Chinese Journal of Physiology 52(4): 264-272, 2009
DOI: 10.4077/CJP.2009.AMK004

Review

Disruption of Conditioned Drug Memories

Chianfang G. Cherng[1] and Lung Yu[2]

[1]*Department of Health Psychology, Chang Jung Christian University, Tainan 711*
[2]*Institutes of Behavioral Medicine and Basic Medical Sciences, Department of Physiology, National Cheng Kung University College of Medicine, Tainan 701, Taiwan, R.O.C.*

Abstract

We first made a brief review on historical development of drug craving theories. A special emphasis was given on the proposal that conditioned drug memories can be a critical psychopathological basis to elicit compulsive drug taking, craving and subsequent relapse. We then discussed the different processes associated with drug learning and memory as well as recent findings pertaining to these processes, specifically using the conditioned place preference (CPP) paradigm as a model for assessing these conditioned drug memories. Over this decade, many factors have been identified to affect the acquisition, consolidation, expression and reconsolidation of such a drug-induced CPP memory in rodents. Since reactivation of the established drug-induced CPP memory and modification of the reactivated memory are two core components for developing potential treatments, a few theoretical and practical considerations in the CPP paradigm are provided and discussed accordingly.

Key Words: abuse drug, drug craving, reinforcement, reward, classical conditioning

Development of Drug Craving Theories

Drug addiction presents as a chronic disorder mainly characterized by compulsive drug-taking and long-lasting drug-seeking behavior (an overt behavior of craving) in spite of illness, disrupted relationships or failures in life roles (22). One of the most challenging problems for drug addiction treatment is addicts' long-term vulnerability to drug craving even following a prolonged period of abstinence (16, 30, 71). An incentive-sensitization theory was proposed a decade or so ago in an attempt to explain the phenomenon that drug craving and drug-seeking behavior occurred even when drug withdrawal symptoms-associated discomfort dissipated (55). In this theory, repeated drug use has been thought to chronically alter the neural systems which are involved in incentive motivation and reward for natural appetitive reinforcers, thus to render addicts enduringly to be hypersensitive to the drug and drug-associated stimuli with ensuing drug craving and drug-seeking behavior. Although this incentive-sensitization theory prevails over many other theories in predicting the cause and underlying mechanism for drug craving, wanting and seeking behavior, it is not satisfactory to predict the roles of the neural system, which normally mediates aversive reinforcer-supported learning and memory, in drug craving and drug seeking behavior (12, 47). Jentsch and Taylor (1999) extended the incentive-sensitization theory by putting forward a possibility that frontal cortical dysfunction-associated inhibitory control impairment can explain the cause of drug-taking behavior (36). However, it remains elusive that how such a drug use-produced frontal cortical dysfunction and loss of inhibitory control on compulsive drug-taking behavior specifically leads to drug craving after a long-term abstinence.

Lately, several groups of investigators have been focusing their attention on the roles of drug habit formation and maladaptive drug associative learning in drug craving and drug seeking behavior (4, 28, 70). It has been well-known that cues associated with

Corresponding author: Dr. Lung Yu, Behavioral Neuropharmacology Laboratory, Institute of Behavioral Medicine, National Cheng Kung University College of Medicine, 1 University Rd., Tainan 70101, Taiwan, R.O.C. Tel: +886-6-2353535 ext. 5114(Lab), 5106(O), Fax: +886-6-2095616, E-mail: lungyu@mail.ncku.edu.tw
Received: January 23, 2009; Revised (Final Version): July 4, 2009; Accepted: July 8, 2009.
 ISSN : 0304-4920. http://www.cps.org.tw

previous drug use can provoke drug craving and conditioned emotional response in addicts, that is, they are associated with relapse during drug use or after a period of abstinence (49, 50). The risk of relapse is elevated when addicts encounter drug-conditioned cues, such as people, places or paraphernalia which has been previously associated with drug use. These drug-conditioned cues can elicit drug-related behavior in animal models (15) and drug craving in human addicts (25). Likewise, imaging studies have indicated that drug-conditioned cues activate prefrontal cortical regions and the amygdala, which are involved in the formation of drug habit and consolidation of stimulus-reward association (27). Thus, cue-provoked relapse can occur in subjects who have strongly resolved never to use drugs again (49, 67). Berke and Hyman (4), accordingly, claimed a core role of associative learning in explaining and predicting eventual relapse for drug addicts. Hyman and Malenka (34) summarized many lines of evidence and further extended this proposal by maintaining that central behavioral features of addiction resulted from drug-usurping normal memory mechanisms in central nervous system. Therefore, drug-taking compulsion and its persistence are predictable based on a pathological usurpation of neural mechanisms that are normally involved in memory. In fact, Di Chiara (18) provided a similar tenet that addiction is the expression of the excessive control over behavior acquired by drug-related stimuli as a result of abnormal associative learning following repeated drug use.

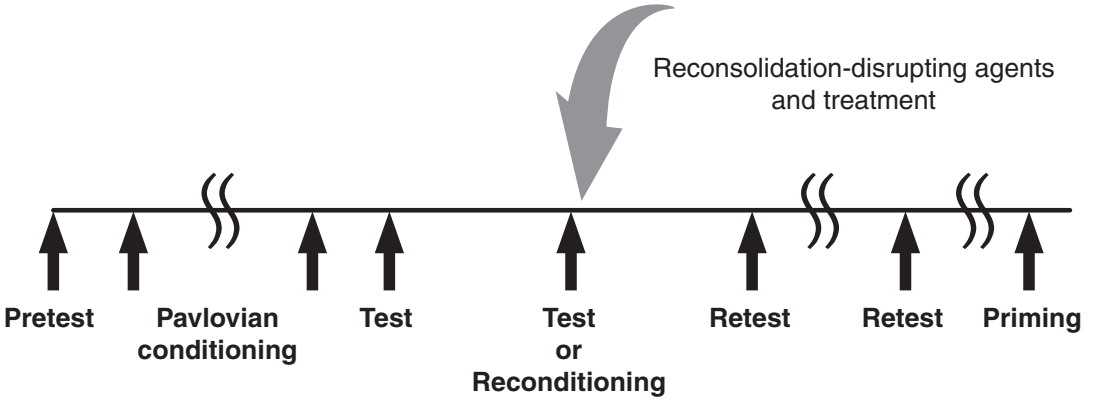
Use of the Drug-Induced CPP Paradigm to Study Craving Treatment

