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Advances in behavioral animal models of alcohol use disorder

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ABSTRACT

Alcohol use disorder (AUD) is a multifaceted neuropsychiatric disease that combines behavioral, psychosocial, and neurobiological aspects. Over the previous decade, animal models have advanced in modeling the major psychological constructs that characterize AUD. These advances pave the road for more sophisticated behavioral models that capture addiction-related aspects, such as alcohol craving, compulsive seeking and intake, dependence, and relapse. In this review, we survey the recent progress in behavioral animal modeling of five aspects of AUD: alcohol consumption, dependence, and seeking; compulsivity in alcohol intake despite adverse outcomes; vulnerability and resilience factors in alcohol addiction; relapse despite treatment; and relapse prevention by manipulating alcohol-associated memory reconsolidation. These advances represent a general attempt to grasp the complexity and multidimensional nature of AUD, and to focus on behavioral characteristics that better reflect and model this disorder.

Introduction

Alcohol use disorder (AUD) is a complex neuropsychiatric condition that combines behavioral, neurobiological, and psychosocial aspects (American Psychiatric Association, 2013), with 5.6% of the USA population aged 12 or older meeting the AUD diagnostic criteria (Substance Abuse and Mental Health Services Administration, 2016). Modeling this disorder in animals has been challenging, and requires fine definition of the psychological constructs that compose this illness. The development of AUD has been characterized as a spiraling distress-addiction cycle, leading from social/recreational alcohol intake to compulsive alcohol seeking, consumption, and dependence, via repeating phases of preoccupation/anticipation (craving), binge/intoxication, and withdrawal and negative affect (Koob & Le Moal, 2001).

Over the previous two decades, animal models have advanced from modeling the mere self-administration of alcohol, which on its own does not necessarily model AUD characteristics, to more sophisticated behavioral models that capture addiction-related aspects, such as alcohol craving, seeking, compulsive intake, dependence, and relapse. However, even alcohol self-administration *per se* is challenging to model, as alcohol may evoke both aversive and appetitive effects. Moreover, although most people consume alcohol throughout their lives, only a minority develop AUD, suggesting that genetic and environmental factors, and their combination through neurodevelopment in particular, may lead to predisposition to AUD.

In the review, we survey the progress over recent years in behavioral animal modeling of five aspects of AUD: the modeling of alcohol consumption, dependence, and seeking; the modeling of the compulsive aspects of alcohol addiction; the modeling of individual differences, vulnerability, and resilience factors in alcohol addiction; the modeling of relapse despite treatment; and the modeling of relapse prevention by manipulating alcohol-associated memory reconsolidation.

Alcohol consumption and seeking

Several rodent strains have been selectively bred for high alcohol preference (e.g., Colombo et al., 2014; Li, Lumeng, McBride, & Waller, 1979; McBride, Rodd, Bell, Lumeng, & Li, 2014), allowing

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consumption of high levels of alcohol without specific "initiation training". However, in outbred rat strains, initiation of stable operant responding for alcohol typically requires prolonged pre-exposure to alcohol, gradually fading saccharin/sucrose supplement, or concomitant water deprivation (Becker, 2013; Carnicella, Ron, & Barak, 2014; Simms, Bito-Onon, Chatterjee, & Bartlett, 2010; Simms et al., 2008). As a result, the initiation phase in a typical operant alcohol self-administration procedure can last weeks or even months, unlike with other drugs of abuse. Moreover, application of sweeteners or water deprivation might raise confounding issues.

Alcohol consumption and dependence

Although these initiation-training procedures are required to initiate a high level of operant responding, Augier et al. (2014) recently showed that Wistar rats can acquire and maintain moderate operant responding for alcohol without the use of water deprivation, extended pre-exposure to alcohol, or sucrose fading. Thus, alcohol-naïve male Wistar rats were trained to press a lever to obtain 0.1 mL of 20% alcohol in 13 short (30-min) sessions. Half of the rats received a 22-h water-deprivation schedule during the first three sessions. While rats with no water deprivation obtained fewer alcohol rewards during the first session, they did not differ from water-deprived rats in responding for alcohol throughout the rest of the training, and reached compatible levels of blood alcohol concentration (BAC) (Augier, Dulman, Singley, & Heilig, 2017; Augier et al., 2014). The levels of alcohol self-administration, the motivation to obtain alcohol, and stress-induced reinstatement were reduced by the pharmacological treatments previously shown to suppress these behaviors in other alcohol consumption paradigms. These findings suggest that it is possible to achieve moderate alcohol consumption levels and stable operant responding in outbred rats in a simple and short self-administration procedure. Thus, it allows the saving of valuable time and resources, while avoiding possible confounding issues. It is important to note that this procedure does not model excessive alcohol intake or dependence, but rather offers a protocol to measure alcohol-related behavior in non-dependent animals.

