CHAPTER

2

Animal models of drug relapse and craving: From drug priming-induced reinstatement to incubation of craving after voluntary abstinence

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Abstract

High rates of relapse to drug use during abstinence is a defining feature of drug addiction. In abstinent drug users, drug relapse is often precipitated by acute exposure to the self-administered drug, drug-associated cues, stress, as well as by short-term and protracted withdrawal symptoms. In this review, we discuss different animal models that have been used to study behavioral and neuropharmacological mechanisms of these relapse-related phenomena. In the first part, we discuss relapse models in which abstinence is achieved through extinction training, including the established reinstatement model, as well as the reacquisition and resurgence models. In the second part, we discuss recent animal models in which drug relapse is assessed after either forced abstinence (e.g., the incubation of drug craving model) or voluntary (self-imposed) abstinence achieved either by introducing adverse consequences to ongoing drug self-administration (e.g., punishment) or by an alternative nondrug reward using a discrete choice (drug vs. palatable food) procedure. We conclude by briefly discussing the potential implications of the recent developments of animal models of drug relapse after voluntary abstinence to the development of medications for relapse prevention.

Progress in Brain Research, Volume 224, ISSN 0079-6123, http://dx.doi.org/10.1016/bs.pbr.2015.08.004

Keywords

Voluntary abstinence, Forced abstinence, Conflict, Context, Cue, Extinction, Drug self-administration, Choice, Punishment, Reinstatement, Relapse, Resurgence, Reacquisition, Review

1 INTRODUCTION

The central problem in the treatment of drug addiction is high rates of relapse to drug use after periods of forced or voluntary (self-imposed) abstinence (Hunt et al., 1971; Leshner, 1997; O'Brien, 2005). In human drug addicts, drug relapse and craving during abstinence typically involve one or more of the following factors: acute exposure to the self-administered drug (de Wit, 1996; Jaffe et al., 1989), drug-associated cues or contexts (O'Brien et al., 1986, 1992), stress (Sinha, 2001; Sinha et al., 2011), or short-term and protracted withdrawal symptoms (Wikler, 1948, 1973).

Since the 1970s, this clinical scenario has been modeled in monkeys (Stretch et al., 1971), rats (Davis and Smith, 1976; de Wit and Stewart, 1981), and mice (Highfield et al., 2002) by using a reinstatement model in which drug seeking induced by different experimental manipulations is assessed after extinction of the drug-reinforced responding (Bossert et al., 2013; Shaham et al., 2003). However, human abstinence is typically either forced (e.g., incarceration or inpatient treatment) or voluntary due to either the negative consequences of chronic drug use or the availability of alternative nondrug rewards in the drug user's environment (Epstein and Preston, 2003; Katz and Higgins, 2003; Marlatt, 1996). Therefore, during the last 15 years, investigators have incorporated these facets of human abstinence into "alternative" models of drug relapse in which abstinence is not achieved by extinction training (Caprioli et al., 2015a; Cooper et al., 2007; Lu et al., 2004; Marchant et al., 2013a; Panlilio et al., 2005).

In Section 2, we discuss relapse models in which abstinence is achieved through experimenter-imposed extinction training: the reinstatement model (Shaham et al., 2003), the reacquisition model (Carnicella et al., 2008), and the resurgence model (Podlesnik et al., 2006). In Section 3, we discuss animal models in which drug relapse is assessed after either forced or voluntary abstinence. The latter is achieved either by introducing adverse consequences (punishment) to ongoing drug self-administration or by introducing an alternative nondrug reward using discrete choice (drug vs. palatable food) procedures. These include the incubation of drug craving and related forced abstinence-relapse models (Fuchs et al., 2006; Lu et al., 2004), punishment- and conflict-based relapse models (Cooper et al., 2007; Panlilio et al., 2005), and the recent choice-based voluntary abstinence-relapse model (Caprioli et al., 2015a). Our goal in this review is to introduce the different relapse models and then briefly provide a historical perspective on each model. In Tables 1 and 2, we provide a summary of these models and Fig. 1 depicts the number of published papers using the different models since 1970.

Table 1 Extinction-Based Relapse Models

	Number of Papers	Key Historical Citations
Drug priming		
Self-administration	464	de Wit and Stewart (1981), Ettenberg (1990), McFarland and Kalivas (2001), Mueller and Stewart (2000), Self et al. (1996), Stewart (1984), and Stretch et al. (1971)
CPP	187	
Runway	3	
Discrete cues		
Self-administration	372	Davis and Smith (1976) and Meil and See (1996, 1997)
Discriminative cues		
Self-administration	58	Ciccocioppo et al. (2001), McFarland and Ettenberg (1997), Weiss et al. (2000), and Katner et al. (1999)
Runway	2	
Context		
Self-administration	60	Bossert et al. (2007), Crombag et al. (2002), Fuchs et al. (2005), and Hamlin et al. (2007)
Stress		
Self-administration	169	Erb et al. (1996), Shaham and Stewart (1995b), and Wang et al. (2000)
CPP	55	
Withdrawal states		
Self-administration	4	Stewart and Wise (1992) and Shaham et al. (1996)
Reacquisition		
Self-administration	12	Davis et al. (1978) and Leri and Rizos (2005)
CPP	5	
Resurgence		
Self-administration	3	Quick et al. (2011)

