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Using Conditioned Place Preference to Identify Relapse Prevention Medications

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Abstract

Stimuli, including contexts, which predict the availability or onset of a drug effect, can acquire conditioned incentive motivational properties. These conditioned properties endure after withdrawal, and can promote drug-seeking which may result in relapse. Conditioned place preference (CPP) assesses the associations between drugs and the context in which they are experienced. Here, we review the potential utility of CPP procedures in rodents and humans to evaluate medications that target conditioned drug-seeking responses. We discuss the translational potential of the CPP procedure from rodents to humans, and review findings with FDA-approved treatments that support the use of CPP to develop relapse-reduction medications. We also discuss challenges and methodological questions in applying the CPP procedure to this purpose. We argue that an efficient and valid CPP procedure in humans may reduce the burden of full clinical trials with drug-abusing patients that are currently required for testing promising treatments.

Indexing terms

Conditioned place preference; amphetamine; methamphetamine; mirtazapine; baclofen; varenicline; naltrexone; addiction therapy; rodents; humans

1. Introduction

Substance use disorders are difficult to treat, and relapse is extremely common even in individuals who are highly motivated to stop using their drug of choice. Currently, FDA-approved pharmacotherapies exist for the treatment of alcohol, nicotine, and heroin dependence but not for cocaine, amphetamine, or methamphetamine dependence. Most often, medications are designed to target the direct effects of drugs, rather than learned associations with the drugs that might precipitate craving or drug use. Here, we address the possibility of using conditioned place preference (CPP) procedures to identify medications that target conditioned incentive responses as a means to reduce relapse. The CPP method is commonly used in laboratory animals, and has recently been extended to humans. We argue

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that CPP provides a promising laboratory model of incentive conditioning and relapse in both laboratory animals and humans. In the following sections, we examine the potential of CPP to be used to identify effective therapies.

2. Conditioned drug effects

Pavlov (Pavlov, 1927) first showed that strong associations are formed between contextual stimuli and psychoactive drugs such as morphine. By repeatedly pairing environmental stimuli with a psychoactive drug, the stimuli begin to elicit some of the responses elicited by the drugs themselves. Such conditioning also occurs with motivational properties of drugs; that is, stimuli paired with drugs that produce positive motivational effects acquire some of the motivational properties themselves. These acquired, conditioned properties are believed to underlie the ability of drug-related stimuli to promote relapse (Ludwig, 1986; O'Brien et al., 1992; Robinson and Berridge, 1993; Stewart, 1983; Wikler, 1973). Conditioned stimuli may be either discrete stimuli (e.g., visual, olfactory, gustatory and auditory stimuli) or they may be complex 'contexts' consisting of multiple stimuli that can make up an environment (Hogarth et al., 2010; Mucha et al., 1998; Panlilio et al., 2005; Tolliver et al., 2010; Crombag et al, 2008). Many drugs of abuse serve as unconditioned stimuli (e.g., the amphetamines, cocaine, alcohol, nicotine, morphine, heroin), and drug-induced conditioning has been demonstrated in many animal species (Tzschentke, 1998, 2007; Cunningham et al, 1993; Stephens et al, 2010). Conditioned responses are believed to play an important role in eliciting relapse, even long after an individual has been drug-free (see Crombag et al., 2008).

The conditioned place preference (CPP) procedure is commonly used to study drug reward processes in rodents (Bardo and Bevins, 2000; Tzschentke, 1998; 2007). In CPP, the animals receive a drug in one environment or 'context' and an inactive substance in another environment. Following these pairings, the animals, typically in a drug-free state, are given a choice to move freely between the two environments, and the amount of time spent in the drug-associated environment is taken as an index of preference for the drug. In other words, greater amount of time spent in the drug-paired context is taken to mean the context has acquired incentive salience, or value, that reflects the rewarding properties of the drug. In rodents, CPP remains robust for weeks after conditioning and it is highly resistant to extinction (de Wit and Stewart, 1981; Heinrichs et al., 2010; Herrold et al., 2012; Mueller et al., 2002; Stewart et al, 1984; Voigt et al., 2011a).

