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Neurobiology of Relapse to Heroin and Cocaine Seeking: A Review

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***Abstract*——The objective of this article is to review data from studies that used a *reinstatement* model in rats to elucidate the neural mechanisms underlying relapse to heroin and cocaine seeking induced by exposure to the self-administered drug (drug priming), conditioned drug cues, and stressors. These factors were reported to contribute to relapse to drug use in humans following prolonged abstinence periods. In the reinstatement model, the ability of acute exposure to drug or nondrug stimuli to reinstate drug seeking is determined following training for drug self-administration and subsequent extinction of the drug-reinforced behavior. We will review studies in which pharmacological agents were injected systemically or intracranially to block (or mimic) reinstatement by drug priming, drug cues, and stressors. We also will review studies in which brain lesions, in vivo microdialysis and electrochemistry, and gene expression methods were used to map brain sites involved in relapse to drug seeking. Subsequently, we will discuss theoretical issues related to the processes underlying relapse to drugs and address methodological issues in studies on reinstatement of drug seeking. Finally, the implications of the findings from the studies reviewed for addiction theories and treatment will be discussed. The main conclusion of this review is that the neuronal mechanisms involved in relapse to heroin and cocaine seeking induced by drug priming, drug cues, and stressors are to a large degree dissociable. The data reviewed also suggest that the neuronal events mediating drug-induced reinstatement are to some degree dissociable from those mediating drug reinforcement.**

I. Introduction

A. Background and Overview

High rates of relapse to drug use following prolonged withdrawal periods characterize the behavior of experienced heroin and cocaine users (Mendelson and Mello, 1996; O'Brien, 1997). In heroin- or cocaine-free individuals, drug craving and relapse to drug use can be triggered by exposure to the self-administered drug (Meyer and Mirin, 1979; Jaffe et al., 1989; de Wit, 1996), by stimuli previously associated with drug taking (Childress et al., 1992; Carter and Tiffany, 1999), or by exposure to stressors (Kosten et al., 1986; Kreek and Koob, 1998; Sinha et al., 1999).

Over the last several decades, some laboratories have been using an animal model, termed the *reinstatement* model, to study factors that underlie relapse to heroin and cocaine seeking induced by exposure to the self-administered drug, drug cues, and stressors. The use of this procedure has become increasingly popular as indicated in Fig. 1, which depicts the number of studies that used the reinstatement model from 1971 to 2001 in laboratory animals. In the learning literature, reinstatement refers to the resumption of a previously extinguished conditioned response after acute noncontingent exposure to the unconditioned stimulus (Bouton and Swartzentruber, 1991; Catania, 1992). In the studies reviewed below, reinstatement typically refers to the resumption of extinguished lever-pressing behavior after noncontingent exposure to drug or nondrug stimuli (Stewart and de Wit, 1987). In studies on cue-induced reinstatement (*Section III.*), reinstatement also refers to

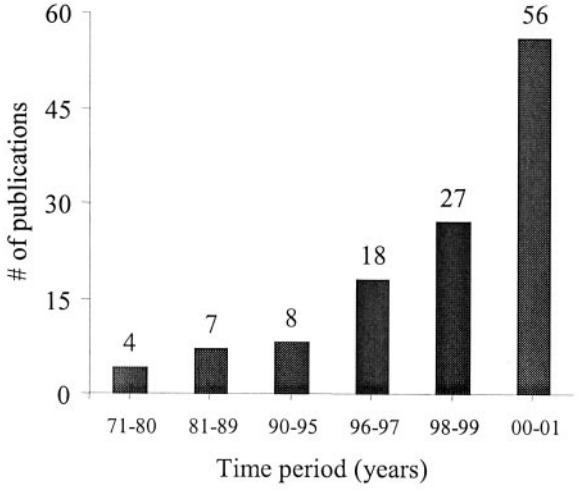

FIG. 1. Number of publications of studies which used reinstatement models in laboratory animals (mice, rats, and monkeys). Studies of reinstatement of heroin, cocaine, nicotine, and alcohol seeking are included.

the resumption of drug seeking after exposure to the drug cues following extinction of the lever-pressing behavior in the absence of these cues. Common terms used in reinstatement studies are defined in Table 1.

In the reinstatement model, laboratory animals are initially trained to self-administer drugs by pressing a lever for intravenous drug infusions in operant conditioning chambers. Subsequently, the drug-reinforced behavior is extinguished by substituting the drug solutions with saline or by disconnecting the infusion pumps. After extinction of the drug-reinforced behavior, the ability of acute exposure to drugs (i.e., drug priming) or nondrug stimuli to reinstate drug seeking is determined under extinction conditions (Stretch et al., 1971; Stewart and de Wit, 1987). There are two main dependent variables during tests for reinstatement: nonreinforced responses on a lever that previously delivered the drug, the *active* lever; and responses on a lever not associated with drug infusions, the *inactive* lever. Responses on the active lever are interpreted to reflect reinstatement of drug seeking. Inactive lever responses are typically interpreted to reflect nonspecific activity, but they may also reflect response generalization (Catania, 1992).

It has been argued that the reinstatement model does not mimic most situations in humans that lead to drug abstinence and thus may not be suitable to model relapse (Marlatt, 1996; Bergman and Katz, 1998). In addition, based on data demonstrating different neurochemical and behavioral effects of contingent versus noncontingent drug injections (Dworkin et al., 1995; Hemby et al., 1997; Markou et al., 1999), it has been argued that the effect of priming drug injections in the reinstatement model may not be relevant to drug addiction (Everitt and Robbins, 2000). Furthermore, it has not been established that opioid withdrawal, which is associated with relapse in humans (Himmelsbach, 1943; O'Brien et al., 1986; Wikler, 1973), can reinstate heroin seeking in the reinstatement model. Naloxone-precipitated withdrawal does not reinstate heroin seeking following extinction (Stewart and Wise, 1992; Shaham and Stewart, 1995b; Shaham et al., 1996). In contrast, spontaneous 24-h heroin withdrawal was found to reinstate heroin seeking, but it cannot be concluded from this study whether this effect was due to the motivational effects of opioid withdrawal or from state-dependent mechanisms (see Shaham et al., 1996).

Despite these limitations, the reinstatement model has good predictive validity because conditions that reliably reinstate heroin and cocaine seeking in laboratory animals such as drug re-exposure, drug cues, and stress (Self and Nestler, 1998; Shaham et al., 2000a; Stewart, 2000) also were reported to provoke drug relapse and craving in humans (see above). Thus, the model can be used to study neuronal mechanisms underlying relapse to drugs despite the fact that the conditions that lead to drug abstinence in laboratory animals are different from those in humans.

In this review we will summarize data from studies that used the reinstatement model in laboratory rats on the role of specific neurotransmitter systems in relapse to heroin and cocaine seeking. Although most studies used heroin or cocaine as the self-administered drug, several studies in which rats were trained to self-administer amphetamine or morphine also are reviewed. Studies using the reinstatement model with monkeys or those using this model with alcohol-trained rats are not reviewed here Lê and Shaham, 2002); for recent reviews, see (Spealman et al., 1999 . The section below provides an overview of several procedures used in reinstatement studies.

B. Experimental Approaches

Using monkeys, initial studies on reinstatement of amphetamine or cocaine seeking by drug priming were conducted by Stretch and Gerber in the early 1970s (Stretch et al., 1971; Stretch and Gerber, 1973; Gerber and Stretch, 1975). Goldberg, Schuster, and colleagues also have shown that stimuli paired with morphine or cocaine injections in monkeys reinstate drug-taking behavior after the lever-pressing behavior is extinguished in their absence (Schuster and Woods, 1968; Kelleher and Goldberg, 1977; Goldberg et al., 1981). Davis and Smith (1976) and de Wit and Stewart (1981, 1983) were the first to study reinstatement of drug seeking in rats. Over the years, several types of reinstatement procedures were used (Fig. 2).

Stretch et al. (1971) and Davis and Smith (1976) used a "between-session" reinstatement method, in which training for drug self-administration, extinction of the drug-reinforced behavior, and tests for reinstatement were conducted during different daily sessions. The advantage of the between-session model is that it mimics somewhat the human situation of relapse to drugs at times that are beyond the acute withdrawal phase. A

TABLE 1
Glossary of terminology

Active lever. Responses on this lever lead to drug infusions during drug self-administration training. During extinction training and tests for reinstatement, responses on this lever are not reinforced by the drug and serve as a measure of "drug seeking".

Between-session reinstatement procedure. A procedure in which drug self-administration training, extinction training, and tests for reinstatement of drug seeking are conducted on separate daily sessions.

Between-within session reinstatement procedure. A procedure in which drug self-administration training is conducted over days, and then extinction training and tests for reinstatement of drug seeking are examined on the same day following different periods of drug withdrawal.

CPP procedure. A classical conditioning procedure used to study the conditioned reinforcing effects of drugs or nondrug reinforcers. During training, one portion of a test chamber is associated with injections of a drug and another portion is associated with injections of a vehicle. During testing for CPP, conducted in a drug-free state, the subject is allowed to choose between the drug-paired and the vehicle-paired environment. An increase in preference for the drug-paired context serves as a measure of the conditioned reinforcing effects of the drug.

Conditioned reinforcer. A previously neutral stimulus (e.g., tone, light) that acquired reinforcing effects through its prior association with a primary or unconditioned reinforcer (e.g., food, drug).

Contextual drug cue. A diffuse set of "background" stimuli (e.g., operant chamber fan, time of day) in the drug self-administration context that becomes associated with the availability and the effects of the drug following repeated daily training sessions.

Cross-reinstatement. Reinstatement of drug seeking, following extinction of the drug-reinforced behavior by drugs that are different from the self-administered drug.

Discrete conditioned drug cue. A neutral stimulus (e.g., cue light, tone, sound of infusion pump) that becomes a conditioned reinforcer following repeated pairing with drug infusions and effects during self-administration training.

Discriminative drug cue. An environmental stimulus that after discrimination training sets the occasion for drug self-administration behavior (rendering the behavior more likely). During training, this stimulus termed the S^+ (or S^D) is presented just before the drug becomes available or throughout the period of self-administration; a different stimulus, termed the S^- (or S^Δ), is presented when the drug is not available either on alternate days or sessions.

Drug self-administration procedure. In this procedure, laboratory animals typically lever press for drug injections. The premise of this procedure is that psychoactive drugs control behavior by functioning as positive reinforcers. A high concordance exists between drugs self-administered by laboratory animals and those abused by humans.

Extinction. In the terminology of operant conditioning, extinction refers to discontinuing the reinforcement (e.g., food, drug) of a response (e.g., lever press). In the terminology of classical conditioning, extinction refers to the presentation of a conditioned stimulus(i), previously paired with a given unconditioned stimulus (e.g., food, drug), in the absence of the primary reinforcer. In studies of cue-induced reinstatement, extinction may refer to lever pressing in the absence of both the drug and the conditioned cues that had previously been paired with drug injections.

FR schedule of reinforcement. A reinforcement schedule in which the reinforcer (e.g., drug, food) is delivered following an invariant number of responses.

Inactive lever. Responses on this lever do not lead to the delivery of drugs during self-administration training. In reinstatement studies, responses on this lever during testing are thought to measure nonspecific activity and/or response generalization.

Negative reinforcer. A stimulus is defined as a negative reinforcer if its removal or postponement, following a response, increases or maintains the likelihood of a response.

Positive reinforcer. A stimulus is defined as a positive reinforcer in operant conditioning if its presentation, following a response, increases or maintains the likelihood of the response.

Primary reinforcer (or unconditioned reinforcer). Any stimulus that has reinforcing effects without the need for any explicit conditioning operation.

Predictive validity. A measure of how well a manipulation in the model predicts an analogous manipulation in the modeled condition.

Rate-dependent effects of drugs. Refers to the observation that the effects of drugs on operant responding are related to the rate of the response in the absence of the drug. Typically low rates of responding increase proportionally more than higher rates following drug administration; the very high response rates are often decreased by drug administration.

Reinstatement. In the learning literature reinstatement refers to the recovery of a learned response (e.g., lever-pressing behavior) that occurs when a subject is exposed noncontingently to the unconditioned stimulus (e.g., food) after extinction. In studies of reinstatement of drug seeking, reinstatement typically refers to the resumption of drug seeking after extinction following exposure to drugs, drug cues, or stressors.

Relapse. The term commonly used in the clinical literature to describe the resumption of drug-taking behavior following drug-free periods.

Renewal. Recovery of extinguished behavior that can occur when the context is changed after extinction, when the subject returns to the learning environment after extinction in a different environment. In studies of reinstatement of drug seeking, rats are trained to lever press for a drug in one environmental context, the lever-pressing behavior is extinguished in a different context, and renewal of drug seeking occurs when rats return to the original drug self-administration context.

Second-order schedule of reinforcement. A complex schedule of reinforcement in which completion of the response requirements of one schedule (often referred to as the unit schedule) is treated as a unitary response that is reinforced according to another schedule. Often a stimulus is briefly presented at the completion of the unit schedule requirements, and this stimulus can acquire conditioned reinforcing effects.

Within-session reinstatement procedure. A procedure in which drug self-administration training, extinction training, and tests for reinstatement are conducted on the same day.

Sources: Bouton and Swartzentruber, 1991; Catania, 1992; Stolerman, 1992.

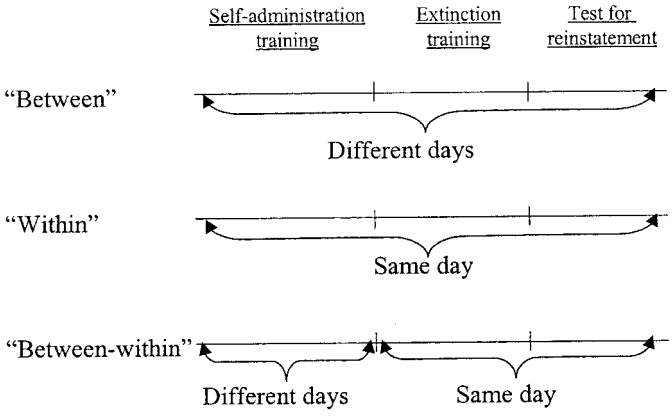

FIG. 2. A depiction of the timeline of within-session, between-session, and between-within-session reinstatement procedures. See Table 1 and text for a full description of these procedures.

limitation of this method, however, is that repeated testing under extinction conditions results in the attenuation of responding to the reinstating stimulus. Thus, subjects that are trained for prolonged periods cannot be tested after extinction more than two to three times, leading to the use of many subjects.

de Wit and Stewart (1981) introduced a "within-session" reinstatement method. In this method, rats are initially trained to self-administer cocaine or heroin. Subsequently, tests for reinstatement are carried out several times a week in a daily session of 1 to 2 h of drug self-administration, 3 to 4 h of extinction of the drug-reinforced behavior, and a subsequent test for reinstatement. Rats are given regular drug self-administration training between the test days. The advantage of this method is that rats can be repeatedly tested for reinstatement (de Wit and Stewart demonstrated that neither tolerance nor sensitization is evident after repeated testing with priming drug injections). The limitations of the within-session method are that it does not simulate long-term relapse in humans, and the rats are not "truly" drug-free at the time of testing (i.e., they are tested several hours after last exposure to drug).

A more recent variation of the reinstatement procedure is the "between-within" method (Tran-Nguyen et al., 1998). In this method, rats are initially trained for drug self-administration. Subsequently, extinction training and tests for reinstatement are conducted on the same day after different days of drug withdrawal. The advantage of this method is that it can be used to study the relationship between the duration of the drug withdrawal period and reinstatement of drug seeking (see *Section V. Discussion*). At present, however, it is not clear whether this method is suitable for repeated testing. Thus, different groups of rats, tested at each withdrawal period, are needed for a clear interpretation of the data (Tran-Nguyen et al., 1998).

Two other reinstatement models were developed in recent years. Ettenberg and colleagues introduced a "*runway* " reinstatement model to study the role of discriminative drug cues in relapse (Ettenberg, 1990; Ettenberg et al., 1996; McFarland and Ettenberg, 1997). In this model, the dependent measure is the "*run time* " from a "*start box* " to a "*goal box* " where a drug infusion is given. During the initial discrimination training (Catania, 1992), rats are given a drug injection when they reach the goal box in the presence of one discriminative cue (e.g., specific odor) or saline injections in the presence of a different cue. The discriminative cues are presented at the start box. Over time, rats decrease their run time in the presence of the drug predictive cue, but not the saline cue. Rats are then given sessions in the absence of the discriminative cues and the drug during which run time progressively increases (extinction). During testing, a single presentation of the drug-associated cue leads to a decrease in the run time to reach the goal box (cue reinstatement). In addition, a single drug infusion in the goal box during extinction decreases the run time on the subsequent drug-free day (drug reinstatement).

The advantage of the runway method is that the impact of drug priming on behavior is studied on a subsequent, drug-free day. Thus, alternative interpretations for the effects of pharmacological manipulations given prior to drug priming (e.g., locomotor activation/sedation) on behavior during testing can be ruled out. The limitation of the runway model is that rats are not exposed to more than several drug infusions/day, and consequently drug intake is much lower than in self-administration studies. Thus, the runway model can only mimic some aspects of recreational drug use but not compulsive use of high amounts of drugs. This model also reveals a complex behavioral pattern in cocaine-trained animals, which do not decrease their run time during training, presumably due to the "anxiogenic" effects of cocaine (Ettenberg and Geist, 1991, 1993). Thus, this model is not suitable for studying relapse to cocaine because it is difficult to establish that cocaine serves as a reinforcer in this model. Finally, rats are given the drug priming contingently when they reached the goal box during an extinction session. Thus, the priming manipulation in the runway method is different than that of the traditional reinstatement method.

Most recently, several laboratories have developed a conditioned place preference (CPP[2]) reinstatement

[2] Abbreviations: CPP, conditioned place preference; DA, dopamine; GABA, γ-aminobutyric acid; VTA, ventral tegmental area; PKA, protein kinase A; NAc, nucleus accumbens; AMPA, α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid; mPFC, medial prefrontal cortex; IEG, immediate early genes; CeA, central nucleus of the amygdala; NMDA, *N*-methyl-D-aspartate; CNQX, 6-cyano-2,3-dihydroxy-7-nitroquinoxaline; 5-HT, 5-hydroxytryptamine; CRF, corticotropin-releasing factor; NA, noradrenaline; SSRI, selective serotonin reuptake blocker; HPA, hypothalamic-pituitary-adrenal; Δ9-THC, Δ9-tetrahydrocannabinol; ADX, adrenalectomy; CB1, cannabinoid type 1; CS, conditioned stimulus; BLA, basolateral amygdala; PKC, protein kinase C; TTX, tetrodotoxin; TH, tyrosine hydroxylase; PENK, proenkephalin; BNST, bed nucleus of the stria terminalis;

model (Mueller and Stewart, 2000; Parker and McDonald, 2000). In these studies, rats are initially trained to associate one distinctive environment with a drug injection and a different environment with a saline (vehicle) injection. Following training, rats spend more time in the drug-paired environment, when given a choice between the two environments, on a drug-free test day. This acquired preference for the drug-paired environment can be extinguished by daily injections of saline in the previously drug-paired environment (extinction). It was found that after extinction, injections of cocaine (Mueller and Stewart, 2000) or morphine (Parker and McDonald, 2000) reinstate the extinguished CPP for the drug. Finally, it was recently reported that both morphine injections and footshock stress "reactivate" CPP for morphine (that is no longer observed) after 9 (Wang et al., 2000) or 36 (Lu et al., 2000) drug-free days, during which the rats are not exposed to extinction conditions. The advantage of the CPP reinstatement model is that nonspecific motor effects of pharmacological manipulations are less likely to influence behavior because the dependent measure is not lever-pressing behavior. This model also does not require the expertise of intravenous surgery and the need to maintain catheter patency. However, as in the case of the runway model, total drug exposure is low and thus the relevance of this model to compulsive and chronic drug use is limited.

In conclusion, several experimental procedures can be used to study reinstatement of drug seeking in rats, each with its advantages and disadvantages. In the sections below, we will review studies that used these different procedures.

II. Drug Priming-Induced Reinstatement

Many studies have reported reliable heroin- or cocaine-induced reinstatement using the different reinstatement methods described above (Self and Nestler, 1998; Stewart, 2000). The drug priming effect also was reported in alcohol- and nicotine-trained rats (Chiamulera et al., 1996; Shaham et al., 1997a; Lê et al., 1998). As described below, this effect is demonstrated following systemic and intracranial administration. Agents from the same pharmacological class of the self-administered drug reliably reinstate heroin and cocaine seeking (Carroll and Comer, 1996; de Wit, 1996). Several studies, however, also demonstrated "cross-reinstatement" with drugs that are from different classes than the self-administered drug (Davis and Smith, 1976; De Vries et al., 1999). The magnitude of drug-induced reinstatement is positively correlated with the priming dose. In addition, doses that are higher than the unit dose of the self-administered drug are needed to reliably reinstate the behavior (de Wit, 1996). Also, at higher doses, peak responding occurred later and continued for longer periods than with low doses (de Wit and Stewart, 1981). Finally, Lynch and Carroll (2000) reported that female rats are more responsive to cocaine-induced reinstatement than male rats. However, the priming effect is reliably observed with male rats, which were used in most of reinstatement studies. In the section below, we describe studies in which pharmacological and neurochemical methods were used to elucidate the role of specific neurotransmitter systems underlying reinstatement by heroin and cocaine priming. Table 2 summarizes data from substitution (cross-reinstatement) studies in which the effect of pharmacological agents on reinstatement of heroin and cocaine seeking was determined. Table 3 summarizes data on the effect of pharmacological agents on reinstatement induced by heroin or cocaine priming.

A. Dopamine

A large body of evidence indicates that the mesocorticolimbic dopamine (DA) system (Fallon and Moore, 1978) contributes to the acute reinforcing effects of heroin and cocaine (Koob and Bloom, 1988; Wise, 1996b). Cocaine, an indirect DA agonist, increases DA release by blocking the DA transporter (Heikkila et al., 1975). Heroin and other μ-opioid receptor agonists increase DA release in terminal regions by inhibiting GABAergic neurons in the VTA, which provide tonic inhibition of DA neurons, resulting in increased DA release in terminal regions (Di Chiara and North, 1992). The data reviewed indicate that the mesocorticolimbic DA system also is involved in reinstatement by cocaine or heroin priming.

1. Cocaine Priming. The effect of cocaine priming on reinstatement is mimicked by systemic injections of amphetamine (a DA reuptake blocker and a DA releaser), DA reuptake blockers (GBR-12909, methylphenidate) and D2-like receptor agonists (7-hydroxy-2-dipropylaminotetralin, quinpirole, bromocriptine) (de Wit and Stewart, 1981; Wise et al., 1990; Self et al., 1996; De Vries et al., 1999; Schenk and Partridge, 1999). On the other hand, mixed DA agonists (apomorphine) or direct D1-like agonists (SKF 82958, SKF 81297, ABT 431) do not mimic the effect of cocaine priming on reinstatement

FR, fixed ratio; VNAB, ventral noradrenegic bundle; LC, locus coeruleus; ABT 431, (−)-trans-9,10-diacetyloxy-2-propyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[c]phenanthrene hydrochloride; CP-154,526, butyl-ethyl-(2,5-dimethyl-7-(2,4,6-trimethylphenyl-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)amine; HU210, 11-hydroxydimethylheptyl-8-tetrahydrocannabinol; PD 128,907, *S*(+)(4a*R*,10b*R*)-3,4,4a,10b-tetrahydro-4-propyl-2*H*,5*H*-[1]benzopyrano[4,3-b]-1,4-oxazin-9-ol hydrochloride; SCH 23390, 7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine; SCH 39166, (−)-trans-6,7,7a,8,9,13b-hexahydro-3-chloro-2-hydroxy-*N*-methyl-5a-benzo-(d)-naphtho-(2,1b)azepine; SKF 81297, (±)-6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide; SKF 82958, (±)-6-chloro-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromide; SR14176A, *N*-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide; WAY 100625, *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinyl-cyclohexane carboxamide.

