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Differential effects of dorsal hippocampal inactivation on expression of recent and remote drug and fear memory☆

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HIGHLIGHTS

- Systems consolidation predicts that retrieval of remote memories can occur independent of the hippocampus.
- Hippocampal inactivation impairs expression of recent and remote cocaine CPP, but only affects only recent contextual fear.
- We discuss models of substance abuse and issues in the translation of memory mechanisms to clinical therapies.

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ABSTRACT

Drugs of abuse generate strong drug-context associations, which can evoke powerful drug cravings that are linked to reinstatement in animal models and to relapse in humans. Work in learning and memory has demonstrated that contextual memories become more distributed over time, shifting from dependence on the hippocampus for retrieval to dependence on cortical structures. Implications for such changes in the structure of memory retrieval to addiction are unknown. Thus, to determine if the passage of time alters the substrates of conditioned place preference (CPP) memory retrieval, we investigated the effects of inactivation of the dorsal hippocampus (DH) with the GABA-A receptor agonist muscimol on expression of recent or remote CPP. We compared these effects with the same manipulation on expression of contextual fear conditioning. DH inactivation produced similar deficits in expression of both recent and remote CPP, but blocked expression of recent but not remote contextual fear memory. We describe the implications of these findings for mechanisms underlying long-term storage of contextual information.

1. Introduction

A key finding from studies of substance abuse is that drug-conditioned contexts and cues generate strong cravings, even years after cessation [1–4]. A better understanding of the processes that support long-term maintenance of drug-associated memories may allow generation of targeted therapies to disrupt drug-context associations or facilitate extinction of drug-seeking [5]. While many compounds have shown promise in animal models of drug-seeking [5–10], part of the problem may be translation from animal models to clinical populations. Many complex factors, such as number of drug administrations, environmental complexity, social factors, individual differences, and time since initial drug exposure, separate animal models of drug-seeking from human addiction [11].

A primary goal of drug abuse research is to develop animal models that are well matched to human drug addiction. In humans, addiction forms over months and years, whereas animal models of drug abuse generally acquire drug-seeking behavior on the order of days and weeks. This difference is compounded by associative learning models that predict that different neural substrates support expression of recent and remote memories [12]. Much of what is known about the ability to modulate drug-associated memories comes from the study of memories that have been recently acquired; much less is known about modulation of these memories after long retention intervals. Thus, age of drug-associated memories is one factor that could contribute to a mismatch between human addiction and animal models of substance abuse.

Many studies have demonstrated that memories that require the hippocampus for initial consolidation become less dependent on the hippocampus over time [13–17]. This observation has led to the idea of systems consolidation, where hippocampus-dependent memories become hippocampus-independent in the weeks

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following acquisition [12]. This effect has been most demonstrated in contextual fear conditioning, though it also occurs in other forms of hippocampus-dependent learning, such as trace fear conditioning [15,16]. In each case, hippocampal disruption interferes with expression of recent but not remote memories. Systems consolidation is thought to support formation of long-lasting memories, since context learning in the absence of the hippocampus is less stable over time [18]. Although it is notable that systems consolidation effects can be difficult to replicate and are open to other interpretations [19–22], investigation of these processes may prove valuable, because similar time constraints have also been shown for reactivation-dependent impairments in memory [23,24], an approach that has been applied to models of drug abuse treatment [25,26]. Thus, understanding what tasks are affected by these processes may help identify clinical problems that could be treated by targeted disruption of particular consolidation mechanisms.

As systems consolidation is most reliably demonstrated in contextual fear learning [22], it is of interest to determine if hippocampus-dependent systems consolidation also occurs in other forms of contextual learning. In conditioned place preference, hippocampal structures have been implicated in acquisition of context-drug associations [27,28]. However, it is not clear to what extent the hippocampus is involved in retrieval of a previously learned context-drug association, or if that involvement changes over time. Thus, we used cocaine-induced conditioned place preference (CPP) to determine if hippocampal involvement in context-drug memory retrieval changes over time. To investigate this, we used muscimol to inactivate the dorsal hippocampus (DH) of mice prior to testing for cocaine-induced CPP that was either 1 or 28 days old, time points regularly used to examine long-term memory consolidation [14,17]. Additionally, we examined the effects of DH inactivation on expression of recent and remote contextual fear conditioning.

2. Materials and methods

2.1. Subjects

These studies were conducted with 108 8–16 week old, male, C57BL6/J mice, which were singly housed with ad lib. food and water and maintained on a 12 h/12 h light/dark cycle. All procedures were approved by the Oregon Health & Science University Animal Care and Use Committee and were in accordance with the ethical guidelines of the National Institutes for Health.

