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Scheduled access alcohol drinking by alcohol-preferring (P) and high-alcohol-drinking (HAD) rats: modeling adolescent and adult binge-like drinking

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Abstract

Binge alcohol drinking continues to be a public health concern among today's youth and young adults. Moreover, an early onset of alcohol use, which usually takes the form of binge drinking, is associated with a greater risk for developing alcohol use disorders. Given this, it is important to examine this behavior in rat models of alcohol abuse and dependence. Toward that end, the objective of this article is to review findings on binge-like drinking by selectively bred alcohol-preferring (P) and high-alcohol-drinking (HAD) lines of rats. As reviewed elsewhere in this special issue, the P line meets all, and the HAD line meets most, of the proposed criteria for an animal model of alcoholism. One model of binge drinking is scheduled ethanol access during the dark cycle, which has been used by our laboratory for over 20 years. Our laboratory has also adopted a protocol involving the concurrent presentation of multiple ethanol concentrations. When this protocol is combined with limited access, ethanol intake is maximized yielding blood ethanol levels (BELs) in excess, sometimes greatly in excess, of 80 mg%. By extending these procedures to include multiple scheduled ethanol access sessions during the dark cycle for 5 consecutive days/week, P and HAD rats consume in 3 or 4 h as much as, if not more than, the amount usually consumed in a 24-h period. Under certain conditions, using the multiple scheduled access procedure, BELs exceeding 200 mg% can be achieved on a daily basis. An overview of findings from studies with other selectively bred, inbred, and outbred rats places these findings in the context of the existing literature. Overall, the findings support the use of P and HAD rats as animal models to study binge-like alcohol drinking and reveal that scheduled access procedures will significantly increase ethanol intake by other rat lines and strains as well.

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Keywords

animal model of alcoholism; blood alcohol concentration; discrete bout; drinking-in-the-dark; excessive intake; extreme drinking; limited access; loss-of-control drinking; nocturnal drinking

Introduction

A majority of adult Americans have a family member with an alcohol use disorder (AUD) (Research Society on Alcoholism, 2009). Moreover, close to half of adults in the US meeting life-time diagnostic criteria for alcohol dependence do so by the age of 21, and this percentage increases to approximately two-thirds by the age of 25 (Hingson, Hereen, & Winter, 2006). Today's youth are initiating alcohol use earlier and experiencing more alcohol-related problems than ever before (Bava & Tapert, 2010; Gore et al., 2011; Miller, Naimi, Brewer, & Jones, 2007; Miller, Turner, & Marlatt, 2001; Pitkänen, Lyyra, & Pulkkinen, 2005; Quine & Stephenson, 1990; Winters, 2001). Also, approximately 80% of US high school seniors have consumed alcohol, with half initiating drinking before the 8th grade (Johnston, O'Malley, & Bachman, 1999). This is alarming since an early onset of alcohol use is a predisposing factor for developing alcohol dependence (Anthony & Petronis, 1995; Chou & Pickering, 1992; Clark, Kirisci, & Tarter, 1998; Grant & Dawson, 1997; Hawkins et al., 1997).

Binge alcohol drinking (defined in general terms as consuming 4–5 drinks in ~2-h period and achieving blood ethanol levels of 80 mg% or more (NIAAA, 2004) appears to be a behavior primarily engaged in by adolescents and young adults (< 24 years old) compared with older adults (c.f., Courtney & Polich, 2009; Marczinski, Grant, & Grant, 2009; Martinic & Measham, 2008; Plant & Plant, 2006). In the US, close to 30% of high school seniors engage in binge drinking (Johnston, O'Malley, & Bachman, 1991, 1993), with 70% of college students having engaged in this behavior during high school (Wechsler, Lee, Kuo, & Lee, 2000). It has been estimated that greater than 1 out of 3 male college students in the US engage in binge drinking and that a significant proportion of these achieve blood alcohol concentrations (BACs) between 100 and 200 mg% (e.g., Wechsler, Lee, Kuo, & Lee, 2000; White, Kraus, & Swartzwelder, 2006). The seriousness of this problem is underscored by the fact that adolescents drink 11 percent of all alcohol consumed in the US, with practically all of it consumed in the form of binge drinking (NIAAA, 2012). As discussed by L.P. Spear (2010), along with Bell and colleagues (2013), parallel developmental ages between rats and humans have been estimated (estimated body weights are included for rats in Table 1, because most rat studies do not give the animal's age) using behavioral and neurobiological milestones—see Table 1.