The table depicts the number of published papers in which investigators used the different extinction-based relapse models. We also include in the table selected historical citations. Note*: Many papers published results that fit more than one category (e.g., assessment of both drug-priming- and cue-induced reinstatement). Such papers are counted in more than one category in Tables 1 and 2. The data in both tables are based on PubMed research.*

Table 2 Abstinence-Based Relapse Models

	Number of Papers	Key Historical Citations
Forced abstinence		
A single test during abstinence	37	Fuchs et al. (2006), Grimm et al. (2001), Tran-Nguyen et al. (1998), Shalev et al. (2001), and Neisewander et al. (1996)
Incubation of drug craving	67	
Adverse consequences-imposed abstinence		
Punishment-based model	9	Cooper et al. (2007), Marchant et al. (2013a), Panlilio et al. (2003), and Economidou et al. (2009)
Conflict model	5	
Voluntary abstinence		
Incubation of drug craving	1	Caprioli et al. (2015a)

The table depicts the number of published papers in which investigators used the different abstinence-based relapse models. We also include in the table selected historical citations.

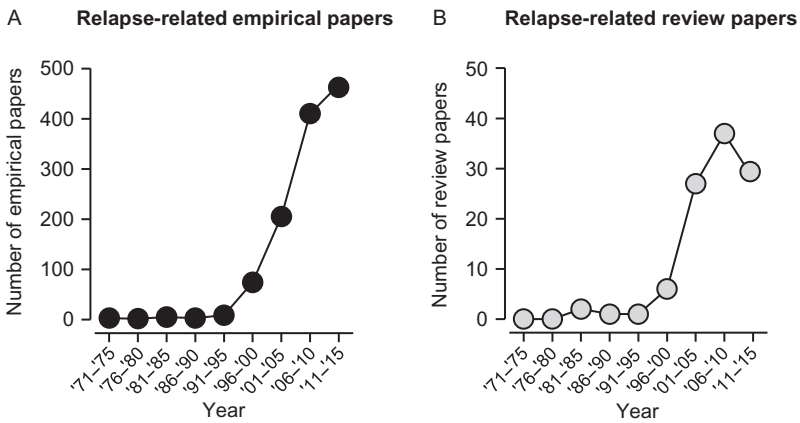

FIGURE 1

Number of relapse-related empirical papers and reviews per 5-year period since 1970.

Note: Data for 2011-2015 do not include papers published after August 2015.

Our review does not include theoretical discussions of the validity of animal models of relapse or a comprehensive summary of the main findings in studies using animal models of relapse. We refer the interested reader to earlier and more recent reviews in which we covered these topics (Bossert et al., 2005, 2013; Epstein et al., 2006; Lu et al., 2004; Marchant et al., 2013b; Pickens et al., 2011; Shaham et al., 2003; Shalev et al., 2002). Additionally, our review does not cover the more recent

adaptation of the reinstatement model and the incubation of craving model to study relapse to palatable food seeking (Calu et al., 2014; Grimm et al., 2002, 2005; Nair et al., 2009). We also do not cover the "alcohol-deprivation effect"—the increase in alcohol intake after an abstinence period (Sinclair and Senter, 1968)—that is widely used in the alcohol field to study alcohol relapse (Le and Shaham, 2002; Vengeliene et al., 2014).

2 EXTINCTION-BASED RELAPSE MODELS

2.1 REINSTATEMENT

In the learning literature, reinstatement refers to the recovery of a learned response (e.g., lever-pressing behavior) that occurs when a subject is exposed, noncontingently, to the unconditioned stimulus (e.g., food) after extinction (Bouton and Swartzentruber, 1991). In the drug addiction literature, reinstatement typically refers to the resumption of drug seeking after extinction following exposure to drugs, drug cues or contexts, or stressors (Shaham et al., 2003).

In the operant self-administration variation of the reinstatement model, laboratory animals are trained to self-administer a drug. During the extinction phase, lever pressing (or nose poking) is extinguished in the absence of the drug. During the reinstatement test, the ability of acute exposure to the drug or nondrug stimuli to reinstate drug seeking is determined under extinction conditions. Non-reinforced responding on the previously active lever or nose poke device is the operational measure of drug seeking (Stewart and de Wit, 1987).

In the operant runway variation of the reinstatement model, the dependent measure is the *run time* from a *start box* to a *goal box* where a drug infusion is given. During the training phase, rats are given a drug injection when they reach the goal box and over time, their run time decreases. During the extinction phase, the rats increase their run time when drug injections are not available in the goal box. During reinstatement testing, noncontingent exposure to drug priming or drug-associated cues results in decreased run time to the goal box (reinstatement) (Ettenberg, 1990; McFarland and Ettenberg, 1997).

In the conditioned place preference (CPP) variation of the reinstatement model, laboratory animals are trained to associate one distinct compartment (context) with drug injections and a second compartment with injections of the drug vehicle. Subsequently, rats are subjected to extinction training during which they are exposed to both contexts in the absence of the drug. Reinstatement of the preference for the drug-paired compartment is then determined after noncontingent exposure to drug or nondrug stimuli (Mueller and Stewart, 2000; Sanchez and Sorg, 2001).