(Self et al., 1996, 2000; De Vries et al., 1999) (Figs. 3 and 4). Surprisingly, these direct D1-like agonists, some of which are self-administered by rats and monkeys (Self and Stein, 1992; Weed et al., 1993; but see Caine et al., 1999b), also block cocaine-induced reinstatement in rats (Self et al., 1996, 2000) and monkeys (Khroyan et al., 2000). Norman et al. (1999) reported that the D1-like antagonist, SCH 23390, attenuates cocaine-induced reinstatement. In addition, using the runway model in amphetamine-trained rats, Ettenberg (1990) reported that the D2-like receptor antagonist, haloperidol, attenuates drug-induced reinstatement. These pharmacological data indicate that DA plays a crucial role in cocaine-induced reinstatement. In addition, although activation of D2-like receptors provokes cocaine seeking, activation of D1-like receptors inhibits it. The reasons for this pharmacological dissociation are not clear in light of the literature on the similar behavioral effects of the D1- and D2-like agonists on locomotor activity (Self et al., 1996) and cocaine reinforcement (Self and Nestler, 1995).

Studies using intracranial drug injections also provide evidence for the role of the mesocorticolimbic DA system in cocaine priming. Stewart (1984) found that intra-VTA infusions of morphine reinstate cocaine seeking (Fig. 5). A likely mechanism for this effect is that morphine inhibits GABAergic neurons in the VTA, which provide tonic inhibition of DA neurons (Di Chiara and North, 1992). More recently, Self et al. (1998) studied the effect of manipulations of the intracellular signaling of the D1- and D2-like receptors by using an activator (S_P-cAMPS) and an inhibitor (R_P-cAMPS) of protein kinase A (PKA). These agents mimic activation of the D1- and D2-like receptors by receptor agonists, respectively (Kebabian and Calne, 1979). They found that intra-NAc infusions of R_P-cAMPS reinstate cocaine seeking, whereas infusions of S_P-cAMPS nonselectively increase responding on both levers. The data with the PKA inhibitor are in agreement with those obtained with systemic injections of direct D2-like agonists. However, it cannot be ruled out that the effect of R_P-cAMPS on reinstatement is mediated via its action on non-DA receptors in the NAc that also inhibit cAMP formation (e.g., μ-opioid receptors) (Taylor and Fleming, 2001). The mechanisms underlying the effect of the PKA activator on the lever-pressing behavior and their relationship to DAergic activity are even less clear, as this effect is different from that observed with D1-like agonists. Cornish and Kalivas (1999) found that activation of AMPA receptors in the NAc reinstate cocaine seeking, and PKA modulates AMPA receptor activity (Banke et al., 2000). Thus, the effect of the PKA activator on cocaine seeking may be due to its action on the AMPA receptor. More recently Cornish and Kalivas (2000) reported that direct infusions of DA into the NAc reinstate cocaine seeking. Surprisingly, these authors found that intra-NAc infusions of the nonselective DA antagonist, fluphenazine, had no effect on cocaine-induced reinstatement. These data, together with the data described above suggest that DA neurotransmission in components of the mesocorticolimbic DA system other than the NAc is involved in cocaine-induced reinstatement. In agreement with this idea, McFarland and Kalivas (2001) recently found that infusions of fluphenazine into the medial prefrontal cortex (mPFC) attenuate cocaine-induced reinstatement.

Other evidence for the role of DA in cocaine-induced reinstatement comes from studies using in vivo microdialysis and electrophysiology, and immediate early gene expression (IEG) methods. Using in vivo microdialysis, it was reported that priming injections of cocaine increase extracellular dopamine levels in the NAc (Neisewander et al., 1996) and the amygdala (Tran-Nguyen et al., 1998), a terminal projection of the mesocorticolimbic DA system (Fallon and Ciofi, 1992). Di Ciano et al. (2001) reported that in rats trained to self-administer *d*-amphetamine, priming injections of the drug increased DA signal in the NAc, as measured by chronoamperometry. Finally, Neisewander et al. (2000) reported that priming cocaine injections increase Fos protein expression, a cellular marker of neuronal activity (Morgan and Curran, 1991), in the VTA and several terminal DA projections [the caudate putamen, central nucleus of the amygdala (CeA), lateral amygdala and the anterior cingulate cortex].

Other indirect evidence for the role of DA in reinstatement comes from studies demonstrating that caffeine (an antagonist of adenosine receptors) reliably reinstates cocaine seeking (Worley et al., 1994). This effect may be due to an interaction between adenosine A2a and D2-like receptors, which are negatively coupled (Fuxe et al., 1998). Thus, blockade of adenosine A2a receptors by caffeine can lead to activation of D2-like receptors and consequently to reinstatement of cocaine seeking. It has been shown that D2-like receptor antagonists can attenuate the effects of adenosine receptor antagonists (Garrett and Holtzman, 1995).

Converging evidence implicates the mesocorticolimbic DA system in cocaine-induced reinstatement. Surprisingly, D1- and D2-like receptors play fundamentally different roles in this effect. Finally, the recent data of Cornish and Kalivas (2000), together with the previous pharmacological data, suggest that the action of DA in regions of the mesocorticolimbic DA system (e.g., the prefrontal cortex), other than the NAc, mediates cocaine-induced reinstatement. Nevertheless, DA in the NAc still plays a role as intra-NAc infusions of DA reinstate cocaine seeking (Cornish and Kalivas, 2000).

2. Heroin Priming. Indirect DA agonists (cocaine, amphetamine) were found to reinstate heroin seeking after prolonged withdrawal periods (3 weeks) (De Vries et al., 1998a, 1999) (Fig. 3). Intra-NAc infusions of amphetamine also reinstate heroin seeking in the within-session reinstatement procedure (Stewart and Vezina, 1988) (Fig. 5). In contrast, using the within-session pro-

TABLE 2

Reinstatement of heroin or cocaine seeking by pharmacological agents that are different from the self-administered drug

Neurotransmitter System	References	Procedure; Training Dose (mg/kg/infusion); Schedule; Session Duration (h/day)	Cocaine-Trained	Heroin-Trained
Acetylcholine				
Cholinergic agonist:				
Nicotine: (0.038–0.6 mg/kg, s.c.)	Schenk and Partridge, 1999	W; 0.5; FR-1; 2 h	Some effect	
Nicotine: (0.05–0.1 mg/kg, i.v.)	Wise et al., 1990	W; 1.0; FR-1; 2 h	No effect	
Adenosine				
Nonselective receptor antagonist:				
Caffeine (5.0–40.0 mg/kg, i.p.)	Worley et al., 1994	W; 0.25; FR-1; 2 h	Reinstatement	
Caffeine (20.0 mg/kg, i.p.)	Schenk et al., 1996	B-W; 0.25; FR-1; 2 h	Reinstatement	
Caffeine (1.25–20.0 mg/kg, i.p.)	Schenk and Partridge, 1999	W; 0.5; FR-1; 2 h	Reinstatement	
Cannabinoids				
Cannabinoid agonist:				
Δ9-THC (0.3–3.0 mg/kg, i.p.)	Schenk and Partridge, 1999	W; 0.5; FR-1; 2 h	No effect	
HU210 (4–100 μg/kg, s.c.)	De Vries et al., 2001	B; 0.5; FR-5; 2 h	Reinstatement	
Dopamine				
Dopamine (30.0 μg/side, NAc)	Cornish and Kalivas, 2000	B; 0.5–1.0; FR-1; 2 h	Reinstatement	
Indirect agonists:				
Amphetamine (1.0 mg/kg, i.p.)	De Vries et al., 1998a	B; H, 0.05; C, 0.5; FR-1; 2–3 h	Reinstatement	Reinstatement
Amphetamine (0.1–2.0 mg/kg, i.v.)	de Wit and Stewart, 1981	W; 1.0; FR-1; 2–3 h	Reinstatement	
Amphetamine (0.3–3.0 mg/kg, i.p.)	Schenk and Partridge, 1999	W; 0.5; FR-1; 2 h	Reinstatement	
Amphetamine (0.5 mg/kg, i.p.)	Sutton et al., 2000	B; 1.0; FR-1; 4 h	Reinstatement	
Amphetamine (10.0 μg/side, NAc)	Stewart and Vezina, 1988	W; 0.1; FR-1; 2–3 h		Reinstatement
Cocaine (10.0 mg/kg, i.p.)	De Vries et al., 1998a	B; H, 0.05; C; 0.5; FR-1, 2–3 h	Reinstatement	Reinstatement
Cocaine (0.5–2.0 mg/kg, i.v.)	de Wit and Stewart, 1983	W; 0.1; FR-1; 2–3 h		No effect
Cocaine analogs:				
WIN 35,428 (0.1–3.0 mg/kg, i.p.)	Schenk et al., 2000	W; 0.5; FR-5; 2 h	Reinstatement	
RTI-55 (0.05–0.5 mg/kg, i.p.)	Schenk et al., 2000	W; 0.5; FR-5; 2 h	Reinstatement	
Nonselective DA agonist:				
Apomorphine (0.1–1.0 mg/kg, s.c.)	De Vries et al., 1999	B; H, 0.05; C, 0.5; FR-1; 2–3 h	Suppression	Suppression
Apomorphine (0.0625–0.5 mg/kg, i.v.)	de Wit and Stewart, 1981	W; C; 1.0; FR-1; 2–3 h	No effect	
DA reuptake inhibitor:				
GBR 12909 (10.0–20.0 mg/kg, i.p.)	De Vries et al., 1999	B; H, 0.05; C; 0.5; FR-1; 2–3 h	Reinstatement	Reinstatement
GBR 12909 (3.0–30.0 mg/kg, i.p.)	Schenk et al., 2000	W; 0.5; FR-5; 2 h	Reinstatement	
Methylphenidate (2.0–20.0 mg/kg, i.p.)	Schenk and Partridge, 1999	W; 0.5; FR-1; 2 h	Reinstatement	
D1-like receptor agonist:				
SKF 82958 (1.0 mg/kg, s.c.)	De Vries et al., 1999	B; H, 0.05; C, 0.5; FR-1; 2–3 h	No effect	No effect
SKF 82958 (0.3 or 1.0 mg/kg, s.c.)	Self et al., 1996	W; 0.05; FR-1, 2 h	No effect	
D2-like receptor agonist:				
Quinpirole (0.5 mg/kg, s.c.; prolonged withdrawal)	De Vries et al., 1999	B; H, 0.05; C, 0.5; FR-1; 2–3 h	Reinstatement	No effect
Quinpirole (0.05–1.0 mg/kg, s.c.; early withdrawal)	De Vries et al., 2002	B; H, 0.05; C, 0.5; FR-1; 2–3 h	Reinstatement	Reinstatement
Quinpirole (0.03–3.0 mg/kg, i.p.)	Self et al., 1996	W; 0.05; FR-1, 2 h	Reinstatement	
Bromocriptine (0.5–2.0 mg/kg, i.v.)	Wise et al., 1990	W; H, 0.1; C, 1.0; FR-1; 2 h	Reinstatement	Reinstatement
D2/3-like receptor agonist:				
7-OH-DPAT (0.3 mg/kg, s.c.)	Self et al., 1996	W; 0.05; FR-1, 2 h	Reinstatement	
GABA				
$GABA_B$ agonist:				
Baclofen (1.25–2.5 mg/kg, i.p.)	Campbell et al., 1999	W; 0.4; FR-1, 7 h	No effect	
Others				
Ethanol (1.0–10.0 mg/kg, i.v.)	de Wit and Stewart, 1981	W; 1.0; FR-1; 2–3 h	No effect	
Ethanol (2.0 g/kg, i.v.)	Wise et al., 1990	W; 1.0; FR-1; 2 h	No effect	
Methohexital (1.0–2.0 mg/kg, i.v.)	de Wit and Stewart, 1981	W; 1.0; FR-1; 2–3 h	No effect	
Methohexital (0.5–1.0 mg/kg, i.v.)	Wise et al., 1990	W; 1.0; FR-1; 2 h	No effect	
Glutamate				
AMPA receptor agonist:				
AMPA (0.4 nmol/side, NAc)	Cornish and Kalivas, 2000	B; 0.5–1.0; FR-1; 2 h	Reinstatement	
AMPA (0.04–0.4 nmol/side, NAc)	Cornish et al., 1999	B; 0.5–1.0; FR-1; 2 h	Reinstatement	
NMDA agonist:				
NMDA (83.0 pmol/side, VTA)	Vorel et al., 2001	B; 1.0; FR-1; 3 h	Reinstatement	
cis-ACDA (1.0–3.0 nmol/side, NAc)	Cornish et al., 1999	B; 0.5–1.0; FR-1; 2 h	Reinstatement	

TABLE 2
Continued

Neurotransmitter System	References	Procedure; Training Dose (mg/kg/infusion); Schedule; Session Duration (h/day)	Cocaine-Trained	Heroin-Trained
NMDA antagonist:				
MK-801 (0.1–0.25 mg/kg, i.p.)	De Vries et al., 1998b	B; 0.5; FR-1; 2–3 h	Reinstatement	
Noradrenaline				
α 2-Adrenoceptor agonist:				
Clonidine (0.0625 or 0.125, i.v.)	Wise et al., 1990	B; 1.0; FR-1; 2 h	No effect	
Opioids				
Agonists:				
Morphine (0.3–3.0 mg/kg, i.p.)	de Wit and Stewart, 1981	W; 1.0; FR-1; 2–3 h	No effect	
Morphine (0.1–10.0 mg/kg, i.p.)	Schenk and Partridge, 1999	W; 0.5; FR-1; 2 h	No effect	
Morphine (18.0 μg, VTA)	Stewart, 1984	W; H, 0.1; C, 1.0; FR-1; 2–3 h	Reinstatement	Reinstatement
Morphine (5.0 or 10.0 μg, NAc)	Stewart and Vezina, 1988	W; 0.1; FR-1; 2–3 h		No effect
Heroin (0.05–0.2 mg/kg, i.v.)	de Wit and Stewart, 1981	W; 1.0; FR-1; 2–3 h	No effect	
Heroin (0.25 mg/kg, s.c.)	De Vries et al., 1998a	B; H, 0.05; C, 0.5; FR-1; 2–3 h	No effect	Reinstatement
Butorphanol (8.0 mg/kg, s.c.)	Lynch et al., 1998	W; 0.4; FR-1, 7 h	No effect	
Partial agonist:				
Buprenorphine (0.025–0.4 mg/kg, i.v.)	Comer et al., 1993	W; 0.2–1.0; FR-1; 24 h	No effect	
μ-Receptor selective agonist:				
Etonitazene (2.5 or 5.0 mg/kg, i.v.)	Comer et al., 1993	W; 1.0; FR-1; 24 h	No effect	
Preferential μ-receptor antagonist:				
Naltrexone (1.0–5.0 mg/kg, i.p.)	Stewart and Wise, 1992	W; 0.1; FR-1; 3 h		No effect
Naltrexone (1.6 or 3.2 mg/kg, i.v.)	Comer et al., 1993	W; 1.0; FR-1; 24 h	No effect	
Naltrexone (0.1 mg/kg, s.c., with heroin minipumps)	Shaham et al., 1996	B; 0.1; FR-1; 7–12 h		No effect
Other manipulations				
PKA inhibitor:				
R_p-cAMPS (40.0 or 80.0 nmol/side, NAc)	Self et al., 1998	W; 0.5; FR-1; 2 h	Reinstatement	
PKA activator:				
S_p-cAMPS (40.0 or 80.0 nmol/side, NAc)	Self et al., 1998	W; 0.5; FR-1; 2 h	Nonspecific activation	

Abbreviations: B, between-session reinstatement procedure; B-W, between-within session reinstatement procedure; C, cocaine; FR, fixed ratio schedule of reinforcement; H, heroin; W, within-session reinstatement procedure.

TABLE 3
Effect of pharmacological manipulations on heroin- or cocaine priming-induced reinstatement

Neurotransmitter System	References	Type of Procedure; Training Dose (mg/kg/inf); Schedule; Session Duration (h/day); Priming Dose (mg/kg)	Cocaine-Trained	Heroin-Trained
Corticosterone				
Adrenalectomy	Shaham et al., 1997	B; 0.1; FR-1; 6–12 h; 0.25 (s.c.)		No effect
	Erb et al., 1998	B; 1.0; FR-1; 3 h; 20 (i.p.)	No effect	
Adrenalectomy + CORT replacement	Erb et al., 1998	B; 1.0; FR-1; 3 h; 20 (i.p.)	No effect	
Corticosterone synthesis inhibitor:				
Chronic metyrapone (100.0 mg/kg, s.c., 4–8 days)	Shaham et al., 1997	B; 0.1; FR-1; 6–12 h; 0.25 (s.c.)		No effect
Acute metyrapone (100.0 mg/kg, s.c.)	Shaham et al., 1997	B; 0.1; FR-1; 6–12 h; 0.25 (s.c.)		No effect
Ketoconazole (50.0 mg/kg, i.p.)	Mantsch and Goeders, 1999b	B; 0.5; FR-4; 2 h; 5–20 (i.p.)	No effect	
Cannabinoids				
Cannabinoid antagonist:				
SR141716A (0.3–3.0 mg/kg, s.c.)	De Vries et al., 2001	B; 0.5; FR-1; 2 h; 1.0 (i.v.)	Attenuation	
CRF				
CRF antagonists:				
D-Phe CRF 12–41 (0.1–1.0 μg, i.c.v.)	Erb et al., 1998	B; C; 1.0; FR-1; 3 h; 20 (i.p.)	No effect	
α-Helical-CRF (3.0–10.0 μg, i.c.v.)	Shaham et al., 1997	B; H; 0.1; FR-1; 6–12 h; 0.25 (s.c.)		No consistent effect
α-Helical-CRF (1.0–10.0 μg, i.c.v.)	Lu et al., 2001	B; 10.0 (i.p.), CPP; 10.0 (i.p.)	Attenuation	
CRF1 receptor antagonists:				
CP-154,526 (1.0–10.0 mg/kg, s.c.)	Lu et al., 2001	B; 10.0 (i.p.); CPP; 10.0 (i.p.)	Attenuation	
CRF2 receptor antagonists:				
AS-30 (1.0–10.0 μg, i.c.v.)	Lu et al., 2001	B; 10.0 (i.p.); CPP; 10.0 (i.p.)	No effect	
Dopamine				
Amphetamine (0.5–2.0 mg/kg, i.p.)	Lynch et al., 1998	W; 0.4; FR-1; 7 h; 3.2 (i.v.)	Potentiation	
D1-like receptor antagonist:				
SCH 23390 (0.01 mg/kg, i.v.)	Norman et al., 1999	B-W; 0.05–4.0; FR5 or FR1; 2 h; 20–100 μg/kg (i.v.)	Attenuation	
SCH 23390 (0.05–0.1 mg/kg, i.p.)	Shaham and Stewart, 1996	B; 0.1; FR-1; 12 h; 0.25 (s.c.)		Attenuation
D2-like receptor antagonist:				
Haloperidol (0.075–0.3 mg/kg, i.p.)	Ettenberg et al., 1996	B; Runway; 0.06; 0.06 (i.v.)		Attenuation
Haloperidol (0.15–0.3 mg/kg, i.p.)	McFarland and Ettenberg, 1997	B; Runway; 0.1; 0.1 (i.v.)		Attenuation
Raclopride (0.25–0.5, i.p.)	Shaham and Stewart, 1996	B; 0.1; FR-1; 12 h; 0.25 (s.c.)		Attenuation
D1-like receptor agonist:				
SKF 82958 (0.3–1.0 mg/kg, s.c.)	Self et al., 1996	W; 0.5; FR-1; 2 h; 0.5–2.0 (i.v.)	Attenuation	
SKF 81297 (0.3–3.0 mg/kg, s.c.)	Self et al., 1996	W; 0.5; FR-1; 2 h; 2.0 (i.v.)	Attenuation	
ABT-431 (0.1–3.0 mg/kg, s.c.)	Self et al., 2000	W; 0.5; FR-1; 2 h; 2.0 (i.v.)	Attenuation	
D2/3-like receptor agonist:				
7-OH-DPAT (0.3 mg/kg, s.c.)	Self et al., 1996	W; 0.5; FR-1; 2 h; 0.5 (i.v.)	Potentiation	
Nonselective dopamine antagonist:				
Flupethixol (3.0–6.0 mg/kg, i.m.)	Shaham and Stewart, 1996	B; 0.1; FR-1; 7–12 h; 0.25 (s.c.)		Attenuation
Fluphenazine (10.0 nmol/side, NAc)	Cornish and Kalivas, 2000	B; 0.5–1.0; FR-1; 2 h; 10 (i.p.)	No effect	
GABA				
Agonist:				
Baclofen (1.25–2.5 mg/kg, i.p.)	Campbell et al., 1999	W; 0.4; FR-1; 7 h; 3.2 (i.v.)	Attenuation	
Glutamate				
NMDA antagonist:				
D-CPPene (0.3–3.0 mg/kg, i.p.)	Bespalov et al., 2000	B; 0.32; FR-1; 3 h; 1.0 (i.v.)	Nonspecific effect	
CPP (0.1 nmol/side, into NAc)	Cornish and Kalivas, 2000	B; 0.5–1.0; FR-1; 2 h; 10 (i.p.)	No effect	
Memantine (1.0–10.0 mg/kg, i.p.)	Bespalov et al., 2000	B; 0.32; FR-1; 1.0 (i.v.)	Nonspecific effect	
AMPA receptor antagonist:				
CNQX (1.0 nmol/side, into NAc)	Cornish and Kalivas, 2000	B; 0.5–1.0; FR-1; 2 h; 10 (i.p.)	Attenuation	
Noradrenaline				
α2-Adrenoceptor agonists:				
Clonidine (10.0 or 40.0 μg/kg, i.p.)			No effect	
Lofexidine (50.0–200.0 μg/kg, i.p.)	Erb et al., 2000	B; 0.5; FR-1; 3 h; 20 (i.p.)	No effect	
Guanabenz (640.0 μg/kg, i.p.)			No effect	

TABLE 3
Continued

Neurotransmitter System	References	Type of Procedure; Training Dose (mg/kg/inf); Schedule; Session Duration (h/day); Priming Dose (mg/kg)	Cocaine-Trained	Heroin-Trained
Opioids				
Agonists:				
Butorphanol (8.0 mg/kg, s.c.)	Lynch et al., 1998	W; 0.4; FR-1, 7 h; 3.2 (i.v.)	Attenuation	
Morphine (0.3–3.0, s.c.)	Lynch et al., 1998	W; 0.4; FR-1, 7 h; 3.2 (i.v.)	No effect	
Chronic heroin (3.0 mg/kg/day via osmotic pump)	Shaham et al., 1996	B; 0.1; FR-1; 7–12 h; 0.25 (s.c.)		Attenuation
Partial agonist:				
Buprenorphine (0.025–0.4 mg/kg, i.v.)	Comer et al., 1993	W; 1.0; FR-1, 7 h; 3.2 (i.v.)	Attenuation	
μ-Receptor selective agonist:				
Etonitazene (2.5 or 5.0 mg/kg, i.v.)	Comer et al., 1993	W; 1.0; FR-1, 7 h; 3.2 (i.v.)	Some attenuation	
κ-Receptor agonist:				
U69593 (0.16 or 0.32 mg/kg, s.c.)	Schenk et al., 1999	W; 0.5; FR-1; 2 h; 20 (i.p.)	Attenuation	
Antagonist:				
Naltrexone (1.6 or 3.2 mg/kg, i.v.)	Comer et al., 1993	W; 1.0; FR-1, 7 h; 3.2 (i.v.)	No effect	
Naltrexone (2.0 mg/kg, i.p.)	Stewart, 1984	W; 0.1; FR-1, 2–3 h; 0.1 (i.v.)		Attenuation
Naltrexone (1–10 mg/kg, s.c.)	Shaham and Stewart, 1996	B; 0.1; FR-1; 12 h		Attenuation
Serotonin				
Selective serotonin reuptake inhibitor:				
Fluoxetine (3.0 mg/kg/day, i.p., 20 days)	Baker et al., 2001	B; 0.5; FR-1; 6 h; 15 (i.p.)	No effect	
5-HT_{2C} agonist:				
Ro 60-0175 (1.0–3.0 mg/kg, s.c.)	Grottick et al., 2000	B; 0.25; FR-5; 1 h; 15 (i.p.)	Attenuation	
5-HT_2 antagonist:				
Ritanserin (1.0 or 10.0 mg/kg, i.p.)	Schenk, 2000	W; 0.5; FR-1; 2 h; 5.0–20.0 (i.p.)	No effect	
5-HT_{1A} antagonist:				
WAY 100653 (0.1–1.0 mg/kg, s.c.)	Schenk, 2000	W; 0.5; FR-1; 2 h; 5.0–20.0 (i.p.)	Attenuation	
Other manipulations				
Cocaine immunogen GNC-KLH	Carrera et al., 2000	B; 0.25; FR-1; 1 h; 0.25 (i.v.)	Attenuation	
Leptin (2.0 and 4.0 μg, i.c.v.)	Shalev et al., 2001	B; 0.1; FR-1; 9 h; 0.25 (s.c.)		No effect
Acamprosate (50.0–200.0 mg/kg, i.p.)	Spanagel et al., 1998	B; 0.1; 4 h; 0.25 (s.c.)		No effect
PKA inhibitor:				
R_p-cAMPS (40.0 nmol/side, into NAc)	Self et al., 1998	W; 0.5; FR-1; 2 h; 0.5 or 2.0	Potentiation	
PKA activator:				
S_p-cAMPS (40.0 nmol/side, into NAc)	Self et al., 1998	W; 0.5; FR-1; 2 h; 0.5 or 2.0	Nonspecific effect	

Abbreviations: B, between-session reinstatement procedure; B-W, between-within session reinstatement procedure; C, cocaine; H, heroin; W, within-session reinstatement procedure.

