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Preclinical studies of alcohol binge drinking

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Abstract

Binge drinking is prevalent and has serious biomedical consequences. In children, adolescents, and young adults, it is a prominent risk factor for later development of alcohol-use disorders. Many preclinical models have been employed to study the genetic risks for and biomedical consequences of alcohol drinking. However, these models historically did not result in blood-alcohol concentrations (BACs) exceding 80 mg%; this relatively modest level is the threshold that currently defines a binge session, according to the NIAAA and CDC. Nevertheless, in alcohol-dependent rodents, binge drinking has been well documented. Key neurobiological substrates localized to brain reward and stress systems have been identified. Studies of newer models of binge drinking without dependence are reviewed here. In these models, rodents, non-human primates, and flies will drink enough to reach high BACs. They often display observable signs of intoxication. The neurobiological consequences of these episodes of binge drinking without dependence are reviewed, preliminary evidence for roles for GABA, glutamate, opioid peptides, and corticotropin releasing factor are discussed, as is the need for more work to identify the antecedents and consequences of binge drinking in both animal models and humans.

Keywords

binge drinking; alcohol; intoxication; animal models

Introduction

Definitions

Binge drinking is a term whose connotations have evolved over time. The original version of the Oxford English Dictionary (OED1) collated usages through 1928. It defined “binge” only as a verb meaning “to curtsey; to fawn; to cringe” and gave a first usage date of 1562. Additional material cumulated between 1928 and 1933 appear as a first supplement volume. This supplement contains an additional definition as a noun: “a heavy drinking bout; hence, a spree” as well as a verb “to drink heavily, ‘soak.’”[1] Use of terms such as binge drinking continued through the latter part of the 20th century, taken to mean an enduring period of intoxication often lasting for several days. As with all other distinctions between acute and chronic ethanol use and/or effects, the specific demarcations between an acute episode of

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binge drinking and a more extended bout were not clearly defined. In 2003, the new Director of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) of the National Institutes of Health, Dr. T.-K. Li, oversaw the development of a new definition of binge drinking, which was adopted by the National Advisory Council to the NIAAA in 2004.

> A "binge" is a pattern of drinking alcohol that brings blood alcohol concentration (BAC) to 0.08 gram percent or above. For the typical adult, this pattern corresponds to consuming 5 or more drinks (male), or 4 or more drinks (female), in about 2 hours. Binge drinking is clearly dangerous for the drinker and for society.[2]

This definition achieved three main goals. First, it quantified the definition of a binge by anchoring it to a biological indicator of the dose ingested. Second, it implicitly recognized that circumstances other than simply the "number of drinks" (in this case, gender) could influence the defining end point. Third, it established a *de facto* threshold for intoxication of 0.08 gram percent (or 80 mg%), implying that observable behavioral intoxication was a defining characteristic of a binge. By stating the approximate real-life number of standard drinks, it provided researchers and treatment professionals a route to approximately quantify this type of drinking. This has come to be termed "the 5/4 rule."[2] This definition was subsequently adopted by the Centers for Disease Control and Prevention of the USA.

It is interesting to compare these advances to a current lay definition of binge drinking, "Binge drinking is the modern definition of drinking alcoholic beverages with the primary intention of becoming intoxicated by heavy consumption of alcohol over a short period of time." (http://en.wikipedia.org/wiki/Binge_drinking). This definition starts with the assumption that the intent of binge drinking is to achieve intoxication, but subsequently includes discussions of other forms of extreme drinking and also refers to the current NIAAA definition. While achieving intoxication may often be the intent of the non-dependent individual, it seems unlikely to be the motivation for the unfortunate drinker in all cases. Intent is difficult to demonstrate in preclinical models, since, in the absence of self report, it must be inferred from other behaviors. Indeed, as reviewed below, intoxication is infrequently achieved in many common laboratory animal models of drinking.

Importance

The importance of binge drinking to the individual and to society is clear. There are immediate risks from such causes as injury, driving accidents, unwanted pregnancy, and death due to overdose. There are also longer-term risks from repeated episodes of binge drinking consequent to neurotoxicity, as well as adverse consequences to heart, liver, immune system, bone health and other organ systems. The most recent data, from a NESARC nationwide survey in 2001, found that 8.5% of more than 13,000 adults drink to exceed the NIAAA 5/4 binge guidelines 1–2 times per week.[3] For children and adolescents, binge drinking is increasingly frequent. Early onset of binge drinking is a substantial risk factor predicting development of adult alcohol use disorders. Adolescents tend to show lower sensitivity than adults to alcohol's intoxicating effects,[4] as well as to unpleasant withdrawal-related symptoms such as hangover.,[5] This is a particularly virulent alignment of sensitivities that tends to promote excessive experimentation with alcohol. As there are excellent reviews elsewhere covering the neurobiology of adolescent response to ethanol, we will not cover those studies here; for reviews see. [6],[7]

Fetal exposure

Exposure to high dose alcohol during pregnancy often results in craniofacial malformations and behavioral disorders in offspring.[8] A Fetal Alcohol Syndrome (FAS) has been delineated and studied extensively using preclinical models.[9,10] Fetal exposure can also lead to a range of less severe symptoms that are currently termed Fetal Alcohol Spectrum

Disorder (FASD).[11] A new binge drinking model, Drinking in the Dark (see section 2. F.) has been proposed to be useful as a model of FASD.[12] Readers with a specific interest in FAS/FASD are referred to recent reviews. [13–15]

