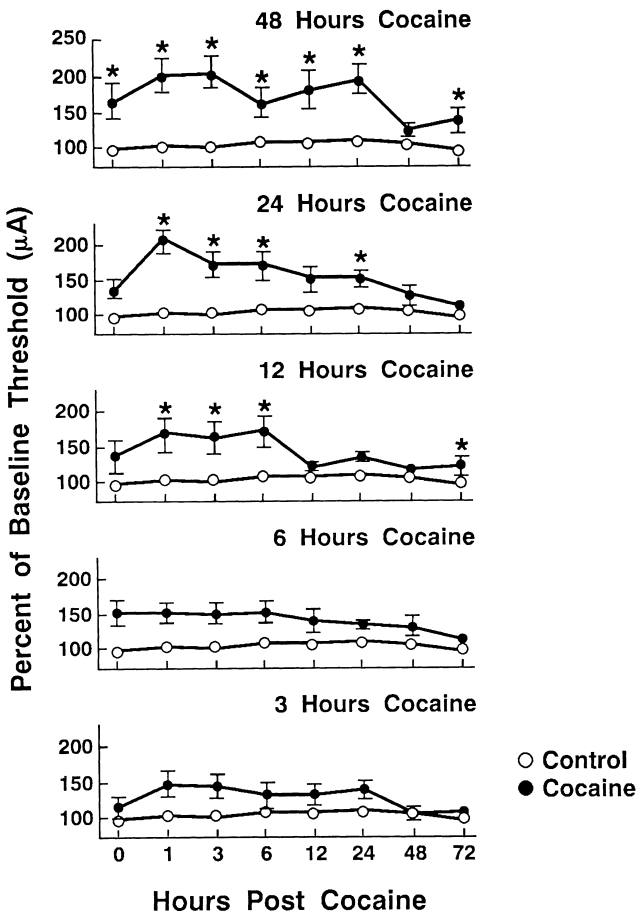

FIG. 6. Intracranial self-stimulation thresholds at several time points after termination of 3–48-h cocaine self-administration sessions. The asterisks indicate statistically significant differences ($p < 0.05$) between control ($n = 9$) and experimental ($n = 12$) groups (Dunnett's test). [Taken with permission from Markou and Koob (37).]

levels in the nucleus accumbens have also been observed during withdrawal from experimenter-administered cocaine injections, although the time course of the effect was different (44,48). Perhaps even more interesting was that extracellular serotonin levels decreased even more dramatically during cocaine withdrawal (see Fig. 7). The duration of the serotonin decrease and the time course of recovery are not known at this time.

Cocaine withdrawal in humans is also characterized by anxiety-like symptoms (21), and withdrawal from repeated cocaine administration produces anxiogenic-like behavior in several tests. There is evidence that 2 days following regimens of repeated injection of cocaine there are anxiogenic-like responses in the defensive burying paradigm (22), drug discrimination (63), defensive withdrawal (65), and the elevated plus-maze (50).

Evidence for a between-systems adaptation following chronic cocaine administration can be found in studies exploring the role of corticotropin-releasing factor (CRF) in cocaine dependence. CRF not only is a major hypothalamic-releasing factor controlling the classic stress response but also appears to have a neurotropic role in the central nervous system in modulating behavioral responses to stress (29). CRF itself has anxiogenic actions, and CRF antagonists reverse a number of behavioral responses to stress (4). Rats treated repeatedly with cocaine showed a significant anxiogenic-like response in the plus-maze following cessation of cocaine administration that was reversed with intracerebroventricular administration of a CRF antagonist (50). Moreover, in a recent study, self-administration of cocaine was associated with an increase in the release of CRF into the amygdala, suggesting that cocaine can activate CRF systems previously implicated in behavioral responses to stress (Richter et al., 1995).

Thus, in the framework outlined above of within- and between-systems adaptations, the neurochemical alterations in dopamine and possibly serotonin neurotransmission during cocaine withdrawal could be considered a within-system adaptation (44,48,60). Here, the same neurotransmitter system, presumably with an important if not essential role in the acute hedonic-like actions of cocaine, may contribute to the motivational effects of cocaine withdrawal. Possible neurotransmitter candidates in the nucleus accumbens involved in a between-systems adaptation include at this time changes in brain CRF, because CRF appears to be an important contributor to the anxiogenic-like effects of cocaine withdrawal (50).

CONTRIBUTION OF OPPONENT PROCESSES TO DEPENDENCE

The modern defining characteristic of dependence is uncontrollable drug use; however, the basis or etiology of that compulsive use has been controversial. Wise and others (58,62) have cogently argued that the positive reinforcing effects of a drug are critical for establishing self-administration behavior, and alleviation of withdrawal symptoms cannot be a major motivating factor in the *initiation* of compulsive drug use. However, such postulates offer little explanation for what the underlying features are that lead to compulsive use and what factors distinguish use from abuse from dependence. The incentive-sensitization theory as outlined by Robinson and Berridge addresses this issue by invoking a shift to an incentive-salience state (wanting) "which is progressively in-

