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Pharmacological and Environmental Determinants of Relapse to Cocaine-Seeking Behavior

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SPEALMAN, R. D., R. L. BARRETT-LARIMORE, J. K. ROWLETT, D. M. PLATT AND T. V. KHROYAN. *Pharmacological and environmental determinants of relapse to cocaine-seeking behavior.* PHARMACOL BIOCHEM BEHAV **64**(2) 327–336, 1999.—Animal models have been developed that simulate relevant features of relapse to cocaine-seeking behavior in humans. These models have provided valuable information about pharmacological and environmental factors that precipitate reinstatement of extinguished cocaine-seeking in rats and monkeys, as well as new insights about potential pharmacotherapies for relapse prevention. Reinstatement of cocaine-seeking behavior in animals can be induced by cocaine priming or by cocaine-paired environmental stimuli; however, maximum reinstatement of drug-seeking appears to be induced when cocaine priming and cocaine-paired stimuli are combined. Drugs that share cocaine's indirect dopamine agonist properties or that act as direct agonists at D_2-like dopamine receptors also induce reinstatement of cocaine-seeking behavior, whereas with some exceptions (e.g., caffeine, morphine) drugs from other pharmacological classes do not. D_1-like receptor agonists block rather than mimic the priming effects of cocaine, suggesting different roles for D_1- and D_2-like receptor mechanisms in cocaine relapse. Although considerable overlap exists, drugs that exhibit cocaine-like discriminative stimulus and/or reinforcing effects in other situations do not invariably induce cocaine-like reinstatement of drug-seeking and vice versa, implying that these effects are not simply different behavioral expressions of a unitary neurobiological process. Finally, recent findings with D_1-like receptor agonists, partial agonists, and antagonists suggest that some of these drugs may be viable candidates for development as antirelapse pharmacotherapies. © 1999 Elsevier Science Inc.

Relapse Reinstatement Drug cues Drug priming Stress Cocaine Dopamine agonists and antagonists D_1- and D_2-like receptor mechanisms Medications development

COCAINE abusers are highly vulnerable to relapse, and treatment prognosis is disappointingly poor, even following successful detoxification (15,57,91). Although the factors responsible for the high rate of relapse are not completely understood, there is now a substantial body of evidence implicating environmental stimuli associated with previous drug use (cues) and acute reexposure to cocaine (priming) as triggers of craving and relapse (42,70). A more comprehensive understanding of these relapse triggers is likely to lead to more effective treatment strategies. As in humans, relapse to cocaine-seeking behavior in animals can be precipitated by cocaine-associated stimuli and cocaine primes, providing a valuable laboratory model for elucidating pharmacological and environmental determinants of relapse and for developing new treatment interventions (16,75). The purpose of this review is to integrate recent advances in our understanding of the relapse phenomenon in these models, to identify potential neurobiologic mechanisms, and to explore implications for medication development.

COCAINE-ASSOCIATED STIMULI AND RELAPSE TO COCAINE-SEEKING BEHAVIOR

Abstinent cocaine abusers frequently report that craving (the self-reported desire for drug) and relapse can be precipitated by features of their environment previously associated with drug use, and there are numerous examples from both the animal and human experimental literature demonstrating the powerful control that drug-associated stimuli can exert

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over drug-seeking and drug-taking behavior (18,34,96). Despite the recognized importance of drug-associated stimuli in maintaining persistent drug self-administration in animals (36,68,72), there have been relatively few studies investigating the role of such stimuli in experimental models of relapse. In perhaps the earliest study of this type, Davis and Smith (21) trained rats to self-administer morphine under conditions in which an auditory stimulus was paired with each drug injection. Drug self-administration then was extinguished by substituting vehicle for morphine injections and omitting presentation of the stimulus. During subsequent test sessions, in which only vehicle was available for self-administration, reintroduction of the stimulus alone temporarily restored drug-seeking behavior to levels approaching those maintained by morphine self-administration. Subsequent studies have extended these findings by showing that a stimulus previously paired with cocaine self-administration can also induce a temporary reinstatement of extinguished drug seeking in rats (23,58). Although the magnitude and persistence of reinstatement induced by cocaine-paired stimuli is typically low compared to the more robust effects induced by cocaine priming (see below), these findings illustrate the impact that environmental cues can have in initiating the relapse process. The results also provide a preclinical foundation for therapeutic strategies to control relapse and craving by modifying "cue reactivity" (17,61,70).