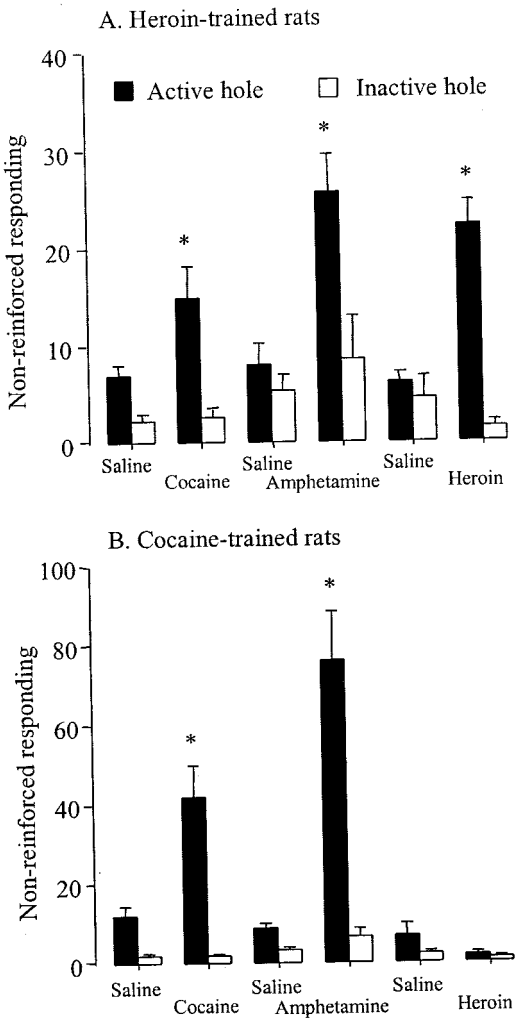

FIG. 3. Reinstatement following long-term extinction (3 weeks) of heroin and cocaine self-administration: mean (± S.E.M.) number of nose poke responses in the previously active (drug-paired) and inactive hole during the 2-h test for reinstatement. A, priming effects in rats previously trained to self-administer heroin; B, priming effects in rats previously trained to self-administer cocaine. Saline, cocaine (10 mg/kg, i.p.), amphetamine (1.0 mg/kg, i.p.), or heroin (0.25 mg/kg, s.c.) were injected 10 min before the start of the reinstatement session. *, significantly different from preceding saline injection ($p < 0.05$). Data are from De Vries et al., 1998, reprinted ©1998 with permission from Blackwell Science Ltd.

cedure, it was reported that cocaine does not reliably reinstate heroin seeking (de Wit and Stewart, 1983). The discrepant results between the effect of cocaine in the between- and within-reinstatement procedures may be related to the development of sensitization to the DA-dependent behavioral activating effects of cocaine following prolonged, but not short, withdrawal periods (De Vries et al., 1999; Vanderschuren and Kalivas, 2000).

Using the within-subjects method, the direct D2-like agonist, bromocriptine, was found to reinstate heroin seeking (Wise et al., 1990). Interestingly, De Vries et al. (1999, 2002) found that the D2-like agonist, quinpirole, reinstates heroin seeking following short withdrawal periods (within 1 week) but not following 3 weeks of withdrawal. The nonselective DA agonist, apomorphine, and the D1-like receptor agonist, SKF 82958, do not reinstate heroin seeking (de Wit and Stewart, 1983; De Vries et al., 1999). In other studies it was found that D2-like receptor antagonists block heroin-induced reinstatement (Ettenberg et al., 1996; Shaham and Stewart, 1996; Lu et al., 2001b). Blockade of the D1-like receptors by SCH 23390 also attenuated heroin-induced reinstatement (Shaham and Stewart, 1996). However, nonspecific sedative effects of the relatively high dose of the D1-like antagonist (0.05–0.1 mg/kg, i.p.) may have contributed to this effect.

Together, the available data suggest that DA is involved in heroin-induced reinstatement. The recent data of De Vries and colleagues suggest that activation of D2-like receptors plays an important role in heroin reinstatement during early but not late withdrawal. A role of D1-like receptors in heroin-induced reinstatement, however, has not been established.

B. Opioids

Activation of μ-opioid receptors is critically involved in heroin reinforcement (Mello and Negus, 1996). The rewarding effects of heroin are mediated via dopamine-dependent mechanisms within the VTA (Wise, 1996b) and dopamine-independent mechanisms within the NAc (Koob, 1992). On the other hand, despite the fact that manipulations of opioid receptors were found to alter cocaine self-administration and CPP in several studies (Shippenberg and Elmer, 1998; Van Ree et al., 1999), it has not been established that activation of opioid receptors is critical for cocaine reward and in many studies opioid receptor antagonists failed to alter cocaine reward (Mello and Negus, 1996). Several studies have examined the effect of opioid receptor agonists and antagonists on reinstatement of heroin and cocaine seeking.

1. Cocaine Priming. The role of opioid receptors in cocaine priming has not been clearly established and the data reviewed below mirror the conflicting literature on the role of opioid receptors in cocaine reinforcement. The preferentially μ-opioid antagonist, naltrexone, has no effect on cocaine-induced reinstatement (Comer et al., 1993). In addition, systemic injections of μ-opioid receptor agonists (heroin, morphine, etonitazene), a mixed μ-agonist/κ-antagonist (buprenorphine) or a mixed μ/κ-agonist (butorphanol) do not reliably reinstate cocaine seeking (de Wit and Stewart, 1981; Comer et al., 1993; De Vries et al., 1998a; Lynch et al., 1998). Furthermore, butorphanol, etonitazene, and buprenorphine (Comer et al., 1993; Lynch et al., 1998), but not morphine (Lynch et al., 1998), attenuate cocaine-induced reinstatement. However, the interpretation of these data is complicated because in opioid-naive rats, systemic injections of opioid agonists have a biphasic effect on behavior: an initial sedative effect that is followed by behavioral activation (Babbini et al., 1975). These initial sedative effects may have masked the expression of the motivational effects of the opioid receptor agonists on reinstatement. Thus, when morphine is infused acutely into the VTA, where it

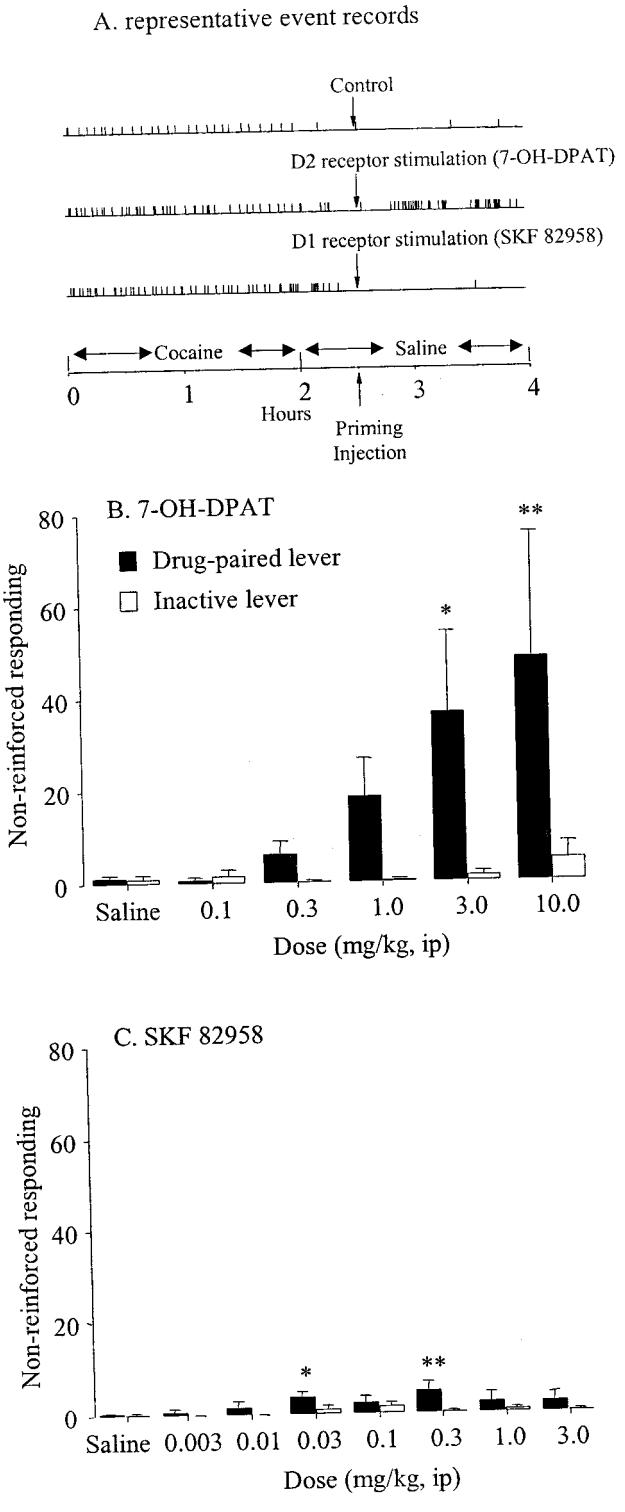

FIG. 4. Effects of intraperitoneal (i.p.) injections with vehicle (saline), the D2-like dopamine agonist 7-hydroxy-2-dipropylaminotetralin, or the D1-like agonist SKF 82958 on reinstatement of nonreinforced lever-press responding. Priming injections were given after extinction from 2 h of intravenous cocaine self-administration when only intravenous saline injections were available. A, lever-press responding in a representative animal. Hatch marks denotes the times of each self-infusion of cocaine in the cocaine phase and of saline in the saline phase. B and C, mean number (± S.E.M.) of nonreinforced lever-press responses during the final hour of the saline phase in the drug-reinstatement paradigm. Asterisks indicate significant differences from saline treatment (*, $p < 0.05$; **, $p < 0.01$). Data are from Self et al., 1996. Copyright 1996 with permission from Science (Wash DC).

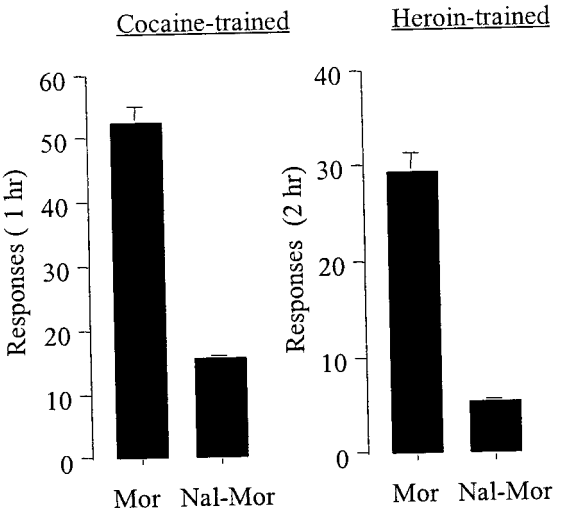

FIG. 5. Responses (mean ± S.E.M.) on the previously active (cocaine- or heroin-paired) lever following priming injections of morphine (Mor) into the ventral tegmental area (cell body region of the mesolimbic dopaminergic neurons), in rats previously trained to self-administer cocaine (left panel) or heroin (right panel). Rats were tested with (Nal-Mor) or without (Mor) pretreatment with the opioid receptor antagonist naltrexone (Nal), administered i.p. Data are from Stewart, 1984, reprinted ©1984 with permission from Elsevier Science.

induces behavioral activation (Joyce and Iversen, 1979), it reinstates cocaine seeking (Stewart, 1984). More recently, Schenk et al. (1999, 2000) reported that the κ-opioid receptor agonist, U69593, decreases cocaine-induced reinstatement. This effect may be related to the inhibitory effect of κ-opioid receptor activation on DA release (Spanagel et al., 1990; Shippenberg and Elmer, 1998).

Despite the fact that opioid agonists and mixed agonists have been shown to attenuate cocaine priming, the potential sedative effects of these compounds in opioid-naive rats, together with the data on the lack of effect of naltrexone on cocaine-induced reinstatement, suggest that activation of μ-opioid receptors is not involved in cocaine reinstatement. However, it appears that alterations of DA neurotransmission by opioid agents can, under certain conditions (e.g., direct intra-VTA infusions of morphine), lead to cocaine seeking.

2. Heroin Priming. The effect of heroin priming on reinstatement is dependent on activation of μ-opioid receptors. Priming injections of μ-opioid receptor agonists such as morphine mimic the effect of heroin on reinstatement when given systemically (de Wit and Stewart, 1983; Stewart and Wise, 1992) or intra-VTA but not intra-NAc (Stewart, 1984) (Fig. 5). Naltrexone, a preferentially μ-opioid receptor agonist, blocks reinstatement induced by either systemic injections of heroin (Shaham and Stewart, 1996) or intra-VTA morphine (Stewart, 1984). Finally, chronic occupation of the opioid receptors with heroin given via Alzet osmotic minipumps attenuates heroin-induced reinstatement (Shaham et al., 1996). These data suggest that activation of DA neurons in the VTA mediates heroin-induced reinstatement. However, there are recent reports that

infusions of opioid and GABAergic agents into the VTA also have DA-independent rewarding effects (Nader and Van der Kooy, 1997; McBride et al., 1999). Thus, it cannot be ruled out that DA-independent mechanisms within the VTA are involved in heroin-induced reinstatement.

C. Glutamate

Glutamate neurotransmission is involved in the development and expression of behavioral and neurochemical sensitization to opioid and psychostimulant drugs (Pierce and Kalivas, 1997; White and Kalivas, 1998). Based on these reports, several recent studies investigated the effect of systemic or intracranial injections of agonists and antagonists of ionotropic glutamate receptors (NMDA and AMPA/kainate) on reinstatement of cocaine seeking.

De Vries et al. (1998b) reported that systemic injections of the noncompetitive NMDA antagonist, MK-801, reinstate cocaine seeking. In contrast, Bespalov et al. (2000) reported that the competitive NMDA receptor antagonist, D-CPPene, and the low-affinity NMDA receptor channel blocker, memantine, do not reinstate cocaine seeking. These discrepant results are one of many examples of the different effects of noncompetitive and competitive NMDA receptor antagonists on behavior (Willetts et al., 1990). Another finding in the study of Bespalov et al. was that pretreatment with the NMDA receptor antagonists led to increased responding on the inactive lever. The reasons for this nonspecific effect are not clear.

Evidence for the role of glutamate neurotransmission in cocaine reinstatement comes from two studies by Cornish and Kalivas (1999, 2000). They found that intra-VTA infusions of AMPA selectively reinstate cocaine but not sucrose seeking. The NMDA receptor agonist (*cis*-ACDA) increased responding on the active lever during testing, but also somewhat increased responding on the inactive lever. In addition, the AMPA receptor antagonist, CNQX, blocked reinstatement of cocaine seeking induced by cocaine priming (given systemically) and intra-NAc infusions of DA. In contrast, the NMDA receptor antagonist, CPP, had no effect on cocaine priming (Fig. 6). Thus, although activation of AMPA and NMDA receptors in the NAc can induce reinstatement, only the former is directly involved in cocaine-induced reinstatement.

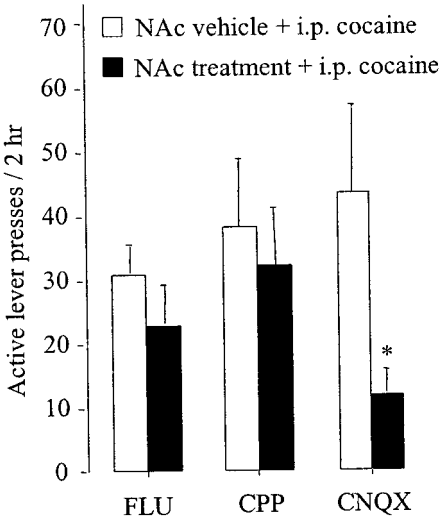

FIG. 6. Effect of intra-accumbens treatment with the mixed dopamine receptor antagonist fluphenazine (FLU; 10 nmol/side), the NMDA receptor antagonist CPP (0.1 nmol/side), and the AMPA receptor antagonist CNQX (1.0 nmol/side) on cocaine- (10.0 mg/kg, i.p.) induced reinstatement of nonreinforced lever-press responding. Data are expressed as mean ± S.E.M. *, significantly different from the vehicle-treated group ($p < 0.05$). Data are from Cornish and Kalivas, 2000, reprinted ©2000 with permission from the Society for Neuroscience.

A study by Vorel et al. (2001) provides additional evidence for the role of glutamate in cocaine reinstatement. Using stimulation parameters previously shown to evoke glutamate receptor-mediated changes in dopamine efflux in the NAc (Blaha et al., 1997), these investigators found that stimulation of the hippocampal-containing glutamatergic neurons in the ventral subiculum reinstates cocaine seeking. They also found that hippocampal stimulation-induced reinstatement is blocked by an intra-VTA infusion of the nonselective ionotropic glutamate antagonist, kynurenic acid, and is mimicked by intra-VTA infusions of NMDA, a manipulation that increases DA release in the NAc (Westerink et al., 1996). The relevance of these provocative data to reinstatement induced by cocaine priming, however, is not known.

Recent data indicate that glutamate action on AMPA receptors within the NAc plays a critical role in cocaine-induced reinstatement. In addition, activation of NMDA receptors within both the NAc and the VTA can reinstate cocaine seeking. The relationship between the glutamatergic mechanisms within the VTA and NAc in cocaine reinstatement is an interesting question for future research. Finally, acamprosate (calcium-acetyl homotaurinate), a compound that alters glutamatergic neurotransmission (Spanagel and Zieglgänsberger, 1997), had no effect on heroin-induced reinstatement (Spanagel et al., 1998). Studies on the effect of specific NMDA or AMPA receptor ligands on heroin-induced reinstatement have not been published.

D. Other Neurotransmitter Systems

Several studies were conducted on the role of several other neurotransmitter systems in reinstatement induced by cocaine or heroin priming. These include 5-HT, corticosterone and corticotropin-releasing factor (CRF), GABA, noradrenaline (NA), acetylcholine, and the endocannabinoids.

1. 5-Hydroxytryptamine. Manipulations of brain 5-HT systems can alter the behavioral effects of cocaine, including drug self-administration and discrimination (Walsh and Cunningham, 1997). Several studies examined the effect of 5-HT agents on cocaine priming-induced reinstatement. The selective serotonin re-

uptake inhibitor (SSRI), fluoxetine, which increases 5-HT levels in terminal regions (Perry and Fuller, 1992), has no effect on cocaine-induced reinstatement (Baker et al., 2001). The 5-HT_{1a} antagonist, WAY 100635, which increases 5-HT cell firing and release (Mongeau et al., 1997), attenuates cocaine-induced reinstatement. In addition, the 5-HT_{2C} agonist Ro 60-0175 (Grottick et al., 2000), but not the 5-HT_2 antagonist ritanserin (Schenk, 2000), attenuates cocaine-induced reinstatement. Ro 60-0175 may attenuate cocaine-induced reinstatement by decreasing DA levels in the NAc and frontal cortex (Millan et al., 1998; Di Matteo et al., 1999). Finally, Tran-Nguyen et al. (2001) reported that 5-HT lesions by 5,7-dihydroxytryptamine shift the dose-response curve of cocaine priming to the left. These data suggest that 5-HT acts on 5-HT_{2C} receptors to attenuate cocaine-induced reinstatement. However, the observation that fluoxetine has no effect on cocaine priming is not in agreement with this idea. Thus, the role of 5-HT in cocaine-induced reinstatement remains to be determined.

2. Corticosterone. The stress hormone, corticosterone, which is released following activation of the hypothalamic-pituitary adrenal (HPA) axis (Selye, 1956), plays an important role in cocaine reinforcement (Piazza and Le Moal, 1998). Cocaine activates the HPA axis (Sarnyai et al., 2001), and inhibition of circulating corticosterone decreases intravenous cocaine self-administration in rats (Goeders, 1997; Piazza and Le Moal, 1997). The data reviewed below, however, suggest that corticosterone secretion does not play a major role in cocaine- (or heroin-) induced reinstatement. The removal of corticosterone by adrenalectomy (ADX) or the administration of CRF receptor antagonists had no effect on cocaine- or heroin-induced reinstatement (Shaham et al., 1997b; Erb et al., 1998). In addition, synthesis inhibitors of corticosterone (ketoconazole or metyrapone) had no effect on cocaine- or heroin-induced reinstatement (Shaham et al., 1997b; Mantsch and Goeders, 1999b). Recently, however, the nonselective CRF receptor antagonist, α-helical CRF, and the selective CRF_1 receptor antagonist, CP-154,526 (Schulz et al., 1996) but not the CRF_2 receptor antagonist antisauvagine-30, were reported to attenuate reactivation of morphine CPP by drug priming after 28 days of withdrawal (Lu et al., 2000). Lu et al. (2001a) also reported that α-helical CRF, but not CP-154,526 or antisauvagine-30, attenuates reactivation of cocaine CPP by cocaine priming. The reasons for the different effects of the CRF receptor antagonists in the CPP model versus the self-administration model are not clear.