While the procedure of Augier et al. (2014) produced relatively moderate alcohol intake and BAC levels, de Guglielmo, Kallupi, Cole, and George (2017) recently presented a novel operant self-administration procedure that leads to considerably higher BACs and to voluntary alcohol dependence in Wistar rats, using alcohol vapor self-administration. The authors developed a new apparatus, in which a response at the active nose-poke hole triggers the release of alcohol vapor into the chamber. Clean air was pushed into the chamber following a vapor-release interval. Rats were trained to self-administer alcohol vapor in 24 sessions of 8 h, conducted every other day. The duration of the alcohol vapor delivery gradually increased from 2 to 10 min. Rats responded for an alcohol vapor, reaching high levels of BAC (~200 mg/dL), comparable with the BAC levels in human alcoholic patients (de Guglielmo et al., 2017). Notably, the voluntary responding of these rats produced high alcohol concentration in the air, similar to the concentration shown to induce alcohol dependence in passive alcohol vapor paradigms (Gilpin, Richardson, Cole, & Koob, 2008). Moreover, prolonged vapor self-administration led to the development of prominent somatic withdrawal signs, boosted anxiety-like behavior, and increased the motivation to obtain alcohol (de Guglielmo et al., 2017). Thus, this novel alcohol vapor self-administration model induces voluntary alcohol dependence in rats, without the use of forced non-contingent exposure to alcohol, sweeteners, water deprivation, or behavioral/genetic selection.

Alcohol seeking

While the alcohol self-administration procedures described above provide a valuable tool for assessment of consumption-related behaviors, assessment of alcohol seeking is possible only after establishment of a strong association between alcohol-associated cues/contexts and the rewarding effect of alcohol. The craving to obtain alcohol in rodents is typically assessed under alcohol-free operant conditions, and defined by the level of engagement in non-reinforced alcohol-seeking behavior (Koob, 2000; Marchant, Li, & Shaham, 2013).

Recently, a new model of alcohol seeking in alcohol-preferring (P) rats was shown to produce long-lasting, cue-driven alcohol seeking without an extinction effect (Giuliano et al., 2015). Specifically, rats were first trained to associate the onset of a light cue with free access to alcohol. During the following training phase, an operant response (lever press) was reinforced by alcohol delivery and the light cue. Next, alcohol seeking was assessed under a second-order schedule of reinforcement, in which the light cue served as a conditioned reinforcer for operant responding in the absence of alcohol reward delivery. After 15 min of the non-reinforced alcohol-seeking testing, during which every 10th lever press resulted in light cue presentation only, responding was reinforced again by the light + alcohol reward, to maintain the reinforcing properties of the light. Alcohol seeking was found to be strongly driven by the presentation of the alcohol-associated cue upon responding, as it decreased when measured in the absence of the light cue, and was reinstated following its reintroduction.

Interestingly, this cue-controlled alcohol seeking was observed in the alcohol-preferring P rats but not in another strain of high-alcohol-drinking (HAD) rats, nor in the alcohol non-preferring (NP) rats (Giuliano et al., 2015). Thus, this new procedure provides a tool to assess long-term cue-controlled alcohol seeking, but is limited to the alcohol-preferring (P) rat strain. Notably, this cue-reinforced alcohol-seeking procedure adds to a series of procedures that assesses the impact of alcohol-associated cues over seeking behavior, described by Everitt and colleagues over the past decade (Giuliano et al., 2018; Milton et al., 2012; Schramm, Everitt, & Milton, 2016).

Compulsive-like, aversion-resistant alcohol intake

Willingness to drink despite adverse consequences is a major characteristic of AUD (American Psychiatric Association, 2013; Centers for Disease Control, 2014). Several animal models have been used to investigate compulsive-like responding, where intoxicant intake persists despite negative consequences (Everitt & Robbins, 2016; Hopf & Lesscher, 2014). Previous studies have identified molecular mechanisms of such compulsive-like alcohol drinking (for review, see Hopf & Lesscher, 2014), including NAc NMDARs (Seif et al., 2013, 2015), glucocorticoid receptors (Vendruscolo et al., 2012), and epigenetic changes within the mPFC (Barbier et al., 2017, 2015; de Paiva Lima et al., 2017). Here, we will focus on recent advances in modeling compulsive-like responding.

Psychological underpinnings of compulsive-like responding

Recently, examination of lickometry of male Wistar rats during quinine-adulterated alcohol solution intake revealed that aversion-resistant alcohol drinking showed reduced variability in almost every measure of lick microstructure, relative to alcohol-only consumption pattern (Darevsky et al., 2018). This finding may reflect greater automaticity, in agreement with previous suggestions that compulsive intake reflects more automatic or habitual responding (Hopf & Lesscher, 2014). In addition, there was higher

motivation and response rate during compulsive-like alcohol intake, especially at the onset of each bout (Darevsky et al., 2018). This concurs with faster responding predicting binge-pattern alcohol intake in humans (Gowin, Sloan, Stangl, Vatsalya, & Ramchandani, 2017), and suggests that there may be an overarching strategy that allows consumption to persist in the face of negative consequences.

Whereas lickometry examination is used to analyze possible psychological underpinnings of compulsive-like alcohol intake, Everitt and colleagues developed a behavioral model capable of dissociating between preparatory and consummatory responses that construct alcohol-seeking and -taking behaviors (Giuliano et al., 2018). Alcohol-preferring (P) rats were trained to respond on an "alcohol-seeking lever" in order to introduce another "alcohol-taking lever", a response on which resulted in the delivery of alcohol. Upon establishment of stable seeking-taking performance, one-third of the responses on the seeking lever resulted in a foot shock, rather than introduction of the taking lever. This unpredictable punishment of seeking responses led to progressive suppression of alcohol seeking in ~30% of rats. In contrast, 34% of rats maintained their seeking response despite punishment, thereby displaying compulsive-like alcohol seeking, whereas the remainder of rats expressed only a moderate decrease in responding (Giuliano et al., 2018).