Effects of high ethanol doses

One method that has been used to achieve high blood ethanol levels is intragastric intubation. Intragastric administration was initially developed to allow studies of physical dependence in rats.[16] Rats were given large doses of ethanol, eg9–15 g/kg/day in 3–5 fractional doses for 4 days. Clear signs of withdrawal were seen after treatment. To avoid lethal overdose, each dose of alcohol must be adjusted based upon the degree of intoxication of each animal.[16] Intragastric administration of a single large dose of ethanol (up to 7 g/kg) was also used in mice to model 'binge drinking.'[17] Single and repeated intragastric administration of large doses of alcohol have also been used in rats and mice to study neurodegeneration, neuroinflammation and neurogenesis.[18–20] There are several caveats to these 'binge' models. First, very large, near lethal, doses of ethanol are given. The toxicities produced by these doses may not be seen with other binge models which produce more modest blood ethanol levels. Second, forced intubation with ethanol solutions is stressful and may not reflect results from self-administration models. In general, the neurochemical actions of passively-administered drugs of addiction are much different from the consequences of self-administration of the same amounts of many drugs.[21] We will not consider studies using these forced, high-dose administrations here as they have recently been reviewed elsewhere.[19] We will consider a related model, intragastric self-administration, in section 2. H.

Scope of this review

In this review, we have sought studies where rats, mice and *Drosophila* will orally ingest sufficient ethanol sufficiently rapidly to reach an intoxicating BAC. We have not identified laboratory studies that have sought to establish the threshold BAC required for behavioral intoxication in rats or mice. However, some authors have declared that the NIAAA level set for humans of 80 mg% can be considered to represent "excessive" drinking in the rat.[22] For mice, which metabolize ethanol somewhat more quickly than rats and which require higher ethanol doses and BACs than rats to show equivalent behavioral responses, we have suggested that 100 mg% is a realistic criterion.[23] Mice with blood levels at or above 100 mg % are intoxicated as measured by several behavioral assays.[23,24] While it has been argued that requiring rodents to drink ethanol during a narrow time window may have the effect of limiting total brain exposure to ethanol and thus defeat the face validity of such models,[25] a wide range of BACs has been reported under paradigms where access is time-limited. Most studies have not tested for visible intoxication. We thus also consider some studies where neither behavioral intoxication nor BAC has been measured, but where intoxication may be inferred from the dose of ethanol ingested.

The compulsive use of alcohol derives from multiple sources of reinforcement. Animal models have been developed for the acute positive reinforcing effects of ethanol. Models also examine the reinforcing effects associated with removal of the aversive effects of ethanol withdrawal or existing aversive states [i.e., self-medication of the aversive effects of abstinence from chronic ethanol or self-medication of a pre-existing negative affective state[26]]. A major early breakthrough was the development of a training procedure in which access to a sweetened solution allowed addition of gradually increasing concentrations of alcohol in ways that avoid the aversiveness of the ethanol taste [for review, see [27]]. Subsequent work extended these so-called "fading" procedures to measures of self-administration in dependent rats and post-dependent rats.[28,29]

In addition, binge-like drinking has been induced by motivational enhancers that include incentives such as sweetened alcohol solutions or production of arousal/drive states such as schedule-induced polydipsia. It is beyond the scope of this review to thoroughly describe each of these methods of excessive ethanol intake, but it is worth briefly describing each and listing some of the advantages and disadvantages of each. We discuss these models, compare them with the standard two-bottle preference models (see next section), and review what we have we learned about the genetic and neurobiological neuroadaptations that ensue.

Preclinical models of binge drinking

Two-bottle preference

Curt Richter showed that rats allocate their drinking between a water bottle and a bottle containing a dilute ethanol solution, pioneering the two-bottle preference test.[30] A rat line (UChB) was created by selective breeding for high ethanol preference in the late 1940's[31] The first demonstration of genetic differences in ethanol preference in mice were published in 1959.[32] This basic test of preference for 10% ethanol vs water, while both fluids are continuously available, has led to hundreds of publications. Several other lines of rats and mice have been selected for high vs low ethanol preference [for review, see [33]]. The most widely studied model is the Preferring (P) rat, the subject of a relatively recent review[22] [for reviews of the other selectively bred lines see [34–39]].

However, rats and mice studied under continuous access conditions drink in sporadic bouts. They generally do not drink enough to attain BACs that exceed 80 mg% (rats) or 100 mg% (mice). This was noted even in studies of C57BL/6 mice, a high preferring strain.[40] The reason for this is not understood. R rodents usually appear to limit their consumption of ethanol to sub-intoxicating BACs. Perhaps this is an evolutionary holdover from taste neophobia, thought to protect species that are unable to vomit if they ingest a poisonous substance.[41] Thus, the standard two-bottle preference test does not offer a convincing model for binge drinking.[42] We will, however, discuss data from the rat and mouse lines that have been selectively bred for high alcohol preference in studies using paradigms that resulted in supra-threshold BACs. The reader is referred to the cited reviews for information about two-bottle preference *per se*.

Chronic intermittent access

Early studies showed that if rats were drinking ethanol and access to the drug was then suspended, they showed increased preference when ethanol was reintroduced.[43,44] Wise[45] subsequently showed that intermittent access (every other 24 hr period) to ethanol in rats led to development of drinking patterns that achieved high levels (9 g/kg/day) of alcohol consumption. BACs were not measured in any of these studies. The availability of ethanol across the 24 hr cycle with a single daily measurement of intake does not allow estimation of whether significant BACs were ever attained. A recent study offered 4.44% beer for 2 hr to adolescent or adult Wistar rats. Daily access was compared with access once each 3 days. Adolescent, but not adult, rats consumed more beer when it was intermittently available. They reached BACs of 60 to more than 150 mg%. Interestingly, those intermittently-exposed adolescents who had been previously exposed to beer for 3 days drank about half as much, and reached lower BACs. The authors characterize this as a "binge-like effect"[46] In another study,[47] intermittent access to 20% ethanol vs water (always available) for 24 hr periods on Monday, Wednesday and Friday each week raised ethanol intake of Wistar and Long-Evans rats to 5–6 g/kg/day within 5–6 drinking sessions. P rats reached 7 g/kg/day. Most rats reached maximal BACs of about 60 mg% in samples taken 30 minutes after the start of drinking, i.e., 45 minutes after the start of the dark cycle; these included all 6 P rats, 8/9 Wistar rats, and 7/10 Long-Evans rats. The remaining 4 rats reached BACs of nearly 100