Recent research in nonhuman primates has confirmed and extended initial findings with cocaine in rodents (4,5). In these studies, squirrel monkeys were trained to self-administer cocaine under a second-order schedule (35) in which persistently high rates of responding were maintained jointly by IV injections of cocaine and by presentations of a visual stimulus paired with cocaine injections (Fig. 1A). After cocaine self-administration was maintained consistently for several months, subjects underwent an extinction phase, during which vehicle replaced cocaine in the infusion pump and the cocaine-paired stimulus was omitted (Fig. 1B). Reintroduction of the cocaine-paired stimulus during a subsequent test session partially reinstated cocaine-seeking behavior, despite the fact that cocaine was unavailable for self-administration, and no priming injections were delivered (Fig. 1C). Although presentations of the stimulus alone characteristically engendered a modest (two- to threefold) increase in response rate, more pronounced and enduring effects were observed in some cases. Figure 2, for example, shows data from one monkey (S-199) that exhibited a particularly robust reinstatement effect during repeated testing over a 20-day period of extinction. These striking individual differences mirror clinical observations and controlled human studies documenting substantial diversity in the effect of drug-paired stimuli among abstinent cocaine abusers (69).

COCAINE PRIMING AND RELAPSE TO COCAINE-SEEKING BEHAVIOR

An increase in craving often is reported by abstinent cocaine abusers following acute reexposure to the drug (42,67), and an analogous priming effect has been observed consistently in laboratory animals. In the typical priming experiment, rats or monkeys are trained to self-administer cocaine

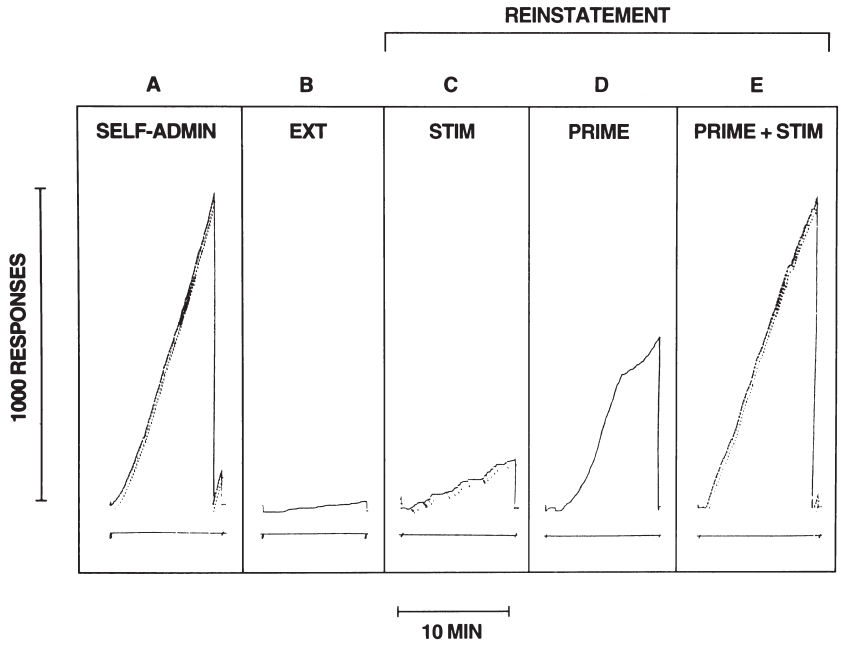

FIG. 1. Representative cumulative records showing performances under a second-order schedule of IV cocaine injection, in which responding was maintained jointly by self-administered cocaine (0.3 mg/kg/injection) and by response-produced presentations of a visual stimulus paired with cocaine (A), and under extinction, in which saline was substituted for cocaine and the cocaine-paired stimulus was removed (B). Reintroduction of the cocaine-paired stimulus (C) or priming with 0.3 mg/kg cocaine (D) partially reinstated extinguished cocaine-seeking behavior. Maximum reinstatement was induced by cocaine priming accompanied by the cocaine-paired stimulus (E). Each panel shows one complete cycle of the schedule (monkey S-223).

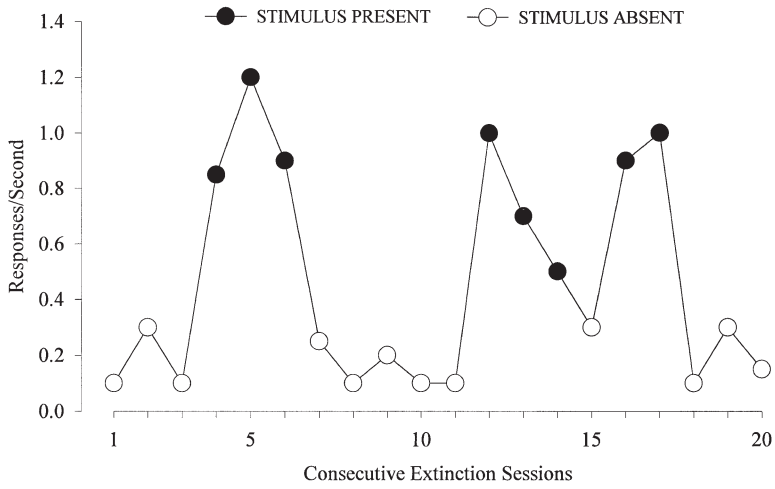

FIG. 2. Repeated reinstatement of extinguished cocaine-seeking behavior by reintroduction of a cocaine-paired stimulus during a 20-day period of extinction (monkey S-199).