Also using the alcohol-preferring (P) rats, Marchant, Campbell, and Kaganovsky (2018) found evidence for a bimodal distribution in the response to punishment of operant alcohol consumption. In this study, alcohol self-administration training was followed by a punishment phase, during which 50% of the responses on the reinforced lever resulted in alcohol delivery combined with a foot shock. Interestingly, this revealed distinct groups of punishment-sensitive and -resistant rats. Thus, while ~43% of rats (116 out of 273) significantly decreased responding to the active lever, the remainder of rats demonstrated persistent responding despite the punishment, with a small sub-population even increasing the number of active lever presses toward the third punishment session.

Individual- and procedural-dependent differences in compulsivity

It is important to note that while some individuals have a greater propensity for developing or expressing compulsive-like behaviors, this is more likely to be a continuum, rather than a dichotomous characteristic, and behavioral responding likely depends on the experimental parameters. Thus, C57BL/6J mice and almost all rat strains drink quinine-adulterated alcohol with quinine levels that are avoided when in water (Lei, Wegner, Yu, & Hopf, 2016; Lesscher, van Kerkhof, & Vanderschuren, 2010; Seif et al., 2015, 2013; Spoelder, Flores Dourojeanni, et al., 2017). However, with higher quinine concentrations, which overall reduces alcohol consumption, some animals drink despite the aversive consequences, while others significantly suppress drinking (Hopf, Chang, Sparta, Bowers, & Bonci, 2010). In addition, about half of rats exhibit shock-resistant alcohol intake when 1 in 8 responses is paired with footshock, but all rats strongly suppress consumption when the shock is delivered for 1 in 3 rewards (Seif et al., 2013). Thus, we have proposed that all individuals have the capacity to exhibit aversion-resistant intake, but the level of compulsive-like behavior (assessed by the magnitude of adversity tolerated during intoxicant intake) will vary across individuals and will depend on the experimental conditions and parameters, allowing the experimenter to decide on the threshold (Hopf & Lesscher, 2014).

Even in selective breeding toward alcohol preference, a subset of subjects initially do not show compulsive-like behavior, yet this behavior emerges after longer-term drinking. For example, a subset of alcohol-preferring (P) rats, initially classified as moderately resistant to punishment of alcohol seeking, became highly resistant to punishment after 10 months of voluntary alcohol drinking (Giuliano et al., 2018). Similarly, in a strain of high-alcohol-preferring (cHAP) mice, 5 weeks of voluntary drinking led to reduced sensitivity to signals of harmful consequences, as mice continued to drink alcohol even when it was mixed with a flavoring previously associated with the emetic effect of lithium chloride (LiCl) (O'Tousa & Grahame, 2016).

Similarly, several groups have shown that longer-term excessive intermittent alcohol exposure leads to development of greater compulsive-like alcohol intake, relative to moderate alcohol intake in continuous access procedures in outbred rats or inbred wild-type mice (e.g., Hopf et al., 2010; Kimbrough, Kim, Cole, Brennan, & George, 2017; Lopez, Becker, & Chandler, 2014; Radke et al., 2017; Seif et al., 2015; Spoelder, Pol, et al., 2017). Together, these results suggest that extended voluntary alcohol drinking can trigger high vulnerability to AUD-related behaviors. Yet, some rodent strains were suggested to be less sensitive to punishment of alcohol intake. For example, DBA/2J mice maintained alcohol self-administration despite negative outcomes for a longer period, compared to several other mouse strains (Halladay, Kocharian, & Holmes, 2017). In addition, expression of higher levels of anxiety has been found to correlate with higher resistance to adverse consequences in male Wistar rats trained to obtain high levels of alcohol (Aoun et al., 2017; Jadhav, Magistretti, Halfon, Augsburger, & Boutrel, 2017).

Finally, an important practical consideration is the nature of the adverse consequence paired with the reward, which in rodents typically involves foot shocks, bad-tasting quinine, LiCl sickness, bright light, or presentation of cues paired with aversion (conditioned suppression). These methods differ in the contingency between alcohol intake and the negative outcome. For example, while quinine is delivered concomitantly with alcohol during intake, foot shocks can be delivered less frequently, adding an anticipatory component. Furthermore, the adverse effects of LiCl can be associated with alcohol taste and odor, with the cues or context, or with the reinforcing psychopharmacological effects of alcohol. Moreover, the aversive effects of LiCl typically occur with a delay after its administration. Indeed, a primary criticism of rodent compulsion-like models is that humans often experience the negative consequences at a time later than drinking, which may resemble the LiCl delayed aversion pattern. A counterargument is that for humans who are treatment-seeking, the adverse consequences can indeed be sometimes immediate. Nevertheless, developing rodent models that incorporate time delays between reward and punishment remains a challenge.