3. γ-Aminobutyric Acid. Roberts and Brebner (2000) found that the $GABA_B$ receptor agonist, baclofen, attenuates cocaine reward. Campbell et al. (1999) reported that baclofen also attenuates cocaine-induced reinstatement (Campbell et al., 1999). This effect may be due to the inhibitory action of baclofen on DA neurons in the VTA (Westerink et al., 1996).

4. Noradrenaline. Several studies found that manipulations of central NA have an effect on opioid and psychostimulant self-administration behavior (Davis et al., 1975; Harris et al., 1996). However, based on other studies, it is generally believed that the involvement of central NA neurons in drug reinforcement is minimal (Wise, 1978, 1996b). Erb et al. (2000) found that the α-2 adrenoceptor agonists, clonidine and lofexidine, have no effect on cocaine-induced reinstatement at doses that decrease NA release in the amygdala and prefrontal cortex. These data suggest that the action of cocaine on the NA transporter (Blakely et al., 1994) is not involved in its effect on reinstatement. The role of NA in heroin-induced reinstatement has not been determined.

5. Acetylcholine. Cholinergic neurons modulate mesocorticolimbic DA neurotransmission in the NAc and the VTA (Di Chiara et al., 1994; Sarter et al., 1999). Nicotine increases DA release in the NAc (Damsma et al., 1989), an effect mediated via the activation of nicotine receptors in the VTA (Nisell et al., 1994). The available data, however, do not implicate nicotinic acetylcholine receptors in cocaine-induced reinstatement. Schenk et al. (1999) found some effect of nicotine on reinstatement of cocaine seeking, but Wise et al. (1990) did not.

6. Endocannabinoids. The endocannabinoid system has been implicated in several neuropsychiatric conditions, including drug addiction (Gardner and Vorel, 1998; Piomelli et al., 2000). The active ingredient of marijuana, Δ9-THC, activates the mesocorticolimbic DA system (Chen et al., 1991; Tanda et al., 1997). In addition, DA through activation of D2-like receptors, releases endogenous cannabinoids in the striatal complex (Giuffrida et al., 1999). Based on these findings, two studies determined the effect of activation or blockade of cannabinoid receptors on cocaine seeking. Using the within-session method, Schenk and Partridge (1999) found that Δ9-THC has no effect on cocaine seeking. In contrast, using the between-session method, De Vries et al. (2001) found that the nonselective cannabinoid agonist, HU210, potently reinstates cocaine seeking following 2 to 3 weeks of withdrawal, whereas the CB1 receptor antagonist SR141716A attenuates cocaine-induced reinstatement. These discrepant results may be due to the time of testing (several hours versus several weeks of withdrawal) and the longer duration of action of HU210 compared with Δ9-THC.

E. Summary

1. Cross-reinstatement or reinstatement by a drug other than the self-administered drug is most commonly observed within a given drug class. This effect, however, also is observed across drug classes and is often not symmetrical (i.e., psychostimulants are more likely to reinstate opioid seeking than vice versa).

2. DA receptors are critically involved in cocaine and heroin-induced reinstatement, whereas opioid receptors are involved in heroin but not cocaine reinstatement.
3. D1- and D2-like receptors play different roles in cocaine reinstatement. Activation of D2-like receptors provokes cocaine seeking, whereas activation of D1-like receptors inhibits it.
4. Glutamate within the VTA and the NAc appears to play an important role in cocaine reinstatement. Surprisingly, within the NAc, blockade of AMPA but not DA receptors attenuates cocaine-induced reinstatement. These data suggest that mesocorticolimbic DA projections to areas other than the NAc mediate the behavioral effects of the systemic injections of DA receptor ligands in the reinstatement model.
5. Recent studies suggest that activation of $GABA_B$ or $5\text{-}HT_{2C}$ receptors attenuates cocaine-induced reinstatement, but future studies are needed to verify the role of GABA and 5-HT in drug-induced reinstatement. The studies reviewed also indicate that cocaine-induced NA and corticosterone release does not contribute to cocaine-induced reinstatement.
6. Recent data suggest that activation of endocannabinoid systems in the brain is involved in cocaine-induced reinstatement.

III. Cue-Induced Reinstatement

In an initial study Davis and Smith (1976) trained rats to press a lever for intravenous injections of morphine; each injection was accompanied by a buzzer presentation (a discrete conditioned stimulus, CS). Lever pressing for morphine was then extinguished by replacing morphine infusions with saline in the absence of the CS. During testing, lever presses resulted in response-contingent presentations of the CS (a conditioned reinforcer), and rats increased their lever-pressing behavior. In contrast, de Wit and Stewart (1981) found that noncontingent exposure to a tone cue following extinction of the lever-pressing behavior for cocaine in the absence of the CS has a weak effect on reinstatement. Similarly, two recent studies found that noncontingent presentations of discrete CSs have a minimal effect on cocaine seeking following extinction of lever pressing in their absence (Fuchs et al., 1998; Tran-Nguyen et al., 1998). It appears that two features are important for obtaining a reliable effect of discrete drug CS on reinstatement (See et al., 1999; Grimm et al., 2000). First, a compound (i.e., tone + light) cue is more effective in inducing reinstatement than a simple tone or light cue (See et al., 1999). Second, as predicted from the studies above, the drug cues should be presented contingently during tests for reinstatement (Grimm et al., 2000).

More recently, Ettenberg et al. (1996) and Weiss et al. (2000) have developed discrimination procedures (Catania, 1992) to characterize the role of discriminative cues, which predict drug availability, in relapse. In these studies, discrete environmental cues (e.g., sound, smell) predict whether drug or no drug (saline) is available during drug self-administration training. These investigators showed that discriminative cues that predict drug availability provoke relapse when they are introduced after the drug-reinforced behavior is extinguished in their absence (McFarland and Ettenberg, 1997; Gracy et al., 2000).

Using a *renewal* procedure (Bouton and Bolles, 1979), we examined the role of contextual stimuli (e.g., physical characteristics of the test environment), which predict drug availability, in relapse to drug seeking (Crombag and Shaham, 2002). In the renewal procedure, conditioned responses to discrete CSs are recovered when they are reintroduced in the original conditioning context (where they were paired with the primary reinforcer) after extinction in a different context. We found that in rats with a history of speedball (a heroin-cocaine combination) self-administration, drug seeking is reinstated when rats are exposed to the drug self-administration context following extinction of the lever-pressing behavior in the presence of drug-contingent CSs (stimulus light, sound of the pump) in a different context (Crombag and Shaham, 2002).

Finally, learning theorists view responding in the absence of a primary reinforcer during extinction as a behavior that is controlled by the CSs previously paired with the reinforcer (Pavlov, 1927; Skinner, 1953). From this perspective, the effect of pharmacological/lesion manipulations on rate of extinction (or resistance to extinction) can be used to study neuronal substrates involved in discrete CS-induced drug seeking (Fuchs et al., 1998). Studies of this type are reviewed below. However, data from studies in which in vivo electrophysiology, microdialysis, and electrochemistry were used during drug self-administration, and thus samples were occasionally taken in response to the drug cues prior to drug infusions, are not reviewed here. Table 4 describes the data from the pharmacological studies on cue-induced reinstatement.

A. Discrete Conditioned Stimuli

Bespalov et al. (2000) reported a decrease in cocaine cues-induced reinstatement following pretreatment with the NMDA receptor antagonist, D-CPPene, but not the low affinity NMDA channel blocker, memantine. See et al. (2001) found that basolateral amygdala (BLA) intra-infusions of an NMDA receptor antagonist (AP-5) or kainate/AMPA receptor antagonist (CNQX) have no effect on cocaine cues-induced reinstatement. These data suggest that NMDA receptors in regions other than the BLA may be involved in cocaine cues-induced reinstatement. Most recently, De Vries et al. (2001) found that the CB1 receptor antagonist SR141716A attenuates cocaine cues-induced reinstatement. These data

TABLE 4
Effect of pharmacological manipulations on cue-induced reinstatement of cocaine and heroin seeking

Neurotransmitter System	References	Type of Procedure; Training Drug; Training Dose (mg/kg/infusion); Schedule; Session Duration (h/day)	Discrete CS	Discriminative or Contextual Cues	Extinction Behavior
Cannabinoids					
Cannabinoid antagonist:					
SR141716A (0.3–3.0 mg/kg, s.c.)	De Vries et al., 2001	B; C; 0.5; FR-5; 2 h	Attenuation		
Dopamine					
D1-like receptor agonist:					
SKF-81297 (1 mg/kg, s.c.)	Weiss et al., 2001	B; C; 0.75; FR-1; 2 h		No effect	
D2-like receptor agonist:					
PD 128,907 (0.3 mg/kg, s.c.)	Weiss et al., 2001	B; C; 0.75; FR-1; 2 h		Attenuation	
D1-like receptor antagonist:					
SCH-23390 (2 μg/side, BLA)	See et al., 2001	B; 0.75; FR-1; 3 h	Attenuation		
SCH-23390 (1–10 μg/kg, s.c.)	Alleweireldt et al., 2002	B; C; 0.75; VR-5; 2 h	Attenuation		
SCH-23390 (2.5–10 μg/kg, s.c.)	Ciccocioppo et al., 2001	B; C; 0.75; FR-1; 2 h		Attenuation	
SCH-23390 (5–10 μg/kg, i.p.)	H. Crombag, J. W. Grimm, and Y. Shaham, submitted	B; C; 0.75; FR-1; 2 h		Attenuation	
SCH-39166 (10 μg/kg, s.c.)	Ciccocioppo et al., 2001	B; C; 0.75; FR-1; 2 h		Attenuation	
SCH-39166 (10 μg/kg, s.c.)	Weiss et al., 2001	B; C; 0.75; FR-1; 2 h		Attenuation	
D2-like receptor antagonist:					
Raclopride (5 μg/side, BLA)	See et al., 2001	B; 0.75; FR-1; 3 h		No effect	
Raclopride (50–100 μg/kg, i.p.)	Crombag et al., submitted	B; C; 0.75; FR-1; 2 h		Attenuation	
HAL (150–300 μg/kg, i.p.)	McFarland and Ettenberg, 1997	B; H; runway; 0.1	No effect		
D2/3 receptor antagonist:					
Nafadotride (1 mg/kg, s.c.)	Weiss et al., 2001	B; C; 0.75; FR-1; 2 h		Attenuation	
Glutamate					
NMDA antagonist:					
AP-5 (1.97 μg/side, BLA)	See et al., 2001	B; 0.75; FR-1; 3 h	No effect		
D-CPPene (0.3–3 mg/kg, i.p.)	Bespalov et al., 2000	B; 0.32; FR-1; 3 h	Attenuation		
Memantine (1–10 mg/kg, i.p.)	Bespalov et al., 2000	B; 0.32; FR-1; 3 h	No effect		
Non-NMDA antagonist:					
CNQX (0.83 μg/side, BLA)	See et al., 2001	B; 0.75; FR-1; 3 h	No effect		
Noradrenaline					
α2-Adrenoceptor agonist:					
Lofexidine (100–200 mg/kg, i.p.)	Highfield et al., 2001	B; 0.025 H+0.25 C; FR-1; 6 h	No effect		
Reuptake inhibitor:					
DMI (10 mg/kg/day for 21 days, i.p.)	Fuchs et al., 1998	B; 0.75; VR-5; 3 h			Attenuation
Opioids					
Antagonist:					
Naloxone (0.5, 1, 3 mg/kg, i.p.)	McFarland and Ettenberg, 1998	B; H; runway; 0.1		No effect	
Serotonin					
Reuptake inhibitor:					
Fluoxetine (3.0 mg/kg/day for 20 days, i.p.)	Baker et al., 2001	B; 0.5; FR-1; 6 h			Attenuation
Tryptophan hydroxylase inhibitor:					
Para-chlorophenylalanine (100 mg/kg 2 days, i.p.)	Tran-Nguyen et al., 1999	B; 0.33; FR-1; 2 h			Attenuation
Depletion of serotonin:					
5,7-DHT (200 μg/20 μl, i.c.v.)	Tran-Nguyen et al., 2001	B; 0.33; FR-1; 2–8 h			Attenuation

Abbreviations: B, between-session reinstatement procedure; B-W, between-within session reinstatement procedure; C, cocaine; H, heroin; HAL, haloperidol; VR, variable ratio schedule of reinforcement; W, within-session reinstatement procedure.

suggest that the brain endocannabinoid system is involved in neuronal processes underlying cue-induced relapse to cocaine seeking.

Alleweireldt et al. (2002) reported that the D1-like receptor antagonist, SCH 23390, attenuates cocaine cues-induced reinstatement. See et al. (2001) also found that SCH 23390 but not raclopride (a D2-like antagonist) injected into the BLA attenuates cue-induced reinstatement of cocaine seeking. These data extend previous reports by See and colleagues on the effect of permanent (excitotoxic) or reversible (tetrodotoxin, TTX; 3 ng/μl) lesions of the BLA on cue-induced reinstatement of cocaine seeking (Meil and See, 1997; Grimm and See, 2000). Interestingly, Grimm and See (2000) found that intra-NAc of TTX (3 ng/μl), which blocks cocaine self-administration, has no effect on cue-induced reinstatement, whereas the BLA reversible lesions had no effect on cocaine self-administration (Fig. 7). These data are of theoretical importance as they demonstrate a double neuroanatomical dissociation between responding controlled by the primary (cocaine) versus the secondary conditioned reinforcer. Most recently, Kruzich and See (2001) demonstrated that TTX infusions (5 ng/μl) into both the BLA and the CeA decreased cocaine cues-induced reinstatement. However, these data cannot be clearly interpreted because a high dose of TTX was used, anatomical controls for spread of the toxin were not used (see Wise and Hoffman, 1992), and the authors did not assess whether the lesions led to motor deficits.

It appears that the BLA and, in particular, D1-like receptors in this area are involved in cue-induced reinstatement of cocaine seeking. These data are in agreement with those from studies on the role of conditioned drug cues in cocaine seeking as measured by the second-order schedule procedure and with those from studies on the effect of BLA lesions on the ability of stimuli paired with natural rewards to control behavior (Robbins et al., 1989; Everitt et al., 1999). Finally, studies on the neuronal mechanisms underlying cue-induced reinstatement of heroin seeking have not been reported. Thus, an interesting question, in light of recent data on the lack of effect of BLA lesions on responding for heroin-associated cues under the second-order schedule (Alderson et al., 2000), is whether the findings from studies on cocaine cues-induced reinstatement generalize to reinstatement induced by heroin cues.

B. Extinction Behavior

Fuchs et al. (1998) found that chronic administration of the NA reuptake blocker, desmethylimipramine, decreases lever pressing during extinction. In two other studies it was found that the tryptophan hydroxylase inhibitor, *para*-chlorophenylalanine, 5-HT lesions with 5,7-dihydroxytryptamine and chronic exposure to fluoxetine also decrease extinction behavior (Tran-Nguyen et al., 1999, 2001; Baker et al., 2001). It is not clear, however, how to interpret these data as both decreases and

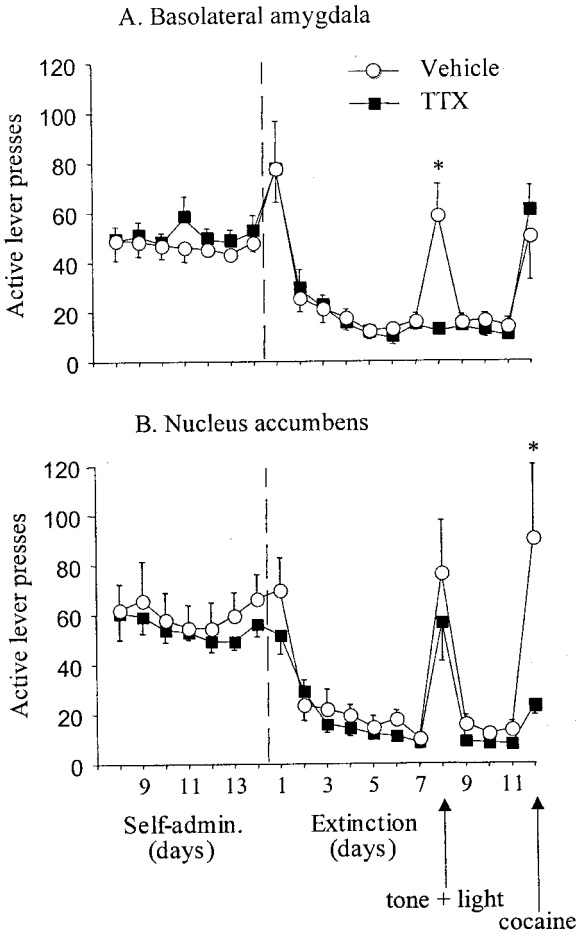

FIG. 7. Responses (mean ± S.E.M.) on the previously active (cocaine-paired lever) during the last week of self-administration, extinction and the two test days. Animals were microinjected with vehicle or TTX immediately prior to test days indicated as "tone + light" and "cocaine". A, lever responses for rats implanted with bilateral cannulae in the basolateral amygdala and microinjected with vehicle or TTX. Rats microinjected with TTX failed to reinstate responding for the tone + light ($p < 0.05$). B, lever responses for rats implanted with bilateral cannulae in the nucleus accumbens and microinjected with vehicle or TTX. Responding of TTX-treated rats for the primary (cocaine) reward was selectively attenuated when compared with vehicle infusion ($p < 0.05$). *, significant group difference for the test session ($p < 0.05$). Data are from Grimm and See, 2000, reprinted ©2000 with permission from Elsevier Science.

increases in 5-HT neurotransmission decrease resistance to extinction.

Using in vivo microdialysis, several studies have examined the effect of exposure to discrete cocaine cues during extinction on DA release in the NAc. Meil et al. (1995) described a precipitous drop in DA levels in the NAc when cocaine was removed from the syringe pumps, even when rats continued to press for a discrete CS light during extinction. Ranaldi et al. (1999) reported a decrease in DA levels in the NAc during extinction when amphetamine was removed, despite an increase in lever pressing for the drug CSs. These data are somewhat difficult to interpret because any effect of the cues on DA release may be masked by the decrease in DA levels due to the clearance of cocaine from the DA transporter. Neisewander et al. (1996) reported that DA levels in the

NAc are not altered when the cocaine-associated cues are reintroduced during extinction testing following 7 days of withdrawal. Together, these data suggest that alterations in DA levels in the NAc are not associated with the lever-pressing behavior controlled by the cocaine cues during extinction. This conclusion is in agreement with those from two recent studies in rats and monkeys, using the second-order procedure, on the lack of effect of contingent cocaine cues on DA release in the NAc (Bradberry et al., 2000; Ito et al., 2000). In contrast, Tran-Nguyen et al. (1998) reported a significant elevation in DA levels in the amygdala when rats returned to a self-administration chamber and were allowed to press the lever for the discrete cocaine cues following one month of withdrawal.

In vivo electrochemistry methods (e.g., chronoamperometry) could potentially clarify the importance of DA in the NAc in cue-induced reinstatement due to the enhanced temporal resolution of the technique. It is possible that the larger sample intervals and sampling of extrasynaptic versus synaptic space used in microdialysis mask the brief alterations in neurotransmitter release. One study used in vivo chronoamperometry to study changes in DA signal in the NAc in response to discrete amphetamine cues (Di Ciano et al., 2001). The authors reported that whereas the amphetamine priming increased the DA signal, the CS had no effect. The limitation of this study, however, is that the DA response to the CS was determined after the behavioral response to the cue was extinguished. Thus, the rats were not actively involved in drug seeking during testing.

Recent studies examined neurochemical and genomic correlates of extinction behavior and exposure to discrete cocaine cues during withdrawal periods. Neisewander et al. (2000) studied Fos protein activation following 21 days of withdrawal after one session of extinction. Exposure to the self-administration environment enhanced Fos expression in several brain areas, including the anterior cingulate, BLA, hippocampal CA1 region, dentate gyrus, and NAc. Thomas and Everitt (2001) used in situ hybridization to image γ PKC (an intracellular signal correlated with neuronal activity) expression in several brain areas during exposure to a cocaine-paired cue. They found selective activation by the discrete CSs previously paired with cocaine infusions in regions of the amygdala and cortex but not the NAc. The relevance of these data to extinction behavior and cue-induced relapse, however, is not clear because the discrete CS were given noncontingently and lever pressing-behavior was not measured following cue exposure.

Schmidt et al. (2001) reported that 12 days of cocaine self-administration reduced tyrosine hydroxylase (TH) immunoreactivity in the NAc shell but not core after 7 days of withdrawal. However, TH immunoreactivity in the NAc was restored in rats that experienced extinction training during this period. Extinction training also increased TH levels in the VTA, whereas TH was not altered in the VTA by cocaine withdrawal alone. The authors concluded that extinction-induced normalization of NAc TH levels could involve increased TH synthesis, stability, and/or transport from the VTA to the NAc. It should be pointed out, however, that because rats in the no extinction group were not exposed to the self-administration environment during the 1-week withdrawal period, it is not known whether repeated exposure to the cocaine self-administration context or the active experience of extinction training (or both) are involved in the effects described above.

Finally, Crespo et al. (2001) studied the expression of proenkephalin mRNA (PENK mRNA) in several brain areas following 0, 1, 5, or 10 days of extinction. One group of rats had previously self-administered cocaine, whereas the other two groups of rats had received either cocaine or saline injections yoked to the rats self-administering cocaine. The main finding in this study was a decrease in PENK mRNA in the CeA of the rats of the contingent group following 5 and 10 days of extinction and withdrawal and a similar decrease in the ventromedial hypothalamus following 5 days but not 10 days. However, because in the paired group both the duration of cocaine withdrawal and the experience of extinction were manipulated (i.e., the rats in the late withdrawal periods also had more extinction training), the relative contribution of these factors to the changes in PENK mRNA is not known.

Although several neurochemical and genomic correlates of extinction behavior were reported, because of the correlational nature of these studies, the neuronal mechanisms underlying drug seeking during extinction remained unknown. In addition, recent studies have shown that manipulations that alter 5-HT utilization can alter extinction behavior. However, as both increases and decreases in 5-HT levels are associated with decreased lever pressing during extinction, the role of 5-HT in extinction behavior remained unclear. Finally, recent data suggest that extinction training can alter the neuroadaptive changes associated with chronic cocaine use.