Over this past decade, the most appreciable development for scientific research on learning and memory should be revival of the concept and interests on memory reconsolidation. Many theorists posit that a well-consolidated memory, when reactivated through retrieval (recall), may return to a transient labile state which is susceptible to modification. Reactivated memory ought to undergo a hypothetical reconsolidation process to be maintained as its original form or modified by introducing contemporary experience into a new memory (1, 23, 24, 48, 62). Reconsolidation process presumably provides a time window for modifying or strengthening a memory trace (68). In fact, intervention of memory reconsolidation processes has its clinical significance, especially for the treatment of psychiatric disorders that are characterized by exceptionally robust and pathological memories, such as drug-supported memory. Since drug-conditioned cues have been thought to play a critical role in eliciting craving, drug seeking behavior and relapse in humans and various other species (9, 21, 29, 46, 49, 54, 70, 74, 76), a growing body of evidence has been focusing on taking advantage of the recall-sensitive window in order to diminish or even demolish conditioned drug memory in recent years. Being aware that to exhaust drug-supported learning and memory paradigms in various animal models is not the purpose of this review, we decide to discuss drug-supported Pavlovian learning, specifically drug-induced CPP learning and memory, that we are particularly interested in. Drug-induced CPP is an ideal paradigm of choice to study drug memory and its disruption due to two reasons. First, drug-induced CPP memory can be established within a few (usually less than 5) conditioning sessions. Second, retention (or expression) of the drug-induced CPP memory seems to be long-lasting, mimicking the log-term nature of drug memory.

In the drug-induced CPP paradigm, experimental animals (usually rodents) are exposed to an apparatus generally consisting of two initially neutral compartments that can differ in terms of a number of stimulus modalities, such as color, illumination, floor texture, temperature and odor. Animals are exposed to one compartment following drug treatment, whereas the other compartment following vehicle treatment. After a number of these conditioning sessions, animals are allowed free access to the apparatus at a drug-free status for testing the acquisition of drug-induced CPP memory. In the test, time spent difference for the drug-paired compartment and the vehicle-paired compartment for individual animal is used to index the magnitude of drug-induced CPP memory. Likewise, drug-induced CPP performance has been frequently used as a convenient means for revealing the rewarding properties of illicit drugs throughout conditioning sessions (Table 1). Given the reconsolidation phase of drug-induced CPP memory is concerned, animals' acquisition of drug-induced CPP has to be assured after completion of conditionings. Drug-induced CPP memory trace is, then, reactivated (retrieved) in different ways, followed by various kinds of treatment (manipulation of related factors) known for their amnesic effects on memory consolidation. Finally, magnitude of drug-induced CPP memory should be tested at several time points following conclusion of the treatment for revealing the reconsolidation-disrupting effect of the treatment (Table 1).

Since drug-induced CPP paradigm has been increasingly used to study what treatment can effectively diminish or demolish such a conditioned drug memory, reliable acquisition and appropriate retention course of such a memory should be taken into account at the beginning of the study. It has been reported that the number of drug-conditioning sessions correlates positively with the magnitude of

Table 1. A frequently-used procedure for the drug-conditioned place preference paradigm



Content	free navigation in place A & B	drug-place A pairing & vehicle-place B pairing	free navigation in place A & B	free navigation in place A & B or another drug-place A & vehicle-place B pairing	free navigation in place A & B	free navigation in place A & B	drug treatment
Purpose	exclusion of unconditioned place preference	learning of drug-place A & vehicle-place B association	ensuring acquisition of the associative memory	reactivation of the associative memory	examining expression of the associative memory	examining probability of spontaneous recovery for the memory	examining probability of spontaneous recovery for the memory

drug-induced CPP, while two conditioning sessions seem to be the least number of conditioning required in establishing a reliable drug-induced CPP memory (10). Both drug doses and the number of drug conditioning sessions correlate positively with the retention of drug-induced CPP memory, while a time-dependent (or test-dependent) decline in drug-induced CPP magnitude has been noticed after the acquisition of drug-induced CPP memory (10, 41).

A Booming Decade for Research on Drug-Induced CPP Memory

Over the last decade, drug-induced CPP paradigm in rodent models had been used to study every phase (including the acquisition, consolidation, retrieval and reconsolidation) of drug-context associative memory. It is of special interest to notice that the penchant of studying drug-induced CPP learning and memory almost starts immediately after the scenario that drug-context associative learning and memory motivates drug craving is proposed. We, hereby, summarize a few factors which have been studied for their impact on different phases of the drug-induced CPP learning and memory.

Factors Affect the Acquisition and Consolidation of Drug-Induced CPP Memory

7-Nitroindazole, a selective neuronal nitric oxide synthase inhibitor, blocked the acquisition of nicotine-induced CPP (42). Inhibition of neuronal activity in amygdala by bupivacaine, a local anesthetic, infusion was found to block the acquisition and consolidation of amphetamine-induced CPP (33). Intra-basolateral amygdaloid scopolamine, a muscarinic inhibitor, infusion blocked the acquisition and consolidation of amphetamine-induced CPP (63). Intra-accumbal infusion with AP5 (an NMDA antangonist), CNQX (an AMPA antagonist), and Rp-cAMPS (a PKA inhibitor) blocked the acquisition of morphine-induced CPP (32). Calcineurin, calcium-calmodulin-dependent protein phosphatase, -overexpressing mice did not acquire amphetamine- or morphine-induced CPP (7). H-89, a selective PKAII inhibitor, was found to inhibit the consolidation of morphine-induced CPP (65). Intra-hippocampal and intra-accumbal infusion of RU38486, a glucocorticoid receptor inhibitor, blocked the acquisition of morphine-induced CPP (20). Amphetamine was found to enhance the consolidation of morphine-induced CPP (8). Zif268-deficient mice did not acquire cocaine-induced CPP (69). Systemic cycloheximide and anisomycin treatment blocked the acquisition of cocaine-induced CPP (39). N-acetylcysteine, a glutathione precursor, facilitated the consolidation of cocaine-induced CPP (3). Anisomycin disrupted the consolidation of morphine-induced CPP (57). FN-439, a broad spectrum, matrix metalloproteinase inhibitor, was reported to diminish the acquisition of cocaine-induced CPP (11). Blockade

