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Drug Wanting: Behavioral Sensitization and Relapse to Drug-Seeking Behavior

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Abstract—Repeated exposure to drugs of abuse enhances the motor-stimulant response to these drugs, a phenomenon termed behavioral sensitization. Animals that are extinguished from self-administration training readily relapse to drug, conditioned cue, or stress priming. The involvement of sensitization in reinstated drug-seeking behavior

remains controversial. This review describes sensitization and reinstated drug seeking as behavioral events, and the neural circuitry, neurochemistry, and neuropharmacology underlying both behavioral models will be described, compared, and contrasted. It seems that although sensitization and reinstatement involve overlapping circuitry and neurotransmitter and receptor systems, the role of sensitization in reinstatement remains ill-defined. Nevertheless, it is argued that sensitization remains a useful model for determining the neural basis of addiction, and an example is provided in which data from sensitization studies led to potential pharmacotherapies that have been tested in animal models of relapse and in human addicts.

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I. Introduction

Substance abuse is a chronic and enduring phenomenon. Extensive investigations regarding the underlying neural mechanisms of addiction have been ongoing for the past 3 decades. Despite these efforts, few effective treatment options are available to treat drug dependence. Animal models of substance abuse include both noncontingent (experimenter-administered) and contingent (self-administered) drug administration. Up until the late 1990s, studies on drug-induced neuroplasticity focused primarily on examining the effects of repeated noncontingent drug treatments (i.e., sensitization) on dopamine and glutamate systems (Kalivas and Stewart, 1991; Vanderschuren and Kalivas, 2000). Although noncontingent drug administration has provided a wealth of data on how repeated drug exposure alters neuronal function, it is not always accepted that these data predict the neuroplasticity associated with contingent drug administration. Therefore, recent studies have focused on contingent drug self-administration and, in particular, reinstatement of drug-seeking behavior. The choice of this model is based on the idea that the treatments of addiction will intervene to prevent relapse, which reinstatement behavior purports to model (Epstein et al., 2006). Both the sensitization and reinstatement models assess the impact of repeated drug exposure on neural function, the primary difference being how the drug is administered. Thus, the present review will compare and contrast the neural consequences of drug treatment in contingent and noncontingent behavioral models of addiction used to study the neural consequences of drug administration. We then explore questions regarding the interchangeability and validity of each model with a goal to determine the extent of predictive validity that behavioral sensitization resulting from repeated noncontingent drug administration provides for the neuroplasticity underlying the reinstatement of extinguished contingent drug self-administration. Furthermore, whether behavioral sensitization is a component of reinstatement of drug seeking behavior will also be considered.

II. Definitions

A. Sensitization

The enhanced response to a stimulus, after repeated exposure to that stimulus, is termed sensitization (Robinson and Becker, 1986; Kalivas and Stewart, 1991). Regarding drugs of abuse, behavioral sensitization is defined by the augmented motor-stimulant response that occurs with repeated, intermittent exposure to a specific drug. Behavioral sensitization is a long-lasting phenomenon; the enhanced behavioral response has been reported to persist for at least a year (Paulson et al., 1991). A number of factors, including number of treatments, interval between treatments, dose, sex, age, and genetics, can affect the strength of behavioral sen-

sitization (Post and Contel, 1983). Behavioral sensitization has been reported to occur in response to cocaine, amphetamine, morphine, ethanol, nicotine, and Δ^9 -tetrahydrocannabinol (Joyce and Iversen, 1979; Robinson and Becker, 1986; Benwell and Balfour, 1992; Cunningham and Noble, 1992; Post et al., 1992; Cadoni et al., 2001). Furthermore, cross-sensitization between drugs has been shown. For example, animals repeatedly exposed to Δ^9 -tetrahydrocannabinol exhibited a sensitized behavioral response to morphine (Cadoni et al., 2001), whereas animals repeatedly exposed to ethanol were sensitized to cocaine and vice versa (Itzhak and Martin, 1999), and animals repeatedly exposed to amphetamine were sensitized to morphine (Lett, 1989; Vezina et al., 1989; Vezina and Stewart, 1990). In addition, animals with a history of repeated exposure to toluene, via inhalation, exhibited a behaviorally sensitized response to cocaine (Beyer et al., 2001). This suggests that common mechanisms underlie the development of behavioral sensitization, despite the fact that different classes of drug have distinct binding sites in the brain.

The development of behavioral sensitization can be separated into two phases: initiation and expression. Initiation is the immediate neural events that induce behavioral sensitization, and expression is the long-term consequences of these initial events (Kalivas and Stewart, 1991). Initiation is commonly linked to the ventral tegmental area (VTA¹), and expression is associated with the nucleus accumbens. The environment can influence both the initiation and expression of behavioral sensitization. Thus, animals repeatedly exposed to drugs such as cocaine, amphetamine, or morphine during the initiation phase expressed more robust sensitization when re-exposed to drug in the same environment (paired) as previous drug exposure during the expression phase, compared with animals tested in an environment that differed (unpaired) from that used during the initiation phase (Vezina et al., 1989; Anagnostaras and Robinson, 1996; Wang and Hsiao, 2003; Mattson et al., 2008; Vezina and Leyton, 2009). Behavioral sensitization in the paired environment is commonly referred to as context-dependent sensitization as opposed to con-

¹Abbreviations: AMPA, α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; CNQX, 6-cyano-7-nitroquinoxaline-2,3-dione; CPP, conditioned place preference; CRF, corticotropin-releasing factor; GluR, glutamate receptor; JNJ16259685, (3,4-dihydro-2H-pyrano[2,3-b]quinolin-7-yl)-(cis-4-methoxycyclohexyl)-methanone; LDT, laterodorsal tegmentum; LTP, long-term potentiation; LY341495, 2-[(1S,2S)-2-carboxycyclopropyl]-3-(9H-xanthen-9-yl)-D-alanine; LY379268, (1R,4R,5S,6R)-4-amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid; mGluR, metabotropic glutamate receptor; mPFC, medial prefrontal cortex; NMDA, N-methyl-D-aspartate; PPT, pedunculopontine tegmentum; PVN, paraventricular nucleus; SCH23390, (R)-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine; SKF 81297, (\pm)-6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide; SKF38393, 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine; SKF82958, (\pm)-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-benzazepine; VTA, ventral tegmental area.

text-independent sensitization, which occurs in an unpaired paradigm. Context-dependent cross-sensitization has also been reported to occur (Vezina et al., 1989).

Behavioral sensitization is commonly assessed by monitoring motor activity. When monitoring motor activity, repeated exposure to drugs leads to an augmented motor-stimulant response. Sensitization to amphetamine-like psychostimulants can escalate to manifest as intensified stereotypic behavior that competes with locomotion. For example, when rats are sensitized to higher doses of amphetamine (e.g., 2.0 mg/kg i.p.), they show an initial reduction in activity in response to amphetamine challenge, followed by a delayed increase in locomotor activity (Leith and Kuczenski, 1982). Behavioral sensitization can also be assessed via conditioned place preference (CPP) or drug self-administration. In the CPP paradigm, sensitization is manifested as enhanced time spent in the drug-paired chamber. Thus cocaine, amphetamine, and morphine-induced CPP was enhanced in animals with a history of repeated exposure to these drugs (Lett, 1989; Shippenberg et al., 1996). The potential involvement of sensitization in drug self-administration is usually determined by the ability of repeated noncontingent drug exposure to enhance the acquisition of drug self-administration, using low drug doses, or by drug self-administration inducing locomotor sensitization in response to a noncontingent drug injection (Vezina, 2004). It was initially demonstrated that animals with a history of experimenter-administered amphetamine, which induced locomotor sensitization, subsequently showed an augmented acquisition of amphetamine self-administration (Piazza et al., 1990). Furthermore, pre-exposure to amphetamine, 3,4-methylenedioxy methamphetamine, or nicotine enhanced vulnerability to self-administration of cocaine (Horger et al., 1992; Fletcher et al., 2001). Subsequent studies demonstrated that animals with a history of intravenous cocaine or heroin self-administration demonstrate a sensitized motor response to a systemic challenge injection of the self-administered drug (Hooks et al., 1994; Phillips and Di Ciano, 1996; De Vries et al., 1998b; Zapata et al., 2003). In addition, it was shown that when motor activity was monitored during self-administration, sensitization to the stimulant properties of heroin developed (Marinelli et al., 1998). Animals that self-administered heroin also showed cross-sensitization to noncontingent amphetamine-induced locomotion (De Vries et al., 1998b). Finally, it has been reported that repeated, noncontingent administration of amphetamine enhances the reinforcing properties of amphetamine and cocaine, as assessed by a progressive ratio schedule of reinforcement (Mendrek et al., 1998; Suto et al., 2002; Vezina et al., 2002). Furthermore, studies have demonstrated that exposure to binge cocaine self-administration followed by abstinence also sensitizes the reinforcing properties of cocaine (Morgan and Roberts, 2004; Morgan et al., 2006).