CPP has face validity for addiction processes in humans. Human drug abusers report strong associations with environments in which they use drugs and the acquired incentive properties of drug-associated places can elicit craving and/or relapse in the abstinent addict. Preliminary evidence described in the next section of this report indicates that the CPP procedure can be used in a laboratory setting with humans. We propose that, with some additional development, human laboratory CPP procedures may model critical aspects of the addiction process, especially during relapse and therefore may have value to test potential relapse medications.

A number of preclinical studies have examined potential treatments on the acquisition of conditioned responses; relatively few have studied pharmacotherapies on the expression of already established conditioned responses (e.g. see, Graves et al., 2012a; Herrold et al., 2009; 2012; Herzig and Schmidt, 2004; Herzig et al., 2005; Kang et al., 2008; Vidal-Infer et al., 2012; Voigt et al., 2011b; Ye et al., 2004). Testing potential therapies in the laboratory at the time of expression of conditioned responses may be more clinically relevant as treatment for human addiction processes have to be effective against conditioning that has already taken place (Brandon et al., 2011; Fox et al., 2012; Franklin et al., 2011; Langleben et al.,

2012; Mogg et al., 2012). The following discussion on identifying novel addiction therapies is based on this premise.

3. Laboratory studies of CPP in humans

Recently, we have applied the CPP procedure to humans, making it a viable paradigm for testing relapse prevention medications (Childs and de Wit, 2009; Childs and de Wit, 2011). We demonstrated that healthy young adults came to prefer a room in which they had experienced two administrations of oral *d*-amphetamine (20 mg), compared to a different room where they had received placebo. These participants did not have previous experience with stimulants, and they were blind to the identity of the drug. The preference depended on the explicit pairings of room with drug, as the room preference did not develop in a separate group of participants who experienced the rooms and drug under unpaired conditions. We also examined participants' conditioned place preference in relation to their ratings of 'liking' of the drug-induced effects during the conditioning sessions. Subjects who reported liking the amphetamine most during the conditioning procedure also showed the strongest preference for the drug-paired room after conditioning. This correlation provides good support for the assumption that drug-induced place preferences are related to the subjectively positive effects of a drug, an observation that cannot be tested in nonverbal animals. Thus, studying CPP in humans is feasible, and initial results support the idea that place preference is related to the positive subjective effects of the drugs.

Despite our finding that positive subjective effects were related to place preference (Childs and de Wit, 2009; Childs and de Wit, 2011), there is an interesting hypothetical possibility that subjective responses may not always predict conditioned drug preferences. For example, abused drugs such as nicotine or morphine, which produce initially unpleasant subjective effects in humans (e.g., nausea) may induce room preference in laboratory settings (but note that following chronic administration can engender robust drug-seeking behavior). Thus, future studies using the CPP procedure in humans with abused drugs of several classes will provide critical and interesting empirical tests of the relation between drug-liking and preference conditioning.

One key difference for CPP procedures between rodents and humans is the nature of the outcome measures. For CPP with rodents, the outcome measure is the amount of time the animal spends in the drug-paired environment, whereas in our human studies the outcome measure was the rating of liking for the drug-associated room. This room-liking rating measure was used for practical reasons, because humans are less likely than other animals to 'explore' their environments. It is difficult to determine whether the outcome measure used for rodents (amount of time spent in a drug-associated place) is comparable to the subjective ratings of room preference by humans. We are currently addressing this question by testing a behavioral measure of 'time spent' in an alcohol-paired environment in humans and initial results are promising (Childs et al, 2012). Further refinements of the human CPP procedure will help to identify commonalities and differences between the nonhuman and human models.

