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Pharmacological enhancement of drug cue extinction learning: translational challenges

K.M. Kantak and **B.Á. Nic Dhonnchadha**
Laboratory of Behavioral Neuroscience, Department of Psychology, Boston University, Boston, Massachusetts

Abstract

Augmentation of cue exposure (extinction) therapy with cognitive-enhancing pharmacotherapy may constitute a rational strategy for the clinical management of drug relapse. While certain success has been reported for this form of therapy in anxiety disorders, in this article we highlight several obstacles that may undermine the efficacy of exposure therapy for substance use disorders. We also review translational studies that have evaluated the facilitative effects of the cognitive enhancer D-cycloserine on extinction targeting drug-related cues. Finally, important considerations for the design and implementation of future studies evaluating exposure therapy combined with pharmacotherapy for substance use disorders are discussed.

Keywords

addiction; anxiety; cognitive enhancement; drugs of abuse; exposure therapy; extinction

Exposure therapy for substance use disorders

Exposure therapy is an effective approach for the treatment of anxiety disorders (for review see1). To implement this approach, patients are confronted repeatedly with feared stimuli under carefully controlled conditions. The goal is to extinguish fear to the degree that patients acquire a sense of safety in the presence of these stimuli. Overall, the efficacy of exposure therapy for anxiety disorders is equivalent or superior to medications.2 Unlike the relapse to anxiety that often is observed when medication is discontinued, short-term exposure therapy can provide long-term relief. Given the high degree of success of exposure therapy for extinguishing emotional reactions to feared stimuli and preventing relapse to anxiety, it is reasonable to assume that a similar degree of success could be attained in the treatment of substance use disorders, as stimuli paired with drug use elicit craving and relapse to drug-taking.3

In 2002, Conklin and Tiffany[4] conducted a meta-analysis of past studies on the efficacy of exposure therapy for substance use disorders. Their main conclusion was that exposure therapy for treating alcohol, nicotine, opiate, and cocaine addictions often fail, as evidenced by an overall non-significant effect size of d = 0.0868. Recent studies confirm earlier findings.

Correspondence: Kathleen M Kantak, PhD Laboratory of Behavioral Neuroscience Department of Psychology Boston University 64 Cummington Street Boston, MA 02215 kkantak@bu.edu.

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Alcohol

In individuals with alcohol misuse and problems controlling consumption when dysphoric, comparisons of Cognitive Behavioral Therapy (CBT) provided either alone, with alcohol cue exposure, or with emotional cue exposure, was performed.5 While average improvements were found across therapy conditions, both treatment retention and effects on alcohol consumption were progressively weaker with CBT + alcohol cue exposure and CBT + emotional cue exposure than with CBT alone. However, changes in alcohol dependence did not differ across therapy conditions. Some may argue6 that the failure to observe a benefit from exposure therapy for substance use disorders is related to the fact that a reduction in cue reactivity does not generalize beyond the treatment setting (context specific extinction) and is restored easily in the natural environment (renewal effect). To address this issue experimentally, Mackillop and Lisman7 studied heavy drinkers who were randomized to one of three groups: single context extinction for three sessions followed by a context shift for the fourth session; multiple context extinction for four sessions; and a pseudo-extinction control where neutral cues were presented for three sessions followed by exposure to alcohol cues for the fourth session. Subjects urge to drink declined over the course of exposure therapy. Contrary to expectations, cue-elicited craving was not restored as a result of a context shift and a greater extinction via exposure in multiple contexts was not exhibited. Others have reported similar findings of no renewal effect in alcohol-dependent outpatients.8 These findings suggest that heavy drinking impairs the extinction learning process per se such that individuals are insensitive to factors that normally impact extinction learning. The renewal effect has been observed, for example, in social drinkers undergoing cue exposure procedures in a context different from the test context9 suggesting intact extinction learning. Interestingly, non-problem drinkers wishing to achieve a goal of moderate drinking showed significantly greater reductions in drinking frequency and consumption on each occasion after exposure therapy compared to standard CBT alone.10 Benefits of exposure therapy have been observed also in patients with moderate severity of alcohol dependence, as determined by drinking behavior at 6-month follow-up.[11] Based on alcohol use studies, it appears that extinction of drug cues is an ineffective way to reduce relapse in severely dependent individuals. Context-specificity of extinction may account for some of the poor efficacy of exposure therapy for substance use disorders, but clearly, other mitigating factors must play a role in severely dependent individuals.

