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Animal models of excessive alcohol consumption: Recent advances and future challenges

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Heavy (excessive) levels of drinking and increased vulnerability to relapse represent hallmark features of alcohol abuse disorders and alcoholism. The development of animal models that incorporate these key behavioral characteristics is critical for advancement of studies aimed at elucidating biological underpinnings and environmental circumstances that engender such maladaptive behavior. Such models also are crucial for identifying new potential therapeutic targets and evaluating efficacy and safety of various treatment strategies.

Over several decades, numerous experimental approaches have been employed in developing rodent models of excessive alcohol self-administration. However, until about a decade ago, one of the major obstacles in this work was that rodents typically do not self-administer alcohol in sufficient amounts to produce overt signs of intoxication. Further, when given the opportunity to voluntarily drink alcohol, even under circumstances when access is unlimited, rodents rarely will consume alcohol in a manner that results in significant elevation in blood alcohol levels (above legal limits). Thus, a major challenge for the field has been to overcome these critical problems so that animal models developed for studying alcohol consumption have greater clinical relevance and, thereby, greater potential for use in both elucidating underlying mechanisms and identifying new and more effective treatment approaches.

In the past decade or so, several new models have been developed and some older ones have been resurrected and refined (Becker, 2013). This has provided the alcohol research field with an armament of new models that will enhance the ability of investigators to advance our understanding of neurobiological mechanisms underlying motivational factors that lead to heavy drinking, as well as the myriad neural and behavioral consequences of excessive alcohol self-administration. In addition, these models have played a key role in providing a

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valuable platform for testing and developing new therapeutics that may hold promise for clinical utility in treating risky and unhealthy drinking behavior.

This special issue is devoted to highlighting recent advancements in developing animal models of excessive alcohol consumption. Specifically, contributors to this issue describe several strategies for rodent models that have been developed to address the aforementioned shortcomings, with advantages and disadvantages of the various approaches highlighted. The following is a brief synopsis of the models of excessive alcohol consumption that are described in this issue.

A number of genetic and experimental manipulations have been employed in developing animal models of excessive alcohol consumption to overcome the general innate tendencies for most rodents to limit their intake of alcohol. Excessive levels of alcohol consumption may be operationally defined as levels of intake that exceed those that would ordinarily be attained in the absence of experimental manipulation. Ideally, such excessive alcohol intake should result in significant elevation of blood alcohol levels and overt signs of intoxication, thereby demonstrating that the amount and pattern of alcohol consumed has both physiological and behavioral relevance. Models described in this special issue are representative of a wide variety of contemporary models involving various experimental procedures that have been shown to generally satisfy these criteria; i.e., engendering excessive levels of alcohol consumption along with significant elevation of blood alcohol levels and behavioral signs of intoxication. This includes models involving: 1) selective breeding for high alcohol preference and drinking, 2) scheduled access to ethanol, 3) scheduled periods of alcohol deprivation, 4) scheduled intermittent access to alcohol, 5) schedule-induced polydipsia, and 6) models involving dependence and withdrawal experience.

Genetic influences in alcoholism have long been appreciated (Enoch, 2013; Schuckit, 2014). Use of selective breeding procedures has been very fruitful in developing several mouse and rat models that exhibit high alcohol preference and drinking (Crabbe, 2008; Crabbe, Phillips, & Belknap, 2010). Through the selective breeding process, genes are segregated based on association with the target phenotype (in this case, amount of alcohol consumed or blood ethanol levels attained through alcohol intake within a given time frame). This experimental strategy has proven to be highly successful in generating a number of unique mouse and rat genotypes that engage in excessive levels of alcohol consumption compared to their respective genetically heterogenous progenitors (Bell et al., 2012; Crabbe et al., 2014; Matson & Grahame, 2013). Dr. McBride and Dr. Crabbe provide papers that highlight this strategy and outline characteristics of rat genotypes (P: alcohol-preferring and HAD: high alcohol drinking lines) and mouse genetic lines (HDID: high drinking-in-the-dark lines), respectively. Of note, these unique genetic models have served as valuable resources for the field, as evidenced by their broad use in various experimental situations including several drinking models described in this issue. Aside from the fact that excessive alcohol consumption can be reliably demonstrated in these animals under a variety of environmental and testing circumstances, another significant appeal of these models is the promise that they can be used to identify sets of genes that confer exaggerated avidity and preference (or avoidance) for alcohol. This continues to be a significant challenge for the field in general.