of NMDA receptors and inhibition of CaMKII impaired the acquisition of amphetamine-induced CPP (59). Novelty played a role in the acquisition of methamphetamine-induced CPP (14). Nitrous oxide impaired the acquisition of morphine-induced CPP (5). Hippocampus and frontal cortex were involved in the formation and maintenance of cocaine-induced CPP (38).

Factors Affect the Expression of Drug-Induced CPP Memory

2-PMPA, a glutamate release inhibitor, was found to block the expression of morphine-induced CPP (51). Repeated low-frequency electrical stimu lations suppressed expression of established mor phine-induced CPP (13). MK-801, an NMDA antagonist, was found to inhibit the expression of morphine-induced CPP (75). Nicotine was found to reduce the expression of morphine-induced CPP (64). Intra-ventral pallidal treatment with AP-5 and CNQX blocked the expression of morphine-induced CPP (17). Intra-dorsal hippocampal infusion with muscimol disrupted the expression of cocaine-induced CPP (43). Nitrous oxide blocked the expression of both cocaine- and morphine-induced CPP (5). Blockade of NMDA receptors and inhibition of CaMKII impaired the expression of amphetamine-induced CPP (59). Scolpolamine (a muscarinic antagonict), MK-801, and D-cycloserine (a partial NMDA agonist) all suppressed the expression of cocaine-induced CPP (37).

Factors Affect the Reconsolidation of Drug-induced CPP Memory

Intra-accumbal core infusion with U0126 and PD98059, the ERK kinase (MEK) inhibitors, attenuated the reconsolidation and later expression of cocaine-induced CPP memory (45). Propranolol, a beta-antagonist, administration blocked the reconsolidation of cocaine-induced CPP memory (6). Likewise, propranolol was found to attenuate reconsolidation of morphine-induced CPP memory (56). Blockade of de novo protein synthesis in hippocampus, basolateral amygdala, and nucleus accumbens all disrupted the reconsolidation and later expression of an established morphine-induced CPP memory (44). 7-Nitroindazole disrupted the reconsolidation of cocaine-induced CPP memory (34). Scopolamine was found to enhance or delay the extinction of morphine-induced CPP memory (66). Cycloheximide was found to enhance the maintenance of methamphetamine-induced CPP memory (41). Stress exposure during reactivation of the cocaine-associated environment abolished established cocaine-induced CPP memory (77). MK-801 was found to disrupt the reconsolidation of cocaine-induced CPP memory (37). Administration of FN-439 during cocaine-primed reactivation of the cocaine-induced CPP memory disrupted reconsolidation and later expression of the memory (11). Amphetamine was found to enhance the reconsolidation of morphine-induced CPP memory (8). Treatment with MK-801 immediately after memory reactivation test was found to reduce later amphetamine-induced CPP expression (58). A general review regarding the effects of pharmacological agents on reactivated memories can be referred to Diergaarde *et al.*'s article (19).

Dilemmas Pertaining to the Study Design in Drug-Induced CPP Paradigm

Given the hypothesis that a robust drug-induced CPP memory is susceptible to modification only when such a memory is reactivated, how to effectively reactivate drug-induced CPP memory becomes indisputably one of the most important issues in this regard. Maintenance for the treatment-induced deficit in drug-induced CPP memory is also an interesting issue because the longevity of treatment-disrupted CPP memory reconsolidation is expected to provide empirical evidence for the functional roles of memory reconsolidation—whether memory reconsolidation is an opportunity for permanent erasure of an old memory, acquisition of a new long-term memory, or a transient time window for inactivating an old memory? For substance dependence clinic, maintenance for a failed expression of the drug memory predicts the endurance of therapeutic effects and the dosing regimen of any potential treatment. Finally and definitely not the least, an appropriate reactivation of drug-context memory, timely and effective treatments in combination may presumably eradicate such a robust and long-lasting drug memory, however, are other survival-related experiences and memories intact under such a treatment condition?

In Which Way to Reactivate the Drug-Context Memory?

Almost all kinds of long-term memory, especially notorious conditioned drug memory, have been known for their resistance to extinction (41, 60). Theorists predict that drug-induced CPP memory can be disrupted when such a memory is reactivated. Therefore, to determine how to sufficiently and effectively reactivate the acquired drug-induced CPP memory is important. Nonetheless, the means to reactivate the drug-induced CPP memory remain argumentative. Exposure of rodents to the drug-conditioned cues and context (conditioned stimuli, CS) in the absence of the drug injection (uncondi-