C. Discriminative and Contextual Drug Cues

1. Discriminative Drug Cues. Using a runway model with heroin-trained rats, McFarland and Ettenberg (1995, 1997, 1998) found that the opioid antagonist naloxone or the preferentially D2-like receptor antagonist haloperidol have no effect on heroin seeking provoked by discriminative heroin cues. Naloxone and haloperidol, however, blocked drug seeking on a test day conducted 24 h after last exposure to heroin (Fig. 8). These data suggest that the motivational processes underlying relapse induced by the discriminative cues and the drug itself are dissociable (McFarland and Ettenberg, 1997). Ciccocioppo et al. (2001) and Weiss et al. (2001) reported

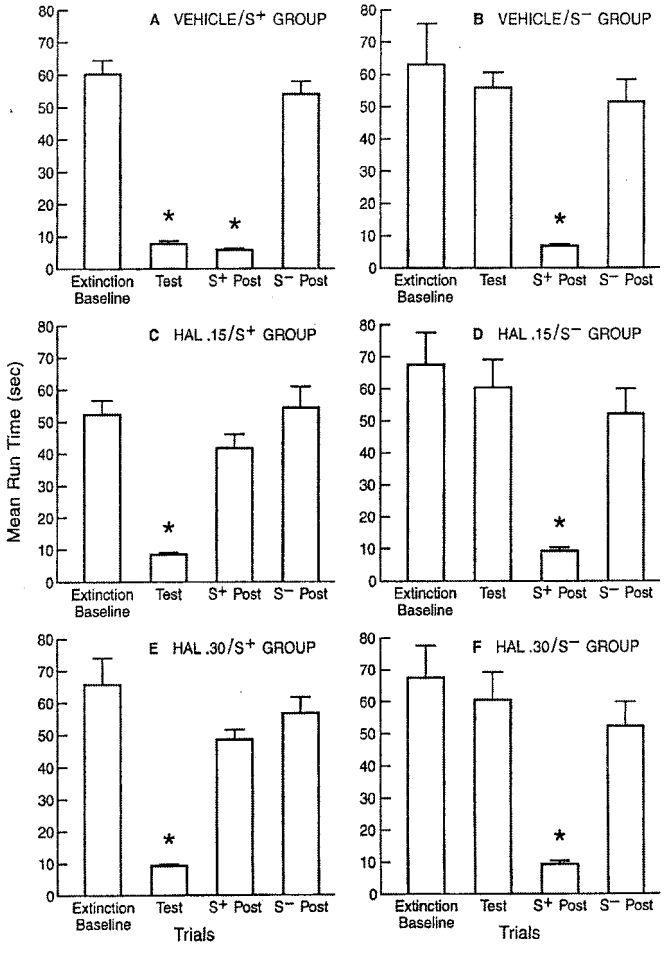

FIG. 8. Mean run times (± S.E.M.) in an operant runway for each treatment group during 3 consecutive days: the final day of extinction (Baseline), a single reinstatement trial (Test), and two post-treatment (Post+ and Post−) conditions, both of which occurred on the same day 24 h after the test trial. Panels A, C, and E show mean run times for animals that experienced the heroin-associated olfactory stimulus (S^+) during the reinstatement test, whereas Panels B, D, and F show the data from animals that experienced the saline-associated olfactory stimulus (S^-) on this trial. Subjects were pretreated with lactic acid vehicle (A and B), 0.15 mg/kg haloperidol (C and D), or 0.3 mg/kg haloperidol (E and F) prior to behavioral testing on reinstatement (Test) day. ⋆, significantly different from baseline ($p < 0.05$). Data are from McFarland and Ettenberg, 1997, reprinted ©1997 with permission from Springer-Verlag.

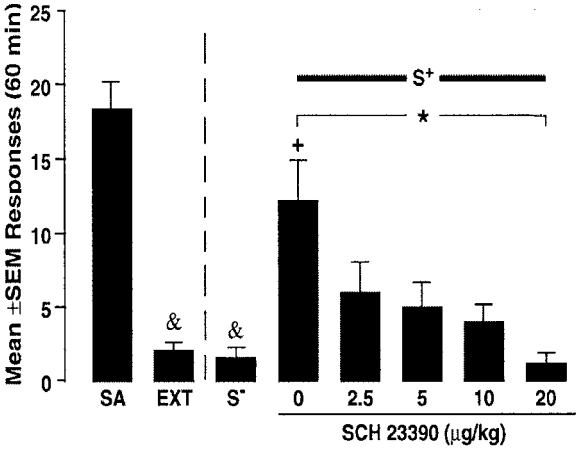

FIG. 9. Effects of the D1 antagonist SCH 23390 on the number of responses (mean ± S.E.M.) induced by the discriminative stimulus for cocaine (S^+). SCH 23390 dose dependently reversed the effects of the S^+. For comparison, the figure also shows the average number of responses during the last 3 days of the self-administration (SA) and extinction (EXT) phases, as well as responses in the presence of the stimulus associated with nonreward (S^-). ⋆, significant linear trend over dose levels ($p < 0.05$); +, different from the EXT and S^- conditions ($p < 0.05$); &, different from cocaine-reinforced responses (SA; $p < 0.01$). Data are from Ciccocioppo et al., 2001, reprinted ©2001 with permission from the National Academy of Sciences, U.S.A.

that SCH 23390 and SCH 39166 (a newer selective D1-like receptor antagonist that binds with low affinity to 5-HT receptors) block reinstatement of cocaine seeking induced by discriminative cues (Fig. 9). Weiss et al. (2001) also reported a similar effect with the D2-like antagonist nafadotride and the D2-like agonist PD 128,907 but not the D1-like agonist SKF 81297. These data should be interpreted with caution because the investigators used a single drug dose of each compound, the effect of the compounds on ongoing extinction behavior (i.e., baseline responding) was not determined, and the same group of rats was tested with the four compounds. The data with PD 128,907 also are different from previous reports on reinstatement of cocaine seeking by D2-like agonists (Self and Nestler, 1998). Finally, in two important studies, Weiss et al. (2000) and Ciccocioppo et al. (2001) reported that cocaine cues increase DA release in both the amygdala and the NAc and that D1-like receptor antagonists decrease cues-induced Fos expression in the BLA and the mPFC (areas Cg1/Cg3).

These findings identify an important role of D1-like receptor activation in relapse induced by discriminative drug cues, whereas a role for the D2-like receptors in relapse induced by these cues is less clear. Specifically, D2-like receptor antagonists have different effects on cue-induced reinstatement of heroin seeking in the runway model versus cocaine seeking in the traditional reinstatement model. The microdialysis and the Fos protein data further implicate the BLA, and possibly the mPFC in discriminative cues-induced reinstatement of cocaine seeking.

2. Contextual Drug Cues. As mentioned above, we found that, in rats trained to self-administer speedball, exposure to the drug self-administration environment, after extinction of the drug-reinforced behavior in a different context, leads to renewal of drug seeking (Crombag and Shaham, 2002). We recently tested the effect of selective D1-like (SCH 23390) and D2-like (raclopride) antagonists on context-induced reinstatement of cocaine seeking (H. Crombag, J. W. Grimm, and Y. Shaham, manuscript submitted). Pretreatment with the D1-like or the D2-like receptor antagonists attenuated context-induced renewal of cocaine seeking at doses that had minimal impact on high rate of operant responding for a sucrose reinforcer. However, raclopride, but not SCH 23390, also decreased lever pressing on the previously active lever in a control group that remained in the extinction context. These data indicate that activation of D1-like receptors is involved in context-induced rein-

statement of cocaine seeking. These data also suggest that activation of D2-like receptors is involved in this effect, but we cannot rule out that some nonspecific effects of raclopride were involved to some degree.

D. Summary

1. Exposure to contingent, but not noncontingent, presentations of discrete CSs associated with drug infusions reinstates drug seeking. Similarly, exposure to discriminative or contextual drug cues, which predict drug availability, also can reinstate drug seeking.
2. Activation of D1-like receptors appears to mediate reinstatement induced by conditioned cocaine cues, including discrete CSs, discriminative cues and contextual cues. The available data suggest that the D2-like receptor is probably involved in discriminative or contextual cues-induced reinstatement of cocaine seeking, but not heroin seeking.
3. The BLA, but not the NAc, is involved in discrete CSs-induced reinstatement. This brain structure is probably also involved in reinstatement induced by discriminative cocaine cues.
4. Activation of NMDA receptors may be involved in discrete CSs-induced reinstatement, but glutamate receptors within the BLA are not involved in this effect. Recent data suggest that activation of brain endocannabinoid systems is involved in cue-induced relapse to cocaine seeking.
5. Increases in DA levels in the amygdala, but not the NAc, as measured by microdialysis, are correlated with cocaine seeking during extinction.
6. The experience of extinction increases immediate early gene expression in several limbic regions, including the BLA and PFC, and recent data suggest that this experience can alter the neuroadaptive changes associated with chronic cocaine use.

IV. Stress-Induced Reinstatement

Intermittent footshock reinstates drug seeking in rats previously trained to self-administer heroin (Shaham and Stewart, 1995b; Ahmed et al., 2000), cocaine (Erb et al., 1996; Ahmed and Koob, 1997; Mantsch and Goeders, 1999a), nicotine (Buczek et al., 1999), and alcohol (Lê et al., 1998; Martin-Fardon et al., 2000). Importantly, in the above studies footshock was found to reinstate heroin and cocaine seeking under different training doses, schedule requirements, shock parameters and strains of rats (Shaham et al., 2000a). Most recently, it was reported that footshock stress also "reactivates" morphine or cocaine conditioned place preference following drug-free periods in rats that were not exposed to extinction conditions (Lu et al., 2000, 2001a; Wang et al., 2000). The effect of footshock also generalizes to an operant behavior controlled by brain stimulation reward into the septum (Shalev et al., 2000) but not to behaviors based on food or sucrose reinforcers (Ahmed and Koob, 1997; Lê et al., 1998; Buczek et al., 1999). Possible reasons for the different effects of footshock on drug versus nondrug reinforcers are discussed elsewhere (Shaham et al., 2000a). In addition, the arousal state induced by exposure to an appetitive stimulus (receptive female) has no effect on reinstatement of heroin seeking, suggesting that arousal per se cannot account for the effect of stress on reinstatement (Shaham et al., 1997c).

Stressors other than footshock, including food deprivation (Shalev et al., 2000) and a stress-like state induced pharmacologically by CRF (Shaham et al., 1997b) reinstate heroin seeking. In addition, the effect of footshock on reinstatement of heroin seeking is mimicked by reversible inactivation of the medial septum with TTX (Highfield et al., 2000). Septal lesions mimic to some degree physiological and psychological responses to stress (Holdstock, 1967; Gray, 1987). In cocaine-trained rats, Comer et al. (1995) reported that food restriction enhances cocaine-induced reinstatement. Carroll (1985) also reported that food restriction reinstates cocaine seeking in rats that experienced this condition during self-administration training.

In heroin-trained rats, exposure to a novel environment, a condition known to induce stress responses (Friedman and Ader, 1967), had no effect on reinstatement (Shalev et al., 2000). In addition, in heroin- and cocaine-trained rats, a conditioned fear stimulus (a tone previously paired with footshock) was not an effective stimulus for reinstatement of lever-pressing behavior (Shaham et al., 2000a). In contrast, using the CPP reinstatement model, Sanchez and Sorg (2001) found that a tone or odor CSs, previously paired with footshock, reinstates cocaine CPP after extinction. The discrepant results of the conditioned fear condition in the self-administration versus the CPP models may be due to the fact that the predominant behavioral effect of the fear stimulus is freezing (LeDoux, 2000), which is incompatible with lever-pressing behavior. Finally, we found in heroin-trained rats that the effect of stress on reinstatement is context and time dependent. Footshock and restraint stressors given outside the self-administration environment are ineffective (Shalev et al., 2000), and the duration of the withdrawal period from heroin is a critical factor in footshock stress-induced reinstatement (Fig. 13C) (Shalev et al., 2000).

The phenomenon of stress-induced reinstatement is both stressor and reinforcer specific, and is critically dependent on the environmental context and the drug withdrawal period. A summary of the pharmacological studies on footshock stress-induced reinstatement is provided in Table 5.

A. Dopamine and Opioids

Exposure to certain stressors, including intermittent footshock, activates endogenous opioid systems (Akil and Morano, 1995). Thus, footshock stress may induce

TABLE 5
Effects of pharmacological/surgical manipulations on footshock-induced reinstatement

Neurotransmitter System	References	Type of Procedure; Training Dose (mg/kg/infusion); Schedule; Session Duration (h/day)	Cocaine-Trained	Heroin-Trained
CRF				
CRF antagonists:				
D-Phe CRF (0.1–1.0 μg, i.c.v.)	Erb et al., 1998	B; 1.0; FR-1; 3 h	Attenuation	
D-Phe CRF (10.0–50.0 ng/side, BNST)	Erb and Stewart, 1999	B; 1.0; FR-1; 3 h	Attenuation	
D-Phe CRF (10.0–50.0 ng/side, AMY)	Erb and Stewart, 1999	B; 1.0; FR-1; 3 h	No effect	
α-Helical-CRF (3.0–10.0 μg, i.c.v.)	Shaham et al., 1997	B; 1.0; FR-1; 6 h		Attenuation
α-Helical-CRF (1.0–10.0 μg, i.c.v.)	Lu et al., 2001	B, CPP, 10 mg/kg, IP	Attenuation	
CRF1 receptor antagonists:				
CP-154,526 (15.0 or 30.0 mg/kg, s.c.)	Shaham et al., 1998	B; H, 1.0, 3 h; C, 1.0, 9 h; FR-1	Attenuation	Attenuation
CP-154,526 (1.0 or 10.0 mg/kg, s.c.)	Lu et al., 2001	B, CPP, 10 mg/kg, IP	Attenuation	
CRF2 receptor antagonists:				
AS-30 (1.0 or 10.0 μg, i.c.v.)	Lu et al., 2001	B, CPP, 10 mg/kg, IP	No effect	
Cannabinoids				
Cannabinoid antagonist:				
SR141716A (1.0–3.0 mg/kg, s.c.)	De Vries et al., 2001	B; 0.5; FR-1; 2 h	No effect	
Corticosterone				
Adrenalectomy	Shaham et al., 1997	B; 0.1; FR-1; 6–12 h		Some potentiation
	Erb et al., 1998	B; 1.0; FR-1; 3 h	Attenuation	
Adrenalectomy + CORT replacement	Erb et al., 1998	B; 1.0; FR-1; 3 h	No effect	
Corticosterone synthesis inhibitor:				
Metyrapone (100.0 mg/kg, s.c.)	Shaham et al., 1997	B; 0.1; FR-1; 6–12 h		No effect
Ketoconazole (25.0 or 50.0 mg/kg, i.p.)	Mantsch and Goeders, 1999a	B; 0.5; FR-4; 2 h	Attenuation	
Noradrenaline				
α2-Adrenoceptor agonists:				
Clonidine (20.0–40.0 μg/kg, i.p.)	Erb et al., 2000	B; 0.5; FR-1, 3 h	Attenuation	
Clonidine (10.0–40.0 μg/kg, i.p.)	Shaham et al., 2000	B; 0.1; FR-1; 9 h		Attenuation
Clonidine (1.0–3.0 μg, i.c.v.)	Shaham et al., 2000	B; 0.1; FR-1; 9 h		Attenuation
Clonidine (1.0–2.0 μg/side, LC)	Shaham et al., 2000	B; 0.1; FR-1; 9 h		No effect
ST-91 (0.5–1.0 μg/side, LC)	Shaham et al., 2000	B; 0.1; FR-1; 9 h		No effect
ST-91 (40 μg/kg, i.p.)	Erb et al., 2000	B; 0.5; FR-1; 3 h	No effect	
Lofexidine (50.0–200.0 μg/kg, i.p.)	Erb et al., 2000	B; 0.5; FR-1; 3 h	Attenuation	
Guanabenz (640.0 μg/kg, i.p.)	Erb et al., 2000	B; 0.5; FR-1; 3 h	Attenuation	
Dopamine				
D1-like receptor antagonist:				
SCH23390 (0.05 or 0.1 mg/kg, i.p.)	Shaham and Stewart, 1996	B; 0.1; FR-1; 12 h		No effect
D2-like receptor antagonist:				
Raclopride (0.25 or 0.5 mg/kg, i.p.)	Shaham and Stewart, 1996	B; 0.1; FR-1; 12 h		No effect
Nonselective dopamine antagonist:				
Flupentixol decanoate (3.0 or 6.0 mg/kg, i.m.; chronic exposure)	Shaham and Stewart, 1996	B; 0.1; FR-1; 12 h		Attenuation
Opioids				
Agonist:				
Chronic heroin (3.0 mg/kg/day)	Shaham et al., 1996	B; 0.1; FR-1; 7–12 h		No effect
Antagonist:				
Naltrexone (1.0 or 10.0 mg/kg)	Shaham and Stewart, 1996	B; 0.1; FR-1; 12 h		No effect
NOP receptor ligand:				
Nociceptin (0.1–2.0 i.c.v.)	Martin-Fardon et al., 2000	B; 0.25; FR-1; 2 h	No effect	
Others				
Acamprosate (50.0–200.0 mg/kg, i.p.)	Spanagel et al., 1998	B; 0.1; 4 h; 0.25 (s.c.)		No effect
Leptin (2.0 or 4.0 μg/kg, i.c.v.)	Shalev et al., 2001	B; 0.1; FR-1; 9 h		No effect

Abbreviations: AMY, amygdala; B, between-session reinstatement procedure; B-W, between-within session reinstatement procedure; C, cocaine; H, heroin; NOP, nociceptin opioid peptide; W, within-session reinstatement procedure.

reinstatement by releasing endogenous opioids, which would in turn activate μ-opioid receptors known to mediate heroin-induced reinstatement. However, naltrexone has no effect on footshock-induced reinstatement of heroin seeking, but blocks heroin-induced reinstatement (Shaham and Stewart, 1996). Furthermore, the occupation of opioid receptors by heroin infused through osmotic minipumps has no effect on footshock-induced reinstatement, but attenuates heroin-induced reinstatement (Shaham et al., 1996).

Exposure to several stressors, including footshock, also activates the mesocorticolimbic DA system (Kalivas and Stewart, 1991; Piazza and Le Moal, 1998), involved in reinstatement of heroin and cocaine seeking by drug priming. Therefore, it was speculated that activation of this system underlies both stress- and drug-induced relapse (Robinson and Berridge, 1993; Shaham and Stewart, 1995b). In agreement with this idea, chronic treatment with the nonselective DA receptor antagonist, flupenthixol, attenuates footshock-induced reinstatement of heroin seeking (Shaham and Stewart, 1996). However, selective D1- or D2-like receptor antagonists (SCH 23390 or raclopride) have no effect on footshock-induced reinstatement. In contrast, raclopride and SCH 23390 attenuated heroin-induced reinstatement. In addition, whereas footshock is at least as effective a stimulus for reinstatement as heroin priming (Shaham, 1996), heroin priming is a more effective stimulus for inducing DA release in the NAc than footshock stress (Shaham and Stewart, 1996). Overall, we interpreted these data to indicate that, unlike the critical role DA plays in drug-induced reinstatement, this neurotransmitter plays only an indirect/modulatory role in footshock stress-induced reinstatement (Shaham et al., 2000a).

It appears that footshock-induced reinstatement is independent of the action of the stressor on the endogenous opioid system. In addition, although basal DA tone may be required for the expression of footshock-induced reinstatement, it is unlikely that brain DA is the critical substrate for this effect.

B. Corticosterone and Corticotropin-Releasing Factor

Exposure to stressors induces the release of the stress-related hormones CRF and corticosterone (Friedman and Ader, 1967; Morimoto et al., 1993). Corticosterone is known to be involved in a variety of behavioral and neurochemical effects of exposure to stressors (Selye, 1956; Johnson et al., 1992). CRF receptors are widely distributed in the brain and CRF has been shown to act at both hypothalamic and extra-hypothalamic sites to mediate behavioral and physiological responses of stress (Dunn and Berridge, 1990; de Souza, 1995).

1. Corticosterone. We found that manipulations of corticosterone levels by ADX or by pretreatment with a synthesis inhibitor of corticosterone, metyrapone, have no effect on footshock-induced reinstatement of heroin seeking (Shaham et al., 1997b). In cocaine-trained rats, ADX attenuates footshock-induced reinstatement. However, in rats with ADX + corticosterone replacement (to maintain basal levels of the hormone) footshock reinstates cocaine seeking (Erb et al., 1998). Thus, it appears that although footshock-induced corticosterone release is not involved in reinstatement of either heroin or cocaine seeking by the stressor, basal levels of the hormone are required for footshock-induced reinstatement of cocaine seeking. Two other studies, however, appear to challenge the above conclusion. Deroche et al. (1997) found that corticosterone infusions reinstate cocaine seeking. Mantsch and Goeders (1999a) reported that inhibition of corticosterone synthesis with the antimycotic agent, ketoconazole, which one of its actions is to inhibit corticosterone synthesis, attenuates footshock-induced reinstatement of cocaine seeking. The results of this study, however, are difficult to interpret due to lack of specificity of ketoconazole, which also acts on several other neurotransmitter and hormonal systems.

There is no evidence that corticosterone is involved in footshock-induced relapse to heroin seeking. In contrast, corticosterone appears to play some modulatory role in footshock-induced relapse to cocaine seeking, but this hormone is probably not the main mediator of this effect.

2. Corticotropin-Releasing Factor. Acute injections of CRF induce reinstatement of heroin seeking (Shaham et al., 1997b). Moreover, the CRF receptor antagonists, D-Phe CRF and α-helical CRF, attenuate footshock-induced reinstatement of heroin and cocaine seeking (Shaham et al., 1997b; Erb et al., 1998; Lu et al., 2000, 2001a). The effect of CRF on reinstatement appears to be mediated by the CRF_1 receptor subtype. Administration of CP-154,526, a selective CRF_1 receptor antagonist, attenuates footshock-induced reinstatement of heroin and cocaine seeking (Shaham et al., 1998; Lu et al., 2000, 2001a). In contrast, administration of the CRF_2 receptor antagonist, antisauvagine-30, has no effect on footshock-induced reactivation of CPP for morphine and cocaine (Lu et al., 2000, 2001a). These data, together with those from the studies of the lack of effect of ADX (heroin-trained rats) or ADX + corticosterone replacement (cocaine-trained rats) on footshock-induced reinstatement, suggest that the effect of the CRF receptor antagonists on reinstatement is mediated via their action on extra-hypothalamic sites, independent of their effect on the HPA axis.

Erb and Stewart (1999) studied the role of CRF in two brain sites involved in stress response and the behavioral effects of CRF, the bed nucleus of the stria terminalis (BNST) and the amygdala (Davis et al., 1997; Koob and Heinrichs, 1999). They found that infusions of CRF into the ventral BNST reinstate cocaine seeking, whereas intra-BNST infusions of D-Phe CRF attenuate footshock-induced reinstatement (Fig. 10). In contrast, infusions of CRF into the amygdala (infusions were aimed at the CeA) have no effect on reinstatement and

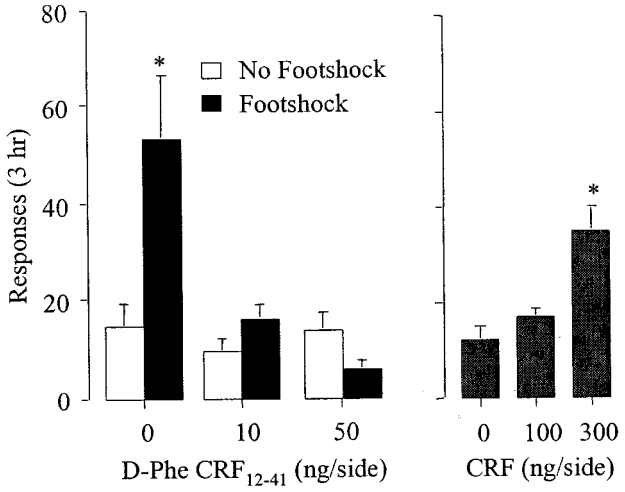

FIG. 10. Mean (± S.E.M.) number of nonreinforced responses on the previously active (cocaine-paired) lever after exposure to 15 min of intermittent footshock in animals pretreated by intra-BNST injections of the CRF receptor antagonist, D-Phe CRF_{12-41} (left panel), and after intra-BNST injections of CRF itself; no footshock was given (right panel). *, significantly different from the other conditions ($p < 0.05$). Similar manipulations in the amygdala had no effects. Data are from Erb and Stewart, 1999, reprinted with permission ©1999 from the Society for Neuroscience.

intra-amygdala infusions of D-Phe CRF do not attenuate footshock-induced reinstatement (Erb and Stewart, 1999). In a subsequent study with heroin-trained rats, however, we found that reversible inactivation of both the CeA and the BNST with TTX blocks footshock-induced reinstatement of heroin seeking (Shaham et al., 2000a). The CeA contains high densities of cell bodies and projection neurons for CRF, but unlike the BNST, the density of the CRF receptors in this area is low (Gray and Bingaman, 1996; Van Pett et al., 2000). Thus, it may not be surprising that CRF or the CRF receptor antagonists had little effect on reinstatement when infused into the CeA (see also Lee and Davis, 1997). Sakanaka et al. (1986) described a CRF-containing projection from the CeA to the BNST, and it has been speculated that this projection may account, in part, for the increase in CRF release in the BNST following exposure to stress (Lee and Davis, 1997).