For several decades, a commonly used approach for studying voluntary alcohol consumption in rodents has involved providing unlimited (24-h) access to alcohol presented along with an alternative fluid (typically water). However, in contrast to providing continuous access to alcohol, restricting availability of alcohol to certain times during the circadian cycle has enabled investigators to more precisely relate alcohol consumption with resultant blood alcohol levels. Further, since rodents are nocturnal, providing scheduled access to alcohol during restricted periods within the dark phase of the circadian cycle (when eating, drinking, and general activity is at its highest levels) has promoted greater alcohol consumption (Bell et al., 2011; Rhodes, Best, Belknap, Finn, & Crabbe, 2005; Rhodes et al., 2007). As detailed in papers authored by Dr. Thiele and Dr. Bell, variations of these general procedures have yielded mouse and rat models, respectively, that reliably exhibit excessive levels of intake, and have been demonstrated to significantly elevate blood alcohol levels and produce behavioral signs of intoxication. While these models have been effectively adopted by many research laboratories and have proven useful in evaluating the ability of various pharmacological agents to modulate drinking in the model, the reasons why animals drink excessively when alcohol access is restricted for brief periods of time each day compared to intake over a similar time period when alcohol is continuously available are not fully understood.

Other models have involved imposing periods during which access to alcohol is removed in rodents that had previously received free continual access for a period of time. Indeed, there is a substantial literature documenting that animals with a long history of daily access to alcohol display a transient, yet robust increase in voluntary alcohol consumption when alcohol is reintroduced after a period of deprivation. This alcohol deprivation effect has been demonstrated in several species using free-choice continuous-access models (Salimov & Salimova, 1993; Sinclair, 1971; Sinclair & Senter, 1968), as well as limited-access operant conditioning procedures (Heyser, Schulteis, & Koob, 1997; Sparta et al., 2009). The alcohol deprivation model has some face validity in that it is thought to model relapse and craving (Sanchis-Segura & Spanagel, 2006; Vengeliene, Celerier, Chaskiel, Penzo, & Spanagel, 2009). However, a few drawbacks related to the model have been noted. One concern relates to the specificity of the phenomenon, since exaggerated intake of other rewarding substances (e.g., sucrose or saccharin solutions) can be demonstrated following similar scheduled periods of deprivation (Avena, Long, & Hoebel, 2005). Additionally, increased alcohol intake after short or long periods of deprivation is typically short-lived, with intake returning to baseline (pre-deprivation) levels within a few days. This latter shortcoming, however, has been recently addressed in studies incorporating repeated periods of deprivation along with concurrent access to several alcohol concentrations (rather than a single choice vs. water) (Rodd et al., 2003, 2009; Spanagel & Hölter, 2000). These procedural manipulations have yielded more robust and durable alcohol deprivation effects. The paper presented from Dr. Spanagel's lab highlights these effects in the alcohol deprivation model along with other characteristics that suggest the model may reflect compulsive aspects of alcohol addiction.