mg%. The highest drinking Long Evans rats, assessed with intermittent access, displayed more inhibition of their drinking by acamprosate or naltrexone than other animals.[47] A subsequent study adapted this method in Long-Evans rats to an operant self-administration schedule with similar results.[48] However, intermittent access does not always yield high ethanol intake.[49]

Thus, allowing access to ethanol on an intermittent basis, starting just after lights out, for example, may offer a methodological route to enhancing intakes. Especially in animals with alcohol-preferring genotypes, intoxicating levels of ethanol are ingested with some consistency. Some studies with variants in this paradigm of periodic exposure to alcohol will be discussed in Section 2. K.

Scheduled high alcohol consumption (SHAC)

Limiting the period of access to an ethanol solution can lead to ingestion of intoxicating doses. Belknap[50] restricted access to water to 90 minutes/day for 4 days. On the 5th day, mice were offered a single bottle of ethanol with concentrations ranging from 1–10%. Both C57BL/6J mice (known alcohol-preferrers) and DBA/2J mice (known alcohol-avoiders) drank about 0.6 – 1.0 ml of fluid in 10 minutes. This led to doses of 0.7 –3.2 g/kg depending on strain and concentration. Many mice of either strain that ingested > 1.4 g/kg showed "… staggering, stumbling, reeling, and falling on the back…". While these mice were likely to have exceeded 100 mg% BACs after their drinking binge, the role of thirst motivation could not be ruled out in this study.[50] Finn and colleagues[51] performed several experiments with C57BL/6J mice as well as with another stock (WSC) that does not show strong ethanol preference. They restricted fluid access to periods starting at 90 minutes and increasing to 10 hr/day over 2–3 weeks. Every 4th day, mice were offered a 10% ethanol solution for either 10 min or 30 min, followed by water during the remainder of their fluid access period. Stable, high ethanol intakes were achieved in both genotypes, leading to ingestion of 2 g/kg in 30 minutes and BACs ranging from 60 to 340 mg% and averaging >100 mg%.[51] In a subsequent study, C57BL/6J female mice given 30 min access to ethanol before their 3 hr fluid access period every second or 3rd day reached BACs of 140–150 mg% and showed motor impairment.[52] The SHAC procedure was subsequently used to seek differences between adolescent and adult drinking. Access to fluid was increased from 4 to 10 hr over 3 weeks. Thirty min access to ethanol was given every 3 days. Adolescents drank more and reached higher BACs (200 mg%) in early tests. Intake declined to adult intake levels as they aged (as in the Hargreaves et al. (2009) study[46] discussed in Section 2. B.). When animals were further tested in a limited access preference test, female mice that were exposed to alcohol in their adolescence retained higher intakes than mice which were not exposed when young.[53]

Alcohol liquid diet

In an alcohol-liquid diet procedure, the diet is typically the sole source of calories (for example, see Moy et al.[54]), forcing rats or mice to consume the alcohol. With a nutritionally complete diet, animals develop alcohol dependence via chronic consumption of liquid diet in the absence of significant health risks.[55] Further, some animals will drink sufficient amounts of ethanol to meet criteria for a binge when alcohol is offered as they are in alcohol withdrawal. Typically, rats are provided a palatable liquid diet containing 5–8.7% v/v ethanol as their sole source of calories.[56–59] Alcohol intake is directly related to the BAC range obtained and the pattern of intermittent high-dose alcohol exposure.[59] However, there are major disadvantages of this procedure. One is individual variability, since the dose, duration, and pattern of alcohol exposure bouts are determined by the animal. Also, experimental designs require pair-feeding control animals so that dietary factors can be dissociated from ethanol-related effects. This is because liquid diets that are unadulterated

with ethanol are highly palatable. If access is unrestricted, control animals will drink extremely large amounts. When control animals are offered their allotment of unadulterated diet, which is limited to that drunk by their pair-fed ethanol animal, they nearly always drink their entire daily allocation immediately. Thus, the pattern of self-administration is also not matched across groups. An technical innovation to overcome this limitation physically yoked the amount of diet available to a control rat temporally and volumetrically to the amount ingested by its paired ethanol-diet rat.[60] The "U-tube" devices that implement this technique, however, are quite expensive and provide other technical challenges, limiting their use.