Erb et al. (2001) studied whether the CRF-containing projection from the CeA to the BNST is involved in footshock-induced reinstatement of cocaine seeking. They used an asymmetric lesion method (Parkinson et al., 2000; Easton and Gaffan, 2001) to functionally disconnect the CRF-containing pathway from the CeA to the BNST. This was achieved by simultaneously injecting TTX into the CeA in one hemisphere and D-Phe CRF into the BNST in the opposite hemisphere. Before testing for footshock-induced reinstatement, rats were given asymmetric injections of TTX (2.5 ng) and D-Phe CRF (50 ng) into the CeA and BNST, respectively, or they were given unilateral injections of either compound alone into the appropriate structure. Functional inactivation of the amygdala-BNST pathway significantly reduced footshock-induced reinstatement compared with that seen when only one hemisphere was manipulated. However, the fact that this attenuation of footshock-induced reinstatement was not complete implies the existence of an additional source of CRF in the BNST other than the CeA-BNST pathway, possibly from cells intrinsic to the BNST (Veinante et al., 1997).

These data suggest that activation of extra-hypothalamic CRF receptors is involved in footshock-induced reinstatement of heroin and cocaine seeking (see also Lê et al., 2000 for similar findings in alcohol-trained rats). In addition, this effect is probably mediated by activation of CRF_1 but not CRF_2 receptors. Finally, it appears that CRF receptors within the BNST and possibly the CRF projection from the CeA to the BNST are involved in footshock-induced reinstatement.

C. Noradrenaline

NA neurons are activated by stressors and are thought to mediate psychological and physiological responses to stress (Stanford, 1995; Bremner et al., 1996). We found that administration of the α-2 adrenoceptor agonists, clonidine and lofexidine, known to inhibit NA cell firing and neurotransmitter release (Aghajanian and VanderMaelen, 1982; Carter, 1997), attenuate footshock-induced reinstatement of heroin, cocaine, and speedball seeking (Erb et al., 2000; Shaham et al., 2000b; Highfield et al., 2001) (Fig. 11). In contrast, these compounds have no effect on cocaine-induced reinstatement (Erb et al., 2000) or discrete CSs-induced reinstatement (Highfield et al., 2001). Clonidine and several other α-2 adrenoceptor agonists also bind to the to the imidazoline type 1 receptor (Piletz et al., 1994). However, the α-2 adrenoceptor agonist guanabenz, which binds at low affinity to imidazoline receptors, also attenuates footshock-induced reinstatement (Erb et al., 2000). Thus, it is unlikely that clonidine and lofexidine attenuate footshock-induced reinstatement by acting on imidazoline receptors.

The effect of the α-2 adrenoceptor agonists on footshock-induced reinstatement is centrally mediated. In cocaine-trained rats, systemic injections of ST-91, a charged analog of clonidine that does not readily cross the blood-brain barrier (Scriabine et al., 1975), have no effect on footshock-induced reinstatement (Erb et al., 2000). In heroin-trained rats, ventricular injections of clonidine block footshock-induced reinstatement (Shaham et al., 2000b).

Subsequently, we studied the brain sites involved in the effect of clonidine on footshock-induced reinstatement of heroin seeking (Shaham et al., 2000b). The brain NA projections arise from two groups of cells, the locus coeruleus (LC) and the lateral tegmental nuclei. The LC neurons project to forebrain areas via the dorsal noradrenergic bundle and provide input to cortical areas such as the hippocampus and frontal cortex (Moore and Bloom, 1979). The lateral tegmental nuclei innervate a

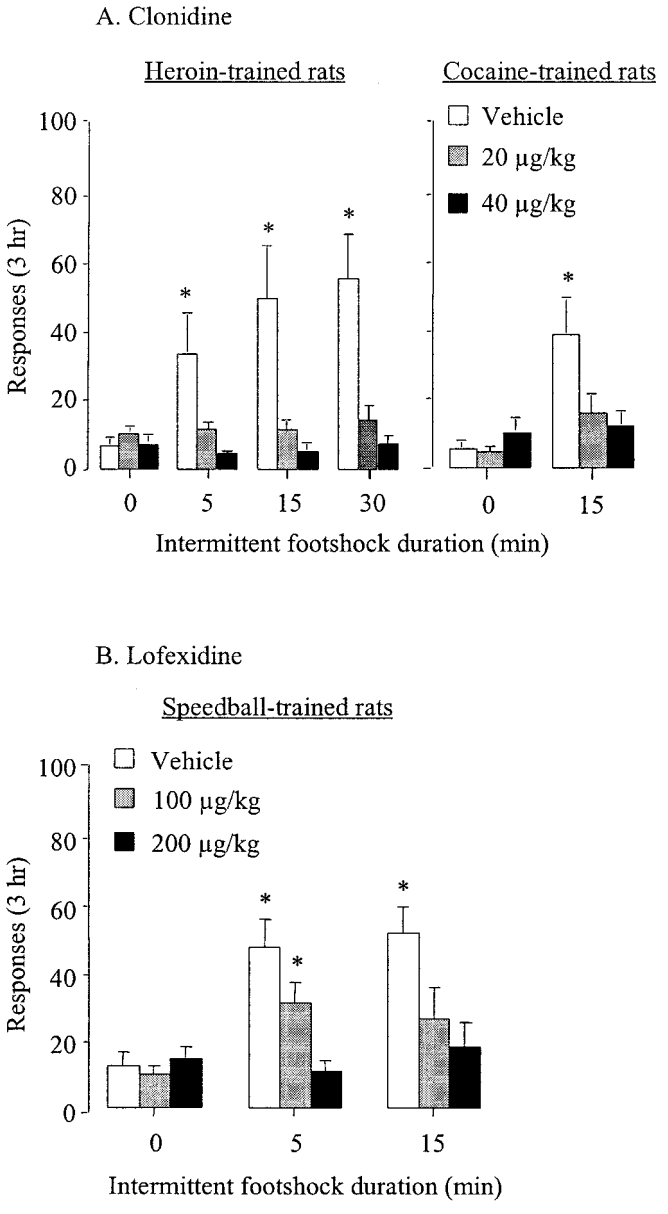

FIG. 11. Mean (± S.E.M.) number of nonreinforced responses on the previously active lever after no shock and exposure to 5 and 15 min of intermittent footshock. A, effects of pretreatment with clonidine in rats that were previously trained to self-administer heroin (left panel) or cocaine (right panel). B, effects of pretreatment with lofexidine in rats that were previously trained to self-administer a heroin-cocaine mixture ("speedball"). Rats were pretreated with saline or lofexidine during days 7 to 10 of training, the extinction phase and during testing. *, significantly different from the same dose under the no-shock condition ($p < 0.05$). Data are from Erb et al., 2000; Shaham et al., 2000; and Highfield et al., 2001, reprinted ©2000 and ©2001 with permission from Elsevier Science and Blackwell Science Ltd.

smaller number of forebrain areas (most of which are also innervated by the LC neurons) via the ventral noradrenergic bundle (VNAB). These include the hypothalamus, CeA, Nac, and BNST (Moore and Bloom, 1979; Fritschy and Grzanna, 1991; Aston-Jones et al., 1999). LC neurons are activated by stressors and play a role in responses to stress (Tanaka et al., 1990), whereas the functions of the lateral tegmental NA system were studied to a lesser degree (Hansen et al., 1980; Cole and Robbins, 1987), and its role in stress responses has not been determined. We found that bilateral injections of clonidine or ST-91 into the LC have no effect on footshock-induced reinstatement of heroin seeking, suggesting that the effects of the α-2 adrenoceptor agonists on reinstatement are not mediated by the LC neurons (Shaham et al., 2000b).

We then studied the possible role of the lateral tegmental NA neurons by making selective 6-hydroxydopamine lesions of the VNAB (Hansen et al., 1980; Delfs et al., 2000) following heroin self-administration training. These lesions reduced NA levels in the hypothalamus and BNST by 60 to 70% and were found to attenuate footshock-induced reinstatement (Shaham et al., 2000b). This finding does not provide direct evidence for the site of action of the α-2 adrenoceptor agonists. However, together with the data on the lack of effect of clonidine and ST-91 in the LC, these data suggest that certain NA nuclei in the lateral tegmentum (e.g., A2 neurons) are involved in footshock-induced reinstatement of heroin seeking. Additional support for this idea is the finding that intra-BNST infusions of a mixture of β-1 and β-2 adrenoceptor antagonists (betaxolol and ICI 181,555) block footshock-induced reinstatement in cocaine-trained rats (F. Leri and J. Stewart, unpublished data). The BNST is the main target for A2 NA neurons (Aston-Jones et al., 1999).

The data indicate that central NA neurons are involved in footshock-induced reinstatement of drug seeking. Somewhat surprisingly, it appears that lateral tegmental NA neurons and their VNAB projections but not LC neurons are involved in this effect. Finally, a question that arises from the data reviewed above is the nature of the interaction between the NA and the CRF systems in the mediation of footshock-induced reinstatement. It appears that two main neurotransmitter systems, CRF and NA, and two main brain structures, the CeA and the BNST, are involved in footshock-induced reinstatement. Several neuronal pathways are likely to be involved in this effect: the VNAB and CRF pathways from the CeA to the BNST and/or from CRF neurons intrinsic to the BNST. The antagonism of CRF receptors in the BNST (but not in the CeA) or blockade of postsynaptic β-adrenoceptors attenuates footshock stress-induced reinstatement, suggesting an interaction between these two systems at least in the BNST. Studies using tracing methods or DSP-4 injections (which selectively destroy LC neurons) have shown that the ventral lateral region of the BNST and the CeA are two of the main targets of the lateral tegmental NA neurons (Fritschy and Grzanna, 1991; Delfs et al., 2000). In the vBNST, lateral tegmental NA neurons form synaptic contact with CRF-containing neurons (Phelix et al., 1994), whereas the nature of the synaptic interactions in the CeA is not known. Using microdialysis, it was found that i.c.v. infusions of D-Phe CRF (1 μg) have no effect on

footshock stress-induced NA release in the BNST (Erb et al., 2001). These data, together with the pharmacological data with CRF receptor antagonists and α-2 adrenoceptor agonists, raise the possibility that activation of VNAB neurons leads to the activation of CRF systems within the BNST and CeA. One possibility is that activation of VNAB neurons by footshock leads to activation of intrinsic CRF systems within the BNST (see Phelix et al., 1994). Another possibility, albeit speculative, is that activation of the VNAB neurons projecting to the CeA activates the CRF pathway from the CeA to the BNST (see Sakanaka et al., 1986). The data on the effect of TTX infusions in the CeA (Shaham et al., 2000a) and on the effect of "disconnecting" the CeA-BNST CRF pathway (Erb et al., 2001) are in agreement with the idea that such an indirect pathway may also be involved in footshock-induced reinstatement.

D. Other Neurotransmitter Systems

Nociceptin/orphanin FQ is the endogenous ligand of the ORL1 receptor (Meunier et al., 1995), and evidence suggests that it may serve as a functional anti-opioid peptide in the control of brain nociceptive processes (Darland et al., 1998). This peptide has been reported to decrease alcohol and morphine CPP and stress- and CRF-mediated effects (Ciccocioppo et al., 2000). Martin-Fardon et al. (2000) tested the effect of nociceptin on footshock-induced alcohol and cocaine seeking and found that the peptide decreases footshock-induced reinstatement in rats with a history of alcohol, but not cocaine self-administration. The reasons for these discrepant findings are not clear.

Leptin is a recently discovered hormone, which is critically involved in energy balance and food consumption (Friedman and Halaas, 1998). In a recent report, leptin was found to reverse the enhancement of lateral hypothalamus brain stimulation reward by chronic food restriction (Fulton et al., 2000). As mentioned above, we found that acute food deprivation reinstates heroin seeking (Shalev et al., 2000), data that extend previous reports on the effect of food deprivation on drug self-administration and reward (Carroll and Meisch, 1984; Carr, 1996). The neuronal mechanisms underlying the potent effect of food deprivation on drug-taking behavior are not known. Based on the report by Fulton et al. (2000), we tested the effect of leptin in our model and found that leptin attenuates acute food deprivation-, but not footshock- or heroin-induced reinstatement (Shalev et al., 2001b) (Fig. 12). This result may suggest that the neuronal mechanisms underlying relapse induced by food deprivation are different from those involved in the relapse induced by footshock stress or heroin priming (see *Section V.B.3.*).

E. Summary

1. Footshock-induced reinstatement of heroin seeking is unaffected by opioid receptor antagonists and is relatively insensitive to dopamine receptor antagonists.
2. CRF-receptor antagonists attenuate footshock-induced reinstatement of heroin and cocaine seeking, an effect mediated by CRF receptors in the BNST. A CRF pathway from the CeA to the BNST may also be involved in footshock-induced reinstatement.
3. Stress-induced release of corticosterone is not involved in footshock-induced reinstatement of heroin or cocaine seeking, but basal levels of corticosterone are required for footshock-induced reinstatement of cocaine seeking.
4. α_2-Adenoceptor agonists, which decrease NA cell firing and release, attenuate footshock-induced reinstatement of heroin and cocaine seeking, but not

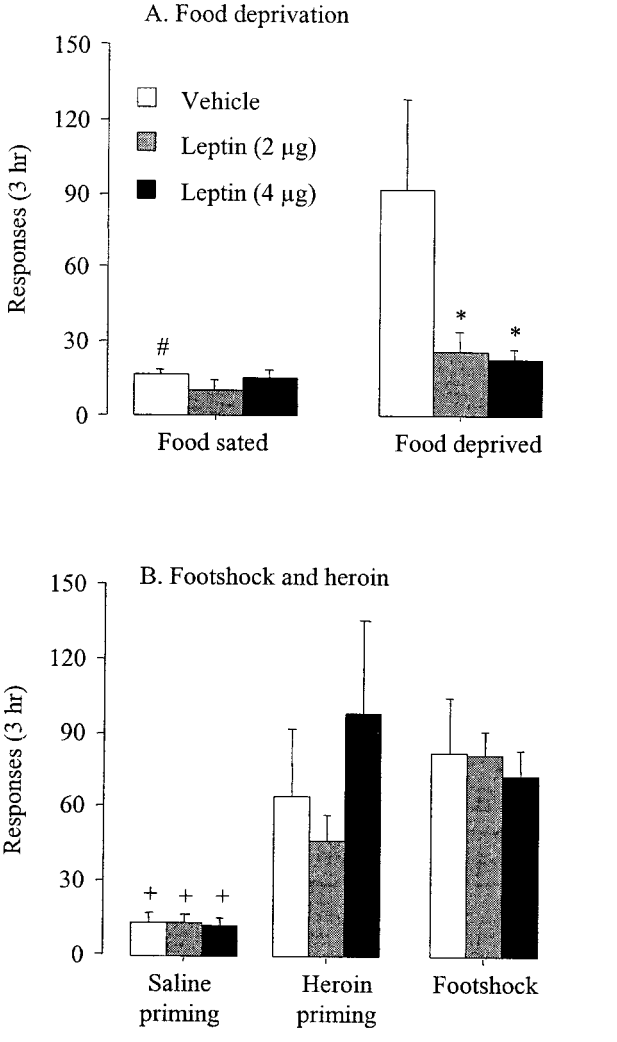

FIG. 12. The effect of pretreatment with leptin (i.c.v.) on the number of nonreinforced responses on the previously active (heroin-paired) lever. A, after exposure to 21 h of food deprivation; B, after exposure to 15 min of intermittent footshock or a priming injection of heroin (0.25 mg/kg, s.c.). *, different from the vehicle condition ($p < 0.01$); #, different from the deprivation condition within each leptin-dose condition ($p < 0.01$); +, different from footshock or heroin priming within each leptin-dose condition ($p < 0.01$). Data are expressed as mean ± S.E.M. Data are from Shalev et al., 2001, reprinted ©2001 with permission from the Society for Neuroscience.

drug- or cue-induced reinstatement. The effect of the α_2-adenoceptor agonists is centrally mediated.
5. Studies with heroin-trained rats indicate that NA neurons originating from the lateral tegmental nuclei, but not LC neurons, are involved in footshock-induced reinstatement.
6. Acute food deprivation reinstates heroin seeking, an effect that is attenuated by central infusions of the hormone leptin.

V. Discussion

In this section we summarize the data reviewed above. Subsequently, we discuss several theoretical issues related to the phenomena of drug priming-, cues- and stress-induced reinstatement. We then address methodological issues associated with the use of the reinstatement procedure. Finally, we discuss emerging issues in reinstatement studies and the implications of the data from these studies for theories of addiction and treatment.

A. Neural Mechanisms Underlying Relapse to Heroin and Cocaine: a Summary

1. Drug Priming-Induced Reinstatement. Activation of μ-opioid receptors is critically involved in heroin-induced reinstatement, and DA mechanisms (likely to be initiated within the VTA) also are involved in this effect. In the case of cocaine priming, the data indicate that D1- and D2-like DA receptors play fundamentally different roles: activation of D2-like receptors promotes cocaine seeking, whereas activation of D1-like receptors inhibits it. In addition, activation of AMPA receptors within the NAc is involved in cocaine-induced reinstatement. An important question for future research, therefore, is what are the brain sites through which DA mediates cocaine-induced reinstatement. Finally, although pharmacological agents acting at receptors of several other neurotransmitter systems (e.g., 5-HT_{2C}, GABA_B) can attenuate cocaine-induced reinstatement, this effect is probably mediated via the effect of these receptor manipulations on DA release.

2. Cue-Induced Reinstatement. The D1-like receptor appears to play a critical role in cocaine reinstatement induced by discrete CSs, discriminative and contextual cues, a finding in agreement with the general role of this receptor in conditioned reward (Sutton and Beninger, 1999). In addition, it appears that the D2-like receptor also is involved in contextual or discriminative cues-induced reinstatement of cocaine, but not heroin seeking. A critical brain site that mediates discrete CSs-induced reinstatement is the BLA, in which D1-like, but not glutamate, receptors are involved in this effect. Indirect evidence from in vivo microdialysis and Fos expression studies also implicates the BLA in cue-induced reinstatement. In contrast, a role for the NAc in cocaine cues-induced reinstatement has not been established. Manipulations of 5-HT neurotransmission (lesions and 5-HT reuptake blockers) can alter lever pressing controlled by the cocaine cues during extinction, but the exact role of 5-HT in extinction behavior is not clear.

3. Stress-Induced Reinstatement. The effect of footshock stress on reinstatement is opioid-independent and DA appears to play some modulatory role in this effect. In addition, footshock-induced corticosterone secretion is not involved in the effect of the stressor on reinstatement. Two main neurotransmitter systems, CRF and NA, and two main brain structures, the CeA and the BNST, are involved in footshock stress-induced reinstatement. The data also suggest that two neuronal pathways are involved in this effect: the VNAB, which originates from the lateral tegmental NA neurons, and possibly a CRF pathway from the CeA to the BNST. Finally, the hormone leptin is involved in reinstatement of heroin seeking induced by food deprivation stress.

An important conclusion from this review is that the neural systems involved in drug priming-, cue-, and stress-induced reinstatement are to a large degree dissociable. In the case of footshock stress and drug priming, a pharmacological double dissociation is evident. Selective D1- and D2-like receptors and μ-opioid antagonists that block heroin-induced drug seeking (Shaham and Stewart, 1996; McFarland and Ettenberg, 1997, 1998) have no effect on footshock-induced heroin seeking (Shaham and Stewart, 1996). Conversely, CRF receptor antagonists and α-2 adrenoceptor agonists that block footshock-induced reinstatement have no effect on drug-induced reinstatement (Shaham et al., 2000a). In the case of cue- and drug-induced reinstatement, Stewart et al. (1984) suggested that drug cues reinstate drug seeking by inducing a "drug-like" state similar to that induced by the drug itself, which is mediated in part by enhanced DA neurotransmission. However, whereas DA appears to be involved in both drug- and cue-induced reinstatement (see above), pharmacological and neuroanatomical dissociations were reported. For example, the NAc appears to be a critical substrate for cocaine-induced reinstatement (Cornish and Kalivas, 2000), but lesions of this structure have no effect on discrete CSs-induced reinstatement (Grimm and See, 2000). On the other hand, reversible lesions of the NAc, which block cocaine self-administration, have no effect on cue-induced reinstatement (Grimm and See, 2000). In addition, in the case of heroin seeking, DA and opioid receptor antagonists block heroin-induced drug seeking, but they have no effect on drug seeking provoked by discriminative heroin cues (McFarland and Ettenberg, 1997, 1998).

Another issue is the degree of overlap between the neuronal substrates underlying cocaine versus heroin seeking. In the case of drug priming, it appears that activation of the mesocorticolimbic DA system is involved in both heroin and cocaine seeking (Stewart, 2000). However, cross-reinstatement between opioid

and stimulant drugs is to a large degree asymmetrical. Indirect DA agonists or D2-like agonists reinstate heroin seeking (Wise et al., 1990; De Vries et al., 1999), whereas μ-opioid receptor agonists (given systemically) do not reinstate cocaine seeking (de Wit and Stewart, 1981; Comer et al., 1993). However, the initial sedative effects of opioid agonists, given acutely to opioid-naive rats, may mask their motivational effect as infusions of morphine into the VTA reinstate cocaine seeking (Stewart, 1984). In the case of footshock-induced reinstatement, the pharmacological data suggest that similar neuronal mechanisms are involved in heroin or cocaine seeking (Shaham et al., 2000a). One exception is that basal levels of corticosterone are required for footshock-induced reinstatement of cocaine but not heroin seeking (Shaham et al., 2000a). There is very little information on similarities/differences in cue-induced reinstatement of heroin and cocaine seeking, but it is possible that these are not identical. For example, although the preferential D2-like antagonist haloperidol has no effect on discriminative cue-induced reinstatement of heroin seeking in the runway model (McFarland and Ettenberg, 1997), selective D2-like antagonists appear to attenuate discriminative (Weiss et al., 2001) and contextual (H. Crombag, J. W. Grimm, and Y. Shaham, manuscript submitted) cues-induced reinstatement of cocaine seeking. In addition, studies using the second-order schedule procedure have shown that manipulations that block drug seeking controlled by CSs in cocaine-trained rats (e.g., a D3 receptor partial agonist, BLA lesions) have no effect on cue-induced drug seeking in heroin-trained rats (Everitt and Robbins, 2000).