Nicotine

Abstinence rates in smokers undergoing exposure therapy have been evaluated through 12-month follow-up.[12] During five sessions of exposure therapy, the urge to smoke decreased from the beginning of treatment to the end of treatment. However, abstinence rates progressively declined from 1-month follow-up (32.3%) to 12-month follow-up (9.1%). Overall, exposure therapy was no more effective than CBT alone, CBT+ nicotine gum, and exposure therapy + nicotine gum in preventing relapse. It was suggested than the use of imagery cues rather than direct *in vivo* cues may have contributed to the failure to observe a benefit from exposure therapy. In a virtual environment version of exposure therapy, craving for cigarettes gradually decreased across six therapy sessions, but this was correlated with the reduction in the smoking count between the morning before the experiment and the start of the experiment.[13] Follow-up procedures were not implemented to determine if any long-term benefits of exposure therapy were evident. Others[14] using *in vivo* cues, reported a small reduction in the urge to smoke within, but not between, two exposure therapy sessions in control subjects. Assessment of smoking behavior at 1- and 4-week follow-up revealed no significant changes. Unfortunately, smoking cue-reactivity was not measured at follow-up, which could have been used to determine whether cue-reactivity outside the therapy sessions

was attenuated or not. In addition, subjects were not asked to refrain from smoking between the therapy sessions.

Opiates

Opiate-dependent individuals undergoing a 10-week inpatient treatment program combined with exposure therapy (six sessions over three weeks) or a control treatment were evaluated for cue reactivity and for cue-elicited craving, withdrawal responses and negative mood at 6 weeks and 6 months post-treatment.[15] While there were decreases in all measures, cue exposure and control subjects did not differ in cue-reactivity during treatment or at follow-up. These findings suggest no added benefit of exposure therapy following withdrawal in opiate-dependent individuals. In another study in opiate-dependent individuals undergoing exposure therapy or a control treatment, decreases in self-reported cue-reactivity also were found in the two groups, which did not differ from one another.16 Further assessments revealed that the group undergoing exposed therapy had higher dropout and relapse rates, suggesting a worse outcome with exposure therapy in opiate-dependent individuals. Recently, it has been shown that opiate-dependent women exhibit stronger heroin craving than opiate-dependent men to imagery cues but no sex differences in heroin craving in response to drug paraphernalia.17 Thus, external contextual cues may be especially meaningful to target for therapy in the majority of opiate-dependent men and at least a subset of opiate-dependent women.

Cocaine

Stimuli that trigger relapse in individuals addicted to cocaine (e.g. sight of a syringe, drug-talk, cook-up paraphernalia) elicit cocaine craving and physiological arousal (e.g. changes in pulse, blood pressure, skin resistance and skin temperature). One of the first exposure-based studies in individuals addicted to cocaine[18] used systematic cue exposure (exposure via audiotape, videotape and simulated cocaine rituals) in abstinent patients (15 sessions over a 2-week inpatient period). Results were preliminary and showed that physiological arousal (a reduction in skin temperature) declined within each exposure therapy session but was greater after session 15 than session 1. In contrast, subjective ratings (“craving”, “high” and “crash”) declined gradually from session 1 through session 15 of exposure therapy. These findings suggest that physiological arousal to cocaine cues is more persistent than psychological arousal. In a follow-up report to this study,19 patients who received exposure therapy rather than the control therapy showed better retention and more cocaine-free urines during outpatient therapy that was continued weekly for 2 months after discharge. Overall, though, the effects were modest and were quickly undermined by concomitant drug use.

Factors contributing to poor efficacy of exposure therapy for substance use disorders

Based on the above accounts, several factors seem to undermine the efficacy of exposure therapy for substance use disorders. These include the severity of the addiction, concomitant use of abused drugs between therapy sessions, and context specificity of exposure therapy. To a certain extent, these three factors may co-vary with a fourth factor, neurocognitive deficits associated with chronic drug use, particularly in individuals who are most severely dependent. This next section explores the relationship between brain sites that are important for effective extinction learning and brain sites whose learning, memory, and executive functions are impaired by chronic drug use.

Neurosubstrates of extinction learning

The identification of the anatomical substrates of extinction learning is an important step in the development and improvement of exposure therapy treatment for substance abuse disorders. In a typical fear conditioning paradigm, a conditioned stimulus (CS), such as a tone, light or odor, is paired with an aversive unconditioned stimulus (US), such as a footshock. After repeated pairing, later presentations of the CS alone elicit a constellation of behavioral and physiological fear responses (conditioned responses, CR) such as freezing and increased startle reflexes. Subsequent repeated presentation of the CS alone, in the absence of the US, leads to extinction of these conditioned fear responses. There is now considerable evidence that extinction is not simply the forgetting of the previously learned association but rather a new, active learning process of inhibitory associations that compete with and ultimately dominate over the previously conditioned response.[20] Evidence indicates that extinction may involve circuits and use mechanism of synaptic plasticity similar to those of conditioned fear learning. Even though the areas and, to an extent, the molecular mechanisms involved in fear extinction learning vary with the task employed, research in rats using pharmacological manipulations, correlative molecular studies and electrophysiology emphasize interactions among several brain regions, most notably the amygdala, the ventromedial prefrontal cortex (vmPFC) and hippocampus in fear extinction learning and memory.