Schedule-induced polydipsia

In schedule-induced polydipsia (SIP) procedures, animals perform "normal" behaviors (e.g., cork-gnawing, wheel running, water or alcohol drinking) in excess during the interim periods between reinforcer deliveries. Schedule-induced alcohol polydipsia is therefore high alcohol drinking produced by the intermittent delivery schedule of another reinforcer, usually small amounts of food provided to food-deprived animals. This procedure produces somatic symptoms of alcohol dependence,[61]. However, it has been largely abandoned in recent years due to several methodological concerns. Most prominent is the concern about the possibilities that food-deprived animals are drinking alcohol for its pharmacological effects and/or due to the motivational drive from the combination of food deprivation and schedule of reinforcement. In a relatively recent study, chronic administration of acamprosate and acute administration of naltrexone both significantly decreased both alcohol SIP and water SIP in mice, further emphasizing the lack of predictive validity as a measure of excessive drinking.[62] There are excellent reviews of the SIP phenomenon[63,64] One area where SIP has been fruitfully applied has been in non-human primates. In these models, it is used to induce drinking that can then be studied for many months. Some of these animals escalate to extremely high levels of intake and are display clear behavioral signs of intoxication. The drinking patterns induced by initial SIP exposure have been shown to predict which animals will subsequently engage in binge drinking.[65]

Drinking in the dark (DID)

It has long been known that rodents ingest most of their daily food and water during the dark phase of their circadian cycle, with peak intake at the beginning and the end.[66] When an alcohol solution is the only source of liquid available to mice, peak intake occurs in the first few hours after lights off,[67,68] The BAC follows this circadian variation closely.[68] Using this information, Ryabinin offered C57BL/6J mice sucrose plus 10% ethanol for 30 minutes during the dark and achieved high intake and BACs in excess of 250 mg%.[69] In a subsequent study, mice were initially fluid restricted. The period of fluid restriction was gradually reduced and alcohol concentration was gradually increased over days during the 30 min access period. By the 8th day, mice were no longer fluid restricted. By the 12th day, mice were drinking enough 10% ethanol to reach BACs of 100–200 mg% and were behaviorally intoxicated.[70]

Rhodes further refined this approach with C57BL/6J mice, omitting the fluid restriction and extending the access period.[71] The basic paradigm was is to offer each mouse a single tube containing 20% ethanol (v/v) in tap water in place of its usual water bottle for a period of 2 hours, beginning 3 hr from the onset of the circadian dark phase. For C57BL/6J mice (known alcohol preferrers), mice drank higher doses (2.3–3.1 g/kg) of 20% ethanol than they did 10% or 30% during 2 hr starting 1 hr into the dark phase. In an experiment offering 2 hr access for three days followed by 4 hr access on the 4th day, mice drank more 20% ethanol starting 3 hr after lights off than starting 1 or 2 hr. We speculate that this is due to the generally higher levels of activity and noise (from eating and drinking) in the test room

during the first hour or two after lights off. Ethanol consumption was consistent within individual mice, and daily intakes were generally stable for most of the first 12 days. Although the first day's intake was essentially uncorrelated with intake on days 2–4, while intakes on days 2–4 were reasonably stable (R^2 values between 0.21 and 0.29). Consumption during the 4 hr test on Day 4 reliably predicted BACs at the end of the drinking period ($R^2 = 0.53$), which nearly all exceeded 100 mg%. This relationship held in C57BL/6J mice bred in house or those obtained from the two Jackson Laboratory sources.[71]

The method, usually instantiated as 3, daily 2 hr access periods followed by a 4 hr test period on Day 4), has come to be known as Drinking in the Dark (DID). Subsequent experiments[72] showed that C57BL/6J female mice reached BACs averaging 130 mg% on the fourth (4 hr) test day and were intoxicated in balance beam and rotarod testing. Evaluating DID in an operant setting where intake was recorded as licks showed that C57BL/6J mice drank ethanol in bouts. As compared with their pattern of drinking water, they drank in about half as many bouts over the session. The average bout duration was shorter for ethanol drinking. However, when drinking ethanol, the rate of drinking was twice that of drinking water. Other more subtle patterns differentiating ethanol DID from water DID were also seen, including some sex-specific differences. Several inbred mouse strains were tested for DID for 4 days and found to differ substantially, with C57BL/6J showing the greatest ethanol DID. These mice were retested for DID. Two bottles were offered each day, containing 20% ethanol vs water. Strains drank nearly the same amount of ethanol when a water bottle was also available, but they also drank some water. BACs were therefore lower than in the single-bottle DID test.[72] However, a comparison of one-bottle vs two-bottle (ethanol vs water) DID in a population of B6xFVBF2 mice did show reduced ethanol intake in the two bottle version of the test.[73]

Among the advantages of this model are its simplicity and its short duration. Some mice will voluntarily drink enough ethanol to become visibly intoxicated. The response is heritable.[72] The principal disadvantage is that no choice is offered. Mice are not fluid deprived, and can choose not to drink. Indeed, many genotypes drink very little in this test.[72] A 4 hr period of voluntary fluid deprivation is not sufficient to greatly challenge mice physiologically.[74] The motivation for ethanol DID is not known: indeed, the motivation for drinking ethanol in the two-bottle preference test is not known, either. In a series of DID experiments with C57BL/6J mice, Thiele asked whether drinking motivation was related to caloric drive. DID intake and BACs were unchanged in food-deprived mice. When leptin was administered peripherally at doses shown in separate groups of animals to reduce feeding, it did not reduce DID or BACs. Peripheral ghrelin administration did not significantly increase DID measures at doses that increased feeding in other mice. These authors concluded that high ethanol intake during DID did not largely reflect calorie-seeking.[75]

Because of the temporal focus offered by the method, DID has been used in several pharmacological experiments. Generally, such studies have used C57BL/6J mice, the 4-day DID procedure described above or a two-day variation, and have administered pharmacological agents peripherally before drinking on Day 4 (or Day 2). Some studies have administered agents intracranially in an effort to elucidate the neuroanatomical substrates of DID. These studies are discussed in Section 3.