In the paragraphs below, we describe the different usages of the model to study reinstatement induced by drug priming, discrete cues, discriminative cues, contextual cues, stress, and drug withdrawal. For each reinstatement-related stimulus, we describe the experimental procedure and then briefly discuss selected historical citations.

2.1.1 Drug priming

2.1.1.1 Experimental procedure

In the drug-priming-induced reinstatement procedure, the effect of noncontingent injections of the self-administered drug, or other drugs on reinstatement of the operant response in the self-administration or the runway procedures, or place preference in the CPP procedure, is determined after extinction of the drug-reinforced learned behavior (de Wit, 1996; Shaham et al., 2003).

2.1.1.2 Brief history

During the early 1970s, Stretch and Gerber showed that noncontingent priming injections of the self-administered drug reinstate amphetamine or cocaine seeking after extinction in monkeys (Gerber and Stretch, 1975; Stretch et al., 1971). Subsequently, Davis and Smith (1976) and de Wit and Stewart (1981, 1983) showed that priming injections of drugs reinstate opiate (heroin, morphine) and stimulant (cocaine, amphetamine) seeking in rats. In 1990, Ettenberg (1990) showed that priming injections of amphetamine reinstate operant responding in the runway model. In 2000, Mueller and Stewart (2000) and Parker and McDonald (2000) showed that priming injections of cocaine or morphine reinstate drug CPP.

In the 1980s, Stewart and colleagues showed that intracranial injections of morphine or amphetamine into ventral tegmental area (VTA) or nucleus accumbens (NAc) reinstate heroin or cocaine seeking, respectively (Stewart, 1984). These results provided the first demonstration for a role of the mesolimbic dopamine system in reinstatement of drug seeking. In 1996, Self et al. (1996) showed that D1-like and D2-like dopamine receptor agonists have opposite effects on reinstatement of cocaine seeking: D1-like receptor agonists inhibit cocaine-priming-induced reinstatement, while D2-like receptor agonists potentiate reinstatement. These results provide the first evidence that mechanisms of reinstatement of drug seeking can be dissociable from those that control ongoing drug self-administration in which the behavioral effects of D1-like receptor and D2-like receptor agonists (and antagonists) are similar (Self and Stein, 1991). In 2001, McFarland and Kalivas (2001) made the first attempt to identify the neuronal circuits that mediate cocaine-priming-induced reinstatement by manipulating dopamine, glutamate, and γ-amino butyric acid transmission in multiple brain areas. This study has been the inspiration for many other studies on the circuitry of drug-priming-induced reinstatement in the last 15 years (Bossert et al., 2013; Kalivas and McFarland, 2003; Schmidt et al., 2005).

During the last two decades, the drug-priming-induced reinstatement procedure has been used in many studies using different drugs of abuse (Bossert et al., 2013; Self and Nestler, 1998; Shaham et al., 2003), including nicotine (Chiamulera et al., 1996) and alcohol (Le et al., 1998), to identify neuropharmacological mechanisms underlying this phenomenon.

2.1.2 Discrete cues

2.1.2.1 Experimental procedure

In the discrete cue-induced reinstatement procedure, rats are first trained to self-administer a drug. During training, lever responding (or nose poking) leads to drug infusions that are temporally paired with a discrete cue (e.g., tone, light, or often a compound tone–light cue). Lever pressing is then extinguished in the absence of the drug and the discrete cue. During the reinstatement test, reexposure to the discrete cue, which is earned contingently by responding on the drug-associated lever, reinstates drug seeking (Davis and Smith, 1976; Meil and See, 1996).

2.1.2.2 Brief history

In 1976, Davis and Smith (1976) showed that contingent presentation of a discrete cue, a buzzer paired during training with an intravenous injection of morphine, reinstates drug seeking after extinction in rats. Subsequently, de Wit and Stewart (1981) showed that noncontingent exposure to a tone cue following extinction of the lever-pressing behavior for cocaine in the absence of the cue has a weak effect on reinstatement. Many years later, See and colleagues showed that contingent but not noncontingent cue presentations during testing reinstate cocaine seeking (Grimm et al., 2000; Meil and See, 1996). During the late 1990s and early 2000s, the See lab used permanent and reversible lesion methods to show a critical role of basolateral and central amygdala (BLA and CeA), and dorsal medial prefrontal cortex (mPFC) in discrete cue-induced reinstatement of cocaine seeking (Grimm and See, 2000; McLaughlin and See, 2003; Meil and See, 1997).

The discrete cue-induced reinstatement procedure is highly reliable and has been used over the years to study neuropharmacological mechanisms of this reinstatement using rats with a history of cocaine (See, 2005), heroin (Fuchs and See, 2002), methamphetamine (Hiranita et al., 2006), nicotine (Forget et al., 2010), and alcohol (Sinclair et al., 2012) self-administration. Recently, this procedure has been used in combination of modern neuroscience techniques to identify circuit and synaptic mechanisms of cue-induced reinstatement of drug seeking (Gipson et al., 2013; Mahler and Aston-Jones, 2012; Mahler et al., 2014).