Taken together, there are a number of valuable rodent models for the assessment of compulsion-like, punishment-resistant drives to obtain alcohol. Importantly, these behavioral models can serve as a platform for identification of individuals who exhibit a collection of symptoms, considered to reflect a pathological urge for alcohol drinking. Indeed, individual differences in level of response for alcohol despite adverse consequences have been suggested as an AUD risk factor (Perkins, 2002; Schuckit & Smith, 2000; Trim, Schuckit, & Smith, 2009). Moreover, there is also variability in the subjective evaluation of the negative value of alcohol-drinking consequences: the less negative the outcome is perceived, the higher is the prospect for heavy alcohol drinking (Mallett, Bachrach, & Turrisi, 2008; Merrill, Read, & Barnett, 2013). Thus, modulation of the experimental parameters, such as punishment severity and alcohol exposure levels, may help to define mechanisms that underlie the subjective resistance to punishment in alcohol users.

Vulnerability and resilience to alcohol addiction

Rodents show high variability in levels of vulnerability and resilience to AUD-like phenotypes, regardless of the alcohol

exposure paradigm. Therefore, identification of vulnerable high-drinking and resilient low-drinking sub-populations can be achieved via a variety of voluntary consumption procedures.

Predictability of AUD phenotypes

Gradual escalation in alcohol drinking is a major characteristic of AUD (Grant et al., 2015). Similar escalation in voluntary alcohol drinking is observed in rodents submitted to intermittent access to alcohol in 2-bottle choice (IA2BC) procedures (Carnicella et al., 2014; Simms et al., 2008; Wise, 1973). Interestingly, Lesscher and colleagues recently reported that drinking escalation in male Lister Hooded rats in an IA2BC procedure occurred only in animals defined as high drinkers upon the first month of exposure to alcohol (Spoelder et al., 2015; Spoelder, Flores Dourojeanni, 2017; Spoelder, Pol, 2017). Furthermore, when tested in an operant setting, the high-drinking rats self-administered more alcohol than low-drinking rats under both fixed ratio and progressive ratio schedules of reinforcement, confirming their higher motivation to obtain alcohol (Spoelder et al., 2015). Higher alcohol drinkers also showed altered decision making, impulsivity, and responding to reward-paired cues (Spoelder, Flores Dourojeanni, et al., 2017), all of which resemble human problem drinking. Moreover, when given intermittent access to alcohol adulterated with increasing concentrations of quinine, high-drinking rats persisted in consuming alcohol despite the aversive taste to a greater extent than low-drinking rats (Spoelder et al., 2015). These findings suggest that the high-drinking rats developed compulsive-like characteristics of alcohol use, another hallmark of AUD in humans (see above). Thus, identification of high-drinking rats at the early stages of voluntary drinking training provides a reliable tool to study different aspects of AUD, while controlling for vulnerability and resilience within the studied population.

Using a similar approach of compilation of existing procedures, Jadhav et al. (2017) trained male Wistar rats in a saccharin-fading alcohol operant self-administration procedure, followed by extended (80 sessions) operant alcohol self-administration training. Rats were then classified as resilient or vulnerable to addiction-like behavior, based on the number of the addiction-related criteria they fulfilled. Specifically, vulnerable rats showed at least 2 out of 3 classification criteria, which included alcohol seeking despite signaled unavailability of alcohol; increased motivation for alcohol seeking and drinking under a progressive ratio reinforcement schedule; and resistance to foot shock punishment (Jadhav et al., 2017). Development of addiction-like behavior was predicted by the levels of alcohol self-administration, and was observed in rats showing higher levels of anxiety-like behavior, as assessed in the elevated plus-maze test (Jadhav et al., 2017), suggesting an anxious profile as another predisposing characteristic for developing AUD in rats.

It is noteworthy that even after chronic usage, only a subset of individuals develops addiction-like behavior (Everitt et al., 2008). Thus, the interaction between high alcohol intake in animals and the emergence of maladaptive alcohol-related behavior should be better characterized, and requires complex, multi-phase procedures that carefully model the spectrum of AUD aspects.

Environmental factors to trigger addiction-like behavior

Early-life stress is another factor documented to increase the vulnerability to develop addiction-like alcohol phenotypes (Butler, Karkhanis, Jones, & Weiner, 2016; Enoch, 2011). For example, adolescent social isolation in male rats resulted in long-lasting increases in a range of behaviors associated with higher risk of AUD, such as greater voluntary alcohol intake and preference, and higher operant alcohol self-administration (Butler & Weiner, 2016; Chappell, Carter, McCool, & Weiner, 2013; Karkhanis et al., 2014). Another early-life stress manipulation, the maternal separation stress procedure, was recently suggested to trigger the development of heavy alcohol drinking (Gondre-Lewis et al., 2016). Specifically, daily maternal separation of Sprague-Dawley pups during their first 3 weeks of life facilitated the acquisition of operant alcohol self-administration and impulsivity during adulthood (Gondre-Lewis et al., 2016). Thus, early-life stress, previously shown to affect brain development and induce long-lasting neuroadaptations (Karkhanis, Rose, Weiner, & Jones, 2016), is a significant risk factor for vulnerability to AUD in adulthood (Enoch, 2011), and these rodent models provide a useful tool to study neurobiological correlates of addiction vulnerability and resilience (Butler & Weiner, 2016).