B. Relapse/Reinstatement

The pharmacological studies outlined above are consistent with repeated noncontingent drug administration producing sensitization to drug-induced motor stimulation, conditioned place preference, and drug reinforcement. However, the most troublesome facet of addiction therapy is perhaps relapse prevention (O'Brien, 1997). Relapse has been modeled in animal studies via measures of reinstated drug-seeking in animals extinguished from drug self-administration training (for review, see Epstein et al., 2006). These studies typically involve establishing an operant response (i.e., lever press or nose poke) for drug, the subsequent extinction of this operant, and then reinstating this operant behavior. Three models are commonly used in reinstatement studies. These include 1) the between-session model, in which self-administration, extinction, and reinstatement occur on different days; 2) the within-session model, in which self-administration, extinction, and reinstatement occur on the same day; and 3) the between-within model, in which self-administration occurs on a day separate from extinction and reinstatement (Shalev et al., 2002). Using these models, it has been shown that after extinction of previously cocaine-reinforced lever pressing, this operant behavior can be reinstated by cocaine priming injections (de Wit and Stewart, 1981). Similar findings have been reported for heroin, nicotine, and amphetamine (de Wit and Stewart, 1983; Chiamulera et al., 1996; Ranaldi et al., 1999). In addition, like cross-sensitization, discussed in section II.A, reinstatement of previous cocaine-supported lever pressing can be induced by amphetamine and morphine (de Wit and Stewart, 1981). However, heroin and ethanol priming failed to reinstate cocaine self-administration (de Wit and Stewart, 1981). In addition to drug-primed reinstatement, re-exposure to the environment associated with drug self-administration in animals not undergoing extinction (context), cues previously paired with drug infusion, or acute stress can reinstate drug-seeking behavior (de Wit and Stewart, 1981; Shaham and Stewart, 1995; Meil and See, 1996; Crombag et al., 2002). Reinstatement can be influenced by a number of factors, including food training before drug training, use of noncontingent drug primes during training, amount of drug intake during training, and the length of withdrawal before reinstatement testing (Shalev et al., 2002).

In addition to the drug self-administration paradigm, the CPP paradigm has also been used to study reinstatement. In the CPP procedure, animals are repeatedly exposed to one distinct environment in the presence of drug and an alternative environment in the presence of vehicle. When given free access to both chambers, animals generally prefer the previously drug-paired environment. Past research has demonstrated that upon extinction, this preference can be reinstated by drug-priming injections with morphine, cocaine, methamphetamine, nicotine, and ethanol or by acute exposure to environmental stress (Mueller and Stewart, 2000;

Parker and McDonald, 2000; Wang et al., 2000; Li et al., 2002; Sanchez et al., 2003; Biala and Budzynska, 2006). Furthermore, similar to sensitization, cross-reinstatement with cocaine or amphetamine injections reinstates morphine CPP or morphine injections reinstates nicotine CPP (Do Ribeiro Couto et al., 2005; Biala and Budzynska, 2006).

C. Behavioral Relationships between Sensitization and Relapse

Among the hypotheses proposed to explain drug relapse, the incentive motivation hypothesis posits that repeated drug use leads to greater salience being attached to drugs and drug-associated cues, suggesting that sensitization might play a role in reinstatement of drug seeking behavior (Robinson and Berridge, 2003). Although the studies outlined above would seem to largely support this contention, direct testing of this hypothesis has provided mixed results. Thus, after extinction of cocaine self-administration, priming injections of cocaine or amphetamine, but not heroin, successfully reinstate cocaine seeking. It is noteworthy that these same cocaine-trained animals also expressed locomotor sensitization to cocaine and amphetamine but not heroin (De Vries et al., 1998b). Animals trained to self-administer cocaine under a long-access paradigm (6 h/day) showed enhanced reinstated cocaine-seeking and locomotor responses to cocaine challenge compared with short-access animals (1 h/day) (Ferrario et al., 2005). In contrast to these findings, reports have demonstrated that both long- and short-access animals develop behavioral sensitization to cocaine or heroin, but only long-access animals exhibit reinstatement of drug-seeking behavior in response to drug-priming injections (Ahmed and Cador, 2006; Lenoir and Ahmed, 2007). However, these studies involved a within-session reinstatement paradigm with a 45-min extinction period, which could be problematic given that long-access animals exhibit enhanced resistance to extinction (Ahmed et al., 2000). In addition, Knackstedt and Kalivas (2007) have reported that the ability of cocaine priming to reinstate cocaine-seeking behavior is not dependent on escalation of drug-seeking behavior or behavioral sensitization. Taken together, the data suggest that sensitization develops to repeated drug exposure occurring during drug-self-administration but that locomotor sensitization does not always correlate with enhanced reinstatement of drug-seeking behavior.

The lack of a clear-cut correlation between locomotor sensitization and reinstatement of drug-seeking behavior might call into question the validity of the sensitization model. When considering face validity, reinstatement is clearly a more valid model than sensitization, given that animals self-administer the drug in the former whereas the experimenter delivers the drug in the latter model. However, the construct validity of the reinstatement model has also been questioned (Epstein et

al., 2006). Thus, the reasons to cease drug use, the contingencies associated with the priming of reinstatement, and the time course of vulnerability to reinstatement differ between animals and humans (Epstein et al., 2006). Furthermore, reinstatement studies typically include extinction procedures that are not common with human drug users (Fuchs et al., 2006). In addition to differences in route of administration, reinstatement and sensitization differ in the amount of drug to which animals are exposed as well as the rapidity with which drug enters the central nervous system. Although both models have shortcomings, as will be discussed below, there seems to be a remarkable overlap between the neurochemical circuitries of behavioral sensitization and reinstated drug-seeking behavior, suggesting that the behavioral sensitization model has construct validity relative to the reinstatement model. Therefore, one could argue that results generated from sensitization studies would, at the very least, be predictive of the impact of repeated contingent drug exposure on central nervous system function. In addition, the possibility remains that sensitization is one factor in reinstatement. In this regard, a recent report suggests that interoceptive stimuli of cocaine can acquire discriminative stimulus properties that would thereby facilitate reinstated drug seeking (Keiflin et al., 2008). When examining the discrepancies in the literature, it should be noted that sensitization of incentive motivation, not locomotion, is important to addiction (Robinson and Berridge, 2008). Thus, it is possible that although the motor circuit might reach a maximum level of sensitization, the motivation circuit continues to sensitize. In this case, long-access animals would exhibit similar levels of locomotor sensitization but greater levels of reinstatement of drug-seeking behavior.

III. Neurocircuitry

A. Neurons versus Circuits

When studying the role of various brain regions in behavioral sensitization or reinstatement, experiments rely on temporary or permanent lesions or injection of receptor agonists or antagonists. Results from these studies can be interpreted to indicate the involvement of neurons in these regions in the behaviors under examination. However, one must remember that the brain regions discussed below work in concert as a circuit to control behavioral responses to drugs. Thus, after the presentation of data that support or refute the involvement of specific brain regions in sensitization or reinstatement, a discussion of the interactions of the various brain regions, based on known anatomical connections, is provided.

B. Sensitization

When discussing the neural circuits that underlie sensitization, one must consider that the augmented motor-

stimulant response has two distinct phases: initiation and expression. Based on intracranial amphetamine injections, it was initially determined that the actions of drugs on the VTA were responsible for the initiation of sensitization, whereas actions within the nucleus accumbens were responsible for the expression of sensitization (Kalivas and Weber, 1988). Lesion studies have also implicated the medial prefrontal cortex (mPFC) in the development of behavioral sensitization. For example, ibotenate lesions of the mPFC, which encompasses both the prelimbic and infralimbic regions, disrupted the induction of sensitization to cocaine and amphetamine (Wolf et al., 1995; Cador et al., 1999; Li et al., 1999). Furthermore, discrete lesions of the prelimbic region of the mPFC with the excitotoxin quinolinic acid also blocked the induction of cocaine-induced sensitization (Tzschentke and Schmidt, 1998, 2000). However, these same authors reported that neither large nor discrete mPFC quinolinic acid lesions altered the induction of sensitization to amphetamine, suggesting that differences exist between cocaine- and amphetamine-induced sensitization (Tzschentke and Schmidt, 2000).