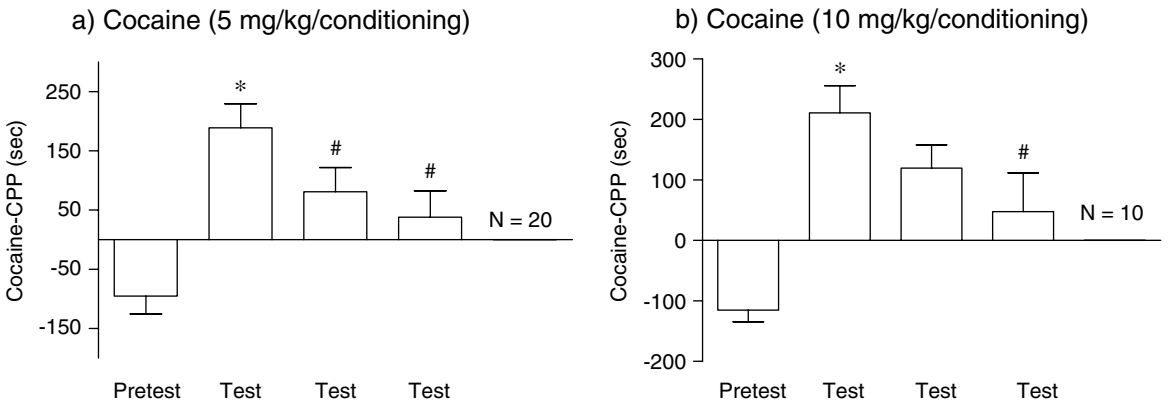


Fig. 1. Magnitude of cocaine-CPP progressively declines with repeated CPP tests. Pretest, cocaine-CPP training, and test were conducted in commercial chambers designed for mouse (MedAssociates Inc., Georgia, VT, USA) (14, 40). An unbiased design was used in this study. On day 1, male C57BL/6NJ mice, aged around 8 weeks, were placed in the center of any randomly chosen chamber and the time spent in each compartment of the chamber was measured for unconditioned preference in a 15-min pretest. Mice spending less than 40% of the time in any one compartment or center were included in the study. For cocaine-CPP training (days 2-4), mice receiving an ip injection of a) 5 mg/kg or b) 10 mg/kg cocaine hydrochloride were immediately confined in the non-preferred compartment of their pretest chambers for 30 min. Eight hours apart, mice received an equivalent volume of saline injection and were immediately confined in the preferred compartment for 30 min in their corresponding chambers. These procedures were repeated for three consecutive days. On day 5 around noon, mice were placed in the center with guillotine doors open and started a 15-min test at a cocaine free status. This test procedure, then, was repeated for another two days. Cocaine-CPP magnitude was represented by subtracting the time spent in saline-paired compartment from the time spent in cocaine-paired compartment in test. Two-tailed paired *t* tests were employed to examine the magnitude (mean ± standard error of mean) of cocaine-CPP. Two doses (5 and 10 mg/kg/conditioning) of cocaine reliably established cocaine-CPP in our experimental animals (*Significantly greater than the pretest results. $t_{19} = 7.095$, $P < 0.0001$ for 5 mg/kg; $t_9 = 7.742$, $P < 0.0001$ for 10 mg/kg). Cocaine-CPP magnitude was notably decreased in the second and third tests under the condition that 5 mg/kg cocaine was used to establish cocaine-CPP ($^{\#}$Significantly lower than the first test result. $t_{19} = 2.28$, $P = 0.0343$ for the second test; $t_{19} = 2.88$, $P = 0.0096$ for the third test). Cocaine-CPP magnitude was decreased in the third test as 10 mg/kg cocaine was used to establish cocaine-CPP ($^{\#}$Significantly lower than the first test result. $t_{19} = 3.127$, $P = 0.0122$).

tioned stimulus, US) has been used to reactivate drug-induced CPP memory by some investigators (6, 45, 37). In contrast, other investigators maintain that co-presentation of the CS and US is required for the reactivation of drug-induced CPP memory (44, 69). Although the use of CS presentation as a reactivation way for retrieving drug-induced CPP memory could be welcome for most of the clinical practitioners, two studies had already stressed the invalidity for using CS alone to reactivate cocaine- or morphine-induced CPP (44, 69). Even more so, we have found a potential flaw accompanying with the use of CS alone for reactivating drug-induced CPP memory. After the acquisition of drug-induced CPP, repeated daily presentations of the drug-conditioned cues and context by allowing animals back into the CPP apparatus for a free navigation result in a fast decline in magnitude of drug-induced CPP (Fig. 1). Such a fast decline in drug-induced CPP performance is not surprising because it can be attributed to a typical memory extinction protocol normally executed by a presentation of the drug-conditioned context and cues without an US (hedonic feelings derived from drug injection). A progressive decline of drug-induced CPP magnitude, in this regard, is unfavorable for revealing the reconsolidation-ameliorating effect of any treatment. Therefore, even presentation of CS alone (an equivalent to the drug-free CPP test) could be a simple means to reactivate the drug-induced CPP memory, the aim to evaluate the reconsolidation-modulating effect of the used treatment can be compromised. It is of interest to note that a high conditioning dose (20 mg/kg) of cocaine and a long inter-test interval (2 to 7 days) have been usually utilized to demonstrate the efficacy of cocaine-conditioned context presentation alone in reactivating cocaine-induced CPP memory (6, 46, 38). Therefore, a retarded development of drug-induced CPP extinction is much likely associated with a high (greater than 10 mg/kg/conditioning) conditioning dose of drug and a long (longer than 24 h) inter-test interval.

Another interesting question regarding the strategy to reactivate drug-induced CPP memory is to assess existence of the memory trace in a reinstatement design. Presentation of an US alone (a priming dose of drug) has been usually used for reactivating drug-induced CPP memory after its extinction in an attempt to assure the persistence of an extinguished drug-

induced CPP memory (26, 40, 72). A disrupted old memory, indeed, can be retrieved by re-exposure to a non-contingent US (53). Nevertheless, recent studies have indicated that presentation of US alone might be insufficient to reactivate the drug-induced locomotor sensitization or CPP memory (44, 69). The observation that a priming injection of the conditioned drug can not facilitate the retrieval of drug-induced CPP memory in any reinstatement design could be due to animals' adaptive choice in several episodes of memory. That is, we argue that reactivation of drug-induced CPP memory, followed by any aversive "treatment" may render animals to acquire a new memory (CS is now pairing with an aversive US, not the previous appetitive US) in those studies that using drug-free CPP test to reactivate the memory. One wants to know whether that "treatment" interrupts the reconsolidation of reactivated CPP memory, several retests are, thus, given afterwards and the magnitude of drug-induced CPP is monitored accordingly. If the premise of aversive "treatment" sustains, animals are not expected to exhibit original CPP during these retests, which has been observed in many studies. Interestingly, repeated drug-free CPP tests could also make the animals learn that current CS predicts no drug or the aversive treatment. If animals behave what they have learned the latest, a priming dose of drug is irrelevant. Even though animals remember that CS once predicts the drug, they are anticipated to remember that CS also predicts the aversive "treatment". In fact, animals do not exhibit original CPP during the retests, possibly suggesting a potent aversion associated with the "treatment". Therefore, a priming injection of drug can not induce an observable recollection of original drug-induced CPP memory. Taken together, we hereby propose to adopt the reconditioning protocol in both situations—use of another CS-US conditioning to reactivate drug-induced CPP memory and to assess the remaining of the previously acquired drug-induced CPP memory following its extinction. After all, a study ever addressed that single drug-pairing session was insufficient to induce a CPP performance (10).