and then advanced to a test phase in which extinction and drug-priming experiments are conducted within a few hours of each other (20,23,73,97) or separated by a few drug-free days (31,80). Although this simple procedure provides an animal model of relapse with face and construct validity, it has not traditionally incorporated some presumably relevant features of drug use and relapse patterns seen in people. For example, human cocaine abusers characteristically have long histories of illicit drug use, and may be abstinent from weeks to months before eventual reexposure to cocaine. Moreover, reexposure occurs most often in the presence of environmental stimuli previously associated with cocaine use.

In an effort to better simulate the relapse patterns of human addicts, recent studies have begun to employ longer drug self-administration and/or extinction periods and to incorporate drug-paired stimuli as part of the training and test procedures (2,4,5,27,58,95). In a study by Barrett-Larimore and Spealman (4), for example, squirrel monkeys were given extensive histories (>6 months) of IV cocaine self-administration under the second-order schedule mentioned previously, followed by a protracted series of extinction sessions interrupted only by occasional tests to determine the effects of cocaine priming. As illustrated in Fig. 3, priming with cocaine in conjunction with restoration of the cocaine-paired stimulus induced marked reinstatement of cocaine-seeking behavior following extinction periods of up to 30 days. Although the degree of reinstatement tended to wane over the extended course of extinction, as might be expected on the basis of clinical observations, the effect was remarkably persistent, given that there were no intervening opportunities to self-administer cocaine. Additional studies showed that although cocaine priming induced appreciable reinstatement of drug seeking in the absence of the cocaine-paired stimulus (Fig. 1D), a large effect typically was seen when the stimulus was restored along with the cocaine prime (Fig. 1E). Under the latter condition, priming-induced reinstatement of cocaine seeking was dose dependent and, at maximally effective doses, engendered high response rates (~1 response/s) similar to those maintained by cocaine self-administration itself (Fig. 4). The robust reinstatement of cocaine-seeking behavior induced by priming accompanied by restoration of a cocaine-paired stimulus suggests an interaction between environmental and pharmacological triggers of relapse, possibly reflecting conditions encountered in real-life situations.

PHARMACOLOGICAL SPECIFICITY OF RELAPSE INDUCTION

In addition to cocaine, several drugs that share cocaine's indirect dopamine (DA) agonist properties or that have prominent agonist effects at D_2-like DA receptors have been found to induce reinstatement of extinguished cocaine-seeking behavior in rats and monkeys (5,23,31,46,73,97). In contrast, drugs from other pharmacological classes (e.g., sedatives, anxiolytics, neuroleptics, antidepressants, and most opioid ag-

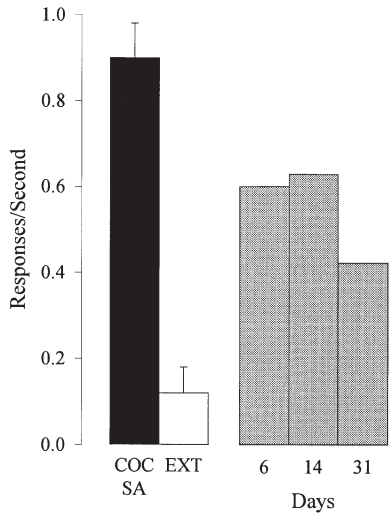

FIG. 3. Repeated reinstatement of extinguished cocaine-seeking behavior by cocaine priming (0.3 mg/kg) accompanied by presentations of a cocaine-paired stimulus after 5, 13, and 30 days of extinction (striped bars). Mean ± SD rates of responding during the last five sessions of IV cocaine self-administration (filled bar) and the first five sessions of extinction (unfilled bar) are shown for comparison (monkey S-151).

