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Review Article

A Brief Review of Dopaminergic Mechanisms of Reconsolidation of Cocaine-Seeking Behaviors

Qingyao Kong and Ming Xu

Department of Anesthesia and Critical Care, The University of Chicago, Chicago, IL 60637, USA
Address correspondence to Ming Xu, mxu@dacc.uchicago.edu

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Abstract Reconsolidation is a process in which memory undergoes a transiently labile stage after its retrieval and needs to be consolidated again in order to be maintained. Disruption of reconsolidation of drug memories dampens previous memories and therefore may provide a useful way to treat drug abuse. Based on the importance of the dopamine D1 and D3 receptors in mediating the acquisition of cocaine-induced behaviors, we studied the effects of manipulating these two receptors on reconsolidation of cocaine memories in mouse models of cocaine conditioned place preference and intravenous self-administration. Pharmacological blockade of D1 or D3 receptors attenuated reconsolidation of cocaine memories, and such attenuation lasted for at least one week. A genetic mutation of D3 receptors attenuated reconsolidation that lasted for at least one week after the memory retrieval. In contrast, with no memory retrieval, pharmacological antagonism of D1 or D3 receptors or the D3 receptor gene mutation did not significantly affect cocaine memories. Here we review our studies on D1 or D3 receptors in reconsolidation of cocaine reward memory and discuss the implications of such studies.

Keywords reconsolidation; cocaine memory; dopamine D1 and D3 receptors; antagonists; gene mutation; intravenous self-administration, conditioned place preference

1. Introduction

Drug addiction is a brain disorder characterized by compulsive seeking and taking of drugs, and by drug craving and relapse after long periods of abstinence [1,2]. Memories of drug effects or learned associations between the rewarding properties of drugs and cues are thought to precipitate craving and relapse [3]. Reconsolidation is a process that renders memory transiently labile after retrieval and needs to be consolidated again in order to be maintained [4,5,6,7]. Pharmacological or molecular manipulations of reconsolidation of acquired drug memory have been shown to dampen or even erase previous memories [3,8,9,10] and disrupt drug-seeking and relapsing behavior as measured by cocaine-induced conditioned place preference (CPP), morphine-induced CPP, intravenous cocaine self-administration (IVSA), and reinstatement [8,9,11,12,13,14,15]. These studies suggest that understanding the molecular basis of reconsolidation of reward memory may help to develop new medications for the treatment of drug addiction [16,17,18].

The mesolimbic dopaminergic system is involved in mediating the effects of drugs of abuse [17,19,20,21,22,23,24,25,26,27]. The D1-like family includes D1 and D5 receptors that interact with Gs proteins. The D2-like family includes D2, D3, and D4 receptors that interact with Gi or G0 proteins [28]. Both D1 and D3 receptors are expressed in mesolimbic dopamine (DA) projection areas. It is generally thought that drugs of abuse produce their initial reinforcing effects by triggering DA release in the nucleus accumbens (NAc) that activate D1 class receptors and inhibit the D2 class receptors as well as related neuronal circuits. Repeated drug administration triggers neuroplastic changes in glutamatergic inputs to the striatum and midbrain DA neurons, enhancing the brain's reactivity to drug cues, weakening self-regulation, and increasing the sensitivity to stressful stimuli, and DA modulates these long-term changes. Indeed, we and others have shown that D1 [29,30,31,32,33,34,35,36,37] and D3 receptors [34,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52] mediate locomotor-stimulant and positive reinforcing effects of cocaine, as well as cue-induced reinstatement of cocaine seeking. However, the roles of D1 and D3 receptors in reconsolidation of cocaine-related memory have not been elucidated. We recently performed such studies. We show that pharmacological blockade of D1 receptors attenuated reconsolidation after retrieval in cocaine memories in mouse models of IVSA, and that mutation of the D3 receptor gene or pharmacological blockade of D3 receptors weakened or attenuated reconsolidation of cocaine-induced CPP and IVSA. Our results suggest that D1 and D3 receptors and their related signaling mechanisms play key roles in reconsolidation of cocaine memories in mice.