2.1.3 Discriminative cues

2.1.3.1 Experimental procedure

The operant runway variation of the discriminative cue-induced reinstatement procedure includes three phases. During the initial discrimination training, rats are given a drug injection when they reach the goal box in the presence of one discriminative cue (e.g., specific odor) or saline injections in the presence of a different discriminative cue. During this phase, run time decreases over time. During the extinction phase, in which the drug- and saline-paired discriminative cues and the drug are not available, run time increases over time. During the reinstatement test, reexposure to the discriminative cue that previously predicted drug availability reinstates

operant responding, as indicated by decreased run time to reach the goal box (McFarland and Ettenberg, 1997).

In the more commonly used operant self-administration variation of the discriminative cue-induced reinstatement procedure, laboratory animals are trained to self-administer a drug in the presence of a distinct discriminative cue and to self-administer saline in the presence of a different discriminative cue. During the extinction phase, lever pressing (or nose poking) is extinguished in the absence of the discriminative cues and the drug. During the reinstatement test, exposure to the discriminative cue that previously predicted drug availability reinstates lever responding (Alleweireldt et al., 2001; Weiss et al., 2000).

2.1.3.2 Brief history

In 1997, McFarland and Ettenberg (1997) used the operant runway model to demonstrate that systemic injections of the mixed dopamine receptor antagonist haloperidol decrease discriminative cue-induced reinstatement of heroin seeking (McFarland and Ettenberg, 1997). Subsequently, the Weiss lab established a self-administration variation of the model using alcohol (Katner and Weiss, 1999; Katner et al., 1999). In subsequent studies with cocaine as the self-administered drug, they showed that discriminative cue-induced reinstatement of cocaine seeking is associated with increased dopamine release in NAc and amygdala. They also showed that blockade of D1-family receptors decreases both discriminative cue-induced reinstatement and discriminative cue-induced Fos (a neuronal activity marker) expression in amygdala and mPFC and that the reinstatement effect of the discriminative cues persists for at least 4 months after cocaine exposure (Ciccocioppo et al., 2001). These investigators also demonstrated that the response to the cocaine-associated discriminative cues is remarkably persistent over repeated testing and that D2-family receptors also play a role in this reinstatement (Weiss et al., 2001).

Since the publications of these studies and related studies (Alleweireldt et al., 2001), the discriminative cue-induced reinstatement procedure has been used to study neuropharmacological mechanisms of this reinstatement in rats with a history of cocaine (Kallupi et al., 2013; Yun and Fields, 2003), heroin (Alvarez-Jaimes et al., 2008), alcohol (Dayas et al., 2007), and nicotine (Cervo et al., 2013) self-administration.

2.1.4 Contextual cues

2.1.4.1 Experimental procedure

In the context-induced reinstatement model, laboratory animals are first trained to self-administer a drug in an environment (termed context A) associated with a specific set of "background" cues (e.g., operant chamber fan, time of day, visual cues, tactile cues, olfactory cues). Lever pressing is then extinguished in a different environment (termed context B) with a different set of "background" cues. During reinstatement testing under extinction conditions, exposure to context A, previously paired with drug self-administration, reinstates operant responding (Crombag et al., 2002). This model is based on the ABA renewal model that has been used to assess the role of contexts in resumption of conditioned responses to aversive

and appetitive cues after extinction (Bouton and Bolles, 1979; Bouton and Swartzentruber, 1991). There are two variations of the context-induced reinstatement model. In the first variation, discrete drug cues are present during training, extinction, and reinstatement (Crombag et al., 2002). In this procedure, contexts may indirectly induce drug seeking by modulating the effects of discrete infusion cues on drug seeking by serving as occasion setters. In the second variation, discrete cues are absent during training, extinction, and reinstatement (Fuchs et al., 2005). In this procedure, contexts may directly induce drug seeking by acquiring Pavlovian conditioned stimulus properties (Crombag et al., 2008).

2.1.4.2 Brief history

Crombag and Shaham (2002) introduced the context-induced reinstatement model to the addiction field in a study using rats trained to self-administer "speedball" (a heroin–cocaine combination). In a subsequent study, they used selective dopamine receptor antagonists to demonstrate a critical role of D1- and D2-family receptor antagonists in this reinstatement (Crombag et al., 2002). In a series of neuropharmacological studies, Bossert and colleagues showed a role of VTA and NAc dopamine and glutamate in context-induced reinstatement of heroin seeking (Bossert et al., 2004, 2006, 2007). An important finding from these studies is that different NAc subregions control reinstatement induced by exposure to heroin-associated contexts (NAc shell) versus discrete cues (NAc core) (Bossert et al., 2007). In 2005, Fuchs et al. (2005) showed that reversible inactivation of BLA, dorsal mPFC, and dorsal hippocampus decreases context-induced reinstatement of cocaine seeking. In subsequent studies, Fuchs et al. continued to map the brain circuits of context-induced reinstatement of cocaine seeking (Fuchs et al., 2007, 2008; Lasseter et al., 2010; Xie et al., 2013). During the mid-2000s, the McNally lab has begun to use elegant anatomical approaches to map the circuitry of context-induced reinstatement of reward (sucrose, alcohol, cocaine) seeking that led to discovery of a critical role of lateral hypothalamus (LH) and paraventricular thalamus in this reinstatement (Hamlin et al., 2006, 2007, 2008; Marchant et al., 2010).

The context-induced reinstatement model is highly reliable and has been used by many investigators over the last decade to study neurobiological mechanisms of this reinstatement in rats with a history of cocaine (Luo et al., 2011), heroin (Bossert et al., 2011), methamphetamine (Rubio et al., 2015), nicotine (Diergaarde et al., 2008), and alcohol (Burattini et al., 2006) self-administration. The Fuchs lab has also recently elegantly modified the context-induced reinstatement model to study neurobiological mechanisms of reconsolidation of memories of contexts associated with cocaine self-administration (Fuchs et al., 2009; Wells et al., 2013).

2.1.5 Stress

2.1.5.1 Experimental procedure

In the operant variation of the stress-induced reinstatement procedure, the laboratory animals are first trained to self-administer a drug in the presence of a discrete cue. Lever pressing is then extinguished in the presence of the discrete cue. During

reinstatement testing under extinction conditions (in the presence of the discrete cue), presession exposure to certain stressors reinstates lever pressing or drug seeking (Shaham et al., 2000a). In the CPP variation, the animals are first trained to associate one context with drug injections and a second context with vehicle injections. Next, the animals are subjected to extinction training and then tested for reinstatement of drug CPP after exposure to different stressors (Sanchez and Sorg, 2001).

2.1.5.2 Brief history

In 1985, Carroll (1985) showed that food restriction reinstates cocaine seeking in rats that experienced this condition during self-administration training. In 1995, Shaham and Stewart (1995b) showed that an intermittent footshock stressor reinstates heroin seeking and proposed that the reinstatement model can be used to study mechanisms underlying stress-induced drug relapse. In the mid-late 1990s, several investigators showed that footshock-induced reinstatement is also observed in rats with a history of cocaine (Ahmed and Koob, 1997; Erb et al., 1996; Mantsch and Goeders, 1999), alcohol (Le et al., 1998; Martin-Fardon et al., 2000), and nicotine (Buczek et al., 1999) self-administration. Subsequently, Wang et al. (2000) showed that an intermittent footshock reinstates cocaine CPP after extinction. Subsequent studies on stress-induced reinstatement explored two main research questions: the generality of intermittent footshock-induced reinstatement to other stressors and the neurobiological mechanisms of stress-induced reinstatement (Mantsch et al., 2015; Shaham et al., 2000a).

Regarding the generality question, in the self-administration model, effective stressors include acute 1-day food deprivation (Highfield et al., 2002; Shalev et al., 2000), delayed (1 day) cold swim stress (Conrad et al., 2010), and the pharmacological stressors corticotropin-releasing factor (CRF) (Erb et al., 1998; Le et al., 2000; Shaham et al., 1997a), kappa-opioid receptor agonists (Valdez et al., 2007), and the prototype alpha-2 adrenoceptor antagonist, yohimbine (Le et al., 2005; Lee et al., 2004; Shepard et al., 2004). However, the validity of using yohimbine as a stressor in reinstatement was recently questioned (Chen et al., 2014). Stressors that reinstate drug preference in the CPP model include swim stress, restraint stress, tail pinch, social defeat, and a cue paired with shock exposure (Kreibich and Blendy, 2004; Ribeiro Do Couto et al., 2006; Sanchez and Sorg, 2001; Sanchez et al., 2003).

Regarding mechanisms, studies in the late 1990s and early 2000s showed a critical role of extrahypothalamic CRF (Erb et al., 1998; Le et al., 2000; Shaham et al., 1997b) and noradrenaline originating from the lateral tegmental nuclei but not locus coeruleus (Erb et al., 2000; Shaham et al., 2000b) in footshock stress-induced reinstatement of drug seeking. Subsequent studies demonstrated a role of dopamine transmission in VTA, NAc, dorsal mPFC, orbitofrontal, and the glutamatergic projections from dorsal mPFC to NAc core (Capriles et al., 2003; McFarland et al., 2004; Xi et al., 2004), as well as a role of VTA CRF and glutamate in this reinstatement (Blacktop et al., 2011; Wang et al., 2005). An important development in studies on stress-induced reinstatement is on the mechanisms underlying the

ability of stressors to potentiate the reinstatement effect of drug cues (Buffalari and See, 2009; Liu and Weiss, 2002) and drug priming (Graf et al., 2013).

2.1.6 Withdrawal states

It has been established for many years that drug withdrawal states provoke drug relapse during abstinence (Wikler, 1948, 1973). Yet historically, it has been a challenge to demonstrate that drug withdrawal can induce reinstatement of drug seeking in animal models (Shalev et al., 2002). To date, the effect of heroin withdrawal on reinstatement of heroin seeking was assessed in three early studies. In the first study, Stewart and Wise (1992) used the within-session variation of the reinstatement model in which rats self-administer heroin for 2–3 h, then undergo extinction training for several hours, and then tested for drug-priming-induced reinstatement (de Wit and Stewart, 1981). They showed that under these limited daily access training conditions, morphine-priming injections reinstate heroin seeking, while priming injections of the opiate antagonist naltrexone do not. This study was followed by two studies in which heroin-dependent rats were trained under extended-access heroin self-administration conditions (daily sessions of 7 or 12 h/day).

In the first study, Shaham and Stewart (1995a) showed that under conditions in which both heroin priming and intermittent footshock reinstate heroin seeking, naltrexone-precipitated withdrawal (induced by injecting morphine 45 min before the test session and the opiate antagonist naltrexone 40 min later) has no effect on reinstatement. In the second study, they showed that in rats implanted with heroin-containing minipumps during the extinction and reinstatement phases, acute injections of the opiate antagonist naloxone (precipitated withdrawal) had no effect on reinstatement of heroin seeking. In contrast, robust reinstatement was observed 24 h after removal of the minipumps (spontaneous withdrawal) (Shaham et al., 1996). Many years later, Zhou et al. (2009) showed that naltrexone injections 1 day but not 14 days after withdrawal from heroin self-administration (4 h/day) potentiate cue-induced heroin seeking as assessed in an extinction test.

Despite the critical role of drug withdrawal states in human drug relapse, currently, there is no active research on mechanisms of withdrawal-induced drug relapse in animal models.

2.2 REACQUISITION

2.2.1 Experimental procedure

In the reacquisition procedure, laboratory animals are first trained to self-administer a drug or nondrug reward. Lever pressing (or nose poking) is then extinguished by removing the reward. During the subsequent reacquisition test sessions, the operant response is again rewarded with the drug or the nondrug reward under experimental conditions identical to those used during training (Bouton et al., 2012).

2.2.2 Brief history

To our knowledge, a formal operant reacquisition procedure was first used in the addiction field by Davis et al. (1978). They showed that ethanol reacquisition after extinction was prevented by drugs that reduce brain levels of noradrenaline and dopamine. Many years later, Li et al. (2003) showed that reacquisition of morphine self-administration is modestly influenced by the reinforcement schedule during initial drug self-administration training. Leri and Rizos (2005) were the first to use a CPP-based reacquisition procedure and subsequently used it to study the role of mPFC in reacquisition of heroin CPP (Ovari and Leri, 2008). A reacquisition-based model has also been used by the Everitt lab in their studies on the ability of cocaine-associated cues to maintain drug seeking under a second-order reinforcement schedule (Di Ciano and Everitt, 2004; Di Ciano et al., 2008).

Since then, this procedure has been used by different investigators to study neuropharmacological mechanisms of reacquisition of drug self-administration and CPP after extinction (Achat-Mendes et al., 2012; Carnicella et al., 2008; Nic Dhonnchadha et al., 2010, 2012; Sticht et al., 2010). The most interesting recent finding from the use of the operant reacquisition procedure is that the cortical and subcortical mechanisms of reacquisition of reinforced alcohol-taking behavior are different from those that control nonreinforced reinstatement of alcohol seeking (Khoo et al., 2015; McNally, 2014; Millan et al., 2013; Willcocks and McNally, 2013). We predict that these findings will have a major impact on future direction of research on neuropharmacological mechanisms of drug relapse.

2.3 RESURGENCE

2.3.1 Experimental procedure

The resurgence procedure includes three phases. In the first phase, rats are trained to press on Lever 1 to receive a reward (drug or food). In the second phase, lever presses on Lever 1 are not reinforced (extinction), while responding on Lever 2 is reinforced by the food reward or Lever 1 is extinguished before Lever 2 training (Winterbauer and Bouton, 2011). In the third test phase, lever responding is not reinforced on either lever, and resumption of responding on Lever 1 serves as the operational measure of "resurgence" or resumption of extinguished reward seeking (Winterbauer and Bouton, 2010).

2.3.2 Brief history

In 2006, Podlesnik et al. (2006) showed resurgence of oral alcohol seeking after extinction in rats. This group also demonstrated resurgence of intravenous cocaine seeking after extinction and that this effect is blocked by a D1-family receptor antagonist (Quick et al., 2011). In these studies, the resurgence effect with cocaine-trained rats was significantly more robust than with alcohol-trained rats.

3 ABSTINENCE-BASED RELAPSE MODELS

3.1 FORCED ABSTINENCE[1] AND INCUBATION OF DRUG CRAVING

3.1.1 Experimental procedure

A typical forced abstinence study includes three phases: training, abstinence (withdrawal), and testing. During the training phase, laboratory animals are trained to self-administer a drug; lever presses (or nose pokes) lead to the delivery of a drug infusion paired with a discrete cue. During the abstinence phase, the subjects are housed in the animal facility for different periods of abstinence. During the test phase, the subjects are brought back to the drug self-administration environment/context (operant chambers) and lever presses (or nose pokes) lead to contingent presentations of discrete cues previously paired with drug infusions but not the drug (Fuchs et al., 2006; Reichel and Bevins, 2009). Nonreinforced lever pressing in this single extinction session is the operational measure of "relapse to drug seeking" and the main dependent measure in forced abstinence studies.

A variation of this general procedure has been used in "incubation of drug craving" studies in which typically different groups of subjects are tested under extinction conditions at different abstinence days (Pickens et al., 2011). Incubation of drug craving refers to the time-dependent increases in cue-induced drug seeking after cessation of drug self-administration training (Grimm et al., 2001). We discuss this phenomenon under the forced abstinence procedure because this procedure is currently used in most, if not all, recent mechanistic studies on incubation of drug craving (see Lee et al., 2013; Li et al., 2014c; Loweth et al., 2014a; Ma et al., 2014). However, incubation of drug craving was initially observed in studies on drug priming (Tran-Nguyen et al., 1998), discrete cue (Grimm et al., 2001; Neisewander et al., 2000), and stress (Shalev et al., 2002) induced reinstatement that used the so-called "between-within" reinstatement procedure (Shalev et al., 2002). In this procedure, the extinction and reinstatement test phases are performed during a single session on different days after drug self-administration training.

3.1.2 Brief history

3.1.2.1 Forced abstinence

The "forced abstinence" model was first introduced to the field by the Neisewander lab in studies in the late 1990s in which the effect of chronic drug treatment, lesions, or striatal dopamine release was determined after several days or weeks of forced abstinence in the home cage on extinction responding and subsequent reinstatement (Fuchs et al., 1998; Neisewander et al., 1996; Tran-Nguyen et al., 1999). In a subsequent important study, Fuchs et al. (2006) used tetrodotoxin reversible inactivation

[1]The word *abstinence*, etymologically, denotes agency on the part of the abstainer. Therefore, strictly speaking, "forced abstinence" is oxymoronic and "voluntary abstinence" (see below) is redundant. We use those terms because they have become entrenched in the literature on this topic and are now the clearest ways to convey the experimental procedures used to study incubation of drug craving discussed in the review.

and showed partial neuroanatomical dissociation between brain areas controlling cue-induced relapse after forced abstinence versus cue- and context-induced reinstatement of cocaine seeking after extinction. Since then, the single extinction session forced abstinence model to measure cue-induced relapse has been used by several investigators to study underlying mechanisms (Berglind et al., 2007; Reichel and Bevins, 2009).

3.1.2.2 Incubation of drug craving

In 1986, Gawin and Kleber (1986) proposed that cue-induced cocaine craving progressively increases over the first weeks of abstinence and remains high over extended periods. An analogous incubation phenomenon was subsequently identified in rats based on observations of time-dependent increases in extinction responding and cue-induced reinstatement after cessation of drug self-administration training (Grimm et al., 2001; Neisewander et al., 2000; Shalev et al., 2001). Incubation of drug craving has been observed in rats trained to self-administer methamphetamine (Shepard et al., 2004), alcohol (Bienkowski et al., 2004), nicotine (Abdolahi et al., 2010), or oral sucrose (Grimm et al., 2002) (see also Youtz, 1938 for an early demonstration of "incubation of food craving"). Incubation of drug craving was also observed in one study using a CPP procedure in which preference for the morphine-paired side increased over time (Li et al., 2008), and in a study, using an acquisition of a new conditioned response-learning procedure (Mackintosh, 1974) in which the response to heroin or cocaine cues to maintain operant responding was determined at different time points after drug self-administration (Di Ciano and Everitt, 2004). Recently, Halbout et al. (2014) showed that robust incubation of cocaine craving occurs after a single session of cocaine self-administration. Finally, several recent studies have demonstrated incubation of nicotine, methamphetamine, and alcohol craving in humans (Bedi et al., 2011; Li et al., 2014a; Wang et al., 2013).

Several recent reviews summarize results from studies on neurobiological mechanisms of incubation of drug craving and environmental modulation (e.g., environmental enrichment) of incubation of drug craving (Dong and Nestler, 2014; Li et al., 2014b; Loweth et al., 2014b; Marchant et al., 2013b; Pickens et al., 2011; Solinas et al., 2010).

3.2 VOLUNTARY ABSTINENCE INDUCED BY ADVERSE CONSEQUENCES OF DRUG INTAKE

3.2.1 Experimental procedure

Laboratory animals are trained to self-administer a drug (or food); typically, each drug delivery is paired with a discrete cue. During the subsequent phase, drug-taking behavior is suppressed by an aversive shock before the relapse tests. In punishment-based relapse models, this is achieved by administering the shock after the rat performs the operant response (Panlilio et al., 2003). In the conflict-based relapse model, drug taking and seeking is suppressed by introducing an electric barrier in front of the drug-associated lever (Cooper et al., 2007). During the test phase, relapse to drug seeking is precipitated by exposure to drug-priming injections or cues.

3.2.2 Brief history

3.2.2.1 Punishment-based relapse models

In an early study, Smith and Davis (1974) showed that morphine-priming injections do not provoke relapse to morphine seeking after high-intensity shock punishment. More recently, Panlilio et al. (2003) used lower intensity shock and showed that priming injections of remifentanil (a short-acting opioid agonist) after punishment-induced suppression of the drug-reinforced responding cause faster reacquisition of remifentanil self-administration. Subsequently, these authors (Panlilio et al., 2005) showed that priming injections of heroin or the benzodiazepine lorazepam also cause resumption of nonreinforced lever responding (relapse). We recently modified the ABA context-induced reinstatement procedure to demonstrate context-induced relapse to alcohol seeking in alcohol-preferring P rats after punishment in a nondrug context (Marchant et al., 2013a). In subsequent studies, Marchant and Kaganovsky (2015) and Marchant et al. (2014) showed an important role of LH and NAc shell in context-induced relapse to alcohol seeking after punishment-imposed abstinence.

A punishment-induced abstinence procedure has also been used to determine neuropharmacological mechanisms of cue-induced relapse to cocaine seeking after home-cage forced abstinence following the completion of the punishment phase (Economidou et al., 2009; Pelloux et al., 2014). Krasnova et al. (2014) also recently showed that incubation of methamphetamine craving is observed after punishment-imposed abstinence and 21 days of home-cage forced abstinence.

3.2.2.2 A conflict-based relapse model

Since the 1920s, experimental psychologists have used conflict-based procedures to assess motivation to seek rewards (Olds and Olds, 1958; Warden, 1931). Cooper et al. (2007) adapted this conflict-based procedure as an animal model of the human condition of self-imposed abstinence and relapse episodes that involve making a choice between the desire for the drug and its adverse consequences. They reported that about half of the rats whose cocaine-reinforced responding was suppressed by increasing shock intensities of the "electric barrier" near the drug-paired lever, resumed drug seeking (in the presence of the electric barrier) during tests for discrete cue-induced relapse. Peck et al. (2013) replicated this observation and also showed that compared with cocaine-trained rats a significantly higher proportion of heroin-trained rats resume drug seeking during the cue-induced relapse test. In an elegant study, Saunders et al. (2013) provided a potential explanation for the large individual differences in cocaine cue responding during the relapse test by showing that only "sign-tracking" but not "goal-tracking" rats relapse to cocaine seeking in the conflict-based relapse model.

3.3 VOLUNTARY ABSTINENCE INDUCED BY INTRODUCING A NONDRUG REWARD IN A CHOICE PROCEDURE

3.3.1 Experimental procedure

The new voluntary abstinence incubation of craving procedure includes four experimental conditions: (1) palatable food self-administration training in the presence of distinct discriminative and discrete food-associated cues, (2) drug self-

administration training in the presence of distinct discriminative and discrete drug-associated cues, (3) voluntary abstinence during which the rats are given mutually exclusive choice sessions between the palatable food and the drug, and (4) tests for cue-induced drug seeking in extinction tests during early or late abstinence. During the voluntary abstinence period in our studies, we expose rats to 20 daily mutually exclusive choice trials between methamphetamine and palatable food, every 10 min; this procedure is based on previous choice studies in rats that self-administered cocaine, heroin, or methamphetamine (Ahmed et al., 2013; Caprioli et al., 2015b; Lenoir and Ahmed, 2007). The alternative food reward is a TestDiet pellet (# 1811155; 12.7% fat, 66.7% carbohydrate, 20.6% protein). We chose this pellet because in food preference tests, rats prefer this pellet type over other pellet types with different compositions of fat and carbohydrate and different flavors (Calu et al., 2014).

3.3.2 Brief history

In a recent study, we used the procedure described above and showed that cue-induced methamphetamine seeking is significantly higher after 21 days of voluntary abstinence than after 1 day (Caprioli et al., 2015a). This incubation effect was observed under two different self-administration procedures that are widely used to model drug addiction: extended daily access drug self-administration procedure (Ahmed and Koob, 1998; Ahmed et al., 2000) and a long-term training procedure used to identify addicted rats based on the DSM-IV criteria (Deroche-Gamonet et al., 2004; Piazza and Deroche-Gamonet, 2013). We also found that AZD8529, a positive allosteric modulator of metabotropic glutamate receptor 2 (mGluR2), decreased "incubated" cue-induced drug seeking on abstinence day 21. We propose that our rat model is analogous to the human condition of relapse to drug use after termination of long-term contingency management treatment (Roll, 2007; Silverman et al., 2012). Our model also mimics, to some degree, relapse that occurs in more natural settings when former addicts lose important alternative nondrug rewards that maintain abstinence (e.g., a steady job, social relationships).

4 CONCLUSIONS

In this review, we provided an overview of the different animal models that have been used over the years to study relapse to drug seeking. Currently, the vast majority of the published papers are from studies in which the reinstatement procedure was used to identify mechanisms of drug-priming- and discrete cue-induced drug seeking, and to a lesser degree, stress-, context-, and discriminative cue-induced reinstatement (Table 1). However, more recently, the number of studies using "alternative" relapse models of forced or voluntary abstinence has significantly increased (Table 2). A critical question for the future is whether the use of the newer relapse models, which more closely mimic the conditions that lead to abstinence in

humans, will result in novel insights on the neuropharmacological mechanisms of drug relapse and subsequently to the identification of new medications for relapse prevention.

ACKNOWLEDGMENTS

Research was supported by the National Institute on Drug Abuse, Intramural Research Program. The authors declare that they do not have any conflicts of interest (financial or otherwise) related to the data presented in this manuscript.

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