Finally, the data reviewed suggest that the neuronal substrates that mediate drug-induced reinstatement are to some degree different from those that mediate drug reinforcement. First, although D1-like receptor agonists substitute for cocaine in the drug self-administration method and some of these agents produce CPP (Self and Nestler, 1995; Abrahams et al., 1998), they do not reinstate cocaine seeking (Self and Nestler, 1998). Second, although NMDA receptor antagonists are self-administered directly into the NAc (Carlezon and Wise, 1996), an NMDA antagonist does not reinstate cocaine seeking (Cornish and Kalivas, 2000). Third, Cornish et al. (1999) found that whereas NMDA and AMPA agonists have a minimal effect on cocaine self-administration behavior, these agonists reinstate cocaine seeking. These investigators also showed that blockade of DA receptors in the NAc, known to be involved in cocaine reinforcement (Wise, 1996b), have no effect on cocaine-induced reinstatement. Fourth, although manipulations of corticosterone secretion have a profound effect on cocaine self-administration behavior (Piazza and Le Moal, 1996; Goeders, 1997), similar manipulations have a minimal effect on cocaine-induced reinstatement (Erb et al., 1998; Mantsch and Goeders, 1999b). Fifth, Vorel et al. (2001) showed that electrical stimulation of the medial forebrain bundle—known to be involved in reward processes (Wise, 1996a)—has no effect on reinstatement of cocaine seeking. In contrast, stimulation of the ventral hippocampus, a brain area that has not been reported to be involved in drug reward, potently reinstates cocaine seeking. Sixth, although blockade of brain CB1 receptors attenuates cocaine-induced reinstatement, this manipulation has no effect on cocaine self-administration behavior (De Vries et al., 2001). Finally, although DA receptor antagonists do not have a consistent effect on heroin self-administration behavior (Ettenberg et al., 1982; Mello and Negus, 1996), they reliably attenuate drug seeking induced by heroin priming (Shaham and Stewart, 1996; McFarland and Ettenberg, 1997).

It appears that multiple and dissociable brain systems are involved in relapse to heroin and cocaine seeking induced by drug priming, conditioned cues, and stress. Somewhat surprisingly, it also appears that the neuronal events that mediate heroin- or cocaine-induced reinstatement are to some degree different from those involved in their reinforcing effects.

B. Theoretical Issues

In this section, theoretical issues concerned with the effects of drug priming, drug cues and stressors are considered.

1. Drug Priming. Several explanations for the drug priming effect have been put forward over the years. It has been suggested that the discriminative stimuli properties of drugs mediate in part drug-induced reinstatement (Stolerman, 1992; Bergman and Katz, 1998). Rats can readily learn to discriminate drugs from saline in a drug discrimination model, wherein deprived rats learn to press one lever for food/water following drug injections and a different lever following saline injections (Stolerman, 1992). The drug discrimination procedure is regarded as an animal model for the subjective effects of drugs in humans (Preston, 1991). According to a discriminative stimulus account of reinstatement, exposure to the self-administration drug during testing elicits a selective increase in responding on the previously active lever because certain drug effects signal the rat that pressing this lever but not the inactive lever will lead to drug infusions. Proponents of this view typically point out that as in the case of drug discrimination response generalization is most likely to occur within the same drug class.

However, studies on the neuronal substrates that mediate the discriminative stimulus effects of heroin suggest that they are different from those that mediate drug-induced reinstatement. Intra-VTA injections of morphine—a manipulation that induces reinstatement of heroin seeking (Stewart, 1984)—do not induce heroin-appropriate responding in the drug discrimination method (Shaham and Stewart, 1995a; Jaeger and van der Kooy, 1996; but see Shoaib and Spanagel, 1994). Jaeger and van der Kooy (1993, 1996) further showed

that the rewarding and discriminative effects of morphine are anatomically dissociable and that the discriminative drug effects are neither necessary nor sufficient for morphine's rewarding effects. Finally, the observations that indirect DA agonists and D2-like agonists reinstate heroin seeking (Wise et al., 1990; De Vries et al., 1999) is not in agreement with most studies from the drug discrimination literature, in which generalization to the training drug is typically observed within a given drug class (Stolerman et al., 1989, 1995).

Stewart and colleagues hypothesized that reinstatement by drug priming is due to the ability of the drug to induce an incentive motivational state, which leads to resumed drug seeking (Stewart et al., 1984). This incentive motivational state refers to the arousing/activating state that occurs following exposure to an appetitive unconditioned stimulus or to stimuli classically conditioned to the unconditioned stimulus (Stewart et al., 1984). They postulated that drug seeking during tests for reinstatement occurs because the presence of the drug in the body (and brain) enhances the incentive value of the extinguished drug cues, previously paired with the drug's rewarding effect. The findings that both heroin and cocaine priming reinstate drug seeking via activation of the mesocorticolimbic DA (Stewart, 2000), thought to be involved in incentive motivation and appetitive goal-direct behavior (Stewart et al., 1984; Robinson and Berridge, 1993; Di Chiara, 1995), provide support to this idea. Additional support for Stewart's hypothesis is the observation that the removal of the drug cues previously associated with amphetamine during testing attenuates amphetamine-induced reinstatement (Stretch et al., 1971). Finally, as argued by Leri and Stewart (2001), the findings that drug priming reinstates an approach behavior toward contextual cues previously associated with the drug's rewarding effects after extinction in the CPP model is consistent with an incentive motivation view but not with a discriminative stimulus view. Specifically, in the CPP procedure the drug is not associated with a specific instrumental responding. Thus, it is unlikely that drug priming acts to induce a habitual form of responding that is elicited by its discriminative stimulus properties (see Bickel and Kelly, 1988).

It appears unlikely that the discriminative stimulus properties of the priming drug injections can account for their effect on reinstatement. In contrast, the available data appear to fit an incentive motivation account of drug priming. It should be pointed out, however, that this state of affairs might be due to the fact that incentive motivation is a theoretical construct, and as such, it is difficult to design experiments that can refute or support its role in reinstatement. It is also likely that incentive motivation is only one of several processes involved in relapse behavior. The data reviewed indicate that multiple neuronal systems are involved in relapse induced by drug priming, cues, and stress, implying that multiple psychological processes are likely to be involved. Finally, as argued by Tiffany (1990), relapse often occurs as a result of automated processes, which are independent of motivational processes.

2. Drug Cues. It has long been established that conditioned drug cues can provoke relapse in rats and monkeys (Goldberg, 1976). Furthermore, drug-associated stimuli can modulate the behavioral and physiological effects of drugs of abuse (Siegel, 1989; Stewart, 1992; Robinson et al., 1998). In the last 6 years, several laboratories have used established learning procedures, including conditioned reinforcement, discrimination learning, and renewal (Catania, 1992; Bouton, 1993) to study neuronal substrates underlying relapse induced by discrete CSs (previously paired with each drug injection) and discriminative and contextual cues, which predict drug availability but are not specifically paired with each drug injection. This distinction is important since previous studies indicate that different neuronal circuits underlie the behavioral effects of discrete CSs versus contextual stimuli (Phillips and LeDoux, 1992; Holland and Bouton, 1999).

In studies using lever-pressing behavior as the dependent measure, it is often difficult to differentiate between the relative contribution of discrete versus contextual cues in extinction behavior or cue-induced reinstatement. For example, a retractable lever that extends at the start of the training sessions can serve as a contextual cue that predicts drug availability. However, the depression of the lever and the associated auditory click can also serve as discrete CSs that are associated with drug injections. The situation is even more complicated in studies in which both discrete CSs associated with drug/saline injections and discriminative cues that predict drug/saline availability are simultaneously manipulated during discrimination training (Gracy et al., 2000). Interestingly, this experimental manipulation results in a persistent effect of the drug cues on reinstatement over many test sessions and up to 4 months of withdrawal periods (Ciccocioppo et al., 2001).

Even with the renewal procedure, in which one set of contextual cues (e.g., specific smell, floor texture) is associated with drug self-administration training and the other set of cues is paired with extinction training while keeping the discrete CS (e.g., cue light, sound of the pump) constant during training and extinction, the interpretation of the data is not straightforward. One possibility is that the effect of the drug context on renewal of drug seeking is due to a nonspecific effect of switching rats to a different environment. This possibility is not likely becasue we found that rats exposed to a novel environment during testing do not resume lever-pressing behavior (Crombag and Shaham, 2002), a finding in agreement with previous reports (Bouton and King, 1983; Goddard, 1999; Nakajima et al., 2000). Alternatively, contextual stimuli, because they reliably signal drug availability, acquire excitatory conditioned stimulus (CS+) qualities, including incentive motivational

properties. In our studies, extinction training occurred in a different environment and therefore contextual cues would have retained their motivational value. Exposure of rats to these (nonextinguished) contextual cues could have elicited cocaine seeking.

Another possibility is that drug-associated contextual stimuli provoke relapse because of their occasion setter (Holland, 1992) or modulator (Rescorla et al., 1985) properties. Unlike traditional CSs, occasion setters do not elicit behavior by themselves, but rather modulate the behavioral effects of other conditioned stimuli (Holland, 1992). According to this view, contexts function as retrieval cues in cases where the meaning of the discrete CSs is ambiguous because they have been paired with both reinforcement and nonreinforcement (Bouton, 1993), as is the case in our studies. Thus, a question that emerges from the above behavioral analysis is whether the DA receptor antagonists block context-induced reinstatement of cocaine seeking by interfering with the putative occasion setting properties of the context or by acting on neuronal systems that underlie conditioned behaviors elicited by discrete CSs.

Thus, unlike studies using classical conditioning paradigms on mechanisms underlying contextual versus discrete cues on behavior (e.g., conditioned fear; conditioned activity), in studies on drug cues-induced reinstatement, it is difficult to differentiate between the relative contribution of discrete CSs associated with drug infusions versus that of discriminative and/or contextual cues associated with drug availability. It is also likely that on many occasions an interaction between discrete CSs and contextual cues underlies cue-induced relapse to drugs.

3. Stress. Several mechanisms have been proposed to explain the effect of footshock stress on relapse to drug seeking. It has been suggested that activation of the mesocorticolimbic DA system by stressors underlies their effect on reinstatement, thus mimicking drug priming (Robinson and Berridge, 1993; Shaham and Stewart, 1995a). This hypothesis, however, is not likely as footshock stress- and drug-induced reinstatement can be dissociated pharmacologically and anatomically (Shaham et al., 2000a). It has also been argued that footshock stress might reinstate cocaine seeking by mimicking certain interoceptive cues of cocaine that were present during training (Ahmed and Koob, 1997). Footshock exposure results in cocaine-appropriate responding in drug discrimination tasks (Mantsch and Goeders, 1999a). However, footshock is often a more effective stimulus for reinstatement than drug priming (Shaham, 1996), an observation that would not be predicted if stressors act by mimicking the cue properties of the drug. In addition, Mantsch and Goeders (1999a) reported that a pharmacological manipulation (ketoconazole administration) that blocks footshock-induced reinstatement does not alter footshock-induced cocaine-appropriate responding in a drug discrimination task. Finally, the pharmacological dissociation between footshock- and drug-induced relapse does not support the idea that the stressor mimics interoceptive drug cues.

Whitehead (1974) suggested that stressors induce a withdrawal-like state, which leads to relapse to heroin use. There are similarities between the stress response and symptoms of opioid withdrawal (Redmond and Huang, 1979). However, this idea seems unlikely as withdrawal precipitated by an opioid receptor antagonist does not reinstate heroin seeking and footshock reinstates drug seeking in the presence of a maintenance dose of heroin (Shaham and Stewart, 1995b; Shaham et al., 1996). Finally, Highfield et al. (2000) provided some evidence that footshock stress may provoke relapse by interfering with a neuronal processes underlying response inhibition, whose function is to stop ongoing activity when reinforcers are not available, as is the case during extinction (Pavlov, 1927; Gray, 1987). Four outcomes suggestive of the interruption of inhibitory processes, and which would be predicted by a "disinhibitory" account of footshock-induced reinstatement, were obtained (Highfield et al., 2000). These include: 1) reinstatement of heroin seeking by inactivation of the medial septum, a brain area involved in response inhibition (Grossman, 1977; Gray and McNaughton, 1983); 2) attenuation of footshock-induced reinstatement by stimulation of the medial septum; 3) summation between reduced activation of the medial septum and mild shock; and 4) increased resistance to extinction by footshock stress.

Another unresolved question concerns the mechanisms underlying food deprivation stress-induced reinstatement. We found that leptin attenuates food deprivation-induced, but not footshock- or heroin-induced reinstatement (Shalev et al., 2001b). Thus, it is possible that the neuronal events that mediate acute food deprivation-induced reinstatement are dissociable from those involved in reinstatement induced by footshock or heroin priming. This hypothesis can be confirmed (or refuted) by determining the effect on food deprivation-induced reinstatement of pharmacological agents that block reinstatement by drug priming or footshock.

It appears that footshock stress reinstates drug seeking by mechanisms that are probably unrelated to the ability of the stressor to induce drug-like or withdrawal-like states. An alternative explanation is that acute exposure to footshock disrupts neural processes that normally exert inhibitory control over prepotent behaviors. Finally, the mechanisms underlying food deprivation-induced reinstatement are yet to be elucidated.

4. Summary. Although a great deal of knowledge has been accumulated on the neuronal mechanisms underlying relapse behavior, the psychological processes involved in relapse induced by drug priming, drug cues, and stressors are not clear. In the case of drug-induced reinstatement, the available data appear to support the idea that incentive motivational processes underlie this

effect. In contrast, the data reviewed do not support the idea that the discriminative stimulus effects of drugs mediate drug-induced reinstatement. In the case of cue-induced reinstatement, an unresolved issue is the degree of overlap between the neuronal mechanisms underlying relapse induced by discrete CSs paired with drug injection versus discriminative or contextual cues that predict drug availability. Finally, little is known about the mechanisms underlying stress-induced reinstatement. The available data do not support the idea that footshock reinstates by inducing drug-like or withdrawal-like states. The stressor, however, may reinstate drug seeking by its actions on neuronal processes involved in response inhibition. Finally, it is not known whether food deprivation reinstates drug seeking by acting on neuronal systems involved in drug priming or footshock, or by its action on a different neuronal circuit that is yet to be elucidated.

C. Methodological Issues

In this section, we address several methodological issues that should be considered in the interpretation of data from reinstatement studies. A distinction that we will make in this section is whether the experimental variable discussed alters behavior during tests for reinstatement in a *quantitative* (i.e., a change in the magnitude of a given behavioral effect by the different levels of the experimental variable) or a *qualitative* manner (i.e., a change in the direction of a given behavior by the different levels of the experimental variable).

1. Prior Training for Food Reinforcement. In many studies, rats are trained to lever press for food prior to drug self-administration training. Although these conditions facilitate drug self-administration training (Carroll, 1999), they may introduce confounds in reinstatement studies. Specifically, when the same experimental setup is used for food training and drug self-administration training, the latter condition comprises a component of extinction training for food. Thus, resumption of lever-pressing responding during testing may be due to reinstatement of food seeking rather than drug seeking. This alternative explanation can be ruled out by using a control group of rats that lever press for food (de Wit and Stewart, 1981; Shaham et al., 1997a), but this condition has rarely been employed in reinstatement studies.

2. Noncontingent Priming Injections during Training. A common practice in drug self-administration studies is to start the training sessions with one or two priming noncontingent drug injections (Caine and Koob, 1994). As in the case of food training, this manipulation facilitates drug self-administration training but it introduces confounds in the interpretation of the data. When noncontingent drug injections are given at the start of each training session they may become discriminative cues (Catania, 1992) that predict drug availability. As these priming injections are not given during the extinction phase, when drug priming is reintroduced during testing it may reinstate drug seeking because of its discriminative stimulus properties (i.e., it informs the rat that the drug is now available or that subsequent lever presses will lead to contingent drug injections). Thus, when priming injections are given during training, their effect on reinstatement after extinction may be due to their discriminative stimulus effects, incentive motivational effects (see *Section V.B.1.*), or both.

3. Response Rates during Training. The effect of pharmacological manipulations on operant behavior maintained by drugs or nondrug reinforcers is dependent on baseline rates of responding, the rate dependence effect (Sanger and Blackman, 1976; Witkin, 1994). For example, DA receptor antagonists increase lever pressing for a high unit dose of cocaine when each lever press is reinforced, a fixed ratio-1 (FR-1) schedule (Wise, 1978; Ettenberg et al., 1982). On the other hand, under an intermittent schedule of reinforcement (FR-15), which leads to a high rate of responding, DA receptor antagonists decrease lever pressing for cocaine (Caine and Koob, 1994). An important question, therefore, is whether the rate of responding during training leads to qualitative differences in the behavioral effects of drug priming, drug cues, and stressors during testing. Response rates during training can be manipulated by changing either the schedule of reinforcement, the unit dose (i.e., the dose per infusion) of the training drug, or both.

Despite the fact that only several studies have addressed this issue empirically (see below), we argue that it is not likely that the response rate during training is a major methodological concern in reinstatement studies. The main reason for this argument is that regardless of the rate of responding during training (and extinction), tests for reinstatement are conducted under low rates of responding after extinction. The available data on the effect of rate of responding during training on reinstatement appear to support this argument. Comer et al. (1995) found that under an FR-1 schedule, the training dose of cocaine (0.2, 0.4, or 1.0 mg/kg/infusion, which leads to high, moderate, or low response rates, respectively) does not alter reinstatement induced by cocaine priming in rats. In addition, regardless of the training dose, food restriction enhanced the effect of cocaine priming on reinstatement. Leri and Stewart (2001) trained rats to lever press for heroin (0.025, 0.05, 0.1, or 0.2 mg/kg/infusion; FR-1 schedule) or cocaine (0.25, 0.5, 1.0, or 2.0 mg/kg/infusion; FR-1 schedule) on alternate days. They found that response rates during training (which are high with low doses and low with high doses) do not predict the response to cocaine or heroin priming after extinction. In contrast, Kruzich et al. (1999) reported that the response rate during training was negatively correlated with the magnitude of cue-induced reinstatement. These data should be interpreted with caution as they are based on correlational analyses rather than on experimental manipulations.

Most important, it was found that regardless of the response rates during training, pharmacological agents have similar effects on reinstatement. For example, the effect of D1- and D2-like agents on reinstatement of cocaine seeking in rats trained on a high unit dose and an FR-1 schedule (Wise et al., 1990; Self et al., 1996), conditions that lead to low response rates, generalizes to monkeys trained on a second-order schedule, which leads to high rates of responding (Khroyan et al., 2000). Furthermore, it has been shown that pharmacological manipulations (e.g., CRF receptor antagonists) that attenuate footshock-induced reinstatement in an operant procedure (Shaham et al., 2000a), also attenuate reactivation of CPP by the stressor in a classical conditioning, rate-independent paradigm (Lu et al., 2000, 2001a).

In conclusion, it does not appear that differences in response rates within and between studies lead to qualitatively different effects on reinstatement of drug seeking. The fact that findings from reinstatement studies based on operant self-administration behavior generalize to those from rate-independent CPP studies further supports this conclusion. However, in agreement with learning studies on the partial reinforcement effect, the increased resistance to extinction after training with intermittent versus continuous reinforcement schedules (Gray, 1987), it appears that reinstatement by drug or nondrug stimuli can be enhanced when rats are trained under intermittent schedules of reinforcement. Thus, training rats on intermittent schedules of reinforcement leads to higher rates of responding after exposure to cocaine priming (Tran-Nguyen et al., 1998) or footshock stress (Mantsch and Goeders, 1999a) than those observed in studies in which an FR-1 schedule of reinforcement was used.

4. Amount of Drug Exposure during Training. Several recent studies indicate that the amount of drug intake during training can influence the effect of drug priming and footshock stress on reinstatement. The effect of prior drug exposure during training on reinstatement, however, is quantitative rather than qualitative. Compared with rats trained for 6 days, Deroche et al. (1999) reported that rats trained to lever press for cocaine for 29 days demonstrated a shift to the left in the dose-response curve in response to cocaine priming (0.2–1.6 mg/kg, i.v.). Sutton et al. (2000) and Baker et al. (2001) reported that total cocaine intake during training is correlated with the magnitude of reinstatement induced by amphetamine or cocaine priming, respectively. In the study of Sutton et al. (2000), however, the amount of cocaine intake during training was not correlated with reinstatement induced by drug cues or a mild footshock. In contrast, Ahmed et al. (2000) reported that, compared with rats trained for 1 h/day, rats trained for 11 h/day to self-administer heroin demonstrated an enhanced response to footshock stress during testing. Thus, it appears that the magnitude of reinstatement induced by drug priming is associated with the amount of cocaine intake during training. At present, however, a clear picture is yet to emerge on the relationship between drug intake and reinstatement induced by stressors and drug cues.

5. The Drug Withdrawal Period Prior to Tests for Reinstatement. Recent studies indicate that the duration of the withdrawal period prior to tests for reinstatement is an important factor, which can lead to quantitative and qualitative differences in reinstatement by drug and nondrug stimuli. Tran-Nguyen et al. (1998) demonstrated that the response to cocaine priming is increased after 1 month of withdrawal compared with 1 day or 1 week (Fig. 13A). In addition, the effect of D2-like receptor agonists on reinstatement of heroin seeking is critically dependent on the withdrawal period. Using a within-session model, Wise et al. (1990) found that the D2-like receptor agonist, bromocriptine, potently reinstates heroin seeking when given several hours after drug self-administration. De Vries et al. (2002) found that the D2-like agonist quinpirole reinstates heroin seeking after short periods (less than 1 week), but not after prolonged periods (greater than 3 weeks) of drug withdrawal.

There also are profound differences in response to drug cues and footshock stress at different time periods after drug withdrawal. In a study with cocaine-trained rats, we found that the response to the cocaine cues progressively increased following withdrawal from cocaine and that, surprisingly, reinstatement was not observed on day 1 of withdrawal (Grimm et al., 2001) (Fig. 13B). In another study with heroin-trained rats, we found that reinstatement of lever-pressing behavior by footshock followed an inverted U-shaped curve with maximal responding after 6 and 12 days of heroin withdrawal (Shalev et al., 2001a) (Fig. 13C). Surprisingly, footshock did not reinstate behavior on day 1 of heroin withdrawal.

6. Side Effects of the Pharmacological and Brain Manipulations. An important issue in reinstatement studies is concerned with the interpretation of data from studies in which pharmacological agents and/or brain manipulations are given prior to tests for reinstatement. The question is what are the necessary control conditions to determine that decreases (or increases) in active lever responding during testing reflect the effects of the experimental manipulations on drug seeking rather than some other nonspecific effects. At present, there is no single behavioral measure that can adequately address this question. Thus, it is necessary to collect data from several dependent measures to rule out that nonspecific effects of the experimental manipulations led to changes in behavior.