In addition to the mesocorticolimbic system (i.e., VTA, nucleus accumbens, and mPFC) the ventral pallidum, hippocampus, amygdala, laterodorsal tegmentum (LDT), and the paraventricular nucleus (PVN) of the thalamus have been suggested to play a role in the development of sensitization. Thus, lesion studies demonstrated that the LDT and PVN, but not the hippocampus, play a role in the development of sensitization (Wolf et al., 1995; Young and Deutch, 1998; Nelson et al., 2007). However, other experiments showed that inactivation of the dorsal but not the ventral hippocampus blocked the expression of amphetamine sensitization (Degoulet et al., 2008). In contrast to this finding, a recent study demonstrated that amphetamine sensitization depends on enhanced activity of ventral hippocampal neurons that increases activity of VTA dopamine neurons (Lodge and Grace, 2008). Ibotenate lesions of the amygdala have been reported to either block or have no effect on the development of amphetamine sensitization (Wolf et al., 1995; Cador et al., 1999). Finally, studies with μ -opioid agonists and antagonists suggest that ventral palladium is involved in both the initiation and expression of behavioral sensitization to morphine (Mickiewicz et al., 2009). As will be discussed further below, it is likely that each of these brain regions affects the development of sensitization by influencing the mesocorticolimbic dopamine system.

The common circuitry for behavioral sensitization includes dopamine projections from the VTA to the nucleus accumbens and glutamate projections from the mPFC to the nucleus accumbens (Pierce and Kalivas, 1997a). In addition to dopamine, GABAergic neurons project from the VTA to the nucleus accumbens and mPFC, whereas dopamine terminals located in the nucleus accumbens also release glutamate (Van Bockstaele

and Pickel, 1995; Tecuapetla et al., 2010). Furthermore, this circuit can be activated by projections from the mPFC to the VTA (Li et al., 1999), probably via the LDT (Omelchenko and Sesack, 2005, 2007). In addition to direct connections, the VTA probably indirectly influences the nucleus accumbens and mPFC via projections to the basolateral amygdala and PVN (Oades and Halliday, 1987; Kita and Kitai, 1990; Takada et al., 1990; Shinonaga et al., 1994; Moga et al., 1995). Finally, the hippocampus is likely to impact the mesolimbic dopamine system via inputs to the VTA (Lodge and Grace, 2008). Thus, as illustrated in Fig. 1A, the mPFC provides excitatory input, either directly or indirectly via the LDT, to the VTA, which provides dopaminergic influence to the nucleus accumbens, either directly or indirectly via the basolateral amygdala and PVN. This circuit can also be influenced by direct hippocampal

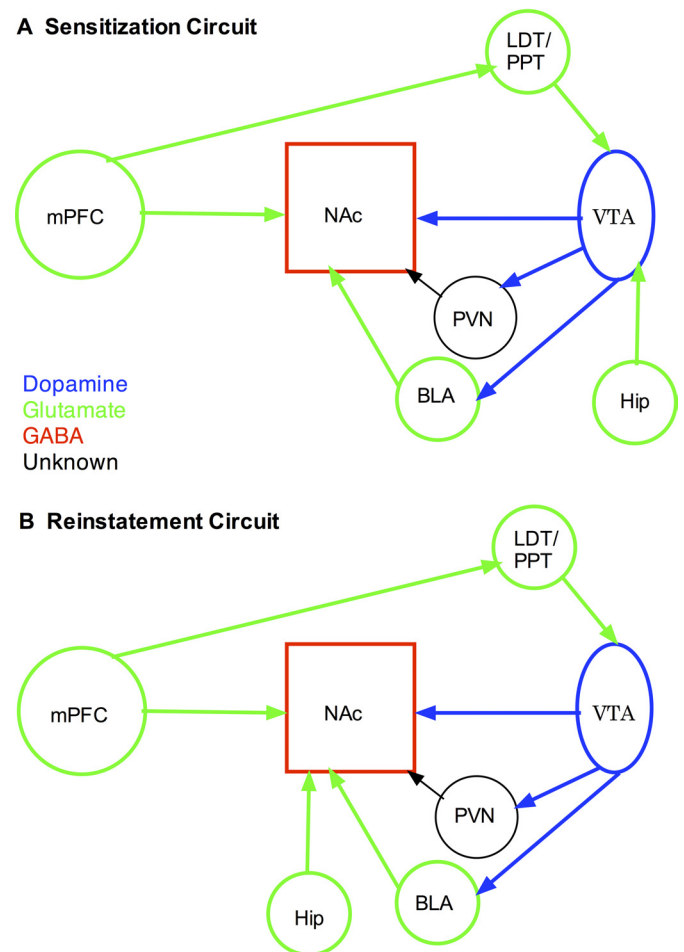


FIG 1. Comparison of the neurocircuitry involved in sensitization and reinstatement behaviors. The nucleus accumbens (NAc) serves as an output to motor circuits. A, in the case of sensitization, the nucleus accumbens is modulated by dopamine input from the VTA that either directly innervates this target or does so indirectly via the PVN and basolateral amygdala (BLA). The nucleus accumbens also receives direct glutamate inputs from the mPFC as well as indirect projections via the LDT/PPT and VTA. Finally, the VTA also receives glutamate input from the hippocampus (Hip). B, the circuitry underlying reinstatement is nearly identical to that of sensitization except that the Hip affects the circuit via the NAc rather than the VTA.

input to the VTA and mPFC input to the nucleus accumbens. The neurochemistry and neuropharmacology of this circuit will be discussed below.

C. Relapse/Reinstatement

Studies exploring the neurocircuitry of reinstatement of drug-seeking behavior have typically involved measurement of Fos synthesis in response to drug, cue, or stress priming or have used lesions or reversible inactivation of select targets to alter reinstatement. Cocaine priming increases Fos synthesis in the VTA, caudate nucleus, and central nucleus of the amygdala, whereas cue priming produces an increase in Fos in the nucleus accumbens, basolateral amygdala, and hippocampus, and both cocaine and cue priming increased Fos in the anterior cingulate cortex (Neisewander et al., 2000). Inactivation of the VTA, nucleus accumbens core, ventral pallidum, and dorsal mPFC all prevent cocaine-primed reinstatement (McFarland and Kalivas, 2001; Capriles et al., 2003). Furthermore, injection of cocaine into the dorsal mPFC or morphine into the VTA reinstates drug-seeking behavior (Stewart, 1984; Park et al., 2002). In addition to the structures discussed with drug-primed reinstatement (Capriles et al., 2003; McLaughlin and See, 2003; Fuchs et al., 2004; McFarland et al., 2004; Chaudhri et al., 2008), the basolateral amygdala is implicated in cue-induced reinstatement of cocaine- and heroin-seeking behavior (Meil and See, 1997; Kruzich and See, 2001; Fuchs and See, 2002; Kantak et al., 2002; McLaughlin and See, 2003), whereas the dorsal and ventral hippocampus have been implicated in context- and cue-dependent reinstatement, respectively (Sun and Rebec, 2003; Fuchs et al., 2005). Finally, the PVN has been implicated in context-dependent reinstatement of beer-seeking (Hamlin et al., 2009). Brain regions shown to be involved in stress-primed reinstatement include the nucleus accumbens shell, central amygdala, bed nucleus of the stria terminalis, and lateral tegmental nuclei in addition to those regions previously discussed for drug-primed reinstatement (Shaham et al., 2000a,b; McFarland et al., 2004). In addition to previously discussed regions, the LDT and pedunculopontine tegmentum (PPT) have been recently shown to be involved in drug-primed reinstatement, although their role in stress- and cue-induced reinstatement has yet to be explored (Schmidt et al., 2009). Thus, although a shared core circuit for reinstatement exists, stress, cues, and context affect this circuitry via additional inputs.

Previous studies suggest that the reinstatement circuit includes a motor subcircuit and limbic subcircuit (Kalivas and McFarland, 2003). The motor subcircuit is the projection from the dorsal mPFC to the core of the nucleus accumbens, which is proposed to be a final common pathway for reinstatement. As illustrated in Fig. 1B, the limbic subcircuit consists of the VTA, basolateral amygdala, the LDT/PPT, hippocampus, and the extended

amygdala, central nucleus of the amygdala, and the bed nucleus of the stria terminalis. As described earlier, reinstatement of drug seeking generally involves priming the animals with drug, cue, or stress, and specific neuroanatomical regions of the limbic subcircuit subserve each of these forms of reinstatement. Thus, the mPFC projects to the VTA directly or via the LDT/PPT and, in the case of stress, via the extended amygdala (Shaham et al., 2000b; Kalivas and McFarland, 2003; McFarland et al., 2004; Schmidt et al., 2009). The VTA projects back to the dorsal mPFC either directly, or in the case of cues, via the basolateral amygdala, (Kalivas and McFarland, 2003). Finally, the dorsal hippocampus and PVN provide contextual information to the limbic circuit by impinging on the basolateral amygdala and nucleus accumbens shell, respectively (Fuchs et al., 2007; Hamlin et al., 2009). It should be noted, however, that much of the literature on the neurocircuitry of reinstatement is based on studies with cocaine. A recent report exploring the neural circuits of heroin-seeking behavior largely confirmed the findings with cocaine but indicated an expanded circuitry for reinstatement of heroin self-administration (Rogers et al., 2008). As with sensitization, a discussion on the neurochemistry and neuropharmacology of reinstatement is provided in section IV.