Amygdala

Given its pivotal role in the learning and expression of conditioned fear 21,[22] it is not surprising that the amygdala is also a site of plasticity in fear extinction learning. Electrophysiological studies have established a strong case for cellular plasticity in the amygdala during the acquisition phase of extinction. When the CS is presented in the absence of the US, neurons in the basolateral amygdala (BLA) show reduced firing [23],24 whereas a different population of neurons show high activity to the CS or resistance to extinction.25 This supports the theory that extinction is not an erasure of the original memory and implies that the amygdala not only supports the maintenance of the original memory, but also facilitates extinction learning.26 Temporary inactivation of BLA neuronal activity [27–30] impairs fear extinction learning, further supporting the dependence of fear extinction learning on intact amygdalar function.

Ventromedial prefrontal cortex

The vmPFC (infralimbic and prelimbic cortex of rats) appears to be an important locus for the consolidation and subsequent retrieval of extinction memory. This is based on studies demonstrating normal extinction learning following lesions or temporary inactivation of the vmPFC.[21] However, impaired extinction recall was observed when animals were exposed to the CS 24hrs after extinction training, showing similar levels of the conditioned response as those animals that had not undergone extinction training.21 Paralleling vmPFC lesion findings, electrophysiological studies have shown that activity of vmPFC neurons remains unchanged across extinction sessions but show increased activity to the CS during extinction retrieval.31,32

Pharmacological manipulations restricted to the vmPFC typically lead to normal inhibition of fear responses across extinction but impaired retention of this inhibition the following day.[33–36] Infusion studies showing that disruption of protein synthesis [34] MAPK blockade [37,35] and administration of a NMDA receptor antagonist [29,33,36] within the vmPFC all impair retrieval of extinction suggest that the plasticity in this region supports consolidation of extinction learning. In each case, delaying the infusion 2 or 4 hours after extinction eliminated the effect, consistent with a time-limited role of molecular processes in

consolidation of extinction.[38] Overall, these findings are consistent with both consolidation and retrieval roles of vmPFC in extinction.

Hippocampus

Several studies have shown that the hippocampus has an important role in encoding contextual information to label and retrieve memories.[39,40] Reversible inactivation of the dorsal hippocampus impairs the context-specific expression of extinction.[41–43] Furthermore, rats with hippocampal lesions show impaired contextual reinstatement of conditioned fear.[44] Contextual information has a critical function in determining whether the original fear memory or the new extinction memory should control fear expression and the hippocampus is thought to have a central role in the contextual modulation of extinction recall.[45,26]

Stimulation of the hippocampus induces bursting in vmPFC [46,35] and modulates the response of vmPFC neurons to BLA inputs.[47] Although clarification of the precise circuitry requires further investigation, there is strong evidence that the hippocampus, through communication with the vmPFC [48] and the amygdala [49,50] regulates the contextual modulation of fear expression during extinction retrieval.[51–54] Thus, the current model of extinction learning proposes that the expression of fear extinction i.e., the reduction of the conditioned response, results from inhibition of the amygdala following activation of the vmPFC. The hippocampus can either excite or inhibit the vmPFC, allowing for the context modulation of extinction.[55] Therefore, the amygdala, the hippocampus, and the vmPFC are critical structures for fear extinction in rats. While much of the information gained so far concerning neurosubstrates of extinction learning is based on fear responses, it is possible that this same network underlies drug cue extinction learning and consolidation.[56]

Neurocognitive deficits associated with abused substance

The majority of clinical studies examining neurocognitive deficits associated with abused substances have focused on executive functions of the prefrontal cortex. This includes effects on attention, working memory and impulsivity. Less well-studied are the effects of abused substances on the neurocognitive functions of other memory systems involved in associative learning and memory, such as the amygdala and hippocampus. Importantly, drug-related deficits in executive functions and associative learning and memory are consistent with studies showing that chronic drug use (cocaine, opiates, alcohol and nicotine) is associated with volume reductions, gray or white matter loss, and/or reduced cellular activity within the prefrontal cortex, amygdala and hippocampus.[57–63]

Attention

Electophysiological (P300 event-related potentials) measures of selective attention consistently have revealed deficits (reduced amplitude) in abstinent cocaine dependent individuals compared to controls.[64–67] A similar deficit was reported in abstinent individuals dependent on opiates, alcohol, or cocaine + alcohol.[66,68] Effects on tasks measuring sustained attention are less consistent in that enhanced performance [69,70] and reduced performance [71,64] have been reported in cocaine dependent individuals. The extent and severity of cocaine use in these studies may have been a mitigating factor for these divergent findings. Notably, research has indicated that recent cocaine use may mask underlying neurocognitive deficits, including deficits on measures of attention.[72,73] Furthermore, use of nicotine, which improves attention, also may mask attention deficits induced by abstinence from other drugs of abuse.[74,75]

Working memory

Among executive functions in polydrug-dependent individuals (alcohol, cocaine, heroin), working memory is the component that shows the highest impairment [76]. In 48% of individuals, moderate to severe impairment in the performance of at least one test of working memory was observed. Recreational polydrug users, on the other hand, do not show working memory performance deficits,77 suggesting that the severity of addiction is an important factor for exhibiting working memory impairments.