Selective breeding for drinking in the dark

Because DID appeared to be heritable, Crabbe and colleagues decided to create mice that drank sufficient ethanol to become intoxicated using genetic selection. Rather than selecting animals that drank the most, they elected to breed selectively for the BAC achieved at the end of the DID test. Because genetic contributions to different measures of intoxication tend to be mostly specific to the particular behavioral assay employed,[24] they also elected not to

test and breed for behavioral intoxication. To facilitate the project (which required screening about 100–200 mice per generation), they adopted a two-day version of the DID test. They offered 20% ethanol in a single tube for 2 hr on Day 1 and 4 hr on Day 2, starting 3 hr after lights off.[23] They started by testing a genetically heterogeneous stock, HS/Npt, a population where as many as 8 alleles may be represented for any gene. These mice drank 4 g/kg ethanol in 4 hr and averaged BACs of 30 mg%. The Crabbe group selected the 15 males and 15 females with the highest BACs and mated them to initiate a High Drinking in the Dark-1 (HDID-1) selected line. With each generation, they tested the offspring as adults and selected the animals with the highest BACs to produce the next generation. In the 11th selected generation, BACs attained during testing averaged more than 100 mg%. More than half the animals exceeded this value. This BAC is accompanied by behavioral intoxication in nearly all mice. Intake had increased by about 50% even though they were not selecting on intake. When naive HDID-1 mice from the 9th selected generation were tested for intoxication immediately after a DID test, they were intoxicated as compared with control mice drinking water. HDID-1 mice drank more ethanol and reached higher BACs in 4 day one-bottle then in two bottle testing, though drinking was generally low in this experiment for unknown reasons.[23]

The Crabbe group has maintained breeding pairs of the HS/Npt stock as a control line, but does not test them each generation. Heritability of this trait is low ($h^2 = .09$). The rate of increase in BACs over generations has therefore been slow. This suggests that this trait may be affected by many genes, no one of which exerts a major effect. These investigators were able to rule out differences in ethanol metabolism between HDID-1 and HS/Npt as a contributor to the BAC differences. A comparison of DID in mice from the 11th selected generation with data from the Crabbe laboratory collected in C57BL/6J mice showed that HDID-1 mice drank more and achieved higher BACs than C57BL/6J.[23]

Selection is continuing, and the investigators are are replicating this selection. A second HDID line (HDID-2) was initiated using essentially the same method The gradual increase in BAC and intake in the HDID-2 line resembles that of the HDID-1 line very closely.[33] The HDID-2 line has not yet been tested for two-bottle DID, intoxication, or other potential correlated responses to selection. However, it will offer a valuable way to confirm interesting findings from the HDID-1 selected line that suggest particular genetic influences. They are currently selecting generations 20 (HDID-1) and 12 (HDID-2).

Intragastric self-administration (IGSA)

Myers and Veale first suggested that a gastric fistula might allow self-administration of ethanol in animals that normally avoided the taste or other sensory properties of the drug.[76] In a series of studies, Anthony Deutsch and colleagues pumped ethanol into the stomachs of rats through an indwelling intragastric (ig) cannula.[77–82] Most of these experiments first infused sufficient ethanol to render the animals tolerant, dependent or both, and then offered them a choice of self-administering the drug. Animals administered as much as 10 g/kg/day, though neither the pattern of administration during the day nor the BACs were reported.[77] In two later studies, P rats were shown to self-administer ethanol by the ig route. The first study showed that P rats could be trained to self-administer up to 9.4 g/kg/day by this route, reaching BACs between 92 and 415 mg%.[83] A second study reported 6 g/kg/day self-administered doses.[84] In both studies, the P rats had been tested more than one month earlier for two bottle alcohol preference, but there was no period of forced infusion before the IGSA test. The time that it took to train rats to self-administer ethanol by the ig route was not stated.

Fidler et al[85] have resurrected the Deutsch method for IGSA. In three experiments in which Sprague-Dawley rats were surgically implanted with intragastric catheters, ethanol was

passively infused for 3–6 days providing 3.3 – 12.2 g/kg/day. During a subsequent 5–6 day self-infusion test, licks on one flavored solution were paired with ethanol infusion while licks on another solution were unpaired. During the self-infusion period, passively infused rats self-administered 4–7 g/kg/day while controls self-administered 0–2.6 g/kg/day. Passively infused rats also took much more of their ethanol in large bouts than controls.[85] In a subsequent study with rats, similar results were obtained. Increasing the duration of the ethanol-free interval between periods of passive exposure to 36 hours significantly reduced ethanol consumption suggesting that massed passive exposure produced stronger dependence than space passive exposure.[86] Blood alcohol levels averaged 0.12 g% measured 30 minutes after the start of a bout in which rats infused 1.5g/kg/30 min. This group has also adapted the procedure for mice and shown that even alcohol-avoiding DBA/2J mice will self-administer significant doses of ethanol IG. While C57BL/6J mice self-administered more ethanol than DBA/2J, DBA/2J took more of their alcohol in large bouts. One animal reached 170 mg% BAC five minutes after starting an infusion.[87]

Together, these studies suggest that IGSA is a viable model that can lead susceptible animals to self-administer substantial amounts of ethanol and achieve significant BACs. While most of these studies have examined intakes over extended periods, analyses could be adapted to the temporal resolution needed to see whether significant binge-like intakes are achieved. One principal strength is that this approach avoids the orosensory properties of ethanol that appear to limit intakes in many rat and mouse genotypes. This procedure also allows the experimenter to control the dose, duration, and pattern of alcohol exposure with some precision in animals. However, the method requires surgery. Animals are more likely to be rendered comatose and/or die of alcohol overdose unless safety procedures are built into the system. Its principal limitation is the degree of technical sophistication required to implement it.