2. Reconsolidation procedures

We used established procedures to train mice to acquire CPP or IVSA [53,54]. For the CPP paradigm, once D3 receptor mutant mice and wild-type (WT) littermates showed

cocaine-induced CPP, all mice were placed in the cocaine-conditioned compartment for 3 min (retrieval). Afterwards, all mice were returned to their home cages. Later, after 24 h and 48 h, the mice were allowed to freely explore the three compartments for 20 min without injections, and the time spent in each compartment was recorded. For saline-conditioning groups, only saline was used for the place conditioning and the experimental timeline was the same. For the no retrieval control groups, D3 receptor mutant mice and WT littermates were subjected to the same preconditioning and cocaine conditioning, but there was neither post-testing nor a three-minute retrieval. On the testing days, mice were allowed to freely explore the three compartments for 20 min without injections, and the time spent in each compartment was recorded. An additional group of D3 receptor mutant mice or WT littermates was subjected to saline-conditioning following the same experimental timeline as a control. For pharmacological studies, once WT mice showed cocaine-induced CPP, mice were placed in cocaine-conditioned compartment for 3 min immediately followed by an IP injection of PG01037 (0–30 mg/kg). All mice returned to their home cages afterwards. Mice were allowed to freely explore the three compartments for 20 min without injections 24 h, 48 h, and one week later, and the time spent in each compartment was recorded. We also included control groups without the three-minute retrieval.

For the IVSA paradigm, once the extinction criterion was met, mice were subjected to reconsolidation testing or no-retrieval control testing. For groups with the memory retrieval, mice were connected to IVSA manipulates for 10 min. Based on our preliminary data and previous reports, a 10-minute interval was selected for the retrieval. During this period, mice were exposed to cocaine-associated cues, but with no infusion of cocaine, after active nose-pokes. If there was no active nose-poke response made in the first 6 min, non-contingent cocaine-associated cues were presented three times with one-minute intervals. Injections of SCH23390, PG01037 or their vehicles were IP administered immediately after the 10-minute retrieval. All mice were returned to their home cages afterwards. Then, 24 h, 48 h, and one week after the 10-minute retrieval, mice were tested for reconsolidation of cocaine IVSA under FR2 schedule for 3 h, during which there were cocaine-associated cues but no cocaine infusions after active nose-poke responses were presented. For control groups with no memory retrieval, mice were taken to the behavioral testing room and they were not connected to IVSA manipulates. Mice were given an IP injection of SCH23390, or its vehicles, and they were returned to their home cages in the housing room. Then, 24 h, 48 h, and one week after the treatment of drugs or vehicles, mice were tested for cocaine IVSA under FR2 schedule for 3 h, during which there were cocaine-associated cues but no cocaine infusions after active nose-poke responses were presented.

For effects of the D3 receptor gene mutation on reconsolidation of cocaine IVSA, D3 receptor mutant mice and WT littermates were connected to IVSA manipulates for 10 min, but were without any drug or vehicle treatment after the 10-minute retrieval. Mice were returned to their home cages afterwards. No-retrieval groups of D3 receptor mutant mice and WT littermates were taken to the behavioral room and they were not connected to IVSA manipulates. Mice were not given drug or vehicle treatment and they were returned to their home cages. Then 24 h, 48 h, and one week afterwards, mice were subjected to testing for reconsolidation of cocaine IVSA under FR2 schedule for 3 h, during which there were cocaine-associated cues but no cocaine infusions after active nose-poke responses were presented.

3. Results

3.1. Pharmacological blockade of D1 receptors attenuates reconsolidation of cocaine memory in mouse models of IVSA

Since our previous studies showed that mice with a mutation of the D1 receptor gene does not acquire cocaine-induced CPP or IVSA [33, 34], we used a pharmacological approach to investigate the role of D1 receptors in reconsolidation of cocaine-related memory. WT mice were trained to acquire cocaine IVSA for consecutive 14 days followed by 4–10 days of extinction training. Then the mice underwent a 10-minute memory retrieval followed immediately by an IP injection of saline or different doses of the D1 receptor antagonist SCH23390. We tested reconsolidation 24 h, 48 h, and one week after retrieval. We found that D1 receptor antagonist, at both 0.08 mg/kg and 0.22 mg/kg doses, attenuated reconsolidation and this attenuation lasted for at least one week. As an essential control for studying the reconsolidation process, we tested the effect of the D1 receptor antagonist on cocaine memories in mice that underwent same cocaine IVSA acquisition and extinction but without retrieval, and the result showed that the D1 receptor antagonist did not affect cocaine seeking 24 h after antagonist infusion. These results demonstrate that the blockade of D1 receptors with SCH23390 attenuated reconsolidation of cocaine memory in mouse models of IVSA.