An important consideration needed when implementing the human CPP procedure is the selection of subjects, in particular, whether the volunteers should be experienced drug users or drug-naïve. In some respects, established drug users provide a more sensitive indicator of preference than do non-drug-using volunteers, because the former have already demonstrated the propensity to engage in drug-associated behaviors (Carter and Griffiths, 2009). On the other hand, individuals with extensive drug and conditioning histories may be tolerant to drug-induced effects, and they may exhibit biases in responding that are related to expectancies, other forms of conditioning, or sensory preconditioning, which would

complicate interpretation of outcomes. There are also problems with using non-drug using volunteers. First, the to-be-conditioned drugs may produce less euphoria in non-users compared to users. Second, non-drug-users may be 'by nature' relatively *insensitive* to acquiring preferences, or conditioned associations, with abused drugs. Third, by contrast, people with a high propensity to acquire conditioned responses to drugs may also be at higher risk for drug abuse problems for there is evidence from laboratory rodents that rapid acquisition of place conditioning predicts robust drug-seeking (Flagel et al., 2009). Indeed, ethical considerations limit use of drugs with non-users because of concerns that drug exposure may lead to future drug-taking. In spite of these potential complications, our initial studies with healthy human volunteers indicate that CPP is a promising model. We predict that this model can be utilized in more heterogeneous subject samples, and that it should be further evaluated for utility in identifying potential medications for drug addictions.

4. Methodological considerations for CPP procedures

A straight forward concept of CPP procedures involves an initially neutral stimulus, i.e., context, that when paired with an unconditioned stimulus, i.e., an abuse drug, will take on the positive reinforcing properties of the drug such that the conditioned individual will show a preference for the drug-paired context. Conceptual concerns about CPP procedures often involve the potential for pre-existing preferences for one environment over another to affect the conditioning process (Bardo and Bevins, 2000). That is, an environmental context may have some intrinsic motivational value even before conditioning, and this may (e.g., see Cunningham et al., 2003) or may not (e.g., Spyraki et al., 1985) influence the acquisition of conditioning. An intrinsic preference may also complicate the interpretation of place preference outcomes. If an environment appears to be 'highly preferred' before conditioning, subsequent conditioning with that context may not increase preference further due to ceiling effects. If an environment appears to be 'non-preferred' before conditioning, one of several scenarios may be involved, including the following: the environment is a neutral context as compared to a preferred context, the environment is a 'lesser of two preferences', the context is truly *'not liked'*, or a context is aversive. If the context is aversive, then conditioning-induced increase in preference for that context may reflect *'less aversion'* and thus not show the true positive motivational value of the drug. While many studies use a *biased* CPP procedure, in which the non-preferred environment is used as the conditioning environment to compensate for initial non-preference (Bardo and Bevins, 2000), it is important to bear in mind the interpretational issues that may accompany this procedure.

We have used both biased and unbiased CPP procedures in our studies with rats (Shen et al., 2006; Voigt et al., 2011b; Herrold et al., 2012) and humans (Childs and de Wit, 2009; 2011). Regarding our human studies, we first used an unbiased procedure (Childs and de Wit, 2009), assigning subjects to room-drug conditions without considering initial preferences. In our second human study, we used a biased procedure (Childs and de Wit, 2011), assigning subjects to receive drug in their initially non-preferred room. Although we detected a slight pre-existing preference for one of the rooms in the first study, conditioning developed similarly in both studies, suggesting that biased and unbiased procedures can yield similar results in humans. It is of interest to determine if these outcomes are obtained with other drugs and other contexts.

An additional consideration with CPP procedures includes the possibility of differential effectiveness across different drug classes. In laboratory rodents, CPP develops readily with opiates, amphetamines, and cocaine, but it is more difficult to demonstrate with ethanol, nicotine or cannabinoids (Cunningham et al., 1993; Tzschentke, 1998). These differences among the various classes of abused drugs may be related in part to differences in the

reinforcing efficacy of the drugs. For example, opiates, amphetamines and cocaine are readily self-administered in rats, whereas alcohol and nicotine are less robust reinforcers. Thus, the different CPP outcomes for different classes of abused drugs may reflect the intrinsic reward properties of the drugs.

It is possible that there are species differences in the reinforcing effects of drugs. For example, rodents appear to find alcohol and nicotine to be less rewarding than do humans. Studies using comparable CPP methods in rodents and humans may help to identify species differences in drug-mediated reward, and/or the ability of various abused drugs to establish conditioning.