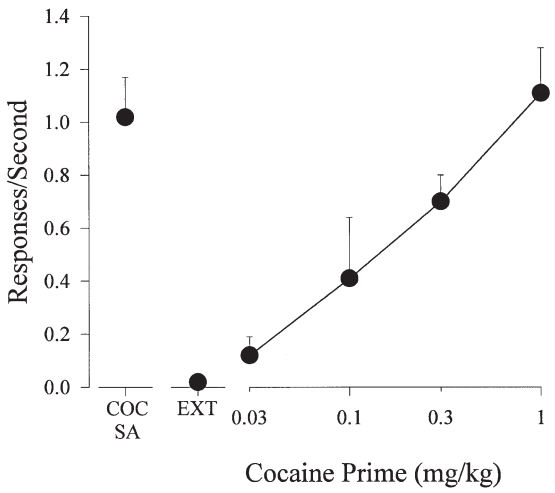

FIG. 4. Effects of dose on reinstatement of cocaine-seeking behavior induced by cocaine priming accompanied by presentations of a cocaine-paired stimulus. Points are means (±SEM, $n = 5$). Unconnected points show responding under the second-order schedule of IV cocaine self-administration (SA; 0.3 mg/kg/injection × five injections/session) and extinction (EXT).

onists and antagonists) typically do not function as primes to reinstate cocaine-seeking behavior (20,23,29,31,53,80). These findings, together with complementary observations that DA receptor antagonists block cocaine-induced reinstatement of drug-seeking (4,95), support the view that stimulation of brain DA activity plays an integral role in mediating cocaine's capacity to precipitate relapse.

A notable exception to the pattern of pharmacological specificity described above is morphine, which has been shown to mimic the priming effects of cocaine in both rats and monkeys (23,80,88). Although the pharmacological profiles of morphine and cocaine differ in several important respects, the cocaine-like priming effects of morphine have sometimes been attributed to the common capacity of the two drugs to stimulate mesolimbic DA activity (25). However, other opiates, including heroin and etonitazene, fail to induce appreciable reinstatement of cocaine-seeking behavior (20,23), and conversely, cocaine does not induce significant reinstatement of heroin-seeking behavior in rats previously trained to self-administer heroin (24). Collectively, these findings suggest that mechanisms other than or in addition to stimulation of mesolimbic DA activity mediate morphine's ability to induce reinstatement of cocaine seeking in animals.

Caffeine also has been found to induce relapse to cocaine-seeking behavior in rats, although the effect appears to be less robust and enduring than that of cocaine (71,102). The neurobiological mechanisms underlying the cocaine-like priming effects of caffeine are poorly understood, but could reflect caffeine's ability to stimulate mesolimbic DA activity indirectly via blockade of central adenosine receptors (28,89). However, because caffeine acts at multiple subtypes of adenosine receptors and affects several neurotransmitter/neuromodulator systems (26), other mechanisms cannot be ruled out. These uncertainties notwithstanding, the results with caffeine illustrate the potential impact that commonly used drugs might have on extinguished cocaine-seeking behavior. Conceivably, exposure to caffeine or other licit drugs could adversely impact abstinence by contributing to a relapse episode.

In addition to morphine and caffeine, IV administration of the stress hormone corticosterone as well as delivery of electric shock have been found to induce reinstatement of extinguished cocaine seeking in some recent studies (2,22,27). This presumably stress-induced reinstatement might be mediated by neural systems in common with those that mediate cocaine priming because both corticosterone and electric shock have been found to enhance cocaine-induced increases in extracellular DA in the nucleus accumbens (6,77), and corticosterone has been reported to maintain IV self-administration in rats (64). Recent studies suggest, however, that this hypothesis may not provide a fully satisfactory explanation for the phenomenon because DA antagonists are largely ineffective in blocking shock-induced reinstatement of drug seeking (78). Furthermore, exposure to shock is less effective than cocaine in stimulating DA release in the nucleus accumbens, but may be even more effective than cocaine in reinstating extinguished drug seeking (27,78). Collectively, these findings imply that there are important differences in the neurobiological processes mediating stress-induced and cocaine-induced relapse. Better delineation of neural mechanisms underlying stress-induced reinstatement of drug-seeking in animals could have important implications for understanding the unresolved role of stress as a trigger of relapse in people (55,62).

D_1-LIKE AND D_2-LIKE RECEPTOR MECHANISMS IN RELAPSE

As noted in the preceding section, D_2-like receptor agonists including bromocriptine, quinpirole, propylnorapomorphine (NPA), as well as the relatively nonselective DA agonist apomorphine have been found to induce robust reinstatement of extinguished cocaine-seeking behavior in rats and monkeys (Table 1). These findings, along with the observation that D_2-like receptor antagonists such as nemonapride and eticlopride dose dependently attenuate the priming effects of cocaine (Fig. 5), strongly support the view that stimulation of one or more subtypes of D_2-like receptors plays an essential role in mediating cocaine-induced relapse. This view is further supported by a recent report that infusion of the protein kinase inhibitor R_p cAMPS into the nucleus accumbens of rats induces significant reinstatement of cocaine-seeking behavior by mimicking the intracellular consequences of D_2-like receptor activation (74).