Drinking induced by chronic intermittent alcohol vapor exposure (CIE)

Alcohol vapor has been used to induce a state of dependence on alcohol for many years.[88] One early study showed that mice would elect to expose themselves to ethanol vapor after dependence had been induced.[89] Reliable self-administration of ethanol in animals made dependent using ethanol vapor exposure has been extensively characterized in rats[90] Such animals drink enough to reach BACs in the 100–150 mg% range.[91,91] Similarly, rats with a history of alcohol dependence show increased self-administration of ethanol when tested even weeks after acute withdrawal.[91] More recent results have shown that chronic intermittent exposure to ethanol (14 h on/10 h off) using ethanol vapor chambers produces more rapid escalation and greater amounts of ethanol intake[28] BACs are reliably above 140 mg% after a 30 min session of self-administration by dependent animals.[92] Although this animal model may have limited face validity considering that alcohol vapor is passively administered to animals, numerous studies have demonstrated that it also has robust predictive validity for alcohol addiction.[93,94]

A similar procedure, sometimes termed withdrawal-induced drinking (WID), has been developed for mice. WID can produce reliable increases in ethanol self-administration during withdrawal. C57BL/6 mice are first exposed to limited-access ethanol preference drinking for several weeks. They are then exposed to intermittent durations of ethanol vapor, 3 or 4 cycles of 16 hours of vapor and 8 hours of air. They are then are retested in a 2 hour limited access ethanol preference drinking test during the circadian dark period.[95–97] Intermittent ethanol vapor exposure significantly increased 15% (v/v) ethanol intake by 30–50%. Testing after multiple cycles of vapor exposure and after at least 24 hours of withdrawal is most effective.[97] Similar results have been reported using an operant response in mice in 60 min test sessions for 10% (w/v) ethanol, when intermittent vapor exposure of 14 hours on/10 hours off was used.[98]

A better term for this type of post-exposure drinking might be "withdrawal-associated drinking," since there is no direct evidence that the withdrawal state *per se* is the determining factor in the increased drinking.

There are several advantages of alcohol vapor inhalation over other methods of chronic forced alcohol administration.[99] First, alcohol vapor inhalation procedures allow for precise control of the dose, duration and pattern of exposure. They are determined by the experimenter and not by the animal. This method also allows control over circadian oscillations in BACs. Second, stable BACs can be maintained for long periods of time in the presence of normal body weight regulation and general ingestive behavior. Third, animals are never rendered comatose, except when experimenters err. They exhibit signs of tolerance and physical dependence upon termination of alcohol vapor exposure. Severity of withdrawal is a joint function of dose, duration and pattern of vapor concentrations.[100,101] Fourth, no surgery is necessary to administer alcohol. Upon removal from chambers, otherwise healthy animals may be tested for a multitude of acute withdrawal-and protracted abstinence-related behaviors.

Although it has been established that genetic factors influence the severity of withdrawal from chronic intermittent vapor exposure to ethanol in mice,[102] no studies of which we are aware have examined the effects of multiple chronic intermittent vapor exposure and withdrawal on the patterns whereby alcohol is subsequently ingested.

Sweet solution ("supersac") binge drinking

Other methods for inducing binge-like ethanol consumption involve either manipulation of the incentive value of the solution (e.g., "supersac" drinking) or manipulation of the deprivation state (schedule induced polydipsia; see previous section). In sweet solution binge drinking, current practice is adds sweeteners to ethanol, a procedure long been used to promote ethanol drinking by rats. This animal model, originally termed sucrose fading, has face validity for the human condition because humans tend to initiate their drinking of alcohol in sweetened forms.[103,104] This is especially true early in the development of alcohol abuse/alcohol dependence, when consumption patterns reflect the NIAAA definition of binge drinking.[2] Adding sucrose or saccharin to sweeten ethanol solutions increases consumption by adult rats relative to ethanol alone in water[105–108] and sweeteners (at specific concentrations) alone in water.[104] Historically, however, studies employing sweetened ethanol have also failed to reliably produce the 80 mg% BACs now deemed by NIAAA to be the defining factor in binge alcohol drinking (e.g.[107,108]). Other studies have not measured blood-alcohol levels (e.g.[104]).

A recent experiment combined saccharin and low glucose concentrations in a solution shown to have high palatability in rats.[109] In one study, rats were trained to self-administer either 10% (w/v) alcohol solution sweetened with "supersac" (3% glucose + 0.125% saccharin) or supersac alone versus water. In a two-bottle choice or operant situation during 30-min daily sessions, rats that drank alcohol in a binge-like pattern reliably consumed amounts of alcohol sufficient to produce BACs > 80 mg%. This occurred in both two-bottle choice and operant situations, in the absence of food or water deprivation.[110] Adding sweeteners to ethanol solutions in order to produce higher ethanol intake is not a new experimental strategy (see above). However, some of the disadvantages of earlier procedures have been circumvented in the supersac model, There is no need for food deprivation (e.g.[111]) or water deprivation (e.g.[112–114]), and blood-alcohol level criteria are defined (e.g.[115–118]).

Other binge-like procedures

When mice or rats are offered multiple bottles of ethanol, whether they contain the same[119] or different[120,121] concentrations of ethanol, the total g/kg dose of ethanol increases. In a study where 5 bottles of 10% ethanol were offered along with 1 bottle of water, male C57BL/6J mice drank more than 23 g/kg/day. By comparison, they drank 9 g/kg/day in a concurrent standard two-bottle preference test. It is not known what the effect of this increased availability has on the temporal pattern of ingestion over the 24 hr day. BACs sampled during the light cycle, when intake is usually low, were quite modest in the C57BL/6J mice.[119] P rats showed a tendency to increase their overall ethanol intake when offered water vs 10%, 20% and 30% ethanol simultaneously. They shifted the distribution of their choices over time to favor drinking the higher concentrations.[120] A similar result was reported with another high-preferring rat strain, sP rats.[122] When multiple concentrations were combined with repeated periods of deprivation and restoration of access, P rats reached BACs averaging 180 mg% after the first 2 hours of drinking during the circadian dark.[120] Similar effects were recently reported in two other rat lines selected for high preference.[123] These latter studies employed a variant of a procedure called the “alcohol deprivation effect,” originally described many years ago.[43]