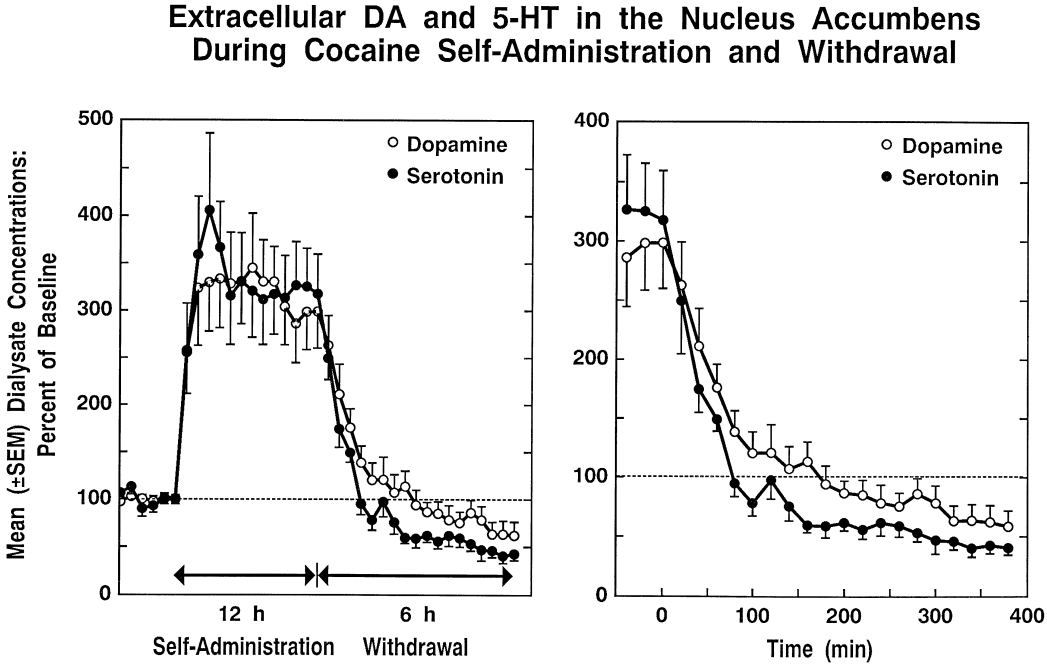

FIG. 7. Profile of dialysate serotonin and dopamine concentrations and a corresponding representative reinforcer delivery record during a 12-h extended-access cocaine self-administration session. Effect of 12-h unlimited-access cocaine self-administration on dialysate serotonin and dopamine levels. The mean (±SEM) presession baseline dialysate concentrations of serotonin and dopamine were 0.98 ± 0.1 nM and 5.3 ± 0.5 nM, respectively (n = 7). All animals self-administered cocaine with regular interinfusion intervals; six out of seven animals self-administered cocaine for the entire 12-h session. The average cocaine intake was 28.8 ± 2.1 mg/12 h (n = 7). [Taken with permission from Parsons et al. (43).]

creased (sensitized) by repeated exposure to drugs" (47). The hypothesized neural basis for this incentive-salience eliciting pathologically strong wanting or craving is a hypersensitive dopamine system (47). Neuroadaptation theories, such as opponent-process theory, in contrast, postulate that the processes of affective habituation (hedonic tolerance) and withdrawal play an important role in the *transition* of drug use to the development of dependence. Thus, whereas initial drug use may be motivated by the positive affective state produced by the drug, continued use leads to neuroadaptation to the presence of drug and to the motivating properties of negative affective consequences of drug termination. Indeed, some have gone so far as to argue that the presence of a negative affective state is the defining feature of addiction (49).

Finally, both the positive and negative affective states can become associated with stimuli in the drug-taking environment through classical conditioning processes, thereby also motivating continued drug use and relapse after abstinence upon reexposure to the conditioned stimuli. Conditioning to the positive affective states induced by drugs has been demonstrated in paradigms in which stimuli associated with drugs of abuse–including psychomotor stimulants, opiates, nicotine, ethanol, and barbiturates–can maintain responding in rats and monkeys when the stimulus is subsequently presented without the drug [for reviews, see (15,40)]. Conditioned withdrawal has been repeatedly observed in opiate-dependent animals and humans; however, there is little evidence to date for such effects with cocaine or amphetamine. It is not clear whether stimuli paired with the negative affective state of cocaine withdrawal can acquire aversive properties, as has been observed with opiates.

The importance of an opponent process conceptualization for understanding addiction and the neurobiology of addiction is that such a formulation makes certain predictions that are different from other hypotheses. First, at the behavioral level, hedonic processes are hypothetical constructs that relate directly to human experience and the persistent disruption of mood states associated with drug abuse and dependence. Indeed, it is the development of a negative affective state that may not only reflect the development of dependence but may even contribute substantially to the *maintenance* of dependence using the hypothetical construct of negative reinforcement. This conceptualization makes wide-ranging predictions about the etiology, vulnerability, and treatment of cocaine dependence. In addition, moved to the neurobiological level of analysis, this opponent process conceptualization predicts that molecular, cellular, and system changes are evoked in the brain by drugs of abuse to counteract the acute hedonic effects of the drugs. Future research identifying the presence or absence of such changes will provide a significant test of this hypothesis.

CONCLUSION: MOTIVATIONAL EFFECTS OF WITHDRAWAL

The present treatise has argued that, despite claims to the contrary (58,62), the motivation for maintenance of compulsive drug use requires negative reinforcement processes in addition to positive reinforcement processes. Abstinence from stimulants results in negative motivational states that can be quantified with a number of behavioral measures. This aversive motivational state is a dysregulator of motivational homeostasis and thus provides a mechanism for a negative reinforcement process wherein the organism is administering the drug to alleviate the aversive state.

Clearly, much remains to be explored about the neurobiology of the unconditioned negative motivational state(s) with stimulants and, in particular, of the *conditioned* negative motivational state(s). The study of the changes in the central nervous system that are associated with these homeostatic dysregulations may provide not only the key to cocaine dependence but also the key to the etiology of psychopathologies associated with mood and anxiety disorders.

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