In contrast to the alcohol deprivation model where long periods of alcohol availability are interrupted with lengthy periods of deprivation before alcohol is re-introduced, a variation of this approach is encapsulated in the intermittent-access model where episodes of continuous alcohol access and deprivation are alternated for relatively short periods of time (1–2 days

rather than weeks). As shown nearly 40 years ago when the intermittent-access model was first introduced (Wise, 1973), recent studies using rats and mice also have demonstrated that alternating relatively brief periods of alcohol access with periods of no access accelerates the pace at which excessive levels of alcohol consumption can be established (within a few weeks) (Carnicella, Amamoto, & Ron, 2009; Hopf, Chang, Sparta, Bowers, & Bonci, 2010; Hwa et al., 2011; Loi et al., 2010; Rosenwasser, Fixaris, Crabbe, Brooks, & Ascheid, 2013; Simms et al., 2008). Another advantageous feature of this model is that escalation of alcohol intake produced by intermittent access (e.g., every other day) can be compared to an independent group of animals that exhibit more moderate and stable levels of intake as a consequence of receiving continuous (daily) access to alcohol. The paper authored by Barak et al. describes some of the experimental parameters that optimize escalation of drinking in this model, along with using the intermittent-access model to then enhance alcohol self-administration behavior using operant conditioning procedures. A paper presented by Dr. Colombo's research group describes a variation of this model, in which varying the temporal pattern of alcohol access each day was found to engender greater alcohol consumption. In this scheme, the unpredictable nature of the daily scheduled access to alcohol is suggested to contribute to higher alcohol intake. Finally, a paper authored by Drs. Hopf and Lesscher describe how excessive levels of alcohol consumption produced in the intermittent-access model (and other drinking models) may satisfy criteria that operationally define compulsive drinking behavior in animals.

It is noteworthy that despite the recent increased popularity and use of the model, mechanisms that underlie or promote the escalation of drinking as a result of chronic-intermittent access remain elusive. Hence, a challenge for future investigations is to gain better insight about the psychological and neurobiological processes engaged by the intermittent nature of alcohol availability in the model (as opposed to continuous access) that contribute to increased motivation and excessive levels of alcohol consumption.

Another experimental procedure that was first introduced about four decades ago and produces high levels of alcohol consumption is schedule-induced polydipsia (Falk & Samson, 1975; Falk, Samson, & Winger, 1972). In this model, regularly scheduled delivery of food reinforcement (typically a fixed time interval) that is not under the animal's control induces excessive behavior, the nature of which depends on the environmental circumstances. When an alcohol solution is available during scheduled reinforcement sessions, the resultant schedule-induced polydipsia refers to an excessive level of alcohol intake that can lead to dependence. The model has been used to produce high levels of alcohol intake in mice and rats (Gilpin, Badia-Elder, Elder, & Stewart, 2008; Mittleman, Van Brunt, & Matthews, 2003). However, one concern with this model is the lack of specificity of the effect since polydipsia can be observed when other fluids (e.g., water) are made available. Additionally, since animals are maintained on a food-restricted diet, there is the question about whether motivation to drink alcohol in the model is related to the drug's pharmacological effects or its caloric value. Another concern is that when the schedule of intermittent food reinforcement is relaxed, alcohol consumption typically reverts back to control levels and the elevated levels of intake are no longer sustained even when alcohol is freely available for longer periods of time (Tang, Brown, & Falk, 1982). These drawbacks have generally hampered broader use of this model. However, recent work has suggested

that more persistent effects may be obtained when experimental parameters used in the model are optimized for facilitating the negative reinforcing effects of alcohol. More specifically, recognizing the stressful nature of the procedure (Ford, Steele, McCracken, Finn, & Grant, 2013; López-Grancha et al., 2006), it has been suggested that the time interval in which food is delivered in the model may be a key factor in establishing the negative reinforcing effects of alcohol. The paper authored by Dr. Ford provides an overview of the schedule-induced polydipsia model and addresses the issue of utilizing experimental conditions that favor an association of alcohol consumption with stress relief (escape from the onerous nature of the intermittent, response non-contingent schedule of food delivery) that may be required for producing long-lasting elevated drinking (even after the reinforcement schedule is removed in connection with alcohol availability). Of note, the schedule-induced polydipsia procedure has been employed to induce alcohol self-administration in non-human primates where a percent of the animals continue to engage in excessive drinking behavior following the removal of the schedule (Grant et al., 2008).