D. Neural Circuitry Relationships between Sensitization and Relapse

It is apparent in Fig. 1 that there is significant overlap in the circuits involved in sensitization and reinstatement behaviors. The mesocorticolimbic dopamine system seems to be the primary circuit, the mPFC projecting to VTA via the LDT/PPT, which then projects to the nucleus accumbens. Projections from the mPFC directly to the nucleus accumbens are also common for reinstatement and sensitization. The PVN and basolateral amygdala can serve as an intermediary destination between the VTA and the nucleus accumbens. The involvement of the hippocampus seems to differ for the two models, with input to the shell of the nucleus accumbens being important for reinstatement and input to the VTA being important for sensitization. A couple of important points should be noted with regard to studies determining the circuits involved in drug-evoked behavior. First, most studies on behavioral sensitization involved lesions before initial drug exposure (i.e., during the initiation of drug-induced neuroplasticity), whereas studies on reinstatement involve interventions that occurred after a history of drug taking (i.e., during the expression of drug-induced neuroadaptations). Second, the studies on sensitization have not isolated subcircuits that might contribute to context-dependent sensitization or stress cross-sensitization between drugs of abuse. Nevertheless, there is remarkable overlap in the neural circuits believed to underlie behavioral sensitization and reinstatement of drug-seeking behavior. These data provide

additional construct validity for the sensitization model in that they seem to accurately predict the neural circuitry of substance abuse. Thus, it is possible that repeated exposure of the circuits described above to drug, be it contingent or noncontingent, produce adaptations that can promote relapse to drug seeking.

IV. Neurochemistry/Neuropharmacology

A. Sensitization

1. *Dopamine.* Early studies suggest that enhanced dopamine transmission in the mesoaccumbens system underpinned locomotor sensitization. Thus, reports demonstrated that cocaine-evoked dopamine release was either enhanced or unaltered in the VTA of sensitized animals (Kalivas and Duffy, 1993; Parsons and Justice, 1993). However, dopamine neuron excitability is enhanced in the VTA in animals with a history of repeated exposure to amphetamine, cocaine, or ethanol (White and Wang, 1984; Henry et al., 1989; Brodie, 2002). Animals behaviorally sensitized to cocaine, amphetamine, nicotine, or morphine (Robinson et al., 1988; Kalivas and Duffy, 1990; Johnson and Glick, 1993; Parsons and Justice, 1993; Shoaib et al., 1994), but not ethanol (Zapata et al., 2006), show enhanced dopamine release in the nucleus accumbens in response to challenge drug exposure. In addition to the mesoaccumbens circuit, more recent studies focused on the mesocortical dopamine system. Most studies have been conducted with cocaine and have shown that repeated cocaine administration produces time-dependent alterations in mPFC dopamine transmission, early withdrawal being associated with decreased cocaine-mediated dopamine transmission and prolonged withdrawal being associated with enhanced dopamine transmission (Sorg et al., 1997; Chefer et al., 2000; Wu et al., 2003; Williams and Steketee, 2005). Amphetamine-induced sensitization was found to be associated with no changes in mPFC dopamine transmission after short withdrawal, but testing at longer withdrawals was not conducted (Peleg-Raibstein and Feldon, 2008). In contrast to these findings, repeated nicotine administration enhances nicotine-evoked dopamine release in the mPFC 24 h after daily treatment (Nisell et al., 1996). Taken together, these data suggest that, in general, behavioral sensitization is associated with augmented dopamine transmission in the mesocorticolimbic dopamine system. However, it should be noted that studies in both human and nonhuman primates indicate that minimal or no sensitization of dopamine release is occurring in cocaine-dependent individuals or monkeys trained to self-administer cocaine (for review, see Bradberry, 2007). This may highlight a difference in dosing in that both humans and primate models tend to involve substantially more cocaine intake than the rodent experiments outlined above. In addition, whereas the primate and human studies involve contingent drug use, the rodent

studies are largely with noncontingent drug use, although a study examining a cocaine challenge in rats trained to self-administer cocaine found sensitized dopamine release in parallel with augmented locomotor behavior (Hooks et al., 1994). In contrast to these findings, human volunteers who received three noncontingent injections of amphetamine in a laboratory setting displayed enhanced dopamine release in the nucleus accumbens in response to an amphetamine challenge injection 2 weeks and 1 year later as measured by decreased [¹¹C]raclopride binding (Boileau et al., 2006). In addition, a recent report demonstrated that in nondependent human cocaine users, intranasal cocaine administration increased dopamine release in the ventral striatum (Cox et al., 2009). Unlike previous studies in humans and nonhuman primates, cocaine-evoked dopamine release was conducted in the presence of drug-associated cues (Cox et al., 2009). It is noteworthy that the degree of dopamine release was positively correlated with history of psychostimulant use, suggesting an enhanced dopamine response with repeated drug use (Cox et al., 2009).

2. *Dopamine Receptors.* In addition to changes in neurotransmitter release, dopamine binding to its receptors plays a key role in behavioral sensitization. For example, enhanced excitability of VTA dopamine neurons that occurs with repeated cocaine is associated with decreased dopamine D2 autoreceptor sensitivity (White and Wang, 1984; Henry et al., 1989). In addition, repeated intra-VTA injections of low doses of the D2 antagonist eticlopride, which are presumably autoreceptor-selective, enhanced subsequent stimulant responses to amphetamine (Tanabe et al., 2004). Blockade of dopamine D1 receptors in the VTA during the initiation phase prevents the development of amphetamine but not cocaine sensitization (Stewart and Vezina, 1989; Vezina, 1996; Steketee, 1998). Furthermore, repeated injections of 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine (SKF38393), a D1 receptor agonist, into the VTA induced sensitization to cocaine (Pierce et al., 1996b). Taken together, these data suggest that reduced autoreceptor inhibition of dopamine neurons in the VTA allows for enhanced dopamine stimulation of D1 receptors in this region that is capable of increasing glutamate release and thus further activation of dopamine projection neurons (Kalivas and Duffy, 1995; Wolf and Xue, 1998).

In the nucleus accumbens, repeated cocaine has been shown to increase dopamine D1 receptor sensitivity (Henry and White, 1991). In addition, injections of (\pm)-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SKF82958), a dopamine D1 receptor agonist, into the nucleus accumbens in combination with systemic cocaine, enhanced the development of cocaine sensitization (De Vries et al., 1998a). Previous studies have demonstrated that injections of (\pm)-6-chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine hy-

drobromide (SKF81297) or SKF38393 into the mPFC blocked the expression of cocaine or amphetamine sensitization (Sorg et al., 2001; Moro et al., 2007), whereas other studies have not found an effect (Beyer and Stekete, 2002). The ability of intra-mPFC quinpirole, a D2 agonist, to inhibit cocaine-induced motor activity was reduced in sensitized animals, whereas repeated injections of the D2 antagonist sulpiride into the mPFC induced sensitization to cocaine (Beyer and Stekete, 2002; Stekete and Walsh, 2005). Although the role of mPFC dopamine D1 receptors in sensitization remains to be clarified, the data above suggest that dopamine D2 receptor function in the mPFC is reduced, that is supported by other studies (Bowers et al., 2004).

3. *Glutamate.* Initial reports demonstrated that in amphetamine- or cocaine-sensitized animals, dopamine neurons in the VTA were more responsive to glutamate, which involved increased α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptor sensitivity (White et al., 1995b; Zhang et al., 1997). Microdialysis studies have revealed that short-term amphetamine administration produces a delayed increase in glutamate levels in the VTA that is not enhanced by repeated exposure, whereas cocaine increases glutamate levels only in the VTA of sensitized animals (Kalivas and Duffy, 1998; Wolf and Xue, 1998). Ibotenate lesions of the mPFC prevent amphetamine from increasing VTA glutamate levels (Wolf and Xue, 1999). In addition, repeated injections of the glutamate uptake inhibitor *L-trans*-pyrrolidine-2,4-dicarboxylic acid into the VTA induced behavioral sensitization to amphetamine, an effect blocked by the *N*-methyl-D-aspartate (NMDA) receptor antagonist 3-(2-carboxy-piperazin-4-yl)-propyl-1-phosphonic acid (Aked et al., 2005). Thus, repeated increases in glutamate levels in the VTA seem to be capable of inducing a sensitized behavioral response to amphetamine or cocaine. These results are consistent with findings that repeated injections of amphetamine or morphine into the VTA also induce sensitization (Vezina et al., 1987; Kalivas and Weber, 1988).