Finally, early exposure to nicotine has been suggested to facilitate the intake of alcohol later in life (Chen et al., 2002; Gold & Frost-Pineda, 2006; Grant, Hasin, Chou, Stinson, & Dawson, 2004; Hanna, Yi, Dufour, & Whitmore, 2001). Recently, it was shown that the mere memory of early-life exposure to nicotine could enhance operant alcohol self-administration during adulthood (Zipori et al., 2017). Specifically, Long-Evans male rats received five nicotine injections during late adolescence (PND 45–59), and were then subjected to an intermittent alcohol self-administration procedure (Carnicella et al., 2014). Although early nicotine treatment itself did not affect subsequent alcohol self-administration, rats that self-administered alcohol in the same context where they previously received nicotine, showed higher alcohol consumption and relapse, compared to control rats that received nicotine in another context, even after nearly 3 months of nicotine cessation (Zipori et al., 2017). Thus, the increase in alcohol consumption was context-dependent, rather than driven by nicotine *per se*. To conclude, adolescent nicotine exposure may provide another risk factor for AUD development later in life via formation of persistent contextual memories.

Models of alcohol relapse

Alcohol addiction is a relapsing disorder; even with successful treatments, nearly 70% of patients relapse within the first year of abstinence (Miller & Hester, 1986; Sinha, 2011). Therefore, understanding the mechanisms that underlie relapse in spite of treatments, using existing (review, Venniro, Caprioli, & Shaham, 2016) and new behavioral models of relapse, is critical for addressing this serious clinical issue. Here, we focused on a couple of animal models of relapse after treatment.

Resurgence models

In the resurgence model, rats cease to seek alcohol when an alternative behavior is reinforced by alternative valuable rewards; however, relapse (resurgence) typically occurs following the loss of the alternative reinforcement (Epstein, 1985; Nall, Craig, Browning, & Shahan, 2018; Podlesnik, Jimenez-Gomez, & Shahan, 2006). This paradigm has been suggested as a pre-clinical model for relapse following “Contingency Management” or “Community Reinforcement Approach” in humans (Davis et al., 2016; Kadden, 2001; Prendergast, Podus, Finney, Greenwell, & Roll, 2006; Roozen et al., 2004; Stitzer & Petry, 2006). Specifically, during the first phase of the resurgence procedure, the target operant responding (e.g., lever pressing) is reinforced by alcohol. During the “treatment” phase, rats can choose between responding on the alcohol-paired lever, which is not reinforced throughout this stage, and an alternative operant response (e.g., chain pulling), reinforced with a non-drug reward (e.g., food). As a result, animals typically reduced lever pressing for alcohol.

During the resurgence phase, both responses are not reinforced, and rats typically show relapse to the alcohol-seeking behavior, in comparison to the alternative food-seeking behavior (Podlesnik et al., 2006; Pyszczynski & Shahan, 2013). Furthermore, alcohol seeking in rats resurged even after prolonged treatment with an alternative reinforcer, consisting of 20 sessions of non-reinforced alcohol task and reinforced food task, and was similar in magnitude to the resurgence following a shorter, 5-sessions treatment (Nall et al., 2018). Thus, resurgence studies are a valuable model for studying the behavioral and neurobiological mechanisms of treatment and relapse despite motivational incentives provided in Contingency Management or Community Reinforcement Approach.

Renewal of alcohol seeking after punishment-imposed abstinence

While the resurgence procedure includes forced abstinence from alcohol during the treatment phase, Marchant, Khuc, Pickens, Bonci, & Shaham (2013) suggested a model of relapse to alcohol seeking after a period of voluntary abstinence. In a context shift-induced reinstatement procedure, rats were trained to self-administer alcohol in context A. Next, lever pressing was punished in a different context (context B) by a foot shock, up to the complete cessation of alcohol intake. Despite punishment-imposed abstinence, renewal of alcohol seeking was usually observed upon returning to context A. This context-induced relapse behavior has been shown to involve the lateral hypothalamus (Marchant et al., 2014), nucleus accumbens (Marchant & Kaganovsky, 2015), and ventral subiculum (Marchant et al., 2016).

Relapse prevention via interference with memory reconsolidation

A main cause of relapse is cue-induced alcohol craving, a process in which retrieval of memories associated with the alcohol evokes strong craving and relapse, even after protracted abstinence. Thus, disruption of the memory for the cue-drug association is expected to reduce or even prevent cue-induced relapse (Milton, 2013).

Contrary to the traditional belief, that after consolidated memories are stable and fixed, current conceptions of memory processes hold that memories are dynamic and changeable entities. Specifically, a well-consolidated memory is stored in an inactive, stable state when unused. However, reactivation of a memory via its retrieval triggers a temporary memory destabilization, which is followed by re-stabilization in a process termed reconsolidation (Dudai, 2006; Lee, Nader, & Schiller, 2017; Nader & Hardt, 2009). Thus, memory reactivation initiates a 5–6-h long "reconsolidation window", during which the memory is labile for interference (Dudai, 2006; Lee et al., 2017; Nader & Hardt, 2009). Indeed, several studies have shown that alcohol-associated memories can be disrupted by interference with their reconsolidation process, leading to reduced relapse (Fig. 1).