The D_2 family of receptors comprises at least three receptor subtypes, designated D_2, D_3, and D_4 (41,82), and growing evidence suggests that these different receptors may function in different ways to mediate cocaine's priming effects. Along these lines, the preferential D_3 receptor agonist PD 128,907 does not induce appreciable reinstatement of cocaine-seeking behavior in monkeys, nor does it enhance the priming effects of cocaine when the two drugs are combined (5). Moreover, the preferential D_3 receptor antagonists AJ-76 and UH-232 (81) correspondingly fail to attenuate the priming effects of cocaine at doses that antagonize the in vivo effects of PD 128,907 (3,4). On the other hand, the D_3/D_4 receptor antagonist YM-43611 attenuates the priming effects of cocaine as effectively as conventional D_2-like receptor blockers (Fig. 5), implying that D_3 and/or D_4 receptor subtypes could play a modulatory role in mediating reinstatement of cocaine-seeking behavior. The development of more selective antagonists targeting the D_2, D_3, and D_4 receptor subtypes should facilitate characterization of the role of different D_2-like receptors in the relapse process.

The role of D_1-like receptors, which comprise the D_1 and D_5 receptor subtypes (41,82), appears to be even more com-

TABLE 1

DRUG PROFILES MIMICKING THE RELAPSE-INDUCING, DISCRIMINATIVE STIMULUS AND REINFORCING EFFECTS OF COCAINE

Drugs*	Cocaine-Like Priming Effects	Cocaine-Like DS Effects	IV. Self-Administration
Indirect DA agonists			
Cocaine	Yes	Yes	Yes
Amphetamine	Yes	Yes	Yes
Methamphetamine	Yes	Yes	Yes
DA receptor agonists			
Apomorphine (D_1/D_2)	Yes	Yes	Yes
Bromocriptine (D_2-like)	Yes	Yes	Yes
NPA (D_2-like)	Yes	Yes	Yes
7-OH-DPAT (D_2-like)	Yes/No[b]	Yes	Yes
PD 128,907 ($D_3 > D_2$)	No	Yes	—‡
SKF 81297 (D_1-like)	No	Yes	Yes/No†
SKF 82958 (D_1-like)	No	Yes	Yes
Opioids			
Morphine	Yes	Yes/No†	Yes
Heroin	No	Yes/No†	Yes
Etonitazene	No	—§	Yes
Other			
Nicotine	No	No	Yes
Caffeine	Yes	No	No

*Additional drugs that do not mimic the priming effects of cocaine include: nalorphine, naloxone, naltrexone, buprenorphine, secobarbital, methohexital, chlorpromazine, desipramine, dimethyltriptamine, and clonidine (see text)

†Individual differences within or across studies.

‡Maintains conditioned place preference (45).

§Not evaluated.

plex. Several studies have convincingly shown that D_1-like full agonists, including SKF 82958 and SKF 81297, can maintain IV self administration (38,76,94) and partially mimic the discriminative stimulus effects of cocaine in rats and monkeys (85,99). Yet neither of these drugs appears to induce reinstatement of cocaine-seeking behavior in either species (5,73). In fact, when administered in combination with cocaine, both drugs as well as the D_1-like partial agonists SKF 38393 and SKF 83959, actually attenuate the priming effects of cocaine in a dose-related manner (Fig. 6). The effects of D_1-like agonists in these studies could imply that stimulation of D_1-like receptors plays an inhibitory role with respect to reinstatement of cocaine-seeking behavior. However, additional experiments have revealed that blockade of D_1-like receptors with ecopipam (SCH 39166) also dose dependently attenuates the priming effects of cocaine in monkeys (Fig. 5). The surprisingly similar ability of D_1-like receptor agonists and antagonists to attenuate cocaine-induced reinstatement of drug-seeking behavior could reflect a generalized suppression of operant behavior rather than a specific effect of either type of drug on cocaine priming. However, doses of D_1-like ligands that block cocaine-induced relapse in monkeys are typically lower than those required to produce comparable reductions in other types of operant behaviors (9,10,86) or to induce motoric side effects that might interfere with cocaine-induced lever pressing (65,66).