Working memory impairments are associated with the abuse of individual drugs as well. Pronounced disruptions are observed in abstinent individuals who have abused alcohol,[78,79] cocaine,[78,80–82] or heroin,[83] and in patients maintained on methadone.[84,85] Nicotine abstinence also produces deficits in working memory, which can be relieved by a resumption of smoking.[86–90]

Impulsivity

While impulsivity is a risk factor that predicts vulnerability for drug abuse, it also is a consequence of chronic drug use.[91] Impulsivity measured via probabilistic reversal learning, response inhibition, or delayed discounting is associated with a number of drugs of abuse in human subjects.

Cocaine-dependent individuals were shown to exhibit greater impulsivity (higher rates of discounted rewards) than controls in a delayed discounting procedure for either hypothetical monetary rewards or crack/cocaine rewards.[92] Cocaine/crack rewards were discounted at a higher rate than monetary rewards. Chronic cocaine users also were shown to engage in perseverative responding in a probabilistic reversal-learning task, demonstrating greater impulsivity compared to non-drug-taking controls, former cocaine users and current or former heroin users.93 Similar differences in the display of impulsivity between cocaine and heroin abusers are reported in other studies measuring response inhibition 94 and delay discounting.95 However, several studies have shown that heroin-dependent individuals exhibit risky choices on a delayed discounting task for hypothetical monetary or heroin rewards. Interestingly, in heroin-dependent individuals, delayed heroin rewards were discounted at a higher rate than monetary rewards.[96–98] When opioid-deprived, discounting of both monetary and heroin rewards was greater than when not deprived of opioids via buprenorphine maintenance therapy.[99] These findings suggest that motivational factors may be important in both cocaine and heroin abusers for acting impulsively.

Smokers also show drug-related impulsive choice. Smokers deprived of nicotine for 24 hr showed an increased preference for immediate cigarettes over delayed money, but did not alter preference for immediate money over delayed money.[100] In a later study, smokers exhibited more pronounced delay discounting of hypothetical cigarette and monetary rewards when deprived of nicotine for 13 hr compared to *ad libitum* smoking.[101] The use of small, real ($10) maximal monetary rewards in the former study vs. large, hypothetical ($10,000) maximal monetary rewards in the latter study may account for these different findings, and suggest that motivational factors are important in smokers as well. Collectively, findings suggest that the nicotine deprivation effect on impulsive choice is associated mainly with the early stages of nicotine withdrawal.

In a comparison of active alcoholics, abstinent alcoholics, and controls, the most rapid discounting rates were measured in active alcoholics, while intermediate rates of discounting were measured in abstinent alcoholics.[102] Control subjects had the slowest rates of discounting. In both alcoholic groups, hypothetical alcohol rewards were discounted more rapidly than hypothetical monetary rewards. Abstinent alcoholics also were shown to be more impulsive than control subjects in studies measuring response inhibition.[103,104]

Moreover, across alcoholic subgroups, cigarette smoking positively correlated with impulsivity,[105] and smoking alcoholics were shown to have higher levels of impulsivity than non-smoking alcoholics.[106] These findings combined with those reviewed above on attention and working memory suggest that co-morbid dependence on alcohol and nicotine is a facilitating risk factor for executive dysfunction in general.

Associative learning and memory

Recognition of facial expression is a commonly used task to assess amygdala-related emotional functioning in human subjects,[107,108] Compared to cocaine naïve participants and occasional cocaine users, recreational cocaine users exhibited a reduced accuracy in recognizing fearful faces.[109] Alcoholic patients also had impairments in the recognizing fearful faces, but in this case, they overestimated the intensity of the amount of fear expressed in the faces.110 These enhanced fear responses were related to the number of previous detoxifications and are consistent with findings showing inappropriate generalization of learned fear responses with chronic alcohol use.111 Current opiate users compared to ex-opiate users were slower to recognize fearful facial expressions, but this was thought to reflect the sedative effects of their maintenance on methadone, as the current opiate users were slower also in recognizing surprise and happy facial expressions.112 In other studies, recently detoxified alcoholics and detoxified subjects with both alcohol and opiate dependence had lower accuracy scores for recognizing a range of emotional facial expressions, including fearful, compared to methadone-maintained opiate addicts and detoxified opiate addicts, who had lower accuracy scores than normal controls.[113] In contrast, nicotine withdrawal was shown not to influence the processing of affective (happy, angry, neutral) facial expression.[114] However, the effects of nicotine withdrawal on fearful facial expression are not known. These findings suggest that among a variety of abused drugs, alcohol may have the most severe impact on emotional facial expression reflecting altered amygdala functioning.