Pharmacological interference with alcohol-memory reconsolidation

Three pharmacological manipulations were shown to disrupt the reconsolidation of alcohol-associated memories: protein synthesis inhibition (Barak et al., 2013; von der Goltz et al., 2009), NMDA receptor blockade (Milton et al., 2012; von der Goltz et al., 2009), and beta adrenoreceptor blockade (Schramm et al., 2016; Wouda et al., 2010).

von der Goltz et al. (2009) were the first to show that interference with the reconsolidation of alcohol-associated memories could reduce alcohol-seeking behavior. To this end, male Wistar rats were trained to self-administer alcohol, and following 3 weeks of abstinence, rats were briefly exposed to the alcohol-associated cues in order to reactivate alcohol-associated memories. The reactivation session lasted 5 min, and was similar to the training phase, except that the alcohol was made available only upon the first two active-lever presses. The authors found that administration of anisomycin (400 μg, intracerebral ventricular) or MK-801 (0.1 mg/kg, intraperitoneal) immediately following memory reactivation reduced the cue-induced increase in alcohol seeking measured 24 h later, as compared to vehicle-treated controls. This effect was still seen 7 days later for the anisomycin group, whereas MK-801-treated rats showed a non-significant trend.

Subsequent studies further demonstrated that alcohol memory reconsolidation could be disrupted by NMDA blockade, whereas the effects of the beta-adrenergic blocker propranolol were inconsistent (Milton et al., 2012; Wouda et al., 2010). Specifically, Wouda et al. (2010) trained Wistar rats to self-administer alcohol by performing a nose poke during the presentation of a light cue, and alcohol delivery was signaled by a tone. After 3 weeks of abstinence, rats were submitted to memory reactivation, consisting of non-reinforced presentation of the alcohol-associated cues (light + tone). Rats were then injected with MK-801 (0.1 mg/kg), or

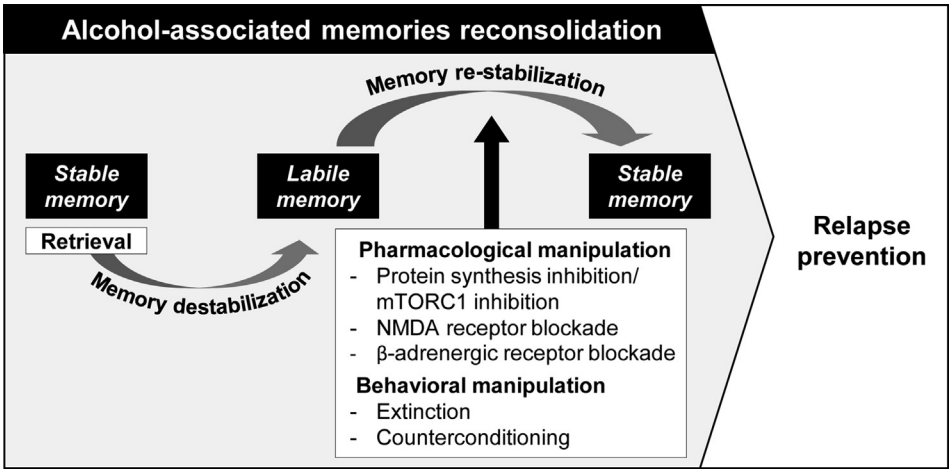

Fig. 1. Relapse prevention via interference with the reconsolidation of alcohol-associated memories. Alcohol-associated memories undergo destabilization upon their reactivation via retrieval. Until their subsequent re-stabilization, memories become labile for a limited period of time, in the process termed "reconsolidation". Pharmacological or behavioral interference with the reconsolidation of alcohol-associated memories can suppress relapse to alcohol seeking and consumption.

with the beta-adrenergic blocker propranolol (10 mg/kg), or vehicle. A day later, rats were tested for alcohol seeking. The reactivation-test procedural blocks were repeated three times, divided by 6 days of rest, and both MK-801 and propranolol reduced alcohol seeking in this series of tests (Wouda et al., 2010).

Milton et al. (2012) trained male Lister-Hooded rats to discriminate between alcohol-predicting and non-predicting cues, and then reactivated the memory by a non-reinforced training session. Unlike most reconsolidation studies, here MK-801 (0.1 mg/kg) or propranolol (10 mg/kg) was injected 30 min *before*, rather than after the reactivation session. Results showed that conditioned approach to the alcohol-paired cue, as well as Pavlovian-to-instrumental transfer (operant response enhanced in the presence of alcohol-paired cue) was impaired in MK-801-treated rats, compared to saline-treated controls (Milton et al., 2012). However, propranolol had no effect on memory reconsolidation in this procedure.

Interestingly, propranolol also failed to affect the reconsolidation of the alcohol-associated memory when given after its reactivation, in an alcohol-conditioned place preference (CPP) paradigm in male DBA/2J mice (Font & Cunningham, 2012). It is possible that interference with memory reconsolidation by propranolol requires more than a single reactivation session, as demonstrated by Wouda et al. (2010). Nevertheless, propranolol administration prior to memory reactivation disrupted the capacity of alcohol to act as a conditioned reinforcer (Schramm et al., 2016). The latter suggests that propranolol can disrupt some aspects (conditioned reinforcement), but not others (conditioned approach and conditioned motivation), of the mechanisms that drive alcohol-seeking behavior (Milton & Everitt, 2010).