The common effects of D_1-like receptor agonists and antagonists on cocaine priming are provocative in light of the qualitatively different influences that these drugs have on other behavioral effects of cocaine. For example, ecopipam attenuates, whereas SKF 82958 and SKF 81297 enhance the discriminative stimulus effects of cocaine in monkeys (85,86). Nonetheless, the available evidence suggests that either agonist-induced stimulation or antagonist-induced blockade of D_1-like receptors is sufficient to blunt the priming effects of cocaine. Such findings imply that there may be a critical range of D_1-like receptor activity that enables reinstatement of cocaine-seeking behavior. If this is the case, the D_1-like receptors may play a crucial modulatory role in cocaine priming, and may constitute viable targets for development of medications to control relapse.

RELATIONSHIP BETWEEN RELAPSE INDUCTION AND OTHER BEHAVIORAL EFFECTS OF COCAINE

It is sometimes assumed that the ability of a drug to induce relapse depends on the degree to which it mimics the subjective and/or reinforcing effects of the self-administered drug. This view has been largely fostered by the finding that many drugs capable of inducing reinstatement of cocaine-seeking behavior also mimic the discriminative stimulus effects of cocaine and maintain IV self-administration in their own right. Although appealing, this view is not well supported by the available data (Table 1, Fig. 7). For example, drugs such as morphine and caffeine, which do not consistently mimic the discriminative stimulus effects of cocaine (19,40,84), induce significant reinstatement of cocaine-seeking behavior (23,71, 80,102). Conversely, drugs such as the D_1-like receptor agonists SKF 82958 and SKF 81297 and the D_3 receptor agonist PD 128,907, which partially mimic the discriminative stimulus effects of cocaine (1,83,85,99) and maintain IV self-administration or conditioned place preference (38,45,76,94), do not

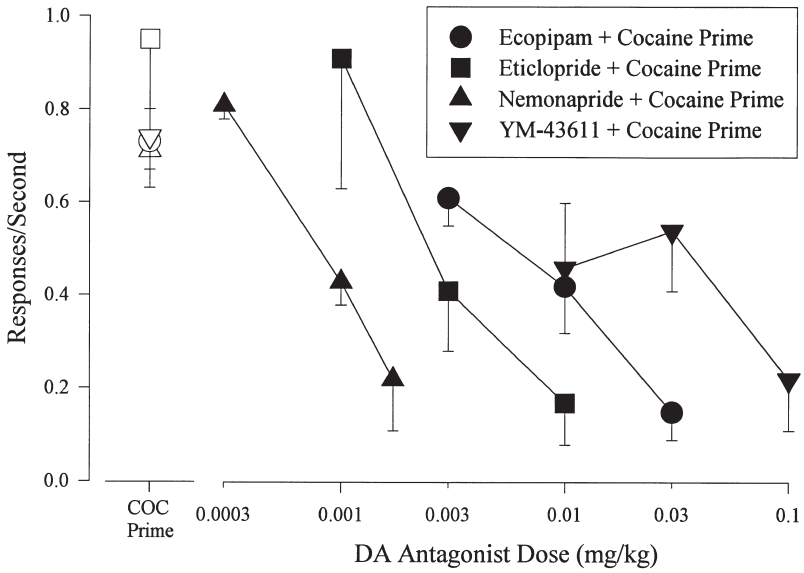

FIG. 5. Attenuation by DA receptor antagonists of relapse to cocaine-seeking behavior induced by cocaine priming (0.3 or 0.56 mg/kg, depending on the monkey) accompanied by presentations of a cocaine-paired stimulus. Data are means (±SEM, $n = 4$) adapted from (4). Unconnected points show the effects of cocaine priming in the absence of DA antagonist treatment (COC prime).

reinstate cocaine-seeking behavior (5,46,73). Thus, although considerable overlap exists, drugs that exhibit cocaine-like discriminative stimulus or reinforcing effects do not invariably induce cocaine-like reinstatement of drug-seeking and vice versa. An important conclusion derived from these observations is that the relapse-inducing, subjective, and reinforcing effects of cocaine are not simply different behavioral expressions of a unitary neurobiological process. Although cocaine-induced enhancement of brain DA activity undoubtedly plays a key role in each of these behavioral phenomena (51,75,98,101), potentially important differences in the contribution of specific DA receptor mechanisms as well as other neurotransmitter/neuromodulator systems warrant investigation. Such differences might be exploited usefully to develop pharmacotherapies targeting different aspects of cocaine addiction.