Recent electrophysiological studies have demonstrated that single or repeated noncontingent exposure to drugs of abuse, including cocaine, amphetamine, ethanol, morphine, and nicotine, induce an NMDA receptor-dependent APMA receptor-induced long-term potentiation (LTP) of VTA dopamine neurons (Ungless et al., 2001; Saal et al., 2003; Borgland et al., 2004). This LTP, which is dependent on activation of dopamine D1 receptors, is of short duration after noncontingent cocaine administration but lasts at least 3 months after contingent cocaine self-administration (Saal et al., 2003; Schilström et al., 2006; Chen et al., 2008). Additional studies have shown that cocaine-induced LTP in the VTA results from insertion of AMPA receptors lacking the GluR2 subunit, which imparts increased Ca^{2+} permeability to these receptors (Bellone and Lüscher, 2005; Mameli et al., 2007; Argilli et al., 2008). Stress, which is known to cross-sensitize with drugs of abuse (Kalivas and Stewart, 1991), also induces LTP in VTA dopa-

mine neurons (Saal et al., 2003). Corticotropin-releasing factor (CRF), which is released in the VTA in response to stress (Wang et al., 2005), potentiates NMDA receptor-mediated transmission, and this potentiation is enhanced in mice with a history of repeated cocaine exposure (Hahn et al., 2009). It is noteworthy that CRF potentiates AMPA receptor transmission in animals repeatedly exposed to cocaine but not cocaine-naïve animals (Hahn et al., 2009). It is postulated that the enhanced response of AMPA receptors to CRF produces enhanced dopamine transmission in the mesocorticolimbic dopamine system (Ungless et al., 2010). Finally, excitatory modulation of VTA dopamine neurons can be further enhanced by CRF-induced attenuation of inhibitory modulation produced by dopamine D2 and GABA-B receptors (Beckstead et al., 2009). Taken together, these data provide a physiological basis for enhanced mesocorticolimbic dopamine transmission associated with expression of behavioral sensitization to drugs of abuse and stress.

Unlike the VTA, repeated cocaine decreases, rather than increases, neuronal responsiveness to glutamate in the nucleus accumbens (White et al., 1995a). Behavioral sensitization to cocaine is associated with reduced basal levels of glutamate in the nucleus accumbens, whereas challenge injections of cocaine or amphetamine produce increased glutamate release in this region (Pierce et al., 1996a; Reid and Berger, 1996; Baker et al., 2002; Kim et al., 2005). It is noteworthy that one report demonstrated that cocaine-induced increases in nucleus accumbens glutamate release occurred only in animals that developed sensitization (Pierce et al., 1996a). In addition, restoration of basal glutamate levels with *N*-acetylcysteine prevented the expression of behavioral sensitization (Madayag et al., 2007). Thus the reduced basal levels of glutamate seen in sensitized animals seems to allow for enhanced glutamate release in response to drug challenge and thus the expression of sensitization (Xi et al., 2002). Additional studies demonstrated that animals withdrawn from repeated cocaine exhibit an increased AMPA/NMDA receptor ratio in the nucleus accumbens, which is indicative of LTP (Kourrich et al., 2007). It is noteworthy that upon challenge with cocaine to test for the expression of sensitization, animals exhibit a decrease in the AMPA/NMDA receptor ratio 24 h later, suggesting a long-term depression-like state of nucleus accumbens neurons (Thomas et al., 2001; Kourrich et al., 2007). Taken together, these data suggest the possibility that reduced basal levels of glutamate produce a compensatory LTP state that is reversed by the enhanced release of glutamate that occurs in response to cocaine (Thomas et al., 2008).

Like the VTA, neurons in the mPFC show an increased responsiveness to glutamate after repeated exposure to amphetamine (Peterson et al., 2000). Furthermore, K^{+} -stimulated glutamate efflux in the mPFC was enhanced in animals after repeated methamphetamine exposure (Stephans and Yamamoto, 1995). Repeated co-

caine was shown to produce time-dependent increases in cocaine-mediated mPFC glutamate overflow, short (but not long) withdrawals from repeated cocaine exposure being associated with cocaine-induced increases in extracellular glutamate concentrations in the mPFC (Williams and Steketee, 2004). It is noteworthy that, as was seen previously in the nucleus accumbens (Pierce et al., 1996a), cocaine only increased mPFC levels of glutamate in animals that expressed behavioral sensitization to cocaine (Williams and Steketee, 2004). These data contrast with those from an earlier study, in which a challenge injection of cocaine failed to effect mPFC glutamate levels in sensitized animals (Hotsenpiller and Wolf, 2002). Finally, physiological studies demonstrate that repeated cocaine exposures induce LTP in the mPFC that is dependent on dopamine D1 receptors and results from a reduction in GABA-A receptor-mediated inhibition of pyramidal neurons (Huang et al., 2007a). In general, the data are supportive of the idea that enhanced glutamate transmission in the mPFC is associated with behavioral sensitization.

4. Glutamate Receptors. As mentioned above, the enhanced glutamate-induced excitability of VTA dopamine neurons seen in behaviorally sensitized animals involves AMPA receptors (Zhang et al., 1997). In support of this, repeated injections of AMPA into the VTA induced cocaine sensitization (Dunn et al., 2005), whereas intra-VTA AMPA injections in sensitized animals increased dopamine and glutamate release in the nucleus accumbens and glutamate release in the VTA (Giorgetti et al., 2001). Studies on the effects of repeated drug exposure on the expression of AMPA receptor subunits in the VTA has been mixed with increased GluR1 levels or no change in GluRs (Fitzgerald et al., 1996; Churchill et al., 1999; Bardo et al., 2001; Lu et al., 2002). On the other hand, more recent studies have shown that repeated cocaine promotes increased insertion of GluR2-lacking AMPA receptors in VTA dopamine neurons, leading to the increased AMPA/NMDA receptor ratio associated with LTP (Bellone and Lüscher, 2005; Mameli et al., 2007; Argilli et al., 2008). With regard to NMDA receptors, coadministration of the competitive NMDA receptor antagonist 3-(2-carboxy-piperazin-4-yl)-propyl-1-phosphonic acid into the VTA with systemic cocaine or VTA amphetamine prevents the development of behavioral sensitization (Kalivas and Alesdatter, 1993; Cador et al., 1999). Systemic injection of NMDA antagonists selective for NMDA receptors containing NR2 subunits also prevents the development of cocaine sensitization as well as the cocaine-induced increase in AMPA/NMDA receptor ratios seen in the VTA (Schumann et al., 2009). Furthermore, sensitization to cocaine or morphine is associated with increased expression of NMDA NR1 subunits (Fitzgerald et al., 1996; Churchill et al., 1999). Finally, injection of a nonselective metabotropic glutamate receptor (mGluR) antagonist into the VTA prevents amphetamine sensitization, whereas re-

peated administration of a nonselective mGluR agonist induces sensitization to cocaine (Kim and Vezina, 1998; Dunn et al., 2005).

Injections of AMPA into the nucleus accumbens produced greater motor activity in cocaine-sensitized animals compared with controls, whereas injection of the AMPA antagonist 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo(f)quinoxaline-2,3-dione blocked the development of cocaine sensitization (Pierce et al., 1996a; Ghasemzadeh et al., 2003). Intra-accumbens administration of 2-[(1*S*,2*S*)-2-carboxycyclopropyl]-3-(9*H*-xanthen-9-yl)-D-alanine (LY341495), a group II mGluR antagonist, induces hyperactivity in amphetamine-sensitized rats but not in control rats (Chi et al., 2006). Repeated exposure to cocaine, followed by withdrawal, increases the levels of GluR1 and AMPA receptor surface expression in the nucleus accumbens after prolonged withdrawal, whereas repeated amphetamine has no effect on AMPA receptor surface expression (Churchill et al., 1999; Boudreau and Wolf, 2005; Boudreau et al., 2007; Boudreau et al., 2009; Ghasemzadeh et al., 2009b; Nelson et al., 2009; Schumann and Yaka, 2009). On the other hand, NMDA receptor subunits have been reported to be increased or decreased in sensitized animals, and surface expression is unaltered (Yamaguchi et al., 2002; Nelson et al., 2009; Schumann and Yaka, 2009). It is noteworthy that the long-term depression induced by a challenge injection of cocaine in sensitized animals that was discussed in section IV.A.3 is paralleled by a decrease in the surface expression of AMPA receptors in the nucleus accumbens (Thomas et al., 2001; Boudreau et al., 2007; Kourrich et al., 2007), which reverses back to the cocaine-induced enhanced surface expression after withdrawal (Ferrario et al., 2010). Taken together, these data suggest that behavioral sensitization is associated with enhanced glutamate transmission via AMPA receptors in the nucleus accumbens that might be reduced by group II mGluRs. In support of the latter point, repeated cocaine administration has been reported to decrease group II mGluR function and expression in the nucleus accumbens, which allows for increased glutamate release in this region (Xi et al., 2002; Ghasemzadeh et al., 2009b). In addition, systemic administration of (1*R*,4*R*,5*S*,6*R*)-4-amino-2-oxabicyclo[3.1.0]hexane-4,6-dicarboxylic acid (LY379268), a group II mGluR agonist, prevents the enhanced nucleus accumbens glutamate overflow seen in response to an amphetamine challenge in amphetamine-sensitized animals as well as the enhanced cocaine self-administration seen in these animals (Kim et al., 2005).