Object recognition and visuospatial memory are the typical measures used to study hippocampal learning functions in human subjects. Chronic heroin or amphetamine abusers both show profound impairments in a test of pattern recognition memory.83 More recently, it was demonstrated that current and former opiate-dependent and amphetamine-dependent individuals were more impaired in pattern recognition memory, particularly for male drug users.115 In alcoholics who did not smoke, visuospatial memory improved over 1 month of abstinence, but in alcoholics who smoked, visuospatial memory improvements were not apparent with alcohol abstinence.116 Thus, while sobriety improves alcohol-induced memory impairments, smoking behavior may undermine these improvements. Alcohol, nicotine, cocaine and opiates all have been shown to disrupt adult neurogenesis in the hippocampus, which may be linked to the deficits in hippocampus-related learning and memory with chronic drug use (for review see117).

Treatment with a cognitive enhancer and exposure therapy

As reviewed above, drugs of abuse have widespread influences on executive functions and associative learning and memory. These deficits reflect reduced functioning of the prefrontal cortex, amygdala and hippocampus. Given that the prefrontal cortex, amygdala and hippocampus are memory systems critical for effective extinction learning and consolidation, the failure of exposure therapy to be effective consistently in reducing drug relapse should not be too surprising. Even for anxiety disorders, exposure therapy is less effective if neurocognitive impairment is present.[118] While neurocognitive impairment may undermine extinction learning, new hope is afforded by research showing improved treatment outcome when extinction training or exposure therapy is combined with the cognitive-enhancing drug D-cycloserine (DCS).

DCS is a partial agonist at the strychnine-insensitive glycine site of NMDA receptors that enhances glutamate neurotransmission.[119,120] Activation of NMDA receptors leads to long-term potentiation and long-term depression, which are mechanisms of synaptic plasticity associated with learning and memory formation[121,122] as well as its extinction.[38,123] Thus, modulation of glutamate activity during extinction training may facilitate the process by which drug-paired cues lose salience and their control over behavior. The first studies showing the facilitative effects of DCS on extinction learning focused on conditioned fear in animals and anxiety disorders in humans. Translational studies have begun to emerge for evaluating the facilitative effects of DCS on extinction targeting drug-related cues. This approach differs significantly from other approaches that attempt to generally overcome the cognitive deficits associated with drug addiction by administering cognitive enhancers to improve treatment retention and outcome (for review see[124])

Fear, anxiety, and D-cycloserine

Numerous pre-clinical studies have demonstrated that DCS is a potent facilitator of fear extinction in rats (see[125] for review). Initial research revealed that rats administered systemic injections or BLA infusions of DCS prior to extinction training exhibited less of a fear response to the CS during a retention test than the saline-treated rats.[126] Furthermore, the effect of DCS on fear retention was observed only in rats that had received extinction training, suggesting that DCS acts specifically to enhance extinction, rather than simply interfering with response expression. The effect of DCS on fear retention was blocked by an antagonist at the glycine site, indicating that the facilitatory effects of DCS on fear extinction were mediated by interactions with the NMDA receptor complex.

Subsequent studies have since replicated these findings in other models of conditioned fear[127,128] in addition to demonstrating that post-extinction administration of DCS also facilitates extinction, implicating consolidation mechanisms.[129] Furthermore, this group established that the effects of DCS are time dependent, as increasing the delay of DCS administration after extinction training led to a linear decrease in the facilitatory effect.[127] Another important aspect of DCS is its ability to enhance the generalization of extinction to other CSs that have been paired with the same US, but not extinguished.[130]

The ability of DCS to prevent fear relapse has been examined using the reinstatement and renewal paradigms. Reinstatement refers to the return of conditioned responding to the CS that occurs when the US is presented after extinction,[131–133] whereas renewal is the recovery of conditioned responding to the CS that occurs when the context is changed after extinction. Reinstatement was not evident in the rats administered DCS after extinction training following US re-exposure.[128] However, despite facilitating extinction, DCS administration did not prevent a renewal effect from occurring when the CS was tested in the original context[134] indicating the context-dependent nature of the facilitatory effects of DCS.

Ressler and colleagues[135] conducted the first translational study on the effects exposure therapy combined with DCS in individuals with acrophobia (fear of heights). Subjects received placebo, 50 mg DCS, or 500 mg DCS 2 to 4 hr prior to two 35 to 45 min virtual reality (glass elevator) therapy sessions spaced 1 to 2 weeks apart. Anxiety and other measures were obtained at baseline, 1 week after the first therapy session, and again 1 to 2 weeks following the second therapy session, with follow-up at 3 months. Subjects treated with DCS experienced lower subjective levels of discomfort and rose to higher floors beginning with the second therapy session. Improvements relative to placebo continued at all post-treatment time points including at 3-month follow-up. A physiological measure of arousal linked to anxiety, fluctuation in skin conductance, was decreased in subjects treated

with DCS. Thus, extinction of fear was enhanced by DCS and was relatively robust and lasting.