In rodents, the CPP procedure is considered to be relatively insensitive to dose magnitude; it remains to be determined whether this is also true in the human CPP procedure. A lack of dose-sensitivity may limit the utility of CPP for studying *acquisition* of the task, and for identifying potential medications that reduce the value (or potency) of a drug *during* conditioning. However, the relationship of dose magnitude of the conditioning drug to response magnitude is less important for investigating medications designed to *reduce expression* of the conditioned response, i.e., behaviors tested in the absence of the conditioning drug and after place preference has been acquired. This distinction is relevant clinically as reduction in expression of CPP by a drug-free but conditioned rodent is likely more applicable to a reduction in context-induced craving or relapse in the drug-withdrawn human addict.

Despite its widespread use as a means to study drug reward-mediated associative learning in animals, the identification of exactly what is learned in the CPP procedure remains unclear (Stephens et al, 2010; 2013). Bardo and Bevins (2000) point out that measures of place preference may be influenced by processes other than reward or associative learning, such as novelty, state-dependence or anxiety. Moreover, processes associated with reward and learning, as they relate to CPP procedures, are not crystal clear (Stephens et al, 2010; 2013). Reward can imply an interoceptive, subjective state of euphoria or well-being, which may occur in nonhuman animals, just as it does in humans, although it cannot be directly measured in nonverbal animals. CPP procedures in humans may shed light on this issue, for these experiments can be designed to determine the relationship (or lack thereof) between pleasurable subjective effects of a drug during conditioning, and the change in place preference after conditioning. As noted above, we found that subjective ‘liking’ of amphetamine was positively correlated with strength of place conditioning in both of our human studies (Childs and de Wit, 2009; 2011). Additional human CPP studies that investigate subjective states or subjective reports of liking or disliking of contextual cues, in relation to behavioral preferences should add clarity to these issues.

With established human drug users, or with rats that have undergone place conditioning, both discrete stimuli (e.g., sight of a cigarette for humans) and contextual stimuli (e.g., environment where drugs were previously administered) can precipitate relapse. Studies with laboratory animals suggest that conditioning with discrete, localizable cues differ fundamentally from conditioning with nonspecific, contextualcues, and the two types of cues rely on different neurobiological processes (Chaudhri et al., 2010; Itzhak et al., 2010). This raises the possibility that medications effective in dampening the expression of responding to drug-related contextual cues, such as those modeled in CPP, may differ from medications that dampen responses to specific discrete drug-related cues. The particular features that become conditioned to a drug in a complex context are often unknown, and individuals may develop associations with specific aspects of the environment that are not easily predicted or controlled (e.g., Vezina and Stewart, 1987). Nevertheless, researchers should bear in mind the possibility that different neurochemical processes are involved in

the expression of conditioned responses to contextual vs. discrete cues, and different medications might be effective for reducing craving or relapse that are engendered by these two forms of condition cues.

5. Medications targeting conditioned drug effects

Ideally, long-term pharmacotherapy for addiction should have the following characteristics: (i) low abuse liability in its own right, (ii) low adverse effects (e.g., sedation or anxiety) that would decrease compliance, and (iii) reduce craving and/or relapse that occur in the drug-withdrawn addict. Focusing on the third characteristic, we propose that identifying efficacious medications for relapse reduction would benefit by identifying treatments that dampen the *expression* of CPP. This outcome could be accomplished by interfering with several processes that are associated with expression of place preference. For examples, therapy could reduce the salience of the contextual cues, or interfere with the retrieval of drug-related memories (e.g., see Fricks-Gleason and Marshall, 2008; Otis and Mueller, 2011). The drug-context link also can be impeded when the individual is repeatedly re-exposed to the drug-paired environment but in the absence of the drug. This process is referred to as extinction learning, and several potential pharmacotherapies have been shown to hasten extinction for stimulant- (Gass and Olive, 2009; Voigt et al., 2011a) and opiate- (Heinrichs et al., 2010) induced CPP in rats. Thus, the mnemonic complexities that comprise place preference expression are rich with potential targets for addiction therapy.

