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Review

Using conditioned place preference to identify relapse prevention medications

T. Celeste Napier[a,*], Amy A. Herrold[b], Harriet de Wit[c]

[a] Department of Pharmacology and Center for Compulsive Behaviors and Addiction, Rush University, Chicago, IL, United States
[b] Center for Management of Complex Chronic Care, Edward Hines Jr. VA Hospital, Hines, IL, United States
[c] Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL, United States

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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.

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   6.3. Mirtazapine (Remeron®) is an FDA-approved atypical antidepressant which may be re-purposed for use in addictions treatment 00
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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

* Corresponding author at: Department of Pharmacology, Cohn Research Building, Suite 424, 1735 W. Harrison Street, Rush University Medical Center, Chicago, IL 60612, United States. Tel.: +1 312 563 2428; fax: +1 312 563 2416.
E-mail address: celeste_napier@rush.edu (T.C. Napier).

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extended to humans. We argue 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 (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., in press; 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, in press; 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., in press; 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, 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, 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 and de Wit, 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

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