2.2. Drugs

Cocaine (Sigma–Aldrich, St. Louis, MS) was dissolved in saline and administered at 20 mg/kg ip, as described previously [8]. Muscimol (Sigma–Aldrich) was dissolved in PBS and administered via bilateral, intra-cranial infusions into the DH (0.5 mg/side, in 0.25 μl, over 1 m), as described previously [29].

2.3. Surgical procedures

On Day 15 of behavioral procedures (CPP or Fear Conditioning) mice were implanted with intra-cranial cannula targeted toward the DH, see Raybuck and Lattal [29]. One caveat to this design that is common to all experiments examining the effects of time on behavior is that recent animals were trained prior to surgery, while remote animals were trained following surgery. However, since performance of vehicle animals did not change over time, it is unlikely that timing of surgical procedures was responsible for our present findings. Cannula placements were visualized with histological nissl staining with cresyl violet and verified by gliosis along infusion cannula tracts. All placements were within the DH (see Fig. 2).

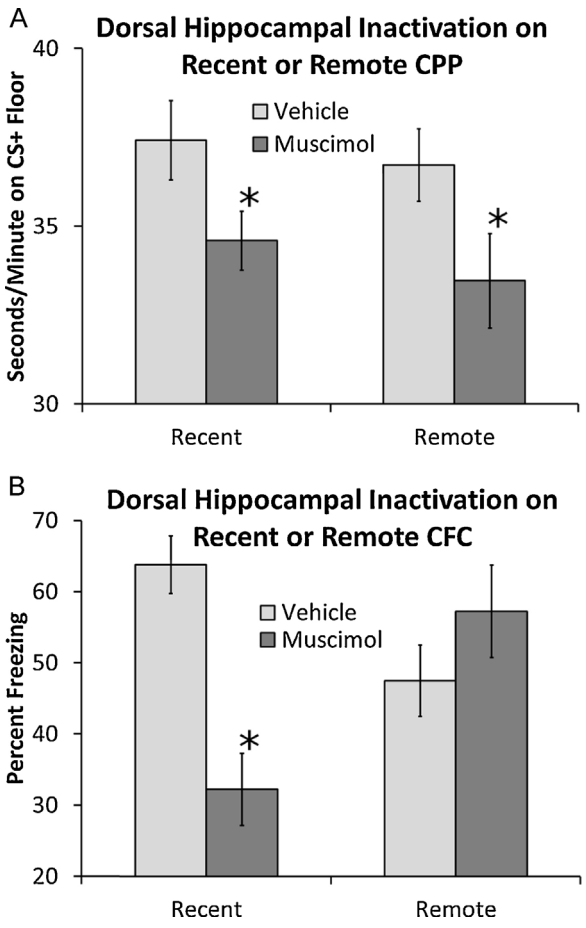

Fig. 1. Effects of DH inactivation on retrieval of recent of remote CPP and contextual fear conditioning. (A) Inactivation of the DH with muscimol produces similar deficits in retrieval of cocaine-induced CPP regardless of training condition. Subjects per group were Recent–Vehicle, 23; Recent–Muscimol 22; Remote–Vehicle 18; Remote–Muscimol 18. (B) In contextual fear conditioning inactivation of the DH produced selective deficits in retrieval of recent contextual fear without affecting remote memory. Subjects per group were Recent–Vehicle, 7; Recent–Muscimol 6; Remote–Vehicle 6; Remote–Muscimol 6. Data are mean ± the standard error of the mean, * denotes $p < 0.05$.

2.4. Behavioral methods

2.4.1. Conditioned place preference

To determine if the hippocampal-dependence of CPP expression changes over time, mice were divided into two experimental groups (recent or remote). For each group, conditioning consisted of alternating exposures (15 min) to unique tactile floor cues (grid or hole floors). Prior to placement on a floor, mice received injection of cocaine (20 mg/kg) or saline, counterbalanced across floor types for a total of two pairings of floor with cocaine (CS+) and floor with saline (CS−); see [8,31]. Mice in the remote training group received CPP training on Days 1–4, whereas mice in the recent training group received CPP training on Days 29–32. Importantly, drug exposure was matched such that during the remote training phase mice in the recent condition received cocaine administration in their home cages and vice versa. Thus, both recency of cocaine exposure and cocaine history were matched across training conditions. All animals were tested for CPP preference on Day 33, 20 min following infusion of muscimol or PBS. The preference test consisted of 15 min of simultaneous access to both tactile floor cues (CS+ and CS−).