Studies of the involvement of mPFC glutamate receptors have revealed that the ability of the group II mGluR agonist (2*R*,4*R*)-4-aminopyrrolidine-2,4-dicarboxylate to block the expression of behavioral sensitization when injected into this region is reduced after prolonged withdrawal from cocaine (Xie and Steketee, 2009a). Furthermore, infusions of LY341495, a group II mGluR an-

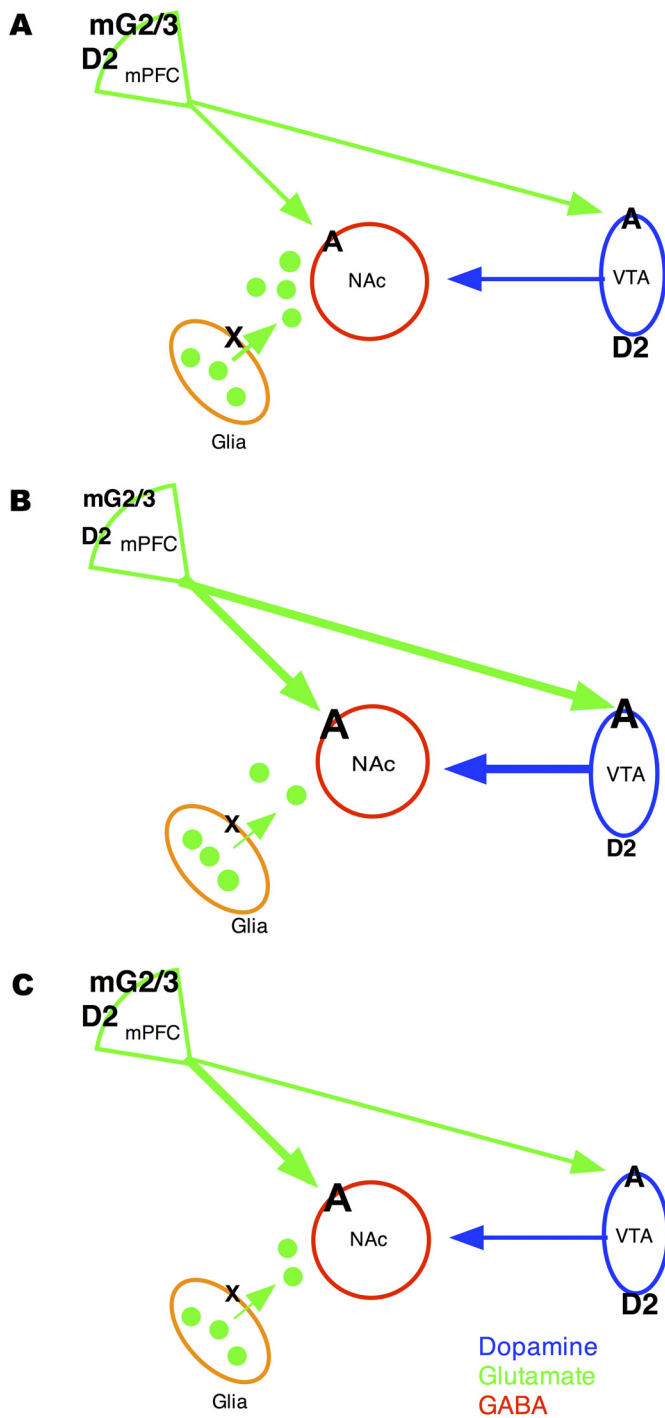


FIG 2. A, the neurochemistry and neuropharmacology of the sensitization and reinstatement circuits compared with normal circuits. B, sensitization is associated with enhanced dopamine transmission from the VTA to the nucleus accumbens that results from reduced D2 autoreceptor function and enhanced AMPA (A) receptor function. Enhanced glutamate transmission from the mPFC to the nucleus accumbens and VTA is also seen in sensitized animals and is thought to result in part from reduced inhibitory modulation produced by D2 receptors and group II mGluRs (mG2/3). In addition, reduced function of the cystine/glutamate antiporter (X) produces lower basal levels of glutamate in the nucleus accumbens that leads to increased AMPA receptor function in this region. Finally, reduced basal levels of glutamate would produce reduced activation of inhibitory group II mGluRs in the nucleus accumbens that would allow for increased evoked release of glutamate in this region (not illustrated). Like sensitization (C), reinstatement is also associated with reduced basal glutamate levels in the nucleus accumbens and enhanced AMPA

agonist, enhanced mesocorticolimbic glutamate transmission in control but not cocaine-sensitized rats, suggesting that repeated cocaine administration reduces tonic inhibition of glutamate transmission (Xie and Stekete, 2009b). In support of this, repeated cocaine administration uncouples group II mGluRs from their G proteins in the mPFC (Xi et al., 2002; Bowers et al., 2004). In addition, repeated cocaine reduced group II mGluR-mediated long-term depression in the mPFC (Huang et al., 2007b). Taken together, these data suggest that long-term cocaine sensitization is associated with a reduction in mPFC group II mGluR function. Finally, long-term withdrawal from repeated cocaine is associated with increased phosphorylation of GluR1 subunits and increased synaptic localization of AMPA and NMDA receptors (Zhang et al., 2007; Ghasemzadeh et al., 2009a). Together, these changes in metabotropic and ionotropic receptors would be expected to increase the excitability of mPFC projection neurons.

The involvement of glutamate in other brain regions that form the sensitization circuit has received limited attention. Morphine sensitization is associated with decreased GluR2 expression in both the amygdala and the dorsal hippocampus with no changes in GluR1 levels in the hippocampus (Grignaschi et al., 2004; Seppehrizadeh et al., 2008). This could lead to enhanced levels of calcium-permeable AMPA receptors thought to underlie synaptic plasticity. Injection of AMPA into the LDT increases glutamate in the VTA, which is enhanced in amphetamine-sensitized animals (Nelson et al., 2007). Thus, glutamate, at various levels of the neural circuitry described in section III, seems to be involved in the development of sensitization.

5. *Summary.* As shown in Fig. 2B and summarized in Table 1, repeated exposure to drugs of abuse produces transient increases in somatodendritic dopamine release in the VTA (Kalivas and Duffy, 1993) as a result of decreased autoreceptor sensitivity (White and Wang, 1984; Henry et al., 1989), which can act on D1 receptors to enhance glutamate release from mPFC projecting neurons and to induce LTP in dopamine neurons (Kalivas and Duffy, 1995; Ungless et al., 2001; Saal et al., 2003). The increase in released glutamate can then act on AMPA receptors to promote dopamine release in the nucleus accumbens (Karreman et al., 1996; Ungless et al., 2010). Long-term, enhanced nucleus accumbens dopamine release occurs as a result of synaptic plasticity at the level of the nucleus accumbens, in particular via an increase in calcium/calmodulin-dependent protein kinase II activity (Pierce and Kalivas, 1997b). Enhanced dopamine release in the nucleus accumbens can act on D1 receptors to promote behavioral sensitization (Giorgetti et al., 2001). The mPFC projections to the VTA are

receptor function in this region along with enhanced drug-evoked glutamate release. Whether other drug-induced changes seen in sensitization are also apparent during reinstatement is not known.

TABLE 1

Summary of drug-induced changes associated with behavioral sensitization and reinstatement

See text for relevant citations.