Finally, the crucial role of protein synthesis in alcohol memory reconsolidation was demonstrated by studying whether alcohol memory reconsolidation involves the activation of the mammalian target of rapamycin complex 1 (mTORC1) pathway (Barak et al., 2013), which is required for the translation of a subset of dendritic proteins (Hoeffer & Klann, 2010; Neasta, Barak, Hamida, & Ron, 2014). In a series of experiments, Barak et al. (2013) showed that alcohol memories could be reactivated not only by the extrinsic stimuli of the operant setting, but also by the intrinsic sensory properties of alcohol (odor-taste cues) *per se*. More specifically, memories were reactivated either by a short (5-min) re-exposure to the operant context with non-reinforced lever presses and an oral alcohol prime delivered at the beginning of the session, or by a 10-min exposure to empty bottles in the home cage, with the tips covered by a few drops of alcohol (Barak et al., 2013).

Reactivation of alcohol-associated memories activated the mTORC1 pathway in the central amygdala, prelimbic cortex, and orbitofrontal cortex, resulting in increased levels of several synaptic proteins (Barak et al., 2013). Furthermore, systemic (20 mg/kg) or central amygdalar (50 μg/side) inhibition of mTORC1 by rapamycin, as well as general inhibition of protein synthesis by anisomycin (62.5 μg/side), during the reconsolidation of alcohol memories led to long-lasting suppression of relapse to alcohol seeking and consumption. Importantly, this effect was present only when rapamycin was injected immediately, but not 5 h after the reactivation session, confirming the essentiality of the interference within the "reconsolidation window".

Taken together, these studies show that disruption of the reconsolidation of alcohol-associated memories by pharmacological manipulations may provide a promising approach for prevention of relapse.

Behavioral interference with alcohol memories reconsolidation

While pharmacological treatment during memory reconsolidation was shown to reduce relapse, some of these treatments may be toxic or induce severe side effects in humans, limiting their translational value. Therefore, behavioral procedures that enable non-pharmacological disruption of drug-memory reconsolidation and prevention of cue-induced craving and relapse are of critical translational value.

Monfils, Cowansage, Klann, and LeDoux (2009) pioneered the behavioral approaches to disrupt fear memory reconsolidation with the "retrieval-extinction" procedure, by showing that extinction training during memory reconsolidation can disrupt the memory. Subsequent studies showed that drug memory reconsolidation can also be disrupted using this approach in animal models (Hutton-Bedbrook & McNally, 2013; Ma, Zhang, & Yu, 2012; Millan, Milligan-Saville, & McNally, 2013; Sartor & Aston-Jones, 2014; Xue et al., 2012) and humans (Xue et al., 2012). Specifically, although typical extinction training suppresses the conditioned response (e.g., craving and drug seeking), this response can recover under certain circumstances, leading to craving and relapse (Barak & Ben Hamida, 2012). In a typical retrieval-extinction procedure, however, extinction is performed following memory reactivation, within the "reconsolidation window", and has been shown to prevent reinstatement, renewal, and spontaneous recovery of the conditioned response, i.e., prevent relapse. Based on these findings, it has been suggested that a new cue-nothing memory is incorporated into the former memory trace of cue alcohol, hence limiting the risk of the cue-induced craving to re-emerge.

Using this approach, Cofresi et al. (2017) showed that memory reactivation prior to extinction training reduced alcohol-seeking behavior. Male Long-Evans rats were trained to consume alcohol from a sipper presented into the training chamber only upon the onset of a visual cue. Next, rats underwent 14 sessions of extinction training, each consisting of 11 trials of an empty sipper presentation signaled by the visual cue. Half of the animals received a 1-h time-out in the home cage between the first two extinction trials, to open the "reconsolidation window". When tested two days later, rats that underwent extinction training during memory reconsolidation showed reduced spontaneous recovery and reinstatement of conditioned responses to alcohol-associated cues, suggesting that the retrieval-extinction procedure can reduce relapse to alcohol seeking.

Interestingly, Millan et al. (2013) also tested the efficiency of the retrieval-extinction paradigm in prevention of alcohol relapse, by training male Long-Evans rats to self-administer decarbonated beer in one context (context A), and then extinguishing the operant response in another, distinct context (B). One group of rats underwent sessions of regular 60-min extinction training. The other group first underwent memory reactivation, consisting of a short (10 min) non-reinforced session. After 70 min, this group was returned for an extinction session. In a test conducted in context A, animals that underwent extinction after memory reactivation showed reduced reinstatement of alcohol-seeking behavior compared to no-reactivation controls. Surprisingly, however, similar reduction in alcohol seeking was found when the reactivation session was performed after, rather than before, the extinction session. (Millan et al., 2013). The authors suggested that the temporal clash of a short memory reactivation and extinction, rather than their order, can reduce seeking response (Millan et al., 2013), thus challenging the interpretation of these results as disruption of memory reconsolidation. However, it was recently shown that behavioral attenuation of cocaine-related memories prevented reinstatement of cocaine seeking only when applied after, but not before, memory reactivation (Goltseker, Bolotin, & Barak, 2017). Therefore, swapping the order of retrieval and the behavioral manipulation may yield different phenomena with similar consequences, and with presumably different underlying mechanisms, which should yet be better characterized.