Valid Consolidation of a New Learning or Disrupted Reconsolidation of the Old Memory

A spontaneous recovery of the learned responses after a period of time lapse and a rapid speed in relearning extinguished responses have been documented even following a complete extinction of the learned responses (52, 61), suggesting that memory extinction may not be intuitively viewed as forgetting or erasure of the original memory trace but an extinction in memory expression. After the consolidation has been completed, memory expression can be defined by employing retrieval tests. A drug-free CPP test is a retrieval test but also a new situation in which previously drug-conditioned compartment is paired with absence of US. A reasonable prediction derived from memory reconsolidation hypothesis is that new information (CS-no US) is inclined to be incorporated into the original memory (CS-US) given the original memory is recalled. A reconsolidation phase is, accordingly, needed for incorporation of new experience into the old memory, to form a new memory. In contrast, use of reconditioning (another pairing of CS and US) protocol to reactive the drug-context memory may not require a reconsolidation owing to the fact that there is little new experience with the reconditioning procedure. Therefore, reconditioning protocol can maintain and strengthen, rather than modify, the original memory (CS contingent on US). In view of the results that reconditioning-induced reactivation of the drug-induced CPP memory followed by potential treatment can be used to abolish later drug-induced CPP performance in a long-lasting manner (44, 69), two possibilities are suspected. First, specific treatment used in this reconditioning design ameliorates the storage or expression of the drug-context memory. Second, even minute differences between new experience and the original memory are capable of motivating a reconsolidation phase once the old memory is retrieved (or reactivated).

As for the findings that many treatments following memory establishment eradicate the CPP memory by utilizing drug-induced CPP test as a reactivation means, treatment-associated reconsolidation disruption seems to be a logical explanation. However, alternative explanations, such as strengthening of a new memory consolidation (CS-no US) and state-dependent memory performance (conditions specifically associated with the treatment, for example intracranial treatment) still need to be partial out.

Is the Drug-Context Memory the Only One Sensitive to Reactivation and Treatment?

Both habit learning for drug use and drug-context association play a critical role in eliciting drug craving and relapse (70, 73). Thus, to modify such a drug-supported memory is a central component of treating drug addiction. Unfortunately, drug-context memories are extremely potent in chronic, binge patients (73). In laboratories, drug-supported memories, including CPP memory, can be reactivated and persistently modified by potential treatment. One reason for explaining such a paradoxical contrast in the drug-context memory strength between addicts and drug-treated animals is that drug-context memories in humans are very likely established by multiple associations of many kinds of CS with drug, many complicated CS

patterns with drug, CS with various amounts of drug. On the contrary, animals receive very few but specific CS modalities and limited times of CS exposure and drug injections in the CPP paradigm. Accordingly, addicts' drug-conditioned memories are resistant to decay over time, while drug-induced CPP in rodents can be recalled and eradicated by appropriate treatment for good. Therefore, one must keep it in mind that even potential treatments for disrupting drug-context memory reconsolidation are defined in the near future, these treatments are not necessarily promising in treating drug addicts. All the difficulties lie in a comprehensive search for all drug-conditioned memories and a full reactivation of them. On the other hand, given the fact that reactivation of the drug-context memory followed by treatment may eradicate the drug-context memory per se, a serious concern will be a general deteriorating effect on many kinds of memory exerted by the treatment. That is, it should be vigorously explored that whether the other survival-related experiences and memories are intact when such a strong drug-context memory is under destructive attack by the treatment.

Conclusions

Approximately a decade ago, a few groups of investigators proposed that drug-taking compulsion, drug craving at abstinence and relapse can be driven by drug-supported pathological memories. Ever since then, drug-induced CPP paradigm in rodent models has been frequently used to study every phase of conditioned drug memory. Many factors thought to affect consolidation phase of the other long-term memories have also been found to affect the reconsolidation phase of drug-induced CPP memory when the CPP memory is recalled. Although reactivation of the drug-induced CPP memory and modification of the memory reconsolidation assist researchers to find potential treatments to disrupt the acquired conditioned drug memory, a few choices in this paradigm are provided. First, it is practical to use reconditioning protocol to reactivate the drug-induced CPP memory and one re-learning trial to assess the magnitude of the drug-induced CPP memory following its extinction. Second, use of reconditioning protocol as a means to reactivate the drug-induced CPP memory can assist to validate some theoretical arguments. Third, the drug-induced CPP memory and other previously-acquired memories should be simultaneously monitored to assure the specificity of memory reactivation and treatment.

Acknowledgments

We thank Ms. Yu-Ting Lai and Ms. Won-Ting Chang for their assistance in literature search. This work is supported, in part, by ROC National Science Council grants 97-2321-B-006-010- and 97-2410-H-006-074-MY3 to L.Y.