Following this study, several others soon followed showing the beneficial effects of DCS combined with exposure therapy for anxiety-related disorders. A facilitation of exposure therapy by DCS was demonstrated for social anxiety disorder,[136,137] obsessive-compulsive disorder,[138,139] and panic disorder.[140] It should be noted that negative outcomes have been observed as well, in particular for obsessive-compulsive disorder[141] and for spider phobia.[142]

Drug addiction and D-cycloserine

Animal studies employing conditioned place preference and drug self-administration procedures have revealed the facilitative effects of DCS on drug cue extinction learning. Conditioned place preference assesses the ability of drugs of abuse to establish learnt contextual associations and provides a measure of conditioned drug reward.[143] The self-administration model uses operant responding (e.g. lever pressing) for drug delivery and measures the reinforcing effects of a drug. In this model, drug-seeking behavior is quantified as responding that is reinforced by the delivery of drug-associated cues in the absence of a drug reinforcer.[144] Drug-seeking behavior is analogous to cue reactivity in humans and is conceptualized as the sensitivity to drug-associated cues. Cue reactivity, as utilized in CBT, is associated with significant physiological arousal and subjective reactions to presentations of drug-related stimuli.145

Conditioned place preference

DCS administered systemically at doses of 15 and 30 mg/kg either before or immediately following extinction training sessions has been shown to facilitate a reduction in preference for a cocaine-paired environment in rats[146,147] and mice.[148,149] This effect in rats could be replicated by local injections made directly into the basolateral amygdala, indicating the involvement of this brain region for the acquisition and consolidation of new associations that are formed during cocaine cue extinction training.[146] Moreover, the effects of DCS were specific for extinction memory as the magnitude of cocaine conditioned place preference (original learning) was not affected when DCS was injected during the conditioning phase rather than the extinction phase.146 Facilitation of cocaine cue extinction by DCS also was shown to be time-dependent in that DCS lost its effectiveness if administered 4 hr after the extinction training sessions ended. Importantly, the effects of DCS on extinction of cocaine-conditioned place preference in rats were long-lasting, with facilitated extinction of preference still evident during tests conducted 2 weeks after the end of extinction training.146 It should be noted that DCS failed to maintain facilitated extinction of cocaine conditioned place preference when mice were tested 1–2 weeks after the end of extinction training.149 This may be explained by the results of a recent study conducted by Paolone and colleagues,147 which demonstrated that DCS did not facilitate extinction of cocaine conditioned place preference when the extinction procedures alone were intensive and effective in control animals (i.e. longer sessions and repeated extinction training). Rats and mice, however, differed in their reaction to a challenge dose of cocaine administered after the end of extinction training, suggesting that there may indeed be species difference in the long-term effects of DCS treatment. Rats treated with DCS during extinction training did not show reinstatement of extinguished cocaine conditioned place preference following a cocaine priming injection.[147] In contrast, extinguished cocaine conditioned place preference was reinstated by a cocaine priming injection in mice treated with DCS during extinction training.148

When examined in mice, similar doses of DCS administered prior to extinction trials failed to enhance the rate of extinction of ethanol conditioned place preference, but did delay subsequent reacquisition (i.e. when ethanol and the cues were re-introduced) of the extinguished place preference.[150] There is some suggestion that the cognitive-enhancing effects of DCS are strain-dependent in mice,151 thus the extinction-facilitating effects of DCS may not be evident in the DBA/2J strain used in this study. However, while facilitation of extinction was not observed directly during the extinction phase, DCS did enhance consolidation of extinction learning to impair the subsequent reacquisition process.

The conditioned place aversion paradigm, in which cues are paired with drug abstinence, can be used to study the withdrawal component of the conditioned response in animals.[152] An opiate receptor antagonist such as naloxone is used to precipitate withdrawal in opiate-dependent animals, thus establishing an aversion to the withdrawal-paired compartment. Administration of DCS immediately before extinction training has been shown to dramatically increase the rate of extinction of the naloxone-induced place aversion in morphine-dependent rats suggesting that extinction of conditioned drug withdrawal involves mechanisms similar to those involved in other types of drug-related extinction.[152] These findings are important because, in humans, drug-paired cues elicit not only drug craving but also conditioned withdrawal, which may trigger relapse.[153]