3.2. A mutation of the D3 receptor gene attenuates reconsolidation of cocaine-induced CPP

To study how D3 receptor is involved in reconsolidation, we first used both genetic and pharmacological approaches in mouse models of cocaine-induced CPP. D3 receptor mutant mice and WT littermates were used to establish cocaine-induced CPP, then, these two groups of mice underwent

retrieval or no-retrieval procedures. We found that the mutation of the D3 receptor gene weakened reconsolidation after retrieval, and it had no effect on cocaine memories in mice with no retrieval. These results suggest that the genetic mutation of the D3 receptor gene dampens reconsolidation of cocaine-induced CPP in a retrieval-dependent manner.

3.3. The selective D3 receptor antagonist PG01037 disrupted reconsolidation of cocaine-induced CPP

To confirm our findings on the role of D3 receptors in reconsolidation of cocaine memory, a similar retrieval-reconsolidation procedure of cocaine-induced CPP was used in WT mice to test pharmacological effects of a selective D3 receptor antagonist PG01037. We found that PG01037 infusion immediately after memory retrieval disrupted reconsolidation of cocaine-induced CPP tested 48 h to one week after retrieval. However, PG01037 alone did not affect cocaine memory without retrieval. These results indicated that a selective D3 receptor antagonist, PG01037, disrupted retrieval-triggered reconsolidation of cocaine-induced CPP in WT mice and this disruption lasted for at least one week.

3.4. The mutation of the D3 receptor gene disrupted reconsolidation of cocaine IVSA

To further study the role of D3 receptors in reconsolidation of cocaine memory, D3 receptor mutant mice and WT littermates were trained to acquire cocaine IVSA for 15 consecutive days followed by daily extinction training until the extinction criterion was met. On the next day, both groups of mice were subjected to a 10-minute retrieval. Mice were tested for reconsolidation 24 h, 48 h, and one week after retrieval. The result suggested that mutation of D3 receptor gene in mice disrupted the reconsolidation of cocaine memory, and this disruption lasted for at least one week. We similarly studied effects of the D3 receptor mutation in no-retrieval groups. The result showed that D3 receptor mutation did not affect IVSA with no memory retrieval. These results suggest that the mutation of the D3 receptor gene disrupted reconsolidation of cocaine memories.

3.5. The selective D3 receptor antagonist PG01037 disrupted reconsolidation of cocaine IVSA

To further confirm the role of D3 receptors in reconsolidation of cocaine memories, we examined the effects of the selective D3 receptor antagonist PG01037 on reconsolidation in WT mice and D3 receptor mutant littermates. Both groups of mice were subjected to 15 consecutive days of cocaine IVSA training followed by daily extinction training until the extinction criterion was met. On the next day, all groups of mice underwent a 10-minute memory retrieval followed immediately by an IP injection of PG01037 or its vehicle. We tested for reconsolidation 24 h, 48 h, and one week after retrieval. We found that PG01037 treatment blocked the reconsolidation of cocaine memories in WT mice but not in D3 receptor mutant mice. Taken together, our results suggest that D3 receptors play a critical role in reconsolidation of cocaine memory in mouse models of drug IVSA.