References

1. Abel, T. and Lattal, K.M. Molecular mechanisms of memory acquisition, consolidation and retrieval. *Curr. Opin. Neurobiol.* 11: 180-187, 2001.
2. Achat-Mendes, C., Ali, S.F. and Itzhak, Y. Differential effects of amphetamine-induced neurotoxicity on appetitve and aversive Pavlovian conditioning in mice. *Neuropsychopharmacology* 30: 1128-1137, 2005.
3. Achat-Mendes, C., Anderson, K.L. and Itzhak, Y. Impairment in consolidation of learned place preference following dopaminergic neurotoxicity in mice is ameliorated by N-acetylcysteine but not D1 and D2 dopamine receptor agonists. *Neuropsychopharmacology* 32: 531-541, 2007.
4. Berke, J.D. and Hyman, S.E. Addiction, dopamine, and the molecular mechanisms of memory. *Neuron* 25: 515-532, 2000.
5. Benturquia, N., Le Guen, S., Cane Strelli, C., Lagente, V., Apiou, G., Roques, B.P. and Noble, F. Specific blockade of morphine- and cocaine-induced reinforcing effects in conditioned place preference by nitrous oxide in mice. *Neuroscience* 149: 477-486, 2007.
6. Bernardi, R.E., Lattal, K.M. and Berger, S.P. Postretrieval propranolol disrupts a cocaine conditioned place preference. *Neuroreport* 17: 1443-1447, 2006.
7. Biala, G., Betancur, C., Mansuy, I.M. and Giros, B. The reinforcing effects of chronic D-amphetamine and morphine are impaired in a line of memory-deficient mice overexpressing calcineurin. *Eur. J. Neurosci*. 21: 3089-3096, 2005.
8. Blaiss, C.A. and Janak, P.H. Post-training and post-reactivation administration of amphetamine enhances morphine conditioned place preference. *Behav. Brain Res.* 171: 329-337, 2006.
9. Bossert, J.M., Busch, R.F. and Gray, S.M. The novel mGluR2/3 agonist LY379268 attenuates cue-induced reinstatement of heroin seeking. *Neuroreport* 16: 1013-1016, 2005.
10. Brabant, C., Quertemont, E. and Tirelli, E. Influence of the dose and the number of drug-context pairings on the magnitude and the long-lasting retention of cocaine-induced conditioned place preference in C57BL/6J mice. *Psychopharmacology* (Berl) 180: 33-40, 2005.
11. Brown, T.E., Forquer, M.R., Cocking, D.L., Jansen, H.T., Harding, J.W. and Sorg, B.A. Role of matrix metalloproteinases in the acquisition and reconsolidation of cocaine-induced conditioned place preference. *Learn. Memory* 14: 214-223, 2007.
12. Burns, L.H., Everitt, B.J. and Robbins, T.W. Differential effects of excitotoxic lesions of the basolateral amygdale, ventral subiculum and medial prefrontal cortex on responding with conditioned reinforcement and locomotor activity potentiated by intra-accumbens infusions of d-amphetamine. *Behv. Brain Res.* 55: 167-183, 1993.
13. Chen, J.H., Liang, J., Wang, G.B., Han, J.S. and Cui, C.L. Repeated 2 Hz peripheral electrical stimulations suppress morphine-induced CPP and improve spatial memory ability in rats. *Exp. Neurol.* 194: 550-556, 2005.
14. Cherng, C.G., Tsai, C.W., Tsai, Y.P., Ho, M.C., Kao, S.F. and Yu, L. Methamphetamine-disrupted sensory processing mediates conditioned place preference. *Behav. Brain Res*. 182: 103-108, 2007.
15. Ciccocioppo, R., Sanna, P.P. and Weiss, F. Cocaine-predictive stimulus induces drug-seeking behavior and neural activation in limbic brain regions after multiple months of abstinence: reversal by D1 antagonists. *Proc. Natl. Acad. Sci. U.S.A.* 98: 1976-1981, 2001.