Drug self-administration

Administration of DCS (30 mg/kg) prior to extinction training resulted in facilitation of extinction learning and subsequent delay in reacquisition of cocaine self-administration in rats.[154] The effects of DCS were time-dependent and specific to its coupling with explicit extinction training. Employing similar conditions, pre-treatment with DCS (10mg/kg) failed to alter extinction training in monkeys; however, subsequent reacquisition of cocaine self-administration was deterred. This effect of DCS was specific for reacquisition of cocaine self-administration following extinction training as pretreatment with DCS prior to a self-administration control session did not reduce cocaine self-administration during the session or alter subsequent reacquisition. These results suggest that DCS augmented consolidation of extinction learning to deter reacquisition of cocaine self-administration in rats and monkeys. Along these same lines, ethanol self-administration studies demonstrated that rats receiving a low dose of DCS (5 mg/kg) prior to extinction sessions exhibited facilitated extinction learning and reduced alcohol-primed reinstatement.155 Collectively, these studies in mice, rats and monkeys suggest that DCS can facilitate extinction of cues associated with a variety of drugs of abuse and deter relapse to drug-seeking behavior.

Drug cue reactivity

Based on these preclinical studies, a critical question is: can DCS enhance the effectiveness of exposure therapy targeting drug-related cues in individuals addicted to drugs? Only two studies have been reported thus far. The first was a pilot study examining the effects of DCS on reactivity to smoking cues.[14] In a double-blind placebo-controlled fashion, subjects received 50 mg oral DCS or placebo 1 hr prior to each of two cue exposure sessions spaced two weeks apart using *in vivo* procedures (removing cigarette from pack and holding it, smelling it and placing it in ashtray in addition to flicking a lighter and holding the cigarette again, etc.). Subjects were assessed for physiological (skin conductance response) and psychological (self-report urge to smoke, questionnaire on smoking urges) aspects of smoking cue reactivity. In addition, smoking behavior (expired carbon monoxide and self-reported smoking) was assessed at 1- and 4-week follow-up. The results showed that both skin conductance and urge to smoke were reduced more in the DCS group than the placebo group after the second exposure therapy session, suggesting enhanced extinction of smoking cue reactivity. Assessment of smoking behavior at 1- and 4-week follow-up revealed no

significant differences. That subjects in this study were not asked to refrain from smoking (the US) between the therapy sessions may have undermined the efficacy of the extinction training for reducing relapse to smoking behavior. Re-exposure to a US strongly reinstates extinguished fear responses in animal studies,[128] suggesting re-exposure to a US interferes with consolidation of extinction learning.

A small pilot study examining reactivity to cocaine cues following exposure therapy combined with DCS treatment also has been reported.[156] In a randomized fashion, subjects received 50 mg oral DCS or placebo 2 hr prior to each of two cue exposure sessions conducted on consecutive days using *in vivo* procedures (handling a small bag of the subject's preferred style of simulated powder or crack cocaine, a crack pipe/lighter or razor blade/mirror, and a $20 bill). Subjects were assessed for physiological (heart rate) and psychological (craving) aspects of cocaine cue reactivity during 1 hr sessions. The craving measure was taken again at 1 week follow-up. Subjects treated with DCS showed a non-significant trend for increased craving during the first therapy session but no difference in craving during the second therapy session compared to placebo. Heart rate measurements were higher in the DCS group relative to the placebo group at baseline and during both therapy sessions. At 1 week follow-up, there were no significant group differences in craving, though the rating was lower in the DCS group than the placebo group. One possibility for these negative findings is that this study was underpowered (48.9%). Moreover, administration of DCS for two consecutive days may have undermined the efficacy of the extinction training. Fear conditioning studies in rats have shown that repeated administration of DCS over short intervals desensitizes the NMDA receptor and prevents a facilitation of extinction learning.[157–159]

Translational challenges

Timing and spacing of DCS therapy

As reviewed above in numerous preclinical studies, it is clear that the general mechanism by which DCS combined with cue extinction training reduces relapse is related to the facilitation of extinction consolidation.160 As 4 hr post-session is the theoretical time window for NMDA-dependent memory consolidation,161 and DCS levels in the cerebrospinal fluid peak more than 2 hr after oral dosing in humans,160 pretreatment times and the length of exposure therapy sessions need to be considered carefully in clinical studies. DCS levels that peak too late after the end of the exposure therapy sessions are likely to result in diminished effectiveness for facilitating drug cue extinction consolidation and preventing drug relapse (see 154). If levels were to peak too early in the exposure therapy sessions, it is likely that instead of facilitating extinction, DCS would facilitate reconsolidation of drug memory and enhance rather than prevent drug relapse (see162). Finally, if exposure therapy sessions with DCS are spaced too closely together, efficacy against relapse to drug-seeking behavior may be lost due to NMDAR desensitization (see146).