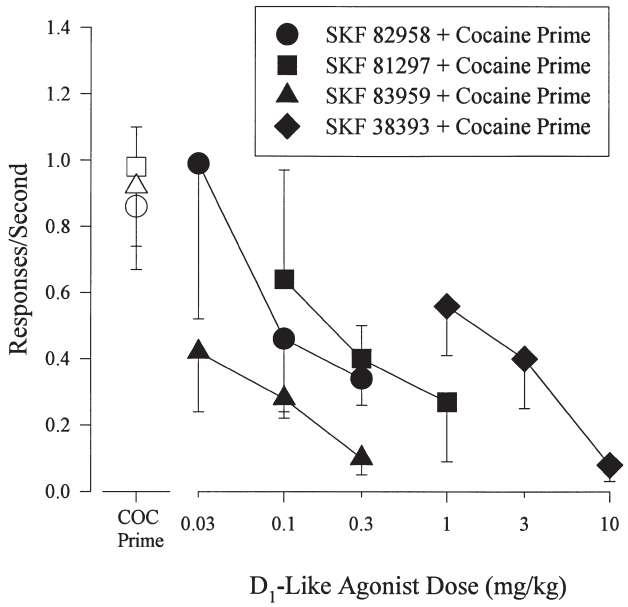

FIG. 6. Attenuation by D_1-like receptor agonists of relapse to cocaine-seeking behavior induced by cocaine priming accompanied by presentations of a cocaine-paired stimulus. Data are means (±SEM, $n = 3$ or 4) adapted from (5) and unpublished observations. Other details as in Fig. 5.

MEDICATIONS DEVELOPMENT FOR RELAPSE PREVENTION

In contrast to clinically approved pharmacotherapies for opiate, alcohol, and nicotine dependence, there are as yet no broadly effective medications for the treatment of cocaine addiction (47,56,60). Based on the use of agonist- and antagonist-based therapies for opiate dependence and the recognized importance of DA mechanisms in cocaine addiction, drug discovery programs have focused, not surprisingly, on compounds that may serve either as pharmacological replacements for cocaine (e.g., DA direct and indirect agonists) or as functional cocaine antagonists (e.g., DA receptor blockers) (43,59). Although opinions differ, there is growing consensus that an effective pharmacotherapy for cocaine addiction might be identified preclinically on the basis of its capacity to reduce cocaine self-administration and block reinstatement of cocaine-seeking behavior. Candidate medications that prevent reinstatement of cocaine-seeking in animals could be effective in controlling craving and relapse in humans.

Preclinical evaluations of both indirect DA agonists and D_2-like receptor agonists provide only limited encouragement for their therapeutic use in cocaine addiction and relapse. Although both types of drugs have been found to reduce IV self-administration of cocaine in animal models (12,14,32,33,48), they also maintain robust self-administration in their own

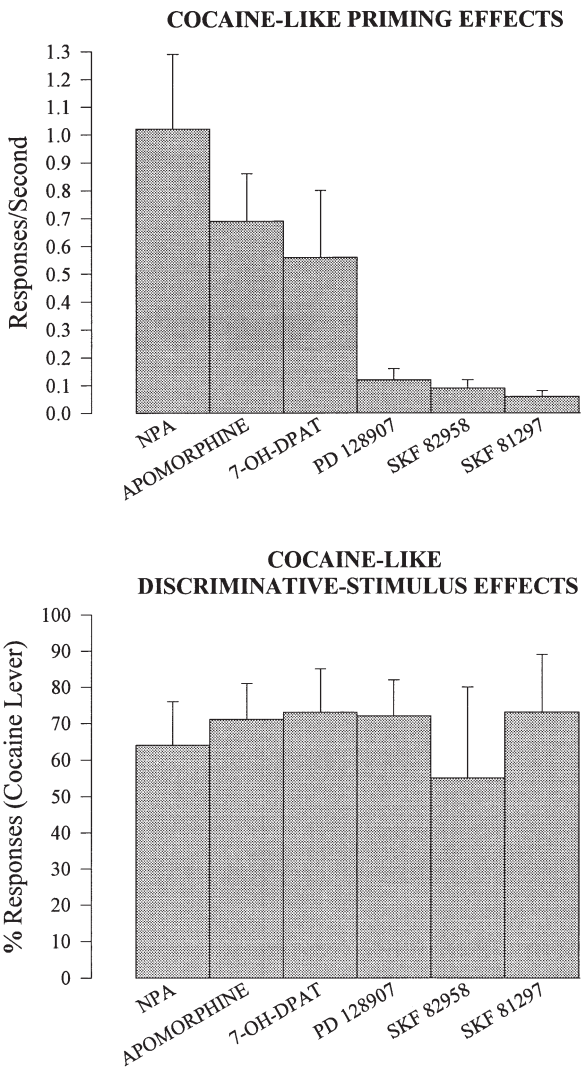

FIG. 7. Comparison of cocaine-like priming effects and cocaine-like discriminative stimulus effects of DA receptor agonists. Top panel shows maximum reinstatement of extinguished cocaine-seeking behavior. Bottom panel shows maximum cocaine-lever responding in monkeys trained to discriminate cocaine from vehicle. Data are means (±SEM, n = 3–5) adapted from (5,83,85) and unpublished observations.

right, suggesting significant abuse potential (8,12,38,100). More importantly, in the present context, D_2-like receptor agonists, with the apparent exception of preferential D_3 receptor ligands, both mimic and enhance cocaine-induced relapse in animals (5,46,73,97). Moreover, human laboratory and clinical studies with indirect DA agonists such as amantadine and methylphenidate, and D_2-like receptor agonists such as bromocriptine and pergolide have shown little or no beneficial effects in suppressing cocaine use or craving (37,39,67,90,92).