Usefulness of selectively bred animal models to study alcohol-associated effects

Animal models have been successfully used to investigate the causes of, and develop treatments for, medical and psychiatric disorders (e.g., Griffin, 2002; McKinney, 2001; Nestler & Hyman, 2010). An animal model has the advantage of allowing the experimenter to control factors such as genetic background, environment, and prior drug exposure. Bi-directional selective breeding is a powerful genetic tool for studying many alcohol-

associated phenotypes (e.g., Crabbe, 2008). Thus, this breeding strategy results in the expression of high vs. low levels of a particular phenotype, such as alcohol intake and/or preference. With this method, the expression levels of a selected phenotype tend to exceed the range of expression displayed by the foundation stock. The alcohol-preferring P and high alcohol-drinking HAD (replicate 1 and 2) rat lines were selectively bred (from a closed colony of Wistar rats and the N/NIH line, respectively) to prefer a 10% alcohol solution over water and consume greater than 5 g of alcohol/kg body weight/day (see McBride, Rodd, Bell, Lumeng, & Li, 2013b). These selectively bred rats have been used to investigate the effects of continuous (24-h/day) and/or binge alcohol drinking across peri-adolescence and adulthood.

Free-choice 24-h ethanol drinking by P and HAD rats

Early work indicated that P rats, when given continuous 24-h access to ethanol (10% v/v) and water in their home cages, consumed most of their ethanol in discrete bouts (~1 g/kg in less than 1 h; resolution was limited to 1-h observations in this study) during the dark cycle (Murphy et al., 1986). These authors also reported that animals with larger bouts tended to have fewer bouts per day. In this same study, it was shown that bout number and size could be manipulated by giving P rats a single 4-h access session/day vs. 24-h continuous access or four 1-h access sessions/day, such that the largest bout size occurred under the 4-h access session, but, again with fewer bouts (Murphy et al., 1986). However, when total ethanol intake was averaged per hour, the four 1-h access sessions/day group drank the most ethanol (~1 g/kg/h) which was 4 times that of the 24-h and 2½ times that of the 4-h groups (Table 2).

In a subsequent study, Bell et al. (2006a, b) examined patterns of daily ethanol (15% v/v) intake by adolescent and adult, male and female P rats in their home cages using a lickometer setup, such that total licks on the water and ethanol bottles were recorded every 6 min across 22 h (12 h dark and 10 h light) for 4 weeks. These studies (Bell et al., 2006a, b) replicated the finding that P rats drink ethanol in bouts (~1 g/kg/6-min) during the dark cycle. In addition, these studies confirmed that, in general, animals that consumed larger bouts (often ~2 g or greater/kg/6–12 min) displayed fewer bouts per 24 h. Regarding peri-adolescence, late pubertal P rats engaged in significantly more bouts/day than their adult counterparts, with an associated decrease in the amount of ethanol consumed/bout. A recent study by Dhaher et al. (2012) used the lickometer setup to examine patterns of daily ethanol (15% v/v) intake of adolescent and adult, male and female HAD1 and HAD2 rats. As with the P rats, HAD rats consume most of their ethanol during the dark cycle and in discrete bouts with the vast majority of these bouts being captured within respective 6-min recording windows. Also comparable with P rats, animals that consumed larger bouts (often ~2 g or greater/kg/6 to 12 min bin) generally displayed fewer bouts per 24 h. Again, similar to P rats, late pubertal HAD1 and HAD2 rats engaged in significantly more bouts/day than their adult counterparts, with an associated decrease in the amount of ethanol consumed/bout (Table 2).

This research (Bell et al., 2006a, b; Murphy et al., 1986) indicates that P rats display repeated bouts (approximately equal to or greater than 1 g/kg in less than 6 min) of alcohol

intake and these occur primarily during the dark cycle. Similarly, HAD rats consume most of their ethanol during the dark cycle in bouts approximating 2 g/kg in less than 6 min (Dhaher, McConnell, Rodd, McBride, & Bell, 2012; Table 2). These levels of alcohol intake within this relatively short time span result in BELs of 80 mg% or higher (Bell et al., 2006a, 2008, 2011). These apparent line differences (Table 2) have been reported elsewhere as well (Files, Samson, Denning, & Marvin, 1998; Samson, Files, Denning, & Marvin, 1998; c.f., Bell et al., 2012). However, even though P and HAD rats consume ethanol in discrete bouts during the dark cycle, the timing of these bouts varies between animals and across days. Therefore, to repeatedly capture these binge-like levels of ethanol intake and their associated elevated BELs, a multiple-scheduled-access procedure during the dark cycle has been adopted by our laboratories. This procedure was developed from past findings when a single-scheduled-access procedure was used.

Free-choice scheduled access ethanol drinking by P and HAD rats

Scheduled access ethanol drinking has been studied with P and HAD rats, using different durations of access and different concentrations of ethanol solutions, as well as home-cage vs. operant access conditions (Table 3). In our laboratory, all of the studies were conducted during the dark cycle, with ethanol intakes satisfying criteria for binge drinking such that BELs of 80 mg% or higher are regularly achieved (NIAAA, 2004). An initial home-cage study (Murphy et al., 1986) