Published in final edited form as:

Curr Top Behav Neurosci. 2013 ; 13: 403–432. doi:10.1007/7854_2012_202.

Modeling Relapse in Animals

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Abstract

Alcohol addiction is a chronically relapsing disorder characterized by compulsive alcohol seeking and use. Alcohol craving and long-lasting vulnerability to relapse presents a great challenge for the successful treatment of alcohol addiction. Therefore, relapse prevention, has emerged as a critically important area of research, with the need for effective and valid animal models of relapse. This chapter provides an overview of the repertoire of animal models of craving and relapse presently available and employed in alcoholism research. These models include conditioned reinstatement, stress-induced reinstatement, ethanol priming-induced reinstatement, conditioned place preference, Pavlovian spontaneous recovery, the alcohol deprivation effect, and seeking-taking chained schedules. Thus, a wide array of animal models is available that permit investigation of behaviors directed at obtaining access to alcohol, as well as neurobehavioral mechanisms and genetic factors that regulate these behaviors. These models also are instrumental for identifying pharmacological treatment targets and as tools for evaluating the efficacy of potential medications for the prevention of alcohol craving and relapse.

Keywords

conditioned reinstatement; conditioned place preference; alcohol deprivation effects; reinstatement; Pavlovian Spontaneous Recovery; alcohol-seeking behavior

1.0. Introduction

Alcoholism is a chronically relapsing condition characterized by compulsive drug seeking and use (American Psychiatric Association, 2000; McLellan et al. 2000; O'Brien et al. 1998; O'Brien and McLellan 1996). Three factors have been implicated in vulnerability to relapse. These include learned responses evoked by environmental stimuli that have become associated with the subjective actions of drug of abuse by means of classical conditioning. Exposure to such stimuli evokes drug desire and drug seeking, effects that have been implicated both in maintaining ongoing alcohol and drug use and eliciting drug seeking and relapse during abstinence (O'Brien et al. 1996, 1998). A second factor with an established role in relapse to alcohol use in humans is stress. Not only is stress a precipitating factor for alcohol seeking, but chronic alcohol use and withdrawal elicit stress-like states and withdrawal-related distress is associated with increased drug craving and conditioned cue

reactivity, thereby compounding relapse risk associated with alcohol cue exposure (e.g., Brown et al. 1995; Kreek and Koob 1998; Marlatt 1985; McKay et al. 1995; Sinha 2000; 2001; Sinha et al. 1999; Sinha et al. 2006). A third major factor in vulnerability to relapse is neuroadaptive dysregulation induced by chronic alcohol use (Koob 2003; Koob and Le Moal 2008). Such disturbances are thought to underlie symptoms of anxiety, mood disturbances, irritability, autonomic arousal, and exaggerated responsiveness to stress that emerge when drug use is discontinued and outlast physical withdrawal and detoxification (e.g., Brower 2010; Heilig et al. 2010; Majchrowicz 1989; Martinotti 2008; Meyer 1996).

To establish the neurobiological mechanisms that mediate ethanol-seeking behavior associated with these risk factors and to identify pharmacotherapeutic targets for relapse prevention animal models are indispensable. This chapter provides an overview of animal models that are most widely employed in contemporary addiction research to study relapse-like alcohol-seeking behavior and its neural, molecular, and genetic basis.

2.0. Models of Craving and Relapse Associated with Conditioning Factors

Alcohol-associated stimuli or events can evoke drug desire and lead to the resumption of drinking in abstinent alcoholics (Cooney et al. 1987; Cooney et al. 1997; Eriksen and Gotestam 1984; Kaplan et al. 1985; Laberg 1986; Monti et al. 1987; Monti et al. 1993; Sinha 2009; Sinha et al. 2009; Sinha et al. 2000). Studies in animals have confirmed that environmental stimuli associated with the reinforcing actions of alcohol -- either by means of classical conditioning or acting as discriminative or contextual stimuli that signal drug availability -- reliably elicit alcohol seeking in animals. Several animal models of alcohol seeking and conditioned reinforcement are used to elucidate the role of learning factors in relapse, to reveal the signaling mechanism that regulate specific aspects of conditioned alcohol seeking, and as a tool in preclinical medication development.

2.1. Conditioned Reinstatement

The initiation of drug seeking in response to alcohol-associated environmental stimuli can be demonstrated in the context of several conditioning procedures. The most prominent among these is the extinction-reinstatement model. Reinstatement refers to the recovery of an excitatory response to an extinguished stimulus produced by noncontingent exposure to the unconditioned stimulus. Conditioned reinstatement in the addiction literature refers to the resumption of responding at a previously drug-paired operandum produced by exposure to drug-associated environmental stimuli (for review, see Le and Shaham 2002; Shaham et al. 2003; Shalev et al. 2002).

An important consideration concerning the significance of learning factors in drug addiction is the role of discrete drug-paired vs. discriminative or contextual stimuli. The latter category of stimuli signals the availability of a reinforcer and thereby sets the occasion to engage in behavior that brings the organism into contact with the reinforcing substance. A condition often associated with drug craving in humans is the cognitive awareness of drug availability. It has been argued, therefore, that the manner in which drug-associated contextual cues attain their incentive properties is likely to involve the predictive nature of these stimuli rather than only classically conditioned stimulus-response associations as modeled with

reinstatement procedures that utilize discrete drug-paired conditioned stimuli (e.g., Ettenberg 1990; Ettenberg et al. 1996; and Ettenberg 2009 for review). Moreover, by virtue of their presence during drug consumption, contextual cues also become associated with the rewarding effects of the drug and thus acquire incentive-motivational value (i.e., elicit memories of previous drug euphoria and the “magnitude” or value of the rewarding effect of drug consumption). Because of this dual action, these stimuli are particularly powerful in eliciting drug seeking and reinstatement.

Both response-contingent and response-noncontingent exposure to ethanol-associated contextual stimuli (or an ethanol-paired environmental context) reliably elicits recovery of extinguished responding at a previously ethanol-paired lever without further alcohol availability (Bienkowski et al. 1999a; b, 2004; Bowers et al. 2008; Burattini et al. 2006; Ciccocioppo et al. 2003a; Ciccocioppo et al. 2003b; Ciccocioppo et al. 2002; Corbit and Janak 2007; Janak and Chaudhri 2010; Katner et al. 1999; Katner and Weiss 1999; Le and Shaham 2002; Radwanska et al. 2008; Zironi et al. 2006). The conditioned effects of, in particular, ethanol-predictive contextual or discriminative stimuli are remarkably resistant to extinction. It has been shown that these stimuli maintain recovery of ethanol seeking significantly above extinction levels when presented repeatedly under non-reinforced conditions (Cannella et al. 2009; Ciccocioppo et al. 2001a; Ciccocioppo et al. 2006) or elicit increased reinstatement with increasing abstinence duration (Bienkowski et al. 2004), a phenomenon that has been referred to as the “incubation of craving” (Grimm et al. 2001; Le and Shaham 2002). The persistence of the motivating effects of drug-associated stimuli in the animal literature resembles the long-lasting, compulsive-like nature of craving and relapse risk associated with exposure to drug cues in humans and provides experimental confirmation of the hypothesis that learned responses to drug-related stimuli are a significant factor in persistent vulnerability to relapse.

Consistent with clinical findings, reinstatement induced by alcohol cues is sensitive to reversal by opioid antagonist administration (Bienkowski et al. 1999a; Burattini et al. 2006; Ciccocioppo et al. 2003b; Ciccocioppo et al. 2002; Katner et al. 1999). In alcoholics, naltrexone attenuates cue-induced craving (Monti et al. 1999; Rohsenow et al. 2000) and reduces relapse rates (O’Brien et al. 1996; Volpicelli et al. 1992). Moreover, excellent correspondence exists between neural mapping data in animals (Dayas et al. 2007; Zhao et al. 2006) and functional brain imaging studies in drinkers (e.g., Braus et al. 2001; George et al. 2001; Kaplan et al. 1983; Kaplan et al. 1984; Kareken et al. 2004; Myrick et al. 2004; Schneider et al. 2001; Vollstadt-Klein et al. 2011) with respect to the neurocircuitry activated by alcohol cue manipulations that, in humans, are closely linked with self-reports of craving. Conditioned reinstatement of ethanol seeking in animals, therefore, has postdictive and, possibly, construct validity as a model of craving and relapse linked to alcohol cue exposure.

2.1.1. Discrete Cues—The original and, until recently, most widely employed method to study the role of conditioning factors in drug-seeking behavior involves the pairing of a response producing the drug reinforcer with brief presentation of an environmental stimulus. In this procedure, animals are trained to respond at a lever. Each response producing the drug reinforcer is contiguously paired with brief presentation of a stimulus, such as a tone or cue light, to establish this cue as a conditioned stimulus (CS). Both the presentation of

alcohol and the CS are contingent on a response. Once reliable ethanol self-administration is acquired, ethanol-reinforced instrumental responding is extinguished by withholding drug delivery and presentation of the CS. Subsequently, tests are conducted in which the degree of recovery of responding at the previously alcohol-paired lever (reinstatement), now maintained by response-contingent presentation of the CS only, is operationally defined as a measure of alcohol seeking or relapse.

2.1.2. Contextual Cues—This model is employed to study the effects of environmental context on the recovery of drug seeking. Here, drug availability is conditioned to stimuli (i.e., olfactory, auditory, tactile, or visual cues) present in the self-administration environment. This model has found increasing application over the past decade and is currently the most widely employed conditioned reinstatement model.

In contextual reinstatement procedures, environmental stimuli neither are paired contiguously with drug infusions, nor is their presentation contingent on a response (Contextual cue manipulations are, however, sometimes combined with the discrete cue conditioning procedures such that reinforced responses result in brief response-contingent presentation of a discrete cue [CS] in the ethanol-predictive environmental context). Owing to their predictive nature for drug availability, contextual stimuli “set the occasion” for engaging in reward seeking (i.e., to lead to the initiation of responding). Except for using context or discriminative stimuli as cue manipulations, these models are identical to the discrete cue (CS) model in terms of the training and experimental sequence, with conditioning followed by extinction in the absence of and, subsequently, reinstatement tests in the presence of the drug-associated cues. Several variants of the model exist. For example, the “basic” conditioned reinstatement model utilizes differential reinforcement of behavior in the presence of discriminative stimuli. In this procedure, during self-administration learning, responses at the operandum are reinforced by the drug only in the presence of this stimulus. In the absence of the stimulus (or the presence of a distinctly different cue), responses remain non-reinforced. Following extinction, presentation of the ethanol-related stimulus elicits ethanol-seeking (relapse-like) behavior (e.g., Ciccocioppo et al. 2001a; Ciccocioppo et al. 2003b; Dayas et al. 2007; Katner et al. 1999; Katner and Weiss 1999; Kufahl et al. 2011; Liu and Weiss 2002b; Zhao et al. 2006). Another widely employed contextual conditioning model pioneered by Bouton and Schwartztruber (Bouton and Swartztruber 1986) to study how the context influences extinction and resumption of learned behavior utilizes distinct environments that provide compound contextual cues (i.e., concurrent presence of olfactory, auditory, tactile, and visual cues). In this model, responding is reinforced by a given drug reinforcer in one context. Reinforced instrumental responding then is extinguished in a second context. Subjects subsequently tested in the second context show low drug seeking because the behavior was extinguished in this context. In contrast, animals tested in the first (drug-paired) context show reactivation or renewal of responding at the previously active operandum (Burattini et al. 2006; Crombag et al. 2008; Crombag et al. 2002; Crombag and Shaham 2002; Zironi et al. 2006; for review, see Janak and Chaudhri 2010).

2.1.3. Neurocircuitry of Conditioned Reinstatement—Drugs of abuse have diverse pharmacological profiles and produce differential behavioral effects. Nonetheless, their conditioned effects share the common feature of activating major components of the brain incentive motivation circuit. With the use of reinstatement models, advances have been made in elucidating the neurocircuitry that mediates ethanol seeking associated with ethanol cue exposure. Consistent with findings from functional brain imaging in humans (e.g., Daglish and Nutt 2003; Goldstein and Volkow 2002; Heinz et al. 2005; Miller and Goldsmith 2001; Heinz et al. 2010; Myrick et al. 2004), animal studies that utilized *c-fos* expression as a marker of neural activation, targeted lesions, and site-specific pharmacological manipulations implicate interconnected cortical and limbic brain regions in response to drug cue-, drug priming-, and stress-induced reinstatement (e.g., Cardinal et al. 2002; Carnicella et al. 2008; Chen et al. 2011; Dayas et al. 2007; Everitt et al. 2001; Janak and Chaudhri 2010; Kalivas and Volkow 2005; See et al. 2003; Steketee and Kalivas 2011; Topple et al. 1998; Tzschentke and Schmidt 2000; Zhao et al. 2006). Major components of this circuitry include the medial prefrontal cortex (mPFC), basolateral amygdala (BLA), central nucleus of the amygdala (CeA), bed nucleus of the stria terminalis (BNST), ventral tegmental area (VTA), nucleus accumbens (NAC), hippocampus, and dorsal striatum, which is thought to participate in consolidating stimulus-response habits via the engagement of corticostriatal loops. Ethanol-associated contextual stimuli elicit specific recruitment patterns within the mPFC, NAC, and hippocampus in rats, similar to those produced by other abused drugs (for discussion see Dayas et al. 2007), as well as brain activation patterns evoked by ethanol cues in alcoholics (Grusser et al. 2004; Maas et al. 1998; Myrick et al. 2004).

In addition to activation of the corticostriatopallidal circuitry, contextual cues conditioned to ethanol produce activation of brain sites not traditionally linked to conditioned drug seeking and reinstatement. These include the medial parvocellular and magnocellular paraventricular nucleus (PVN) of the hypothalamus (Dayas et al. 2007; Zhao et al. 2006). Activation of medial parvocellular PVN neurons is positively correlated with HPA axis activation (Buller et al. 1998; Dayas et al. 1999), suggesting that alcohol cues elicit a stress-like neuroendocrine response. Activation of the magnocellular PVN by ethanol cues represents an effect that is consistent with psychological stress (Dayas et al. 1999), lending support to the hypothesis that ethanol cues produce stress-like effects (see below). In addition to influencing the HPA axis, activated PVN neurons, through descending brainstem projections, may influence autonomic responses associated with the anticipation of ethanol reward predicted by ethanol cues as observed in alcoholic subjects (Sinha et al. 2000; Stormark et al. 1995). Thus, subjective responses to alcohol cues include stress-like reactions, and these may contribute to drug seeking (in animals) and the resumption of alcohol use (in humans) elicited by these cues, given the well-established significance of stress as a risk factor for relapse (see 5.0. Models of Stress as a Risk Factor for Relapse).

2.2. Pavlovian Spontaneous Recovery

Pavlov (Pavlov 1927) was the first to describe the spontaneous recovery of responding by showing that while extinguishing a behavior across a number of days, a small significant increase in responding at the beginning of each new extinction session occurred. In addition, as part of his classic bell-salivation association experiment Pavlov described that following

several extinction trials sufficient to abolish early-session responding, the test subjects would again salivate in response to the ringing bell after a significant time period had elapsed the last extinction session occurred and named this phenomenon spontaneous recovery.

Pavlovian spontaneous recovery (PSR) has been demonstrated in alcohol preferring (P) rats (Rodd-Henricks et al. 2002a; Rodd-Henricks et al. 2002b). Moreover, “pharmacological validation” that the anti-craving agent naltrexone decreases the expression of EtOH PSR (Rodd et al. 2004) confirmed the utility of PSR as a model of EtOH seeking and relapse. As well, the persistence of PSR in the absence of reward is thought to resemble the compulsive nature of drug abuse seen in humans (Anton 1999). PSR appears to be dependent on re-exposure to all stimuli in the environment previously associated with the reinforcer, and PSR increases with time (e.g., Rodd-Henricks et al. 2002a; Rodd-Henricks et al. 2002b). More specifically, PSR is enhanced when a longer period of time has elapsed between the last extinction session (more than 1 week; see Rodd et al., 2004), suggesting that forgetting of extinction learning occurs. Several lines of evidence indicate that, in fact PSR, represents a shift from the expression of extinction learning to what was learned initially (i.e., the association between contextual cues and reward) and not an elimination of either form of learning (Bouton 1988; Brooks 2000; Brooks and Bouton 1993; for review, see Rodd et al. 2004). More specifically, it has been argued that PSR reflects a shift away from extinction learning to motivation to obtain the previously available reward, suggesting that PSR is a model suitable for studying craving-like behavior (Bouton 2002; 2004; Dhaher et al. 2010; Rodd et al. 2006).

2.3 The Operant Runway Model of Relapse

In this model, the time taken in a runway from a start box to a goal box where the drug is administered provides a dependent measure of drug seeking. In this procedure, a discriminative stimulus present in the start box, runway, and goal box is predictive of drug reward obtainable in the goal box, whereas a different discriminative stimulus predicts non-availability of drug reward. Run times eventually decrease in the presence of the drug-predictive discriminative stimulus, but not the non-reward cue. Rats then are placed on extinction conditions under which the discriminative stimulus is absent and no drug is available in the goal box, with the result that run time increases progressively. During subsequent reinstatement tests, reintroduction of the drug-paired discriminative stimulus decreases the runtime for reaching the goal box again. As well, drug availability in the goal box during extinction reduces run time on the subsequent drug-free day. This decrease in the latency to reach the goal box as associated with these manipulations serves as a measure of relapse (Ettenberg 1990; Ettenberg et al. 1996; and Ettenberg 2009). This model has not been utilized extensively to study specifically alcohol relapse processes, but has been employed to examine the effects of ethanol on approach-avoidance conflicts in cocaine-seeking rats (e.g., Knackstedt and Ettenberg 2005, Knackstedt et al. 2006) and the effects of early ethanol exposure on ethanol seeking in adulthood (Walker and Ehlers 2009).

2.4. Conditioned Place Preference Models

An alternative approach to studying ethanol-seeking behavior is the conditioned place preference (CPP) model. CPP reflects the reinforcing value of ethanol by the degree to

which animals seek and spend time in an environment (place preference) previously paired with the systemic administration of alcohol. Place conditioning has advantages over other procedures used to study the rewarding effects of drugs because the procedure is technologically simple and usually brief. The CPP procedure also provides an effective tool to separately examine manipulations that affect the initial learning (acquisition) of the drug-context association and manipulations that affect the performance (expression) of approach responses that result from this learning. Moreover, CPP procedures are effective in establishing dose ranges and post-administration time profiles for ethanol's (and other drugs') reinforcing rather than aversive actions, with implications for understanding actions of the drug relevant for subsequent craving and relapse (for reviews, see Bardo and Bevins 2000; Cunningham et al. 2006; Liu et al. 2008; Schechter and Calcagnetti 1993; Tzschentke 2007).

2.4.1. Expression of Conditioned Place Preference as a Model of Relapse—

Place conditioning procedures permit examination of the neuropharmacological substrates mediating the acquisition and expression of the conditioned reinforcing effects of ethanol (e.g., Camarini et al. 2010; Gremel and Cunningham 2007; Gremel and Cunningham 2008; Maurice et al. 2003; for review see Tzschentke 2007). Manipulations that interfere specifically with the *expression* of CPP, once acquired, provide information on the neural and motivating forces of the conditioned rewarding effects of ethanol leading to ethanol seeking or “craving.” In contrast, interference with the acquisition of CPP is relevant for the understanding of neural mechanisms that mediate the acute reinforcing effects of ethanol, inferred by the establishment of Pavlovian associations between the ethanol reinforcer and place conditioning environment and, therefore, of lesser importance for the understanding of factors that drive the desire to obtain ethanol (craving) and relapse-like behavioral responses.

In CPP expression studies, the degree of preference for a previously ethanol-paired environment provides an index of the strength of ethanol seeking associated with the incentive-motivational effects of the previously alcohol-associated stimulus context. An issue to be considered, however, is that the expression of CPP typically is studied without an intervening period of abstinence before testing such that CPP has some limitations as a valid model of craving and relapse processes during abstinence. As well, CPP studies generally employ involuntary EtOH administration procedures. The reinforcing actions of ethanol under these conditions may differ from those associated with voluntary oral self-administration. As a result, the strength or nature of associations that are formed between ethanol and environmental stimuli may differ in CPP *vs.* self-administration and conditioned reinstatement procedures. Moreover, the number of learning trials in reinstatement models of ethanol-seeking that involve the conditioning of the effects of self-administered ethanol with environmental stimuli typically is considerably greater than in the CPP procedure. Associations that are produced between specific environmental stimuli and ethanol are therefore likely to be weaker in the CPP model. As a result of these differences, the expression of conditioned ethanol-seeking responses may be differentially sensitive to pharmacological manipulation in CPP *vs.* self-administration models and it is likely that the neural substrates of contextual conditioning associated with CPP do not fully overlap with those mediating the effects of stimuli conditioned to the reinforcing effects of actively self-

administered ethanol. Finally, important species considerations apply to ethanol CPP. Typically, ethanol CPP is most effectively obtained in mice. In contrast rats show little ethanol CPP (with the exception of genetically selected ethanol preferring lines) and often develop conditioned place aversion without prior ethanol acclimation procedures (Cunningham et al. 1993; Tzschentke 2007).

2.4.2. Reactivation of Conditioned Place Preference—Another contextual model of ethanol seeking is the reactivation of CPP. This procedure evolved from the traditional CPP procedure and incorporates features of the reinstatement model. Following the extinction of CPP, accomplished by pairings of vehicle rather than drug with the environment, re-establishment, technically termed *reactivation (or reinstatement) of CPP*, is produced by a drug injection. CPP reactivation procedures have been successfully applied in conjunction with abstinence manipulations following which drug injections or stress reactivate CPP. (e.g., Buthada et al. 2011a,b; Itzhak and Martin 2002; Kuzmin et al. 2003; Mueller and Stewart 2000; Romieu et al. 2004; Szumlinski et al. 2002; Thanos et al. 2009; for review see Aguilar et al. 2009; Tzschentke 2007).

The CPP reactivation model incorporates all the advantages of the traditional CPP procedure strengthened by allowing for extinction and abstinence manipulations important for the validity of the procedure as a model of craving or relapse. However, the CPP reactivation model also shares the limitations of the conventional CPP procedure discussed above. A further constraint is that the procedure does not provide a “pure” measure of conditioned reinforcement or contextual reinstatement, but rather of interactions between contextual conditioning and the effects of small “priming” doses of the drug or stress. Indeed, it has been suggested that CPP reactivation data be viewed with caution in terms of their relevance for understanding relapse processes until better information on the neurobiological mechanisms mediating this behavior is available (Aguilar et al. 2009).

3.0 Modeling Craving Induced by “Priming” Doses of Ethanol

It is well established that small doses of drugs of abuse, including ethanol, rather than reducing drug desire, elicit further drug craving (e.g., Jaffe et al. 1989; Ludwig et al. 1974). Moreover, in alcoholics, the first drink after abstinence is often associated with “loss of control,” leading to severe intoxication and a return to continued alcohol abuse (Ludwig et al. 1974). This priming effect can readily be demonstrated in the reinstatement model following systemic administration of low alcohol doses (for review see Le and Shaham 2002). This model provides an effective means to experimentally study the neural and molecular bases of the “loss of control” phenomenon that frequently is at the heart of the relapse process in alcoholics or people who are at risk for alcohol abuse (e.g., Ludwig et al. 1974). Moreover, the model provides a tool for investigating interactive effects of or co-dependence on different substances of abuse in the relapse process as illustrated by findings that nicotine “priming” can elicit reinstatement of ethanol seeking (e.g., Le et al. 2003).

4.0. Seeking-Taking Chained Schedules

Chained schedules consist of a “seeking phase” in which responses at a “drug-seeking” lever are initially required. Following completion of a response requirement or time interval in this first (i.e., seeking) link of the chained schedule, a second link is initiated by making available a “drug-taking” lever. Responses at this lever produce a drug reinforcer and presentation of a CS, followed by a time out period, whereupon the seeking link of the chain is re-initiated. The degree of conditioned drug seeking or relapse is measured by the number of seeking responses during sessions in which responses at the taking lever produce only the CS but do not result in drug availability.

4.1. Dissociation of Alcohol-Motivated Appetitive and Consumatory Behavior

In alcohol addiction research, a variant of “seeking-taking” chained reinforcement schedules is frequently used to dissociate ethanol-reinforced consummatory behavior (i.e., ethanol drinking) from appetitive behavior (i.e., responses induced and maintained by the incentive-motivational effects of ethanol-associated contextual cues (Samson et al. 2000; Samson et al. 1999; Samson et al. 1998). In this procedure, rats engage in ethanol seeking during an “appetitive phase” when they must complete a set of responses at a lever operandum without alcohol being available. The completion of a response requirement within a specific time results in the retraction of the lever and presentation of a sipper tube that contains ethanol solution, from which the rats are then allowed to freely drink for a given amount of time. This is called the “consummatory phase.” Thus, responding during the appetitive phase provides a measure of the day-to-day strength of the animal’s motivation to initiate and engage in ethanol-seeking behavior when exposed to the ethanol-predictive stimulus environment and can also serve as a measure of the desire to drink (Samson and Chappell 2002; Samson et al. 2003). Behavior during the consummatory phase, on the other hand, provides a measure of actual ethanol consumption as an index of the acute reinforcing strength of ethanol. In this model, seeking and consumption are not necessarily correlated. More importantly, this model allows for the investigation of neural mechanisms that control seeking or approach responses (i.e., ethanol “craving”) vs. mechanisms that control the reinforcing effects of ethanol (Saghal 1984). From a drug treatment development perspective, this model provides an effective tool to evaluate the relative efficacy of a potential treatment drugs for preferential “therapeutic” actions on ethanol craving vs. actual ethanol intake (e.g., (Czachowski et al. 2002; Sharpe and Samson 2001).

4.2. Chained Schedules as Potential Measures of Compulsive Alcohol Seeking

In addition to measuring drug seeking, seeking-taking chained schedules provide a potential model of drug compulsion when combined with manipulations designed to establish the degree to which drug seeking becomes resistant to suppression by aversive stimuli. Compulsive EtOH seeking, a hallmark of substance dependence on EtOH, is characterized by its continuation despite adverse consequences (American Psychiatric Association, 2000). Behavior motivated by rewards is suppressed by aversive signals, a phenomenon known as “conditioned suppression” (e.g., Bouton et al. 2008; Kearns et al. 2002; Lauener, 1963). The degree to which conditioned suppression of EtOH seeking is diminished in the presence of EtOH cues on the seeking component of a chained schedule can therefore be thought of as

modeling this aspect of drug compulsion. In the cocaine field, it has been confirmed that conditioned suppression decreases significantly with increasing “severity” of dependence, indicative of the development of compulsive drug seeking (Pelloux et al. 2007; Vanderschuren and Everitt 2004). However, this model still awaits implementation in alcohol field.

5.0. Models of Stress as a Risk Factor for Relapse

Stress has an established role in alcohol abuse in humans and is a major determinant of relapse (Brown et al. 1995; Marlatt 1985; McKay et al. 1995; Sinha 2000; 2001; Sinha et al. 2003; Wallace 1989). The significance of stress in alcohol consumption and reinforcement is also well documented in the animal literature. Stressors can facilitate the acquisition or increase the self-administration of alcohol (e.g., Blanchard et al. 1987; Higley et al. 1991; Mollenauer et al. 1993; Nash and Maickel 1988;) and reliably elicit s reinstatement of ethanol seeking in animal models of relapse (e.g., Le et al. 1998, 1999, 2000, 2006, 2011a, 2011b; Zhao et al. 2006; Liu et al. 2002, 2003; Martin-Fardon et al. 2000; Sidhpura et al. 2010).

Studies of stress-induced reinstatement typically are conducted using the extinction-reinstatement model with footshock stress having been the predominant model. More recently, pharmacological stressors have been employed as an alternative to footshock.

5.1. Footshock Stress

To study stress-induced ethanol seeking in the reinstatement model, rats are trained to self-administer ethanol. Once stable ethanol self-administration is established, ethanol-reinforced responding is extinguished. The reinstatement of ethanol seeking then is studied under extinction conditions after exposure to variable intermittent electric footshock administered through the grid floor of the operant chambers. Several procedural variations have been employed such as exposure to footshock in the reinstatement test environment vs. a different environment (Liu and Weiss 2002a; Liu and Weiss 2003; Le et al. 2000; Martin-Fardon et al. 2000; Sidhpura et al. 2010; Zhao et al. 2006; for review see Le 2002).

This model has been instrumental in the identification of brain regions that are recruited by stress and that may play a pivotal role in stress-induced drug seeking. These brain regions include the bed nucleus of the stria terminalis (BNST) (Erb and Stewart 1999; Shaham et al. 2000; Wang et al. 2006; Zhao et al. 2006), central nucleus of the amygdala (CeA) (Shaham et al. 2003), PVN (Dayas et al. 2007; Zhao et al. 2006), and mesocorticolimbic circuitry components, including the NAC, BLA, and VTA (Wang et al. 2005; Wang et al. 2007; Zhao et al. 2006). Overlap exists in the pattern of neural activation produced by footshock and exposure to ethanol-related contextual stimuli. Ethanol cue exposure, however, produces a stronger activation of brain regions linked to motivation and reward, such as the mPFC and hippocampus, vs. footshock stress, whereas footshock stress induces stronger neural activation within brain stress sites and particularly the PVN (Dayas et al. 2007; Zhao et al. 2006). In addition, both footshock and ethanol-related stimuli activate the CeA and BNST (Zhao et al. 2006), a finding that may reflect possible stress or anxiety-like effects of the ethanol cue. Stress and drug cue exposure may, in fact, induce a similar pattern of neural

activation as suggested by findings showing that in alcoholics craving states associated with drug cue exposure are accompanied by anxiety and HPA activation (Fox et al. 2005; Sinha et al. 2003; Sinha 2009).

5.2. Pharmacological Stressors

Recently, pharmacological stress manipulations have been developed and employed to study the role of stress in relapse using the extinction-reinstatement model. Here, a challenge injection of a pharmacological stressor is administered instead of footshock before reinstatement testing.

To date, the pharmacological stressor of choice has been yohimbine, a α_2 noradrenergic receptor antagonist that is anxiogenic and induces stress responses in both humans and nonhuman primates (Albus et al. 1992; Charney et al. 1983). Early findings revealed that yohimbine elevates drug craving and elicits opioid withdrawal symptoms in methadone-maintained patients (Stine et al. 2002). In animals, yohimbine elicits stress reflected by increased plasma corticosterone, increased arterial blood pressure, increased heart rate, and potentiation of the startle response (Davis et al. 1979; Lang and Gershon 1963; Suemaru et al. 1989), confirming that yohimbine is a suitable pharmacological agent for studying stress-induced drug-seeking behavior.

Yohimbine has since been increasingly used as an alternative stressor to footshock in animal models of drug seeking (Feltenstein and See 2006; Marinelli et al. 2007) and reward seeking (Fuchs et al. 2006; Nair et al. 2006). Yohimbine has been shown to reinstate alcohol seeking (Gass and Olive 2007; Le et al. 2011a; Le et al. 2011b; Le et al. 2005; Stopponi et al. 2011a; Stopponi et al. 2011b) as well as heroin (Banna et al. 2010) and cocaine seeking (e.g., Buffalari and See 2011; Feltenstein and See 2006; Lee et al. 2004), methamphetamine seeking (Shepard et al. 2004).

Yohimbine-induced reinstatement has been validated as a model of stress-induced ethanol seeking or relapse using pharmacological tools. Specifically, it has been shown that “anti-stress” agents including corticotropin-releasing factor (CRF) and hypocretin-1 receptor antagonists effectively prevent the effects of yohimbine on ethanol seeking (Richards et al. 2008; Marinelli et al. 2007). Yohimbine-induced reinstatement is now used extensively for identifying novel pharmacological targets for the prevention of stress-induced ethanol seeking (Le et al. 2011a; Le et al. 2011b; Nielsen et al. 2011; Stopponi et al. 2011a; Stopponi et al. 2011b).

5.3. Interactive Effects Between Stress and Conditioning Factors

Risk factors for relapse are typically studied in isolation, whereas abstinent alcoholics are frequently exposed to multiple external risk factors while at the same time experiencing varying degrees of protracted withdrawal symptoms resulting from ethanol-induced neuroadaptive dysregulation. Important for understanding the significance of drug-related learning in the relapse process, therefore, are findings that the presentation of alcohol cues significantly exacerbates the reinstatement of alcohol seeking produced by stress. Interactive effects of stress and alcohol-related cues were modeled by testing the concurrent effects of footshock stress and an ethanol-associated CS on reinstatement under three conditions: (1)

during response-contingent presentation of an ethanol CS alone, (2) after exposure to very mild footshock stress alone, and (3) during response-contingent presentation of the ethanol CS following exposure to footshock stress (Liu and Weiss 2002a; 2003). Under these conditions, the ethanol CS and footshock, when presented alone, produced only threshold effects on reinstatement of alcohol seeking. However, the ethanol CS elicited strong reinstatement in rats that had been subjected to footshock stress before the session.

The above findings document the existence of interactive effects between two factors implicated in craving and relapse: stress and alcohol-related cues. However, these studies, similar to the majority of research on the neural basis of ethanol seeking, remained confined to ethanol nondependent rats. Rats made ethanol dependent via chronic ethanol vapor inhalation or a chronic ethanol liquid diet show deficiencies in extracellular dopamine in the nucleus accumbens that are likely linked to withdrawal-associated reward deficits (Weiss et al. 2001; Schulteis et al. 1995) as well as hypersecretion of the stress-regulatory molecule corticotropin releasing-factor (CRF) in the central amygdala and BNST (Merlo Pich et al. 1995; Olive et al. 2002). The dysregulation of CRF transmission is long lasting, as are stress and anxiety-like behavioral manifestations of this dysfunction (Zorrilla et al. 2001; Zhao et al. 2007; Valdez et al. 2002). As well, recently abnormal function of metabotropic glutamate receptors with implications for stress-induced reinstatement has been identified in rats with histories of ethanol dependence (Kufahl et al. 2011; Sidhpura et al. 2010). Given that chronic alcohol intoxication leads to profound neuroadaptive dysregulation and, as a consequence, states of negative affect that represent a substantial risk factor for relapse (Koob 2003; Koob and Le Moal 2008), animal models have been employed to investigate the impact of alcohol dependence histories on cue and stress-induced alcohol seeking. These studies revealed that in ethanol dependent rats, the individual effects of an ethanol CS and footshock stress on reinstatement were substantially enhanced compared to nondependent rats, and that the interactive effects of the CS and footshock were, in fact, synergistically enhanced with a nearly 300% increase in ethanol seeking (Liu and Weiss 2002a).

The significance of a dependence history with respect to its role in the effects of alcohol cues and stress is illustrated further by the finding that previously ethanol-dependent rats not only show enhanced reinstatement induced by footshock stress, but also by a CS conditioned to footshock stress as well as the interactive effects of these cues (Liu and Weiss 2003).

The existence of such interactive effects between drug cues and stress has been corroborated in the context of pharmacological stress manipulations). These studies demonstrated that yohimbine greatly potentiated cocaine- and heroin-associated cue-induced reinstatement and that the BNST is a key mediator for the interaction between stress and cues for the reinstatement of cocaine seeking (Banna et al. 2010; Buffalari and See 2011; Feltenstein and See 2006).

Overall, the findings generated with the use of these animal models suggest that the probability of relapse varies as a function of the number and intensity of risk factors operative at any given time, with relapse occurring when the sum of these motivating forces reaches a critical threshold.

6.0. The Alcohol Deprivation Effect (ADE) as a Relapse Model

A well-described phenomenon in the alcohol literature is a marked increase in ethanol consumption that follows periods of alcohol deprivation. Early experiments revealed that rats show marked increases in voluntary ethanol consumption after periods of forced abstinence (Sinclair 1972; 1979; Sinclair and Li 1989; Sinclair and Senter 1967; Sinclair and Senter 1968). This so-called “alcohol deprivation effect” (ADE) has since been confirmed in mice (Salimov and Salimova 1993), rats (Spanagel et al. 1996; Wolffgramm and Heyne 1995), monkeys (Kornet et al. 1990; 1991). It has also been shown that the ADE occurs under both limited- and unlimited alcohol access conditions and with both home cage free drinking and operant self-administration models. However, the ADE appears most robust in the two-bottle free choice procedure using genetically alcohol-preferring animals or after extensive repeated cycles of intoxication and deprivation (Heyser et al. 1997; McBride et al. 2002; Spanagel and Höltér 2000; Spanagel and Kiefer, 2008). Nonetheless, the ADE is well established as a robust and reliable phenomenon in animal models of alcohol drinking.

The ADE is considered a measure of the motivation to seek and consume alcohol (Eravci et al. 1997; Rankin et al. 1979; Sinclair and Senter 1967), loss of control (Wolffgramm and Heyne 1995; Spanagel and Höltér 2000), or relapse (Kornet et al. 1991; McBride and Li 1998). Similarities exist between the ADE in animals and humans, such as enhanced ethanol consumption after abstinence in social drinkers (Burish et al. 1981) and the loss of control phenomenon that surrounds the first drink after abstinence in alcoholics (Ludwig and Wikler 1974; Ludwig et al. 1974; O'Donnel 1984). In view of these similarities, the ADE has appropriate face validity as a model for alcohol relapse process (Vengeliene et al. 2009). Indeed, many consider the ADE a “true” model of relapse compared to reinstatement models that do not measure resumption of actual drug taking and, therefore, perhaps more accurately model craving rather than actual relapse. Moreover, findings that pharmacological agents that suppress ethanol intake and reduce the likelihood of relapse in humans effectively attenuate the ADE in animals further support the predictive validity of this procedure as a model of relapse (Heyser et al. 2003; Heyser et al. 1998; McBride et al. 2002; Schroeder et al. 2005; Spanagel and Kiefer, 2008).

With repeated cycles of deprivation and increased deprivation periods, increased drinking associated with the ADE appears to become resistant to manipulations of ethanol concentration, taste, and environmental factors (Spanagel et al. 1996; Wolffgramm and Heyne 1995; Vengeliene et al. 2009). More specifically, in rats given long-term (8 to 24 months) continuous free access to different concentrations of ethanol and water, interspersed with deprivation periods of varying lengths, ethanol consumption increases significantly over baseline as a result of deprivation episodes (Spanagel et al. 1996; Wolffgramm and Heyne 1995), reaching levels of intake similar to those in rats selectively bred for alcohol preference (Li et al. 1979). The increase in ethanol intake produced by repeated deprivation outlasts long abstinence phases (Spanagel et al. 1996) and may become irreversible (Wolffgramm and Heyne 1995). Under these conditions, the ADE is characterized not only by enhanced preference for ethanol over water but preference for higher ethanol concentrations (> 10% v/v) and resistance to modification by changes in the palatability of ethanol via quinine or sucrose addition, or by manipulation of environmental and social

conditions such as isolation or changing dominance hierarchies (Spanagel et al. 1996; Vengeliene et al. 2009). Moreover, ethanol deprivation under these exposure conditions revealed a behavioral withdrawal syndrome, reflected by lowered thresholds of footshock reactivity, which reached a maximum on the second day of abstinence and persisted for up to 5 days post-ethanol (Heyne et al. 1991; Hölter et al. 2000). Extending these observations, access to multiple concentrations of ethanol and exposure to multiple deprivation cycles can partially overcome the genetic predisposition of NP, LAD-1, and LAD-2 rats for low alcohol consumption. These findings support the unexpected conclusion that the genetic control of low alcohol consumption in rats is not associated with inability to develop an ADE (Bell et al. 2004).

Overall, the ADE, in particular with repeated deprivation, provides an effective model to study the development of compulsive alcohol-seeking behavior and loss of control that characterize substance dependence on alcohol. Given that the ADE can be observed under many different experimental conditions, this phenomenon may have great utility for the exploration of diverse variables that contribute to the relapse process. However, long-term repeated alcohol deprivation procedures that produce the most robust exacerbation of alcohol consumption are time and labor-intensive and have not been employed extensively.

7.0. Conclusions

Alcohol craving and vulnerability to relapse represent formidable challenges for the successful treatment of alcohol addiction. Increasingly sophisticated animal models of ethanol seeking and relapse have become available over the past decade and have been instrumental for expanding our understanding of the neurobiological basis of susceptibility to relapse and for studying the treatment drug potential of pharmacological agents. Nonetheless, the validity of animal models of relapse, in particular of reinstatement models, has not gone unchallenged. The literature contains both critical (e.g., Epstein et al. 2006a; Katz and Higgins 2003) and supportive (Epstein et al. 2006a; Epstein et al. 2006b) appraisals of these models. Taking into account both the limitations and advantages of these models, it is perhaps safe to conclude that reinstatement models are the most effective procedures available to date for investigating the neural bases of craving and relapse and for evaluating the potential of drug treatments for craving and relapse prevention. An effective model also is the “seeking-taking” chained reinforcement schedule that permits concurrent investigation of both the strength of ethanol-seeking behaviors, presumably reflecting craving, and changes in the primary reinforcing effects of ethanol. Expression and reinstatement of conditioned place preference provide relapse models that are easy to implement and considerably less labor intensive than conditioned reinstatement chained schedules or alcohol deprivation procedures. However, as outlined above, CPP procedures have several limitations that require consideration when evaluating data generated by these models for their relevance for understanding the relapse process. The ADE has substantial potential as a model to study the development of compulsive alcohol-seeking behavior and loss of control. However, difficulties in reliably obtaining an ADE with operant ethanol self-administration procedures and the longitudinal nature of repeated ADE procedures required to obtain the most robust effects, somewhat limits the utility of this model.

Clearly, many animal models are available that permit investigation of alcohol-seeking behaviors (craving), the resumption of ethanol consumption following abstinence (relapse, loss of control), as well as neurobehavioral mechanisms and genetic factors that regulate these behaviors. These models also provide valuable tools for identifying pharmacological treatment targets and for evaluating the efficacy of potential treatment drugs for alcohol craving and relapse. At the same time, several important issues for improvement and advancement in our animal model repertoire exist. It will be important to establish the constructs measured by particular models in order to more effectively employ these procedures to study specific aspects or stages of the alcohol addiction cycle. In particular with regard to medications development, a need exists to establish the predictive validity of existing models. Pharmacological agents often do not produce the same modifications in ethanol-seeking behavior across these models and it will be important to understand the implications of these differences for understanding both the construct measured by a given model and its predictive validity.

Perhaps the biggest challenge for the development and refinement of animal models for craving or relapse is the issue of ethanol dependence history. With the exception of animals genetically selected for high ethanol intake, most animals will not voluntarily consume ethanol at levels sufficient to induce dependence. Repeated and long-term alcohol deprivation procedures can accomplish this, but the longitudinal nature of these procedures renders them impractical for everyday applications. Some progress with achieving high voluntary ethanol intake has been made with intermittent ethanol access procedures (Simms et al 2008) that lead to high and quinine-resistant EtOH intake (Hopf et al. 2010) and may provide an avenue to incorporate dependence-like drinking into existing models of relapse, in particular the reinstatement and chained schedule models. The dependence history issue is of special relevance for the understanding of craving and relapse associated with conditioning factors. Present behavioral and neurobiological information on the role conditioning factors in ethanol seeking is limited largely to that from animal studies in nondependent subjects. In alcoholics, a significant positive correlation exists between history of dependence and the severity of cue-induced ethanol craving (Greeley et al. 1993; Laberg et al. 1986; Myrick et al. 2004; Streeter et al. 2002). Thus, cue-induced EtOH seeking in animals without histories of dependence is unlikely to effectively model the learning events and motivating forces that underlie the compulsive nature of EtOH seeking in alcoholics with long histories of heavy drinking and repeated episodes of withdrawal. Ethanol consumption during withdrawal modifies an individual's reinforcement history to include learning about amelioration or avoidance of adverse withdrawal states as a novel and essential aspect of alcohol's reinforcing actions, rendering the drug a qualitatively different, more potent reinforcer. Thus, understanding the control of behavior by stimuli conditioned to ethanol under conditions that encompass the reinforcing dimension of this drug that emerges with the experience of withdrawal states will be essential for advancing the understanding and treatment of alcohol addiction.

Acknowledgments

Supported by grants AA10531, AA014351, and AA018010 from the National Institutes of Health / National Institute on Alcohol Abuse and Alcoholism to FW. The authors thank Michael Arends for editorial assistance.

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Model	Manipulation	Behavioral Measure	Dependent Variable(s)
Conditioned Reinstatement	Alcohol cues (CS) Alcohol-associated contextual cues: alcohol-predictive discriminative stimuli (SD) or environmental context	Alcohol seeking	Non-reinforced responses (e.g., lever presses, nose-pokes)
Pavlovian Spontaneous Recovery	Alcohol-associated environmental context	Alcohol seeking	Non-reinforced responses
Operant Runway	Alcohol SD	Alcohol seeking	Start time latency, time to reach goal
Conditioned Place Preference	Alcohol context	Alcohol seeking	Time spent in alcohol-associated environment
Priming-Induced Reinstatement	Noncontingent administration of alcohol, other drugs of abuse, or pharmacological agents	Alcohol seeking	Non-reinforced responses
Seeking-Taking	Alcohol cues (CS)	Alcohol seeking Alcohol intake	Seeking link: non-reinforced responses Taking link: alcohol drinking
Stress-induced Reinstatement	Footshock stress, pharmacological stress	Alcohol seeking	Non-reinforced responses
Alcohol Deprivation Effect	Alcohol deprivation (intermittent, repeated)	Exacerbation of Alcohol intake	Alcohol drinking/self-administration