Another approach of behavioral interference with the reconsolidation of drug/alcohol-associated memories is based on cue-aversion therapies, in which drug/alcohol-paired cues are re-associated (counter-conditioned) with an aversive consequence. Rewriting the valence of alcohol cues through their re-association with gustatory disgust during the alcohol memory reconsolidation, yielded reduction in alcohol cue valuation, attentional capture, and alcohol craving in humans (Das, Gale, Hennessy, & Kamboj, 2018; Das, Lawn, & Kamboj, 2015).

In animal models, the retrieval-counterconditioning paradigm recently demonstrated efficacy by preventing relapse to cocaine seeking, measured in a place-conditioning paradigm. Relapse was abolished by re-associating the cocaine-associated context with LiCl-induced aversion, only when this aversive counterconditioning was performed after memory reactivation, i.e., within the "reconsolidation window", and this effect was very long lasting (Goltseker et al., 2017). Critically, aversive counterconditioning failed to prevent relapse to drug seeking when conducted before, long after, or without, memory reactivation (Goltseker et al., 2017), suggesting it prevents drug seeking only when applied within the reconsolidation window. It would be interesting to evaluate the efficacy of this approach in alcohol-drinking models as well.

Concluding remarks

We surveyed here several advances in modeling of AUD phenotypes using behavioral rodent models. These advances represent a general attempt to capture and grasp the complexity and multidimensional nature of AUD, and to focus on behavioral aspects that better reflect this disorder. Specifically, it is increasingly accepted that procedures of voluntary alcohol intake in the home cage (e.g., 2-bottle choice paradigms) are not sufficient *per se* to model alcohol addiction. However, these procedures can be used to initiate training in more complicated operant procedures (Carnicella et al., 2014), to induce binge-like drinking (Carnicella et al., 2014; Thiele & Navarro, 2014), to model transition from moderate to excessive alcohol intake (Barak et al., 2015; Even-Chen, Sadot-Sogrin, Shaham, & Barak, 2017), or to model relapse via the alcohol deprivation effect (Vengeliene, Bilbao, & Spanagel, 2014). Combination of these simple self-administration procedures with additional procedures, and designing new behavioral paradigms that would model the complex nature of AUD characteristics, may allow mechanistic insights into these critical aspects of AUD. Relevantly, two recent articles have reviewed the neurobiological mechanisms that underlie behaviors relevant to AUD, at the molecular and system levels (Abrahao, Salinas, & Lovinger, 2017; Ron & Barak, 2016). Below we list three yet unmet challenges, which, in our opinion, should be addressed in future research.

First, predisposition toward AUD is a critical point that should be further explored in animal models of this disorder. As mentioned above, vulnerability and resilience factors in AUD are increasingly acknowledged, and environmental/physiological variables have been identified as risk factors for AUD-like phenotypes in rodents. We believe that additional attempts should be directed to identify and combine genetic, epigenetic, and neurodevelopmental factors that interact with environmental components, to provide a more comprehensive perspective of vulnerability to AUD.

Second, modeling alcohol dependence and consequent withdrawal syndromes is challenging, and has typically utilized a history of chronic non-voluntary alcohol exposure, e.g., via vapor chambers (Lopez & Becker, 2014; Vendruscolo & Roberts, 2014) or intra-gastric alcohol infusion (Lopez & Becker, 2014). While the new procedure of alcohol vapor self-administration model (de Guglielmo et al., 2017) provides an improved validity due to the voluntary exposure to alcohol, the non-physiological route of alcohol exposure through inhalation is still a limitation of this approach. Thus, the development of behavioral procedures with voluntary oral alcohol self-administration that leads to alcohol dependence and significant psychophysiological withdrawal syndrome is still a challenge in the field.

Finally, relapse remains a critical clinical issue in addiction, as most individuals with AUD relapse even after an initially successful treatment. Therefore, additional studies and animal models that would advance the understanding of mechanisms that drive relapse, and more importantly, advance the development of relapse prevention treatments, are extremely valuable. Importantly, disruption of drug-memory reconsolidation as an approach for reducing relapse is still an evolving field (Lee et al., 2017), and only a handful of studies demonstrated this strategy in alcohol addiction. Drug memory reconsolidation studies are typically long, and involve a combination of Pavlovian and operant learning components, which complicates both the procedural considerations and the interpretation of data. Indeed, even from the limited available data, it is clear that disruption of drug/alcohol memories requires a well-controlled setting and fine-tuning of parameters, which complicate the translation of this approach to human studies and treatment development (Spanagel & Bohus, 2015). For example, the effective disruption of reconsolidation has been shown to depend on the strength and age of memories, whereby older and/or stronger memories are less prone to reconsolidation manipulations (Zhang, Haubrich, Bernabo, Finnie, & Nader, 2018). Moreover, memories that involve operant learning are more complicated to disrupt (Zhang et al., 2018). Indeed, alcohol/drug-related memories that evoke relapse are typically old, strong, and involve operant component (Spanagel & Bohus, 2015). Taken together with findings that challenge the memory reconsolidation conceptualization and interpretation of some of the relapse prevention procedures (Baker, McNally, & Richardson, 2013; Millan et al., 2013), future studies will have to better characterize the boundaries of alcohol/drug-memory reconsolidation, investigate its basic mechanisms, and define the optimal settings for its disruption.

Conflicts of interest

The authors declare no competing financial interests.

Author contribution

KG, FWH, and SB wrote the paper.

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