Brain Region	Sensitization	Reinstatement
VTA		
Dopamine release	Increased	Unknown
Autoreceptor function	Decreased	Unknown
Glutamate release	Increased	Unknown
AMPA function	Increased	Increased
LTP	Transient	Prolonged
Nucleus accumbens		
Dopamine release	Increased	Increased or decreased
Basal glutamate	Decreased	Decreased
Glutamate release	Increased	Increased
AMPA function	Increased	Increased
mGluR2/3 function	Decreased	Decreased
mPFC		
Dopamine release	Increased (Delayed)	Unknown
D2 function	Decreased	Unknown
Glutamate release	Increased (Transient)	Unknown
Group II mGluR function	Decreased	Unknown

either direct or indirect via glutamate inputs from the LDT (Omelchenko and Sesack, 2005, 2007; Nelson et al., 2007). Furthermore, within the mPFC, D2 and group II mGluR receptor function is reduced (Beyer and Stekete, 2002; Bowers et al., 2004), allowing for increased excitability of projection neurons. In the nucleus accumbens, basal glutamate levels are reduced, thereby attenuating autoreceptor regulation of release that promotes enhanced drug-induced glutamate release from mPFC neurons in sensitized animals (Pierce et al., 1998; Baker et al., 2002; Xi et al., 2002). The reduced basal glutamate levels are believed to enhance AMPA receptor function (Boudreau and Wolf, 2005; Boudreau et al., 2007; Kourrich et al., 2007). Increased glutamate release in the nucleus accumbens can act on these enhanced AMPA receptors to also promote behavioral sensitization (Pierce et al., 1996a; Ghasemzadeh et al., 2003). Finally, studies indicating the possibility that repeated cocaine produces an increase in calcium-permeable AMPA receptors in the hippocampus and amygdala suggest that neurotransmission within the mesocorticolimbic circuit can be further enhanced by glutamate input to the VTA and nucleus accumbens from the hippocampus and amygdala, respectively (Shinonaga et al., 1994; Lodge and Grace, 2008; Sepehrizadeh et al., 2008).

B. Reinstatement

1. Dopamine. Studies on the role of dopamine in reinstatement of drug-seeking behavior have focused primarily on the nucleus accumbens and have produced mixed results. Thus, cocaine- or amphetamine-primed reinstatement is associated with reduced (Neisewander et al., 1996) or enhanced (Ranaldi et al., 1999; Di Ciano et al., 2001) dopamine release in the nucleus accumbens. Intra-accumbens injections of amphetamine, which would increase dopamine release, have been reported to reinstate ethanol-seeking behavior (Samson et al., 1999). Cue-induced reinstatement of amphetamine- or ethanol-

seeking behavior is associated with either no change or reduced dopamine release, respectively (Katner and Weiss, 1999; Di Ciano et al., 2001). Both D1 and D2 receptors in the nucleus accumbens seem to play a role in reinstatement behavior, although the results are not always consistent. Injection of (*R*)-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SCH23390) into the nucleus accumbens reduces cocaine-primed reinstatement of cocaine seeking or context-primed reinstatement of ethanol seeking (Anderson et al., 2003; Bachtell et al., 2005; Chaudhri et al., 2009; Madayag et al., 2010). In contrast, intra-accumbens SKF81297 reinstates cocaine-seeking behavior (Bachtell et al., 2005; Schmidt et al., 2006). Similar findings have been reported for D2 receptors. Thus, intra-accumbens quinpirole or 7-hydroxy-2-dipropylaminotetralin reinstates cocaine-seeking behavior, whereas eticlopride or sulpiride prevents cocaine-primed reinstatement (Bachtell et al., 2005; Anderson et al., 2006; Schmidt et al., 2006). Although the data seem to consistently show a general role for nucleus accumbens dopamine receptors in reinstatement, discrepancies rise as to the specific involvement of the shell (Anderson et al., 2003, 2006; Schmidt et al., 2006) versus the core (McFarland and Kalivas, 2001; Bachtell et al., 2005; Madayag et al., 2010). Thus, although D1 antagonist microinjection into the shell inhibits reinstated cocaine seeking, similar treatment into the core is ineffective.

In addition to the nucleus accumbens, some reports have also implicated other dopamine systems in reinstatement behavior. Injections of the nonselective dopamine antagonist fluphenazine into the dorsal mPFC prevented cocaine- or stress-primed reinstatement, whereas injections of dopamine reinstated cocaine seeking (McFarland and Kalivas, 2001; McFarland et al., 2004). SCH23390 in the dorsal mPFC blocks cocaine- or heroin-primed reinstatement of drug seeking and cocaine- and stress-primed reinstatement of CPP (Sanchez et al., 2003; Sun and Rebec, 2005; See, 2009). Intra-mPFC microinjection of the D1 agonist SKF81297 induced reinstatement to cocaine seeking (Schmidt et al., 2009). As well, intra-mPFC microinjection of the D2 antagonist eticlopride reduced cocaine-primed reinstatement (Sun and Rebec, 2005). Reinstatement of cocaine-seeking behavior is associated with enhanced cocaine-mediated dopamine release in the amygdala (Tran-Nguyen et al., 1998). Injection of amphetamine into the basolateral amygdala enhanced cue-induced reinstatement, whereas SCH23390 delivered to this same region prevented cue- and cocaine-induced reinstatement of cocaine seeking (See et al., 2001; Ledford et al., 2003; Alleweireldt et al., 2006). Taken together, the data suggest that dopamine stimulation of D1 receptors (in the mPFC, nucleus accumbens shell, and amygdala) and D2 receptors (in the nucleus accumbens) can modulate reinstatement of drug seeking behavior.

2. Glutamate. As with dopamine, the majority of studies conducted on the involvement of glutamate in

the reinstatement of drug seeking focused on the nucleus accumbens. Repeated exposure to cocaine reduces basal glutamate levels in the nucleus accumbens core, which, when returned to normal levels by pretreatment with *N*-acetylcysteine, prevents reinstatement of cocaine seeking (Baker et al., 2003). Injection of (*S*)-4-carboxyphenylglycine, which inhibits the cystine/glutamate antiporter, into the nucleus accumbens core blocks the actions of *N*-acetylcysteine (Kau et al., 2008). Cocaine-primed reinstatement is associated with increased glutamate release in the core of the nucleus accumbens that can be prevented by inactivation of the dorsal mPFC (McFarland et al., 2003). Similar findings have been reported for both heroin and cue-induced reinstatement of heroin seeking behavior (LaLumiere and Kalivas, 2008). Injections of AMPA into the core or shell of the nucleus accumbens can reinstate cocaine seeking, an effect that can be blocked by injection of antisense for the GluR1 subunit into these same regions (Cornish et al., 1999; Ping et al., 2008). Cocaine self-administration produces an increase in surface expression of GluR2-lacking AMPA receptors in nucleus accumbens neurons, which are likely to produce an LTP state, as demonstrated by physiological studies (Conrad et al., 2008; Mameli et al., 2009; Moussawi et al., 2009). 6-Cyano-7-nitroquinoxaline-2,3-dione (CNQX) in the core or shell prevents cocaine-, heroin, or cue-induced reinstatement (Cornish and Kalivas, 2000; Park et al., 2002; Bäckström and Hyytiä, 2007; Famous et al., 2008; LaLumiere and Kalivas, 2008). Disruption of trafficking of GluR2 subunits to the membrane in the core or shell also prevents cocaine-primed reinstatement (Famous et al., 2008). It is noteworthy that, like sensitization, conditioned cues reduce AMPA receptor surface expression 24 h after exposure to these cues (Conrad et al., 2008). In contrast to the consistent findings regarding nucleus accumbens AMPA receptors and reinstatement, injection of the NMDA agonist 1-aminocyclobutane-*cis*-1,3-dicarboxylic acid into the core reinstates cocaine seeking, whereas injection of 2-amino-5-phosphonovaleric acid, an NMDA antagonist, into the core or shell either blocks, has no effect on, or reinstates cocaine seeking (Cornish et al., 1999; Cornish and Kalivas, 2000; Bäckström and Hyytiä, 2007; Famous et al., 2007). Finally, injections of the group II mGluR agonist LY379268 into the nucleus accumbens blocks 1) context-induced heroin seeking and 2) cocaine-primed drug seeking (Bossert et al., 2006; Peters and Kalivas, 2006). Together, these data suggest that cocaine self-administration reduces basal glutamate levels in the nucleus accumbens that in turn reduce group II mGluR modulation of glutamate release (Moran et al., 2005), thus allowing for increased release of glutamate and subsequent stimulation of AMPA receptors that promotes reinstatement. The reduced basal levels of glutamate are offset by increased responsivity of AMPA receptors that can be reversed during reinstatement (Conrad et al., 2008; Mameli et al.,

2009; Moussawi et al., 2009). These effects can be prevented by normalizing basal glutamate, stimulating group II mGluRs, or blocking AMPA receptors (Cornish and Kalivas, 2000; Park et al., 2002; Bossert et al., 2006; Peters and Kalivas, 2006; Bäckström and Hyytiä, 2007; Famous et al., 2008; Kau et al., 2008; LaLumiere and Kalivas, 2008).