Some considerations are needed when using the CPP procedure as an assay for medication development. First, the procedure typically involves newly acquired associations between drug and a context, whereas experienced drug users have many years of experience with drugs and associated stimuli. Thus, it remains to be determined whether medications that effectively dampen newly conditioned place preferences will also dampen long-established conditioned responses. Second, it is not certain that the contextual cues that are typically used in a laboratory study of place preference will model the cues of a ‘real world’ environment associated with drug-taking. These environments often have many features, including sounds, smells, tastes and social stimuli, each of which may acquire motivational properties. This scenario is difficult to model in the laboratory. Third, the CPP procedure usually involves a limited number of pairings of drug and context, whereas drug users may have years of pairings with their drug-related environments. Treatments that effectively dampen newly formed associations (as would be determined in the laboratory setting) may be less effective for long-standing conditioned responses. Finally, the durability of conditioned place preferences, over time or over repeated extinction trials, may present a significant hurtle for therapy. It is clear in rodents, that cues retain their ability to elicit behavior for extended periods of time (Bouton, 2002; Heinrichs et al., 2010; Mueller et al., 2002; Voigt et al., 2011a) a laboratory CPP procedure in humans that characterizes the process of extinction of place preferences requires further development (Ostlund and Balleine, 2008)). Thus, even if a potential therapy is identified using the CPP procedure, given that addiction is known to be a chronic, relapsing disorder, it will be important to also determine the needed treatment duration, whether the pharmacotherapy should be combined with behavioral therapy (e.g., using extinction learning), or if the therapy will need to be life-long.

6. Utility of CPP in medication development for addiction

We suggest here that CPP in the laboratory should be helpful in identifying medications that will prove useful in treating drug addiction in humans. To support this concept, in the following sections, we overview laboratory CPP studies of treatments that now have moved to the clinic for reducing relapse. It is important to note that only a relatively small number

of studies with rodents have targeted the expression of CPP to identify new treatments for drug abuse (Graves et al., 2012a; Herrold et al., 2009; 2012; Herzig and Schmidt, 2004; Herzig et al., 2005; Kang et al., 2008; Vidal-Infer et al., 2012; Voigt et al., 2011b; Ye et al., 2004). Of these, some evaluated potential treatments that now are FDA-approved addiction medications, and others have use compounds approved for other CNS pathologies that may be repurposed for addiction therapy.

6.1. Varenicline is marketed under the trade name Chantix®. Varenicline is a partial α4β2 nicotinic receptor agonist that is approved for smoking cessation treatment (Rollema et al., 2007). Biala and colleagues demonstrated that varenicline blunted nicotine-primed expression of CPP in rats when given on the place preference test day and that it blocked nicotine-primed reinstatement of CPP following extinction (Biala et al., 2010). In both of these cases, the medication was administered in combination with nicotine, and so it remains to be determined whether varenicline also blocks the expression of conditioned preferences established by nicotine, but tested in the absence of nicotine. It also remains to be determined whether varenicline reduces CPP established by nicotine or smoking in humans.

6.2. Naltrexone is a non-specific opioid receptor antagonist marketed in both oral (ReVia®) and injectable (Vivatrol®) formulations. Naltrexone is approved for the treatment of opiate dependence as well as alcohol dependence and relapse following detoxification (O'Malley et al., 2009; Volpicelli, 2001). Consistent with its clinical efficacy, naltrexone reduces the expression of alcohol-induced CPP in rodents when it is administered prior to preference testing (Middaugh and Bandy, 2000). Similar results have been obtained with another opioid antagonist naloxone, which blocks both the expression of alcohol-induced CPP, as well as the reinstatement of alcohol place preference following extinction (Kuzmin et al., 2003).