Dopamine D_1-like receptor agonists offer a potentially more attractive strategy for pharmacotherapy because, unlike other DA agonists, they appear to inhibit initiation of cocaine self-administration (14,73) and dose dependently block reinstatement of cocaine-seeking behavior (5,73). Moreover, although D_1-like receptor agonists have been shown to maintain IV self-administration in animals, the available evidence suggests that the abuse potential of at least some of these drugs is less than that of cocaine (38,76,93). Preliminary observations with one D_1-like receptor agonist, ABT-431, indicate that relatively low doses of this drug reduce cocaine-induced craving in people (54). A potential disadvantage of ABT-431 and other D_1-like receptor agonists, however, is their capacity to induce seizures at higher doses (11,79).

DA receptor antagonists also dose dependently block cocaine-induced reinstatement of drug seeking and attenuate the reinforcing effects of cocaine in rats and monkeys (4,7,13,49). Although antagonist-based therapies for other types of drug addiction have been successful only under restricted conditions (50), findings in animals suggest that DA receptor antagonists could play a role in controlling cocaine use and relapse in appropriately structured situations. The potential usefulness of D_2-like receptor antagonists is likely to be limited, however, by their extrapyramidal side effects, which may be exacerbated in chronic cocaine users (52), and their aversive properties, which may aggravate cocaine withdrawal symptoms (30). The D_1-like receptor antagonist ecopipam, on the other hand, has minimal extrapyramidal effects at doses that block cocaine priming and cocaine self-administration in monkeys (65,66), and appears to be well tolerated in humans (44). Ecopipam or other D_1-like receptor antagonists, therefore, may be viable candidates for medication development. Partial agonists at D_1-like receptors also may be attractive candidates for pharmacotherapy because some of these drugs (e.g., SKF 38393, SKF 83959) dose dependently block the priming effects of cocaine (Fig. 6) as well as its discriminative stimulus effects and IV self-administration in monkeys (65,66). In addition, unlike full agonists, D_1-like partial agonists do not induce seizures in normal animals (87), and may actually be preventive in some animal models of epilepsy (63). Although there are as yet no published reports of D_1-like receptor antagonists or partial agonists in cocaine-abusing people, controlled human studies with both types of drugs have begun.

SUMMARY

Animal models have been developed that simulate relevant features of cocaine use and relapse in people. These models continue to provide valuable information about pharmacological and environmental factors that induce relapse to cocaine-seeking behavior, as well as new insights about potential pharmacotherapies for relapse prevention. As in people, relapse to cocaine-seeking behavior in animals can be induced by cocaine-associated cues and cocaine priming, with maximum effects observed when the two inducing factors are combined. Many drugs that share cocaine's indirect DA agonist effects or that act directly as D_2-like receptor agonists also induce cocaine-like reinstatement of drug seeking. However, D_1-like receptor agonists block the priming effects of cocaine, suggesting important differences in the contribution of D_1-like and D_2-like receptor mechanisms in the relapse process. Nondopaminergic drugs typically do not induce reinstatement of cocaine-seeking behavior; however, cocaine-like priming effects have been reported for caffeine and morphine. A more comprehensive understanding of the roles of both dopaminergic and nondopaminergic processes in cocaine relapse is a desirable goal for future research because it may lead to identification of novel neurobiological targets for therapeutic intervention.

Notwithstanding a considerable degree of overlap, drugs that mimic the reinforcing and discriminative stimulus effects of cocaine do not invariably induce reinstatement of cocaine-seeking behavior. These findings imply that the relapse-inducing, subjec-

tive, and reinforcing effects of cocaine are mediated by nonidentical neurobiological mechanisms—a perspective that may have implications for medications development focusing on different aspects of cocaine addiction. Drugs that block reinstatement of cocaine-seeking behavior in animals might be especially useful for controlling craving and relapse in humans. Although conventional D_2-like receptor ligands do not appear to be beneficial in this regard, recent findings suggest that D_1-like receptor agonists, partial agonists, and antagonists may have more favorable properties.

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