4. Discussion

The process of reconsolidation of memory renders memories re-enter a state of transient instability, requiring further stabilization to be available once again for recall [55]. Reconsolidation has been reported in animal and human models of various types of memories [55]. In rodent models, reconsolidation has been reported in spatial learning [56], object identity or place recognition [57], conditioned-taste aversion [58], as well as in cocaine-related pathogenic memories, such as CPP [59] and cocaine IVSA [60]. In rodent models of cocaine CPP and IVSA, several key neurotransmitters and signaling pathways, such as the NMDA receptor [59], are involved in reconsolidation of cocaine CPP and IVSA. Our previous studies showed that D1 and D3 receptors modulate locomotor-stimulant and positive reinforcing effects of cocaine, as well as cue-induced reinstatement of cocaine seeking. Therefore, our current studies focused on dopaminergic mechanisms of reconsolidation in cocaine memories. Two behavioral paradigms of drug addiction, CPP and IVSA, were used to establish cocaine-related memory and retrieval-reconsolidation paradigm. Both genetic and pharmacological approaches were used to study the role of D1 and D3 receptors in reconsolidation of cocaine memory. We found that DA D1 and D3 receptors play critical roles in reconsolidation of cocaine memories. These findings suggest that D1 and D3 receptors may serve as novel targets for the treatment of cocaine abuse in humans.

4.1. The role of D1 receptors in reconsolidation of cocaine memory

We previously used D1 receptor mutant mice and found that they do not acquire cocaine-induced CPP at several doses [34] and acquire little cocaine IVSA even after extended training [33]. Although the D1 receptor mutant mouse model was useful in studying functions of D1 receptors in the acquisition of cocaine-induced CPP and operant behaviors as well as underlying molecular mechanisms, this mouse model cannot be used for the subsequent reconsolidation studies. To achieve temporal genetic manipulation of D1 receptors, inducible mutation of D1 receptor mouse line is needed in reconsolidation study in the future. We used pharmacological approach to study reconsolidation in our present study. We found that SCH23390, attenuated reconsolidation of cocaine IVSA. Such attenuation in reconsolidation remained at least one

week after the memory retrieval. In the absence of the 10-minute retrieval, mice in the control group showed normal levels of cocaine memory. Our result suggests that D1 receptors contribute to the reconsolidation of cocaine IVSA in mice. To the best of our knowledge, this is the first demonstration that D1 receptors contribute to reconsolidation of cocaine-induced reward memory.

4.2. The role of D3 receptors in reconsolidation of cocaine memory

We used both genetic and pharmacological approaches to study the involvement of D3 receptors in reconsolidation of cocaine memory. To achieve genetic manipulation, we used mice that have a mutation in the D3 receptor gene in both cocaine CPP and IVSA. We previously used D3 receptor mutant mice in cocaine CPP model and found that they exhibited potentiated acquisition of cocaine-induced CPP at lower, but not higher, doses of cocaine compared to their WT littermates [34,41]. Others have shown that D3 receptor mutant mice exhibit enhanced [47] or relatively normal acquisition of cocaine IVSA [61].

To develop equal CPP acquisition between D3 receptor mutant mice and WT mice, we used a high dose of cocaine (20 mg/kg) to induce CPP, and the result showed that the CPP expression level after training has no significant difference between the mutant group and WT group. We performed three-minute retrieval and tested for reconsolidation right after CPP expression. In the IVSA model, our result showed that D3 receptor mutant mice responded more to active nose-pokes than their WT littermates during the mid-phase of acquisition training. Though the progressions of acquisition of cocaine IVSA are not exactly identical between D3 mutants and WT mice, active-response levels in the last three training sessions were similar, suggesting that the acquisition of cocaine IVSA has no overall difference between D3 receptor mutants and WT littermates. Following extinction training and after the extinction criterion has been met, we performed 10-minute retrieval and tested for reconsolidation.

We obtained parallel result using the CPP and IVSA models. We found that the mutation of the D3 receptor gene in mice reduced reconsolidation of cocaine-induced CPP but had no effects in the control group without the three-minute retrieval. Such reduction in reconsolidation of cocaine-induced CPP lasted for at least two days. Mutation of the D3 receptor gene in mice reduced reconsolidation of cocaine IVSA. Such reduction in reconsolidation lasted for at least one week after the memory retrieval. These consistent results further suggest that D3 receptors participate in mechanisms related to reconsolidation of cocaine-induced reward memory.