In recent years, it has become increasingly apparent that experimental procedures that establish both positive and negative reinforcing effects of alcohol are critical for models that demonstrate excessive levels of alcohol consumption in association with dependence (Koob, 2013). While alcohol dependence has long been postulated to play a role in fostering and perpetuating excessive drinking, early studies were not entirely successful in modeling this phenomenon, most likely because they did not employ procedures that optimized the ability of alcohol to serve as a negative reinforcer (Meisch, 1983). However, in the past 10–15 years a growing number of studies have employed several approaches for inducing dependence and linking these with alcohol self-administration procedures (Becker, 2008; Becker, Lopez, & Doremus-Fitzwater, 2011; Roberts, Heyser, Cole, Griffin, & Koob, 2000). As noted above, since rodents will not typically self-administer sufficient amounts of alcohol to produce a state of dependence, these models have employed several procedures involving passive exposure to alcohol in order to induce dependence. Thus, these dependence and drinking models are not designed to address *how* a subject becomes dependent but, rather, the models allow for analysis of how a state of dependence promotes progressive and sustained increases in alcohol consumption. Chronic exposure to ethanol vapor using inhalation has been the predominant approach used to induce dependence in these models. In many instances this chronic alcohol exposure has been delivered in an intermittent manner, allowing subjects to have the opportunity to self-administer alcohol during periods of abstinence (thereby establishing the negative reinforcing effects of the drug). The final set of papers in this issue authored by Drs. Roberts, Griffin, and Lopez provide an overview of these dependence and drinking models where escalation of alcohol intake has been demonstrated in rats and mice under limited- or continuous-access conditions when alcohol is provided in the home cage or in an operant conditioning paradigm. These models are now widely used in the field and have the advantage of enabling direct comparisons between dependent animals that demonstrate escalation of drinking and nondependent animals that exhibit more moderate and stable levels of intake.

In sum, this special issue highlights a number of experimental procedures and approaches that have been adopted in developing several animal models of excessive alcohol consumption. By incorporating various experimental manipulations that entail modifying

genetic and/or environmental factors, these models have generally overcome the natural tendency for rodents to either avoid alcohol or consume it in limited amounts that typically do not produce signs of intoxication. In many instances, the models entail manipulating scheduled access to alcohol (time of day, duration, frequency), periods of time when access to alcohol is withheld, and a history of chronic alcohol exposure and withdrawal experience. As noted in the papers in this special issue, each of the models possesses distinct advantages and limitations. Thus, while no single animal model can fully capture all the complexities of what drives humans to engage in excessive alcohol drinking behavior, collectively these models provide the field with valuable tools to address this important research question. Indeed, many of these models are now widely used nationally and internationally in alcohol research laboratories, playing a significant role in enabling more detailed elucidation of neurobiological mechanisms underlying excessive drinking as well as providing opportunities for evaluating the ability of various pharmacological agents to modulate such drinking.

That said, there are a number of challenges that remain for the field. For example, in an effort to develop more optimal animal models that more closely mimic problem drinking in humans, there is a need to incorporate procedures that reflect cognitive factors that guide decisions about initiating and terminating drinking behavior (i.e., perception and expectations about initial sensitivity and how these change as subjects gain more experience and exposure to alcohol). Future studies using many of these models also should provide more insight regarding risk factors that confer greater vulnerability (or resilience) to known factors that engender excessive drinking. Additionally, greater refinement of these models along with new experimental procedures will be critical for advancing our knowledge about factors that underlie transition from regulated, moderate drinking to uncontrolled, excessive alcohol consumption. This includes more detailed analysis of the compulsive nature of excessive drinking, as reflected in a shift in bias from goal-directed to more habit-like behavior, as well as reduced behavioral flexibility. Ultimately, the validity and usefulness of these models will lie in their ability to enhance opportunities for elucidating underlying neurobiological mechanisms and environmental influences that drive increased alcohol seeking and consumption, as well as providing a platform for evaluating new potential therapies that hold promise of reducing excessive levels of alcohol consumption.

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