Non-human primates have also been studied using sweetened alcohol solutions offered during limited access periods. After training animals to a sweetend solution, alcohol is introduced and animals will drink significant amounts during limited access sessions.[124–126] Some experiments have reported BACs in the 100–200 mg% range.[127] Other studies with non-human primates were discussed in Section 2E.[65]

Finally, we mention a study employing *Drosophila melanogaster*.[128] The powerful genetic tools available to manipulate the fruit fly genome has made this species a favorite of genetics researchers. A recent study offered flies the choice between ethanol-containing food and regular food while monitoring their consumption and preference. Flies elected the ethanol-containing food, which they ingested in quantities sufficient to attain meaningful BACs that had been previously demonstrated to cause behavioral intoxication. Ethanol food preference was not likely to be entirely due to either caloric drive or taste. To test for the role of calories, the experimenters offered food mixtures with ethanol in different ratios. Preference remained stable across these different values. However, the lowest concentration tested still had twice the calories in the ethanol/food combination than in the plain food, so calorie-seeking could not be entirely ruled out.[128] This interesting paper used many of the powerful tools of fly genetics, highlighting the strengths of this model. However, the fact that flies subsist on alcohol as a source of food in the wild may provides cautions for direct comparisons with human addiction or even with rodent models.

Neuroadaptations following binge drinking

Neurochemical and electrophysiological studies of brain changes from binge alcohol consumption are emerging. Consequences of alcohol exposure during adolescence have been reviewed[129] and will not be discussed here. Some studies which purport to study ‘binge drinking’ actually inject ethanol to produce ‘binge-like’ levels of blood ethanol.[130,131] Single injections of alcohol can produce considerable plasticity in brain reward pathways.[132] However, the focus of this review is self-administered alcohol.

Withdrawal-related drinking models in the rat have been extensively studied using neuropharmacological techniques.[133] Both decreases in reward-related neurotransmitter function and recruitment of brain stress neurotransmitter function in the ventral striatum and extended amygdala, respectively, have been hypothesized to contribute to the excessive drinking associated with dependence in rats. In dependent male Wistar rats trained to self-

administer ethanol during withdrawal, the release of dopamine and serotonin was monitored by microdialysis in the nucleus accumbens at the end of a 3–5 week ethanol (8.7% w/v) liquid diet regimen, during 8 h of withdrawal, and during renewed availability of ethanol involving the opportunity to operantly self-administer ethanol (10% w/v) for 60 min, followed by unlimited access to the ethanol liquid diet. In nondependent rats, operant ethanol self-administration increased both dopamine and serotonin release in the nucleus accumbens. Withdrawal from the chronic ethanol diet produced a progressive suppression in the release of these transmitters over the 8 h withdrawal period. Self-administration of ethanol reinstated and maintained dopamine release at pre-withdrawal levels but failed to completely restore serotonin efflux. These findings suggest that deficits in nucleus accumbens monoamine release may contribute to the negative affective consequences of ethanol withdrawal and thereby motivate ethanol-seeking behavior in dependent subjects.[134]

The brain stress system mediated by corticotropin-releasing factor (CRF) systems in both the extended amygdala and hypothalamic-pituitary-adrenal axis also play a key role in the excessive drinking associated with withdrawal. More specifically, alcohol withdrawal reliably produces anxiety-like responses that can be reversed by CRF receptor antagonists.[133] The ability of CRF antagonists to block the anxiogenic-and aversive-like motivational effects of drug withdrawal predicted motivational effects of these CRF antagonists in animal models of extended access to drugs. A particularly dramatic example of the motivational effects of CRF in dependence can be observed in animal models of ethanol self-administration in dependent animals. During ethanol withdrawal, extrahypothalamic CRF systems become hyperactive. There is increased extracellular CRF within the central nucleus of the amygdala and bed nucleus of the stria terminalis of dependent rats.[135–137] When administered directly into the central nucleus of the amygdala, a CRF1/CRF2 antagonist blocked ethanol self-administration by ethanol-dependent rats.[137] Systemic injections of small-molecule CRF1 antagonists also blocked the increases in ethanol intake associated with acute withdrawal.[138–140] These data suggest an important role for CRF, primarily within the central nucleus of the amygdala, in mediating the increased self-administration associated with dependence. Consistent with the sensitization of the withdrawal response associated with repeated alcohol exposure, a CRF antagonist administered during repeated withdrawal also blocked the development of excessive drinking during withdrawal.[141] Results using this model have also implicated dysregulation of norepinephrine, substance P, vasopressin, dynorphin, neuropeptide Y and nociceptin in the excessive drinking associated with withdrawal.[133]

At least four different animal models of binge drinking without dependence have been used for functional studies. No model has been studied in any detail and there are no systematic comparisons among models. The DID limited access paradigm has been used for a number of pharmacological studies. Most treatments reduced drinking. Activation of cannabinoid or GABA-B receptors (using peripheral injection of baclofen induce or enhance binge drinking.[142,143] In contrast, intra-VTA injection of baclofen inhibits drinking in this model.[144] The nicotinic agentscytosine, nicotine and mecamylamine and the aCRF-1 antagonist (CP-154,526) reduced DID drinking.[145,146] Drinking in the DID test was also reduced by GABAergic drugs (muscimol, THIP), a dopamine uptake inhibitor (GBR 12909), urocortin 1 and naltrexone.[142,147,148] Most of these treatments did not reduce water consumption, although both muscimol and THIP showed this effect, suggesting less-specific actions for these agents.[142] Most of these studies did not attempt to determine whether the drugs have any selectivity for high vs lower levels of alcohol consumption. Most did not compare tests that achieve different blood ethanol levels. However, Sparta et al.[145] found that longer access to alcohol (4 hr vs. 2 hr) provided higher BACl (30 vs 80 mg%) and that the CRF 1 antagonist reduced drinking only for the longer access. These results are consistent with the prior discussion regarding dependence-induced drinking.