We further studied role of D3 receptors in reconsolidation of cocaine reward memory using pharmacological approaches using both CPP and IVSA models, in which the behavioral protocols are the same as those used in genetic approach. We chose the D3 receptor high affinity and selectivity antagonist PG01037 to selectively block D3 receptors. PG01037 rapidly penetrates the blood brain barrier and selectively localizes in D3 receptor-rich regions, such as the NAc, Islets of Calleja, and the hippocampus [62], which is ideal for IP injections and targets D3 receptors in the brain. In the CPP model, we administered PG01037 immediately following the three-minute memory retrieval in WT mice and found that PG01037 attenuated retrieval-triggered reconsolidation of cocaine-induced CPP but had no effects in the control group without the retrieval. Such attenuation in reconsolidation of cocaine-induced CPP remained at least one week after the retrieval. Our result in cocaine IVSA is consistent with that in CPP model. Following acquisition and extinction training, we administered PG01037 immediately following the 10-minute memory retrieval in WT and D3 receptor mutant mice. PG01037 attenuated reconsolidation of cocaine IVSA at the 30 mg/kg dose in WT mice, and such attenuation in reconsolidation remained at least one week after the retrieval.

4.3. Potential mechanisms and conclusions

The molecular mechanisms underlying the involvement of D1 and D3 receptors in reconsolidation are still unknown. We and others have demonstrated that D1 and D3 receptors play differential roles in acquiring cocaine-induced behaviors [33,34,35,36,41,52] and the underlying molecular mechanisms are also different. ERK, buy not JNK and p38, is activated in WT mice and D3 receptor mutant mice but not in D1 receptor mutant mice following cocaine CPP acquisition, which suggests that ERK is a potential signaling pathway mediating cocaine CPP acquisition in D3 receptor mutant mice [34,63,64,65,66]. Though D1 and D3 receptors function differentially in acquiring cocaine reward memory, they exert similar function in reconsolidation of cocaine memory. A recent study shows that co-administration of a D3 receptor antagonist and a D1 partial agonist prior to reinstatement significantly reduced reinstatement of cocaine IVSA and CPP, suggesting an interaction between D1 and D3 receptors in cocaine-related behaviors [67]. Since a large percentage of D3 receptor-bearing neurons co-expresses D1 receptors especially in the NAc [68,69], it is possible that D1 and D3 receptors interact to mediate certain functions. One possibility is that D1-D3 receptor heteromers [70,71] in these discrete brain regions may play a role in drug memory reconsolidation by regulating transcription and/or epigenetic modifications in reward circuits (Figure 1). Since mesolimbic dopaminergic system mediates the acquisition of cocaine-induced neurobiological effects including signaling mediated by ERK, PKA, PKC, and CaMKII [19,21,34,41,63,64,66], these

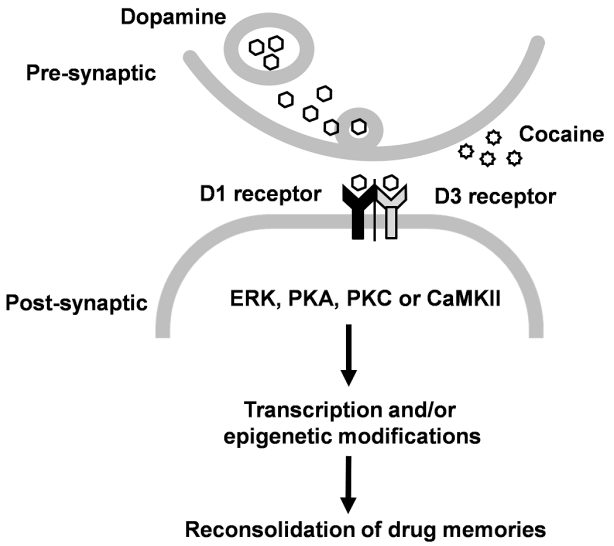

Figure 1: DA D1 and D3 receptors may work in concert to mediate reconsolidation of drug memories by regulating transcription and/or epigenetic modifications in reward circuits. ERK, PKA, PKC, and CaMKII may work alone or in some combination intracellularly to mediate the above process.

signaling pathways may work alone or in some combination intracellularly to mediate the reconsolidation process. Although how these two receptors mediate reconsolidation at the molecular level needs to be answered in the future, our current results suggest that pharmacological blockade of either D1 or D3 receptors in the context of drug memory reconsolidation may be therapeutic for the treatment of cocaine craving and relapse in clinical settings.

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Conflict of interest The authors declare that they have no conflict of interest.

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