16. Dackis, C.A. and O'Brien, C.P. Cocaine dependence: a disease of the brain's reward centers. *J. Subst. Abuse Treat*. 21: 111-117, 2001.
17. Dallimore, J.E., Mickiewicz, A.L. and Napier, T.C. Intra-ventral pallidal glutamate antagonists block expression of morphine-induced place preference. *Behav. Neurosci*. 120: 1103-1114, 2006.
18. Di Chiara, G. Drug addiction as dopamine-dependent associative learning disorder. *Eur. J. Pharmacol*. 375: 13-30, 1999.
19. Diergaarde, L., Schoffelmeer, A.N.M. and De Vries, T.J. Pharmacological manipulation of memory reconsolidation: Towards a novel treatment of pathogenic memories. *Eur. J. Pharmacol.* 585: 453-457, 2008.
20. Dong, Z., Han, H., Wang, M., Xu, L., Hao, W. and Cao, J. Morphine conditioned place preference depends on glucocorticoid receptors in both hippocampus and nucleus accumbens. *Hippocampus* 16: 809-813, 2006.
21. Dravolina, O.A., Zakharova, E.S., Shekunova, E.V., Zvartau, E.E., Danysz, W. and Bespalov, A.Y. MGlu1 receptor blockade attenuates cue- and nicotine-induced reinstatement of extinguished nicotine self-administration behavior in rats. *Neuropharmacology* 52: 263-269, 2007.
22. Diagnostic and Statistical Manual of Mental Disorders, the 4th edi., the *American Psychiatric Association*, 1994.
23. Dudai, Y. Molecular bases of long-term memories: a question of persistence. *Curr. Opin. Neurobiol*. 12: 211-216, 2002.
24. Dudai, Y. and Eisenberg, M. Rites of passage of the engram: reconsolidation and the lingering consolidation hypothesis. *Neuron* 44: 93-100, 2004.
25. Ehrman, R.N., Robbins, S.J., Childress, A.R. and O'Brien, C.P. Conditioned responses to cocaine-related stimuli in cocaine abuse patients. *Psychopharmacology* (Berlin) 107: 523-529, 1992.
26. Engblom, D., Bilbao, A., Sanchis-Segura, C., Dahan, L., Perreau-Lenz, S., Balland, B., Parkitna, J.R., Lujan, R., Halbout, B., Mameli, M., Parlato, R., Sprengel, R., Luscher, C., Schutz, G. and Spanagel, R. Glutamate receptors on dopamine neurons control the persistence of cocaine seeking. *Neuron* 59: 497-508, 2008.
27. Everitt, B.J., Morris, K.A., O'Brien, A. and Robbins, T.W. The basolateral amygdale-ventral striatal system and conditioned place preference: further evidence of limbic-striatal interactions underlying reward-related process. *Neuroscience* 42: 1-18, 1991.
28. Everitt, B.J. and Robbins, T.W. Neural system of reinforcement for drug addiction: from actions to habits to compulsion. *Nat. Neurosci*. 8: 1481-1489, 2005.
29. Feltenstein, M.W. and See, R.E. Potentiation of cue-induced reinstatement of cocaine-seeking in rats by the anxiogenic drug yohimbine. *Behav. Brain Res*. 174: 1-8, 2006. .
30. Feltenstein, M.W. and See, R.E. The neurocircuitry of addiction: an overview. *Brit. J. Pharmacol*. doi:10.1038/bjp.2008.51, 2008.
31. Goldstein, R.Z. and Volkow, N.D. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am. J. Psychit*. 159: 1642-1652, 2002.
32. Harris, G.C., Wimmer, M., Byrne, R. and Aston-Jones, G. Glutamate-associated plasticity in the ventral tegmental area is necessary for conditioning environmental stimuli with morphine. *Neuroscience* 129: 841-847, 2004.
33. Hsu, E.H., Schroeder, J.P. and Packard, M.G. The amygdale mediates memory consolidation for an amphetamine conditioned place preference. *Behav. Brain Res.* 129: 93-100, 2002.
34. Hyman, S.E. and Malenka, R.C. Addiction and the brain: the neurobiology of compulsion and its persistence. *Nat. Rev. Neurosci*. 2: 695-703, 2001.
35. Itzhak, Y. and Anderson, K.L. Memory reconsolidation of cocaine-associatedncontext requires nitri oxide signaling. *Synapse* 61: 1002-1005, 2007.
36. Jentsch, J.D. and Taylor, J.R. Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology* 146: 373-390, 1999.
37. Kelley, J.B., Anderson, K.L. and Itzhak, Y. Long-term memory of cocaine-associated context:disruption and reinstatement. *Neuroreport* 18: 777-780, 2007.
38. Kransnova, I.N., Li, S.M., Wood, W.H., McCoy, M.T., Prabhu, V.V., Becker, K.G., Katz, J.L. and Cadet, J.L. Transcriptional responses to reinforcing effects of cocaine in the rat hippocampus and cortex. *Genes Brain Behav*. 7: 193-202, 2008.
39. Kuo, Y.M., Liang, K.C., Chen, H.H., Cherng, C.G., Lee, H.T., Lin, Y., Huang, A.M., Liao, R.M. and Yu, L. Cocaine- but not methamphetamine-associated memory requires de novo protein synthesis. *Neurobiol. Learn. Mem*. 87: 93-100, 2007.
40. Li, Y-Q., Li, F-Q., Wang, X-Y., Wu, P., Zhao, M., Xu, C-M., Shaham, Y. and Lu, L. Central amygdale extracellular signal-regulated kinase signaling pathway is critical to incubation of opiate craving. *J. Neurosci*. 28: 13248-13257, 2008.
41. Lien, W.H., Yeh, T.L., Yang, Y.K., Cherng, C.F., Chen, H.H., Chen, P.S. and Yu, L. Cycloheximide enhances maintenance of methamphetamine-induced conditioned place preference. *Chinese J. Physiol*. 47: 23-30, 2004.
42. Martin, J.L. and Itzhak, J. 7-Nitroindazole blocks nicotine-induced conditioned place preference but not LiCl-induced conditioned place aversion. *Neuroreport* 11: 947-949, 2000.
43. Meyers, R.A., Zavala, A.R., Speer, C.M. and Neisewander, J.L. Dorsal hippocampus inhibition disrupts acquisition and expression, but not consolidation, of cocaine conditioned place preference. *Behav. Neurosci*. 120: 401-412, 2006.
44. Milekic, M.H., Brown, S.D., Castellini, C. and Alberini, C.M. Persistent disruption of an established morphine conditioned place preference. *J. Neurosci*. 26: 3010-3020, 2006.
45. Miller, C.A. and Marshall, J.F. Molecular substrates for retrieval and reconsolidation of cocaine-associated contextual memory. *Neuron* 47: 873-884, 2005.
46. Moffett, M.C. and Goeders, N.E. CP-154,526, a CRF type-1 receptor antagonist, attenuates the cue-and methamphetamine-induced reinstatement of extinguished methamphetamine-seeking behavior in rats. *Psychopharmacology* (Berlin) 190: 171-180, 2007.
47. Moore, H. and Grace, A.A. Interaction between amygdale and prefrontal cortical afferents to the nucleus accumbens and their modulation by dopamine receptor activation. *Soc. Neurosci. Abstr*. 22: 1088, 1996.
48. Nader, K., Schafe, G.E. and LeDoux, J.E. The labile nature of consolidation theory. *Nat. Rev. Neurosci.* 1: 216-219, 2000.
49. O'Brien, C.P., Childress, A.R., Ehrman, R. and Robbins, S.J. Conditioning factors in drug abuse: can they explain compulsion? *J. Psychopharmacol.* 12:15-22, 1998.
50. O'Brien, C.P., Childress, A.R., McLellan, A.T. and Ehrman, R. Classical conditioning in drug-dependent humans. *Ann. N.Y. Acad. Sci*. 654: 400-415, 1992.
51. Popik, P., Kozela, E., Wrobel, M., Wozniak, K.M. and Slusher, B.S. Morphine tolerance and reward but not expression of morphine dependence are inhibited by the selective glutamate carboxypeptidase II (GCP II, NAALADase) inhibitor, 2-PMPA. *Neuropsychopharmacology* 28: 457-467, 2003.
52. Rescorla, R.A. Retraining of extinguished Pavlovian stumuli. *J. Exper. Psychol.: Anim. Behav. Process*. 27: 115-124, 2001.
53. Riccio, D.C. and Richardson, R. The status of experimentally induced amnesias: gone, but not forgotten. *Physiol. Psychol*. 12: 59-72, 1984.
54. Rogers, J.L. and See, R.E. Selective inactivation of the ventral hippocampus attenuates cue-induced and cocaine-primed reinstatement of drug-seeking in rats. *Neurobiol. Learn. Mem*. 87: 688-692, 2007.
55. Robinson, T.E. and Berridge, K.C. The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res.*