6.3. Mirtazapine (Remeron®) is an FDA-approved atypical antidepressant which may be re-purposed for use in addictions treatment. It is inexpensive (off patent), and through its widespread clinical use for several mental health disorders, is known to be safe and well-tolerated. We have studied the effects of mirtazapine in rats at several stages of the CPP conditioning process and contend that mirtazapine should be considered for addiction treatment (Graves et al., 2012b). Most notably for the present argument, mirtazapine blocked the expression of CPP that was established by methamphetamine in rats (Herrold et al., 2009; Voigt and Napier, 2011). Further, when rats were repeatedly treated with mirtazapine in the home cage after acquisition of methamphetamine CPP, but tested in the drug free state, their preference for the drug-associated place was reduced (Voigt et al., 2011c). This suggests that mirtazapine interferes with the maintenance of methamphetamine-induced associative learning. These observations indicate that mirtazapine may disrupt the reconsolidation of salient memories. Mirtazapine reverses the effects of methamphetamine in other animal models of drug-taking: It blocks expression of methamphetamine-induced motor sensitization (McDaid et al., 2007), and in rats trained to self-administer methamphetamine, mirtazapine blocks methamphetamine-seeking in response to cues whether or not the animals have undergone extinction training before the cue test (Graves and Napier, 2011). Mirtazapine also antagonizes the expression of CPP established in rats with morphine (Graves et al., 2012a; Kang et al., 2008). Consistent with these preclinical observations, there is clinical evidence that mirtazapine reduces methamphetamine use (Colfax et al., 2011) and craving for alcohol in humans (Altintoprak et al., 2008; Yoon et al., 2006), although it did not change cocaine consumption in a small study with depressed cocaine-dependent human subjects (Afshar et al., 2012). The results of ongoing clinical trials, including double-blind placebo-controlled studies should provide important evidence for the ability of mirtazapine to reduce drug-craving and relapse (see ClinicalTrials.gov). It will be of particular interest to test this drug at the time of preference testing in humans who have undergone the conditioning phase of CPP.

6.4. Baclofen is a $GABA_B$ receptor agonist and an FDA-approved muscle-relaxant used for the treatment of spasticity. Although it has some sedating properties, it is well-tolerated in the clinic for patients with multiple sclerosis and tardive dyskinesia (From and Heltberg, 1975; Sawa and Paty, 1979; Stempien and Tsai, 2000). Baclofen has also been studied in the context of addiction in both humans and laboratory animals. In rodents, baclofen facilitates the extinction of CPP established with methamphetamine or morphine (Heinrichs et al., 2010; Voigt et al., 2011a). Specifically, when baclofen is administered following re-exposure to the previously drug-paired environment, fewer extinction sessions are necessary to reverse the drug-induced CPP. Baclofen also reduces nicotine-primed reinstatement of nicotine-induced CPP in rodents after extinction has taken place (Fattore et al., 2009). Baclofen has been tested clinically for addictions to opiates and alcohol. It was not effective in one, single site, moderately sized randomized control trial with human opiate users (Assadi et al., 2003), but in another human study, baclofen, combined with an opiate antagonist or a benzodiazepine, reduced opiate-craving and use (Gerra et al., 2000). In a study with alcohol abusers, baclofen reduced the number of drinking days, compared to placebo (Addolorato et al., 2011). With this pattern of results in the clinic, combined with the preclinical evidence in rodents, it would be interesting to examine the effects of baclofen on expression of human CPP, established by opiates, alcohol or stimulants.

7. Summary and Conclusions

CPP in the laboratory setting for both rodents and humans may be a promising method to study medications to prevent relapse. The procedure has excellent translational potential: the findings with humans can inform the interpretation of studies in rodents, and the rodent procedures can be used to address questions that are difficult to study in humans (e.g., underlying neural mechanisms, potential toxicity or adverse effects of drugs). CPP targets contextual conditioning, which may represent a neurobiologically unique, and until now, relatively understudied process that contributes to relapse. Full clinical trials are expensive and time-consuming, and therefore a method that predicts the effectiveness of treatments, using a more efficient controlled method, may be of great value to the field.

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Highlights Bullet Points

- Conditioned place preference (CPP) measures drug reward in humans and in rats.
- CPP is highly translational and has predictive value for addiction medication development.
- CPP studies with FDA-approved, and potential, addiction therapies are reviewed.
- Commonalities and differences in using humans and rodent models are also reviewed.