A common practice is to determine the effect of the experimental manipulations on responses on the inactive lever as a measure of nonspecific activity. However, given that baseline rates of responding on this lever are low, nonspecific sedative effects cannot be adequately

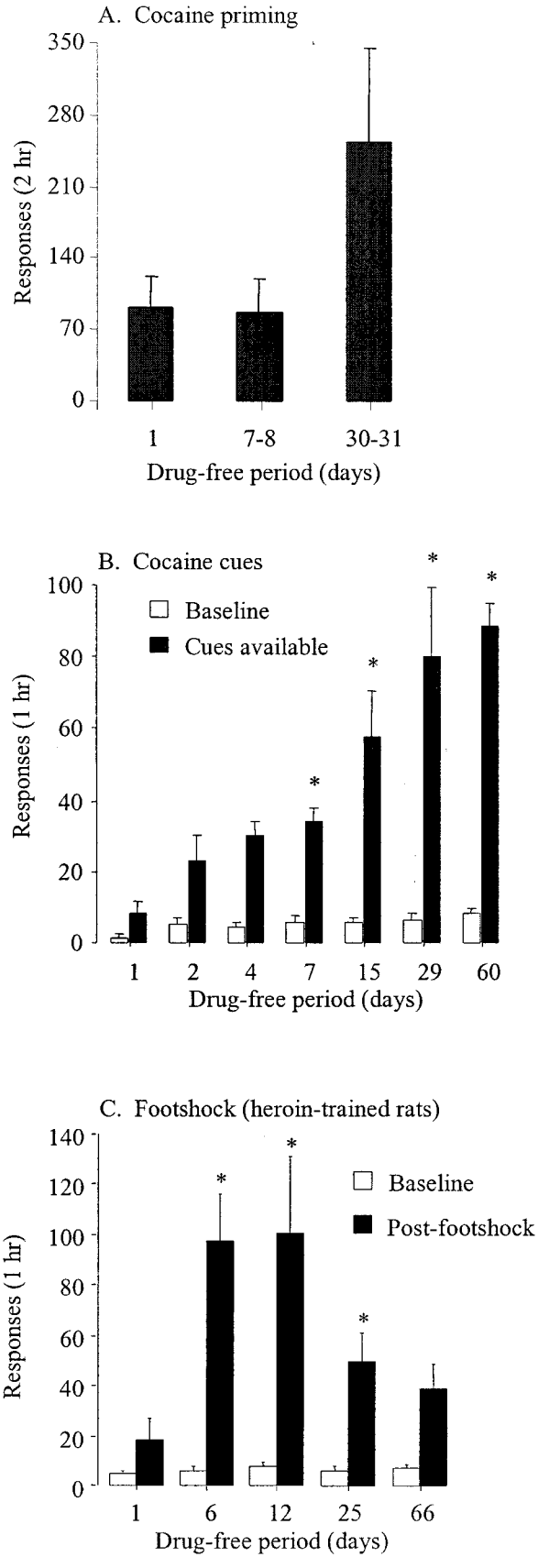

FIG. 13. Mean (± S.E.M.) number of nonreinforced responses on the previously active lever during tests for reinstatement following exposure to cocaine priming, cocaine cues, and intermittent footshock (heroin-trained rats). A, cocaine (15 mg/kg, i.p.)-induced reinstatement following 1, 7 to 8, and 30 to 31 days of drug withdrawal. B, cue-induced reinstatement of cocaine seeking at different withdrawal periods. Baseline (no cues), the last 60-min extinction session wherein the rats reached the extinction criterion prior to exposure to the cocaine cues; cues available, the 60-min session wherein lever presses led to the presentation of the tone and light cues previously paired with cocaine self-administration. Rats were trained to lever press for cocaine for 10 days and were tested after 1, 2, 7, 15, 29, or 60 days of withdrawal from cocaine. *, significantly different from day 1 withdrawal ($p < 0.05$). C, footshock-induced reinstatement of heroin seeking. Baseline, the last 60-min extinction session on which the rats reached the extinction criterion prior to exposure to footshock; postfootshock, the 60-min session after exposure to 10-min intermittent footshock stress. Rats were trained to lever press for heroin for 10 days and were tested under extinction conditions after 1, 6, 12, 25, or 66 days of withdrawal from the drug. *, significantly different from day 1 withdrawal ($p < 0.05$). Data are from Tran-Nguyen et al., 1998, reprinted ©1998 with permission from Elsevier Science; Grimm et al., 2001, reprinted ©2001 with permission from Nature; and Shalev et al., 2001, reprinted ©2001 with permission from Springer-Verlag.

assessed. In addition, even if the experimental manipulations increase responding on the inactive lever, it does not necessarily indicate that it is due to nonspecific behavioral activation. When tests are conducted under extinction conditions, increased responding on the inactive lever may reflect response generalization, which commonly occurs during extinction (Catania, 1992).

Another way to assess nonspecific effects of the pharmacological/brain manipulations is to determine their impact on lever pressing after extinction but in the absence of the reinstating stimulus. However, as in the case of inactive lever responses, because response rates on the active lever are low after extinction, nonspecific sedative effects are difficult to assess. In addition, even if an experimental manipulation selectively increases responding on the active lever but not on the inactive lever, the increased responding may be in part due to nonspecific behavioral activation. Early studies on the rate dependence effects of methamphetamine have shown that the drug does not increase low rate baseline responding that was never reinforced (Verhave, 1958).

Potential sedative effects can be determined by examining the effect of the experimental manipulations on ongoing high rate of responding for a nondrug reinfrocer such as sucrose (Weissenborn et al., 1995; Erb et al., 2000). The specificity of the experimental manipulations on drug seeking, for example, can also be studied by determining their impact on reinstatement of food seeking (de Wit and Stewart, 1981; Cornish et al., 1999) or reinstatement of lever pressing previously maintained by another drug (De Vries et al., 1999). For example, Leri and Stewart (2001) have shown that in rats trained on alternate days to lever press for cocaine and heroin, each with its associated lever and distinct cues, cocaine or heroin priming selectively reinstates lever pressing on its drug-associated lever. However, although the interpretation of the data is clear if the experimental manipulations do not alter response rates under the above control conditions, a change in response rates for a nondrug reinforcer or for a different drug may not be necessarily due to nonspecific effects. To the extent that

drugs of abuse act on brain systems underlying natural rewards (Wise and Rompre, 1989), experimental manipulations that decrease drug seeking may also decrease operant responding for food reward or reinstatement of responding previously maintained by other drug or nondrug reinforcers. Finally, the selectivity of a given manipulation can be studied by determining its effect on more than one reinstating stimulus. For example, CRF receptor antagonists selectively attenuate footshock-induced reinstatement but not reinstatement induced by drug priming (Shaham et al., 2000a).

The measurement of changes in responding on the inactive lever during tests for reinstatement is not an optimal measure of nonspecific effects. Thus, it is necessary to collect converging evidence from several measures. These may include the effect of the manipulations on high rate of operant responding for a nondrug reinforcer, reinstatement of food/water seeking, and reinstatement by other stimuli.

7. Summary. A number of methodological issues should be considered in the design and interpretation of reinstatement studies. To avoid confounds in reinstatement studies, rats should not be food trained prior to drug self-administration training and should not be given noncontingent drug injections at the onset of the training sessions. Based on limited evidence, it appears that the response rate during training does not lead to qualitative changes in responding during tests for reinstatement. Training rats under intermittent schedules of reinforcement, however, can lead to increased responding during testing. Another factor associated with increased responding during tests for reinstatement is the amount of drug intake during training. Recent evidence indicates that the duration of the drug withdrawal period prior to testing is an important factor in reinstatement by drug or nondrug stimuli. Finally, to assess potential side effects of pharmacological and brain manipulations given during tests for reinstatement, data should be collected from several control conditions (e.g., operant responding for food, reinstatement of food seeking), in addition to inactive lever responses.

D. Emerging Issues

In this section we will discuss two issues that emerge from recent reinstatement studies and from other developments in the neuroscience field: the relationship between reinstatement of drug seeking and drug-induced behavior and neurochemical sensitization and the application of the reinstatement model to mice for studies on the genetic bases of vulnerability to relapse.

1. Does Drug Sensitization Contribute to Relapse to Heroin and Cocaine? Repeated exposure to opioid and stimulant drugs results in enhanced behavioral and neurochemical responses to the drugs (sensitization) or stressors (cross-sensitization) after withdrawal periods (Kalivas and Stewart, 1991; Piazza and Le Moal, 1996). These sensitized behavioral and neurochemical responses to drugs and stressors peak at time points that are beyond the acute withdrawal phase and persist for many months, and the mesocorticolimbic DA system is involved in the manifestation of these sensitized responses (Pierce and Kalivas, 1997; White and Kalivas, 1998). These observations, and those demonstrating that pre-exposure to drugs and stressors facilitate the initiation of drug self-administration in rats (Goeders, 1997; Schenk and Partridge, 1997; Piazza and Le Moal, 1998), were the basis for the hypothesis that drug sensitization also contributes to drug relapse (Robinson and Berridge, 1993; Piazza and Le Moal, 1996; De Vries et al., 1998a; Kalivas et al., 1998).

a. Drug Priming and Drug Cues. Evidence in support of the view that processes underlying drug sensitization are involved in relapse to drugs emerges from studies on reinstatement of heroin and cocaine seeking induced by drug priming. First, Tran-Nguyen et al. (1998) found that lever pressing during tests for cocaine-induced reinstatement is higher after 1 month of cocaine withdrawal compared with 1 or 7 to 8 days (Fig. 13A). They also found that these time-dependent changes in behavior are correlated with cocaine-induced DA release in the amygdala. Second, De Vries et al. (1998a, 1999) found a high correlation between the effect of opioid and DA agonists on reinstatement of heroin and cocaine seeking and their ability to induce sensitized locomotor responses after prolonged withdrawal periods. Third, Cornish and Kalivas (2000) found that activation of AMPA receptors in the NAc, known to be involved in the expression of sensitization to psychostimulants after drug withdrawal (White and Kalivas, 1998), mediates cocaine-induced reinstatement. Finally, we found time-dependent changes in cue-induced reinstatement in the first 2 months of cocaine withdrawal (Fig. 13B), which resemble to some degree the time course of the expression of behavioral sensitization to psychostimulant drugs after withdrawal (Paulson et al., 1991).

These data support the idea that sensitization processes within the mesocorticolimbic DA reward circuitry are involved in relapse induced by drug or drug-related cues after prolonged withdrawal periods. However, it must be emphasized that the above data are correlational. Thus, a causal relationship between the expression of locomotor sensitization and relapse has yet to be demonstrated. Also, there is one negative report on the relationship between behavioral sensitization and reinstatement of cocaine seeking. Sutton et al. (2000) reported that the sensitized locomotor responses to amphetamine following cocaine self-administration was not correlated with the magnitude of responding during tests for reinstatement after exposure to amphetamine, cocaine cues, or footshock. However, it is difficult to draw conclusions from this study because a single highly effective dose of amphetamine (0.5 mg/kg, s.c.) was used during tests for sensitization and reinstatement. Thus, it is possible that the lack of correlation is due to a

ceiling effect. In addition, the drug cues in this study were given noncontingently, a manipulation that does not effectively reinstate drug seeking (Grimm et al., 2000).

b. Stress. It was hypothesized that the enhanced responsiveness of the mesocorticolimbic DA system to stressors following withdrawal from repeated exposure to opioid and stimulant drugs may mediate, in part, stress-induced reinstatement (Robinson and Berridge, 1993; Shaham and Stewart, 1995b). Unlike drug priming (and possibly drug cues), the available data suggest that this hypothesis cannot adequately explain stress-induced reinstatement (see *Section V.B.3.*). Repeated exposure to drugs of abuse, however, may induce neuronal adaptations or sensitize neuronal systems involved in stress responses (Kreek and Koob, 1998; Sarnyai et al., 2001).

Two recent studies reviewed above provide some tentative support for this idea. Ahmed et al. (2000) reported that rats trained to lever press for heroin for 11 h per day (long access) demonstrate higher rates of responding during tests for footshock-induced reinstatement than rats trained for 1 h per day (short access). In addition, we found profound time-dependent changes in the effect of footshock on reinstatement of heroin seeking (Shalev et al., 2001a) (Fig. 13C). These data are in agreement with a neuroadaptation model, which argues that drugs induce long-term neuronal changes that take time to develop after drug withdrawal, are long-lasting, and are dependent on the amount of prior drug exposure (Pierce and Kalivas, 1997).

It should be pointed out, however, that changes in sensitivity in brain systems involved in footshock stress-induced reinstatement (i.e., NA and CRF) in response to the stressor are yet to be reported, and in our initial neurochemical characterization of the time-dependent changes in footshock-induced reinstatement, we found that alterations in CRF mRNA in the CeA and BNST in response to the stressor are not correlated with the lever-pressing behavior during testing (Shalev et al., 2001a). Thus, whereas recent behavioral evidence suggests that drug-induced sensitization of brain systems involved in stress response may contribute to vulnerability to stress-induced relapse, the neuronal systems involved in these putative "sensitization" processes are yet to be determined.

2. Application of the Reinstatement Model to Mice. The rat reinstatement model may not be the most suitable mean for studying genetic factors in drug addiction and relapse. Methods for over-expressing genes via viral vectors or inactivating genes by antisense oligonucleotides have contributed to the understanding of the mechanisms of drug reward in rats (Nestler, 2000, 2001). For several reasons, however, the mouse is a more appropriate species to study genetic factors in drug addiction. There are a number of inbred mouse strains and several molecular genetic techniques in mice that allow them to either inactivate (knockout methods) or over-express (transgenic methods) specific genes potentially involved in drug effects (Crabbe et al., 1999; Nestler, 2001). Mice self-administer opioid (Elmer et al., 1996; Roberts et al., 1997) and stimulant (Rocha et al., 1998; Caine et al., 1999a) drugs and also demonstrate CPP for these drugs (Cunningham et al., 1992; Laviola et al., 1992).

There are two published reports on reinstatement in mice, both of which used the CPP procedure. Manzanedo et al. (2001) trained mice (OF1 albino strain) to acquire morphine (40 mg, i.p.) place preference for 4 days. Subsequently, mice were repeatedly tested for morphine CPP in the absence of the drug 5, 15, 20, 35, and 45 days after last exposure to morphine (extinction). CPP for morphine was not observed on the last 3 test days, but a priming injection of morphine (40 mg/kg) led to reinstatement of CPP 46 days after training. Itzhak and Martin (2002) trained Swiss-Webster mice for cocaine CPP and then extinguished this behavior by administering saline injections (8 days) in the previously cocaine- and saline-paired compartments. Subsequently, they found reinstatement of CPP following injections of cocaine, methamphetamine, and methylphenidate but not phencyclidine.

We trained male mice of the 129X1/SvJ strain for 14 to 16 days to self-administer cocaine (0.75 mg/kg/infusion, 4 h per day; infusions were paired with a light-tone compound cue). Next, the lever-pressing behavior was extinguished in the presence or absence (for subsequent tests for cue-induced reinstatement) of the cocaine cue. Subsequently, tests for reinstatement were conducted in different groups of mice after exposure to priming injections of cocaine (0, 1.5, 3.0, and 6.0 mg/kg, i.v.), response-contingent presentations of the cocaine-associated cue or food deprivation stress (1 and 22 h). We found that the effect of cocaine priming on reinstatement was relatively modest and was only observed at the highest dose tested. On the other hand, reinstatement of cocaine seeking was observed following exposure to the cocaine-associated cue and food deprivation stress. These data tentatively suggest that factors contributing to relapse to drugs can be studied in the reinstatement model using the common 129X1/SvJ mouse inbred strain (D. Highfield, A. Mead, J. W. Grimm, B. A. Rocha, and Y. Shaham, manuscript submitted). The reasons for the weak effect of the priming cocaine injections in mice are not clear.

Although species differences in response to reinstating stimuli may exist, both operant and classical conditioning models of reinstatement can be used in mice. Studies using molecular genetic methods are likely to provide information on the role of specific genes in relapse to heroin and cocaine.

E. Concluding Remarks and Implications for Addiction Theories and Treatment

We reviewed data from studies on the neuronal mechanisms underlying relapse to heroin and cocaine. Based

on the data reviewed, we conclude that the neuronal mechanisms involved in relapse induced by drug priming, drug cues, and stressors are to a large degree dissociable and also are likely to be different from those involved in the acute reinforcing effects of these drugs. The data reviewed on the time-dependent changes in the propensity to relapse following withdrawal from heroin and cocaine also suggest that the organism may be most vulnerable to relapse to drugs at time periods that are well beyond the acute drug withdrawal phase. We conclude this review by briefly discussing the potential implications of the data from reinstatement studies to addiction theories and for the treatment of relapse in humans.

1. Implications for Addiction Theories. Negative reinforcement theories postulate that compulsive drug use and drug relapse occur because the addict is seeking drugs to alleviate the aversive symptoms of drug withdrawal; symptoms that can also be elicited by cues previously paired with drug withdrawal (Himmelsbach, 1943; Lindsmith, 1947; Wikler, 1973). Over the years, several drug-opposite physiological and psychological adaptations have been hypothesized to underlie habitual drug use and relapse (Goldstein and Goldstein, 1968; Solomon and Corbit, 1974; Collier, 1980; Koob et al., 1989; Siegel, 1989). The self-medication hypothesis, which argues that compulsive drug use and relapse is due to the drug's effects on the individual's well being, is another form of a negative reinforcement model (Khantzian, 1985; Markou et al., 1998). It is beyond the scope of this paper to describe these negative reinforcement theories in detail and to discuss the degree to which they account for drug self-administration behavior (see Schuster and Thompson, 1969; Stewart et al., 1984; Wise and Bozarth, 1987). In the context of relapse to heroin and cocaine seeking as measured in the reinstatement model, however, we argue that there is little evidence that negative reinforcement models are compatible with the data on relapse induced by drug priming, drug cues, or stressors.

In many of the studies reviewed, rats were trained under conditions that are not sufficient to induce measurable withdrawal symptoms (i.e., 1–2 h/day of drug self-administration or only a single daily exposure to low drug doses in the runway and CPP models). As mentioned, attempts to induce relapse to heroin seeking by precipitating opioid withdrawal were not successful (Shaham and Stewart, 1995b; Shaham et al., 1996). Cues associated with drug administration can induce drug-opposite withdrawal-like effects (Siegel, 1989), but there is no evidence to date that such effect of cues can induce relapse in the reinstatement model. Finally, in our studies, in which rats were trained for 6 to 9 h/day leading to drug intakes that are sufficient to induce withdrawal symptoms during early withdrawal (1–2 days) from heroin (Shaham et al., 1996) and cocaine (Sarnyai et al., 2001), we found that extinction behavior, cue-induced reinstatement, and footshock-induced reinstatement were maximal at time points that are well beyond the acute withdrawal phase. These data are in agreement with those from a different model of drug seeking, the second-order schedule, in which Arroyo et al. (1998) found that during early withdrawal from 12-h cocaine self-administration, a decrease in lever-pressing behavior controlled by the cocaine cues is observed.

The limitations of negative reinforcement theories in explaining compulsive drug use led to the developments of several addiction theories, which were primarily based on the observations that drugs are powerful positive reinforcers and maintain behavior in the absence of physical dependence (Weeks and Collins, 1968; Schuster and Thompson, 1969). Wise and Bozarth (1987) argued that "a common brain mechanism of psychomotor activation is stimulated by all positive reinforcers and that the same mechanism mediates the psychomotor stimulant effects and the positive reinforcing effects of these agents" (Wise, 1988). These authors also argued that drugs elicit approach behavior or forward locomotion (Glickman and Schiff, 1967; Bindra, 1974), which leads to compulsive drug use. Stewart et al. (1984) argued that drugs or drug-associated cues elicit a positive incentive motivational state that leads to approach behavior toward these stimuli, and consequently to compulsive drug use and relapse upon exposure to these stimuli. Robinson and Berridge (1993) hypothesized that incentive sensitization processes or increased responsiveness to drug and drug-associated cues following repeated drug exposure may underlie compulsive drug use and relapse. More recently, Di Chiara (1999) argued that compulsive drug use occurs because repeated stimulation of DA in the NAc shell by drugs of abuse in the presence of drug-associated cues leads to the attribution of excessive motivational value and abnormal control over behavior by these cues. Again, it is beyond the scope of this paper to review these theories in detail, to discuss their similarities and differences, the degree to which they account for compulsive drug use, and the degree to which these theories fit with the data from studies on the role of the mesocorticolimbic DA system in goal-directed behavior (see Berridge and Robinson, 1998; Ikemoto and Panksepp, 1999; Schultz and Dickinson, 2000).

However, a common denominator of all four theories is that the mesocorticolimbic DA system is involved in compulsive drug use, albeit via the elicitation of somewhat different motivational processes, and that the presence of drugs in the body (and brain) rather than drug withdrawal is the critical factor in compulsive drug use and relapse. Stewart et al. (1984) and Robinson and Berridge (1993) also argued that drug cues elicit drug-like effects and consequently drug seeking via their action on the mesocorticolimbic DA system.

To a certain degree, the data reviewed are in agreement with these theories. As mentioned above, the available data tentatively support the view that the putative

incentive motivational effects of heroin and cocaine priming may underlie their effect on reinstatement (Stewart et al., 1984). The findings of De Vries et al. (1998a, 1999), that the ability of drugs to induce locomotor activity is correlated with their effects on reinstatement, are in agreement with all four theories. In addition, as discussed in detail above (*Section V.D.1.*), recent data suggest that psychomotor sensitization (a phenomenon that served as the basis for the incentive-sensitization theory) is associated with drug- and possibly cue-induced reinstatement. Finally, the observations that the mesocorticolimbic DA system is involved in both drug priming- and cue-induced reinstatement is in agreement with the four theories.

Importantly, however, the anatomical (Grimm and See, 2000) and pharmacological (McFarland and Ettenberg, 1997) dissociations between reinstatement by drug priming and drug cues are not predicted by the theories of Stewart et al. (1984) and Robinson and Berridge (1993). In addition, all four theories would not predict the partial dissociation between the neuronal mechanisms underlying acute heroin or cocaine reinforcement and drug-induced reinstatement (*Section V.A.*). Furthermore, although Robinson and Berridge (1993) argued that stressors provoke relapse by mimicking the effect of drugs on the mesocorticolimbic DA system, this does not appear to be the case (Shaham et al., 2000a).

Finally, Koob and Le Moal (2001) proposed an "allostasis" model of drug addiction, in which they argued that repeated and compulsive use of high amounts of drugs induces changes in the drug's "hedonic" set point. Allostasis is a process wherein chronic disturbances of homeostasis of a given physiological (and psychological) system lead to a new stable set point (which is outside of the normal homeostatic range) to cope with the chronic internal and/or external demands (Schulkin et al., 1998). Ahmed and Koob (1998, 1999) provided evidence in support of this view by demonstrating that rats given access to cocaine for 6 h/day, but not 1 h/day, escalate their drug intake over time. However, it does not appear that the allostasis model can account for the results obtained in reinstatement studies. Specifically, following 35 days of withdrawal, cocaine intake returned to normal pre-escalating values in rats which previously self-administered cocaine for 6 h/day (Ahmed and Koob, 1998). On the other hand, in reinstatement studies, the time course of extinction behavior and cocaine- and cue-induced reinstatement has an opposite pattern, i.e., low responding on day 1 of withdrawal and high responding following 1 to 2 months of withdrawal (Tran-Nguyen et al., 1998; Grimm et al., 2001). In other words, drug seeking is inversely related to the changes in the putative hedonic set point.

It appears that negative reinforcement and opponent processes theories and the recent allostasis model cannot adequately explain the data obtained in reinstatement studies. In contrast, incentive motivation, incentive sensitization, and psychomotor theories of addiction can account for certain findings from reinstatement studies. However, even these theories cannot account for the pharmacological and anatomical dissociations between drug priming, drug cues, and stressors and for the partial neuronal dissociation between drug-induced reinstatement and drug reinforcement.

2. Implications for Treatment. As mentioned in the Introduction, the reinstatement model appears to have good predictive validity because conditions that provoke drug relapse and craving in humans (drug re-exposure, drug cues, and stress) also reinstate heroin and cocaine seeking following prolonged withdrawal periods in laboratory animals. Over the past several decades, medication development studies have screened potential clinical compounds for their ability to attenuate drug withdrawal symptoms, to substitute for the abused drug in drug self-administration or discrimination models, or to block the reinforcing or discriminative stimulus effects of the abused drug in these models (Bhargava, 1994; Mello and Negus, 1996). The data reviewed here, however, suggest that effective compounds derived from the above screening methods may not prevent relapse to drug seeking. As mentioned, the data reviewed suggest that the neuronal processes that mediate drug-induced reinstatement are to some degree different from those involved in drug reinforcement or discrimination. Furthermore, even compounds that can effectively block relapse induced by drug priming or drug cues are not likely to block stress-induced relapse and vice versa. In addition, the recent data of McFarland and Ettenberg (1997, 1998) on the differential effect of naltrexone and haloperidol on heroin-induced drug seeking versus cue-induced heroin seeking suggest that potential medications screened for the effect on drug priming may not always alter relapse induced by drug cues. Finally, the data reviewed suggest that a pharmacological therapy that combines agents that are effective against relapse induced by drug or drug cues with agents that attenuate stress-induced relapse should be considered for relapse prevention in humans.

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