The SHAC model of limited access drinking was found to produce an imbalance between excitatory and inhibitory systems in the nucleus accumbens and to suggest that mGluR5-Homer-PI3K signaling in this brain is strengthened by, and critical for, binge drinking.[149,150] An electrophysiological study of the daily intermittent access model of 24 hr two bottle choice drinking showed enhanced glutaminergic activity, especially enhancement of AMPA receptor function, in the ventral tegmental area.[151] This is the opposite of the changes in AMPA receptor function seen after single injections of alcohol.[132] Both acamprosate and naltrexone decreased excessive drinking in this model.[47]

A new rat model that is said to produce 'binge-like' drinking uses P rats with one hour access to ethanol 3 times daily (Multiple Scheduled Access, MSA) during the circadian dark phase for 8 weeks. Rats drinking on this schedule were used for gene expression (Affymetrix array) studies.[152] Analysis of the shell of the nucleus accumbens and central nucleus of the amygdala found only small changes in gene expression, with distinct changes for the two brain regions. Another study compared gene expression in nucleus accumbens of rats consuming only water (control), continuous access to alcohol or MSA for eight weeks. MSA produced no significant changes in gene expression, although continuous access produced changes in 374 named genes.[153] It will be of interest to determine whether other binge models produce reliable changes in gene expression or if other brain regions are more sensitive to binge drinking.

Genetic similarities and differences across drinking models

There are genetic contributions to individual differences in ethanol drinking for any model for which we have data. There appears to be a fair amount of overlap in the genes that contribute to drinking when assessed in different ways. There is an older genetic literature on certain drinking models that resemble DID. As discussed earlier, Belknap reported that C57BL/6J and DBA/2J mice differed in the degree to which they would drink ethanol solutions when thirsty.[50,154,155] McClearn[156] had tested six inbred strains of mice using a similar test, termed "alcohol acceptance under thirst motivation." Mice were singly housed and had their water intake measured for two days. Water was then removed for 24 hr, and on the 4th day a single tube of 10% ethanol was offered for 24 hr. Mice differed significantly in amount of ethanol drunk. The strain rank order of alcohol acceptance was essentially the same as that for two other ethanol preference tests. A subsequent project selectively bred High (HEA) and Low (LEA) Alcohol Acceptance lines of mice from a heterogeneous stock for 14 generations. The trait was heritable ($h^2 = 0.21$). A separate experiment established that alcohol acceptance with or without thirst motivation and two-bottle preference drinking were reasonably correlated across individual animals, suggesting that there was some commonality in the genetic contributions to these different assays. Unfortunately, these lines were not continued.[157]

A substantial literature is devoted to attempts to identify the locations of genes affecting two-bottle alcohol preference drinking. Several quantitative trait loci (QTL) have been rigorously located. These regions of the genome are thus likely to harbor a gene or genes whose variants affect the trait. However, which genes harbor these variants remain generally unknown. Reviews of this literature are available.[33,158,159] Alcohol acceptance under thirst motivation has also been the subject of a number of QTL analyses.[160–165] However, for the alcohol acceptance trait, intakes are not examined in a way that is informative about binge drinking.

Since there are so few neurobiological data from the more promising binge-like models that we have discussed above, it is unfortunately not feasible to compare neurobiological results across models at this time.

Conclusions and need for future research

Historically, animal models of binge drinking have progressed from a) acute injections of quantities of alcohol hypothesized to be intoxicating or sufficient to produce intoxication-like symptoms to b) two-bottle choice procedures over 24 h periods to c) discrete bouts of self-administered alcohol that produce blood alcohol levels equivalent to those defining binge drinking in humans. Thus, the field of animal models of binge drinking has gained both face validity and some construct validity. Here, construct validity refers to the interpretability, "meaningfulness," or explanatory power of each animal model and incorporates most other measures of validity in which multiple measures or dimensions are associated with conditions known to affect the construct.[166] An alternative conceptualization of construct validity is the requirement that models meet the construct of functional equivalence, defined as "assessing how controlling variables influence outcome in the model and the target disorders."[167] The most efficient process for evaluating functional equivalence has been argued to be through common experimental manipulations that should have similar effects in the animal model and the target disorder.[167]

Animal models of binge drinking in the context of dependence, such aswithdrawal-associated drinking in rats or mice, clearly display some construct validity. They have demonstrated high blood alcohol levels. Drugs such as acamprosate, gabapentin, and GABA modulators will block or attenuate such excessive drinking. The new and exciting data on stress systems and excessive drinking during withdrawal hold promise for understanding the neurobiological underpinnings of binge drinking associated with dependence.

Of the limited-access binge models, two models present themselves with significant face validity: DID, and sweetened alcohol. From the perspective of construct validity, both these and the SHAC model have demonstrated blood alcohol levels of 0.08 g% in rats or 0.10 g% in mice. It remains to be determined whether such binge drinking will respond pharmacologically to treatments that also dampen binge drinking in humans. Initial data from naltrexone appear to support this hypothesis. A critical future goal is to determine whether brain changes induced by binge drinking in humans can be reproduced in these animal models. In addition to studies of animal models, this will require more detailed human studies to resolve this difficult issue.

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