Drug reexposure

Preventing drug re-exposure before cue exposure therapy is completed would be difficult to achieve, yet it may be critically important for several reasons. First, it has been shown in animal studies that DCS-facilitated extinction learning using a single dosing strategy is perturbed when CS-US pairings are subsequently reintroduced, leading to reacquisition of fear.[130] Furthermore, when a second cycle of extinction training was attempted shortly after CS-US re-exposure, DCS failed to facilitate re-extinction of fear.[163] The authors suggested that in contrast to initial extinction, re-extinction processes are NMDA-independent, as evidenced by the lack of a facilitatory effect with DCS. These findings may be relevant

when considering treating individuals following a drug relapse episode shortly after exposure therapy is begun.

Post-session arousal

Post-session arousal may be particularly important to include when treating drug addicts with DCS combined with exposure therapy because DCS pretreatment times are selected in clinical studies to ensure peak brain levels near the end of the exposure therapy session when therapeutic extinction learning is undergoing consolidation.[164] Converging evidence suggests that arousal and accompanying release of endogenous glucocorticoids are critical for post-session memory consolidation.[165] Furthermore, elevated levels of glucocorticoids at the end of extinction training may be an important factor for observing augmented consolidation of extinction learning by post-session administration of DCS.[166] Along these lines, post-session administration of DCS during extinction training was not effective in reducing reacquisition of cocaine self-administration in rats unless arousing stimulation in the form of brief handing also was provided.[154] Brief handling in rats is a mild stressor that induces release of glucocorticoids[167] and has been shown to augment consolidation of fear extinction.[168] It should be noted that post-session arousal typically is not used in exposure therapy for anxiety disorders. Research in rats has shown that plasma glucocorticoid levels are significantly elevated for a substantial amount of time after fear extinction training ends, [169] which likely provides sufficient arousal to augment consolidation of fear extinction by post-session DCS administration. In contrast, in rats with a history of cocaine self-administration, plasma glucocorticoid levels are elevated primarily during the early stage of extinction training and then return to basal levels as the session progresses.[170] Thus, enhanced consolidation of drug cue extinction learning by DCS in human subjects may be difficult to achieve unless critical arousing stimulation is provided post-session to release endogenous glucocorticoids.

Cognitive restructuring

CBT for anxiety disorders typically includes several components, including cue exposure and activities designed to complement exposure interventions.[171] Additional activities include teaching patients to identify and challenge maladaptive thinking style and providing home practice strategies for redirecting attention away from cues that provoke anxiety. These activities are used to stabilize exposure treatment gains and assist in cognitive restructuring. In six of the eight studies reviewed above concerning anxiety disorders treatment with exposure therapy and DCS administration, multiple strategies were implemented in addition to cue exposure to provide a complete CBT package. Interestingly, in the DCS study showing facilitated extinction of smoking-related cues, guided imagery scripts were provided between the exposure sessions to highlight the health aspects of not smoking and encourage positive smoke-free living.[14] Exposure therapy was the sole intervention provided in the DCS study targeting cocaine-related cues, which showed no significant reduction in craving and no added benefit of DCS.[156] It is noteworthy that even without adjunct DCS, exposure therapy alone is highly efficacious for the treatment of anxiety disorders.[1] The main benefit of DCS coupled with exposure therapy for anxiety disorders is to dramatically lessen the number of exposure therapy sessions needed to reduce anxiety symptoms and prevent their return. CBT for substance use disorders typically has consisted of exposure therapy alone, and treatment outcomes were mainly negative.[4] As reviewed above, drugs of abuse impair both the structure and function of brain sites important for extinction learning. Thus, exposure therapy alone may not be sufficient to prevent relapse to drug-seeking behavior. Likewise, adding DCS to exposure therapy alone in addicts may not be sufficient in this regard; additional cognitive restructuring activities may be required. It is tempting to speculate that these additional activities may assist in re-

engaging the amygdala, hippocampus and prefrontal cortex for processing new learning that was experienced during exposure therapy sessions.

Conclusions

DCS, which targets the glycine site of NMDA receptors, shows some promise for augmenting exposure therapy in individuals with substance use disorders, though much more work is needed to establish its efficacy for facilitating drug cue extinction and attenuating drug relapse. Alternatives to treatment with DCS include D-serine, which also is an agonist at the glycine site. Relatively low doses (100 mg/kg) have been shown to facilitate the effects of extinction to reduce cocaine-primed reinstatement of drug-seeking behavior in rats trained to self-administer cocaine.[172] Another promising lead is through the use of glycine transporter-1 (Gly-T1) inhibitors that increase synaptic levels of glycine. Recently, it was shown in rats that by combining a GLY-T1 inhibitor with three weekly cocaine cue extinction-training sessions, extinction learning was facilitated, and subsequently, reacquisition of cocaine self-administration was attenuated.173 Thus, there may be other viable options for augmenting exposure therapy in drug addicts if DCS does not show sufficient efficacy in well-designed clinical studies.

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