Rev. 18: 247-291, 1993.
56. Robinson, M.J. and Franklin, K.B. Central but not peripheral beta-adrenergic antagonism blocks reconsolidation for a morphine place preference. *Behav. Brain Res*. 182: 129-134, 2007a.
57. Robinson, M.J. and Franklin, K.B. Effects of anisomycin on consolidation and reconsolidation of a morphine-conditioned place preference. *Behav. Brain Re*s. 178: 146-153, 2007b.
58. Sadler, R., Herzig, V. and Schmidt, W.J. Repeated treatment with the NMDA antagonist MK-801 disrupts reconsolidation of memory for amphetamine-conditioned place preference. *Behav. Pharmacol.* 18: 699-703, 2007.
59. Sakurai, S., Yu, L. and Tan, S.E. Roles of hippocampal N-methyl-D-aspartate receptors and calcium/calmodulin-dependent protein kinase II in amphetamine-produced conditioned place preference in rats. *Behav. Pharmacol*. 18: 497-506, 2007.
60. Sanchez, C.J. and Sorg, B.A. Conditioned fear stimuli reinstate cocaine-induced conditioned place preference. *Brain Res*. 908: 86-92, 2001.
61. Santini, E., Muller, R.U. and Quirk, G.J. Consolidation of extinction learning involves transfer from NMDA-independent to NMDA-dependent memory. *J. Neurosci*. 21: 9009-9017, 2001.
62. Sara, S.J. Retrieval and reconsolidation: toward a neurobiology of remembering. *Learn. Memory* 7: 73-84, 2000.
63. Schroeder, J.P. and Packard, M.G. Posttraining intra-basolateral amygdale scopolamine impairs food- and amphetamine-induced conditioned place preferences. *Behav. Neurosci*. 116: 922-927, 2002.
64. Shams, J., Sahraei, H., Gholami, A., Haeri-Rohani, A., Alaf-Javadi, M., Sepehri, H., Salimi, S.H. and Ghoshooni, H. Effects of ultra-low doses of nicotine on the expression of morphine-induced conditioned place preference in mice. *Behav. Pharmacol*. 17: 629-635, 2006.
65. Sharifzadeh, M., Haghighat, A., Tahsili-Fahadan, P., Khalaj, S., Zarrindast, M.R. and Zamanian, A.R. Intra-hippocampal inhibition of protein kinase AII attenuates morphine-induced conditioned place preference. *Pharamcol. Biochem. Behav*. 85: 705-712, 2006.
66. Tan, H., Liu, N., Wilson, F.A. and Ma, Y. Effects of scomolamine on morphine-induced conditioned place preference in mice. *Addict. Biol*. 12: 463-469, 2007.
67. Tiffany, S.T. A cognitive model of drug urges and drug-use behavior:role of automatic and nonautomatic processes. *Psychol. Rev*. 97: 147-168, 1990.
68. Tronson, N.C. and Taylor, J.R. Molecular mechanisms of memory reconsolidation. *Nat. Rev. Neurosci.* 8: 262-275, 2007.
69. Valjent, E., Corbille, A.G., Bertran-Gonzalez, J., Herve, D. and Girault, J.A. Inhibition of ERK pathway or protein synthesis during reexposure to drugs of abuse erases previously learned place preference. *Proc. Natl. Acad. Sci. U.S.A.* 103: 2932-2937, 2006.
70. Volkow, N.D., Wang, G-J., Telang, F., Fowler, J.S., Logan, J., Childress, A-R., Jayne, M., Ma, Y. and Wong, C. Cocaine cues and dopamine in dorsal striatum: Mechanism of craving in cocaine addiction. *J. Neurosci*. 26: 6583-6588, 2006.
71. Wagner, F.A. and Anthony, J.C. From first drug use to drug dependence; developmental periods of risk for dependence upon marijuana, cocaine and alcohol. *Neuropsychopharmacology* 26: 479-488, 2002.
72. Wang, X-Y., Zhao, M., Ghitza, U.E., Li, Y-Q. and Lu, L. Stress impairs reconsolidation of drug memory *via* glucocorticoid receptors in the basolateral amygdale. *J. Neurosci*. 28: 5602-5610, 2008.
73. Wolfling, K., Flor, H. and Grusser, S.M. Psychophysiological responses to drug-associated stimuli in chronic heavy cannabis use. *Eur. J. Neurosci*. 27: 976-983, 2008.
74. Yan, Y., Yamada, K., Nitta, A. and Nabeshima, T. Transient drug-primed but persistent cue-induced reinstatement of extinguished methamphetamine-seeking behavior in mice. *Behav. Brain Res*. 177: 261-268, 2007.
75. Yonghui, L., Xigeng, Z., Yunjing, B., Xiaoyan, Y. and Nan, S. Opposite effects of MK-801 on the expression of food and morphine-induced conditioned place preference in rats. *J. Psychopharm.* 20: 40-46, 2006.
76. Zhao, Y., Dayas, C.V., Aujla, H., Baptista, M.A., Martin-Fardon, R. and Weiss, F. Activation of group II metabotropic glutamate receptors attenuates both stress and cue-induced ethanol-seeking and modulates c-fos expression in the hippocampus and amygdala. *J. Neurosci*. 26: 9967-9974, 2006. .
77. Zhao, M., Zhang, Z.Y., Zhai, H.F., Qiu, Y. and Lu, L. Effects of stress during reactivation on rewarding memory. *Neuroreport* 18: 1153-1156, 2007.