In addition to the nucleus accumbens, studies have shown that blocking ionotropic receptors with kynurenic acid or CNQX in the VTA blocks cocaine-induced reinstatement, whereas injections of LY379268 prevented context-induced heroin seeking (Bossert et al., 2004; Sun et al., 2005; Schmidt et al., 2009). CNQX in the LDT/PPT also has been reported to inhibit cocaine-seeking behavior (Schmidt et al., 2009). The mGluR1 agonist (3,4-dihydro-2*H*-pyrano[2,3-*b*]quinolin-7-yl)-(cis-4-methoxycyclohexyl)-methanone (JNJ16259685) in the dorsal hippocampus blocks context-dependent cocaine reinstatement (Xie et al., 2010). In contrast, neither CNQX nor 2-amino-5-phosphonovaleric acid in the basolateral amygdala disrupts cue-induced cocaine seeking (See et al., 2001). Thus, inhibition of glutamate transmission in the VTA or dorsal hippocampus, but not the basolateral amygdala, can affect reinstated drug seeking. Finally, infralimbic AMPA administration suppresses cocaine seeking by activating an infralimbic-cortex-to-nucleus accumbens shell circuit during extinction (Peters et al., 2008). This suggests that activation of this circuit plays a role in learning to inhibit drug seeking behavior when drug is no longer available.

3. Summary As seen in Fig. 2C and summarized in Table 1, reinstatement primarily involves enhanced glutamate transmission from the dorsal mPFC to the core of the nucleus accumbens that results from reduced basal levels of glutamate in the nucleus accumbens that allows for reduced autoreceptor control of glutamate release and thereby increased drug-induced glutamate release that activate AMPA receptors (Cornish et al., 1999; Cornish and Kalivas, 2000; Baker et al., 2003; McFarland et al., 2003; Moran et al., 2005; Bäckström and Hyytiä, 2007; Famous et al., 2008; LaLumiere and Kalivas, 2008). These AMPA receptors have been shown to have increased function that is reduced by exposure to previously drug-paired cues (Conrad et al., 2008). The mPFC also affects reinstatement via glutamatergic projections to the LDT/PPT and VTA acting on AMPA receptors in both sites (Schmidt et al., 2009). Dopamine projections from the VTA to the nucleus accumbens, mPFC, and basolateral amygdala also seem to be involved in reinstatement. Specifically, dopamine acting on D1 receptors would be capable of stimulating glutamate projection neurons in the amygdala and mPFC (See et al., 2001; Sun and Rebec, 2005; Alleweireldt et al., 2006; Schmidt et al., 2009; See, 2009), whereas dopamine acting on both D1 and D2 receptors in the nucleus accumbens shell (Anderson et al., 2003; Bachtell et al., 2005; Anderson et al., 2006; Schmidt et al., 2006)

could act in concert with AMPA receptors to reduce GABAergic transmission to the ventral pallidum, which has been shown to be important in reinstatement (O'Connor, 2001; Torregrossa et al., 2008).

C. Neurochemical/Neuropharmacological Relationships between Sensitization and Relapse

Many similarities are noted in a comparison of the neurochemistry and neuropharmacology of behavioral sensitization and relapse. In both cases, basal glutamate levels in the nucleus accumbens are reduced (Baker et al., 2002, 2003) but re-exposure to drug increases glutamate in this region (Pierce et al., 1996a; Moran et al., 2005), which can then act on AMPA receptors to promote the behavioral response (Pierce et al., 1996a; Cornish et al., 1999). Both contingent and noncontingent drug administration induce LTP in nucleus accumbens neurons that involves insertion of GluR2-lacking AMPA receptors into the membrane, which can be temporarily reversed by re-exposure to drug or drug-paired cues (Thomas et al., 2001; Boudreau and Wolf, 2005; Boudreau et al., 2007; Kourrich et al., 2007; Conrad et al., 2008; Mameli et al., 2009; Moussawi et al., 2009; Ferrario et al., 2010). Loss or reduction of glutamate input from the mPFC to the nucleus accumbens prevents the expression of sensitization and reinstatement (Pierce et al., 1998; McFarland et al., 2003). In addition, mPFC glutamate projections to the VTA via the LDT/PPT that act on AMPA receptors have also been shown to be important for both behavioral responses (Nelson et al., 2007; Schmidt et al., 2009). Although the role of glutamate systems in reinstatement and sensitization seem to mirror each other, the role of dopamine systems does not. For example, sensitization, but not reinstatement, is associated with transient reductions in autoreceptor sensitivity in the VTA that allows, in part, for increased excitability of dopamine neurons (White and Wang, 1984; Henry et al., 1989). However, these VTA dopamine responses to repeated cocaine exposure are typically thought to underlie the initiation rather than the expression of sensitization. In addition, although injections of a D1 agonist into the mPFC reinstated cocaine-seeking behavior, it did not lead to the expression of sensitization (Beyer and Steketee, 2002; Schmidt et al., 2009). Taken together, the data suggest that glutamate circuits are the key player in uniting sensitization with relapse. Furthermore, these data point to the need to use the reinstatement model to verify the importance of findings from the behavioral sensitization model in relapse to drug seeking.

V. The Role of Sensitization in Relapse to Drug-Seeking Behavior

The neurocircuitry that underlies behavioral sensitization and relapse to drug seeking behavior are similar, as are the neurochemical and neuropharmacological

mechanisms. However, studies have been less convincing that behavioral sensitization plays a role in reinstatement. Thus, drugs that can reinstate drug seeking in animals extinguished from cocaine self-administration have been shown also to produce a sensitized behavioral response in these same animals, whereas drugs that do not induce reinstatement do not produce sensitization (De Vries et al., 1998b, 2002). Other studies have compared the impact on reinstatement of short-access versus long-access drug self-administration with mixed results (Ferrario et al., 2005; Ahmed and Cador, 2006; Knackstedt and Kalivas, 2007; Lenoir and Ahmed, 2007). Hence, long-access animals escalate their intake of cocaine and exhibit a more robust reinstatement response compared with short-access animals, but differences in behavioral sensitization are not always apparent. It is possible that the lack of difference in behavioral sensitization could result from a ceiling effect. Thus, use of a training regimen that minimizes the amount of drug exposure before testing for sensitization or reinstatement would presumably allow one to determine whether sensitization plays a role in reinstatement. In this regard, a previous study demonstrated that previous experimenter-administered amphetamine that produced behavioral sensitization enhanced not only the reinforcing effects of cocaine but also reinstatement induced by intra-accumbens administration of AMPA (Suto et al., 2004). In this same study, it was shown that with extended withdrawal from cocaine self-administration differences between amphetamine-presensitized animals and controls were no longer apparent. Taken together, these data suggest that presensitized individuals [such presensitization might occur as a result of genetics or exposure to environmental stressors (Altman et al., 1996) or with a limited history of drug use] would be more vulnerable to relapsing to drug seeking. Thus, sensitization is likely to play a role in reinstatement in the early stages of substance abuse. With more prolonged drug exposure, regardless of whether the short- or long-access paradigm is used, other factors, such as the interoceptive stimuli of cocaine becoming discriminative stimuli, could facilitate reinstatement behavior above and beyond that produced by sensitization (Keiflin et al., 2008).

VI. Therapeutic Implications

The present review discusses research efforts that have revealed a neurocircuitry that seems to underlie behavioral sensitization and reinstatement of drug-seeking behavior, at least in rodent models. Moreover, recently reviewed imaging data in human studies, although limited, is largely in agreement with the animal research (Koob and Volkow, 2010). Thus, methylphenidate-induced craving that occurs in cocaine abusers in the presence of cues, activates prefrontal cortical regions, including the orbital and medial prefrontal corti-

ces (Volkow et al., 2005). In addition, imaging research has demonstrated that cues activate both the hippocampus and amygdala in experienced drug users (Grant et al., 1996; Childress et al., 1999; Kilts et al., 2001; Volkow et al., 2004). Given the importance of alterations of glutamate systems in sensitization and reinstatement behaviors (see above), further exploration of neurocircuitry underlying relapse in human drug abusers awaits development of appropriate ligands for the glutamate systems (Koob and Volkow, 2010).

Although behavioral studies have not firmly established a role for sensitization in the relapse to drug-seeking behavior, experiments have demonstrated a remarkable overlap in the neurocircuitry. Thus, by providing more efficient experimental throughput, sensitization could serve as a useful model to determine the mechanisms by which repeated drug exposure alters brain function to enhance behavioral responses to drugs of abuse. Positive results for these studies would then be confirmed in more time-consuming and technically challenging reinstatement studies. As an example, sensitization studies revealed a deficit in basal glutamate levels in the nucleus accumbens that was confirmed in animals with a history of cocaine self-administration. This led to experiments demonstrating that restoring basal glutamate levels in the nucleus accumbens could reduce relapse to drug-seeking behavior in animal models and humans (Baker et al., 2003; Mardikian et al., 2007; Zhou and Kalivas, 2008; Knackstedt et al., 2009, 2010; Sari et al., 2009). This type of progression from studies with behavioral sensitization to validation using models of reinstated drug-seeking and to clinical trials is especially useful to consider for potential pharmacotherapeutic targets identified from genomic and proteomic screens, which do not provide a priori evidence for the involvement of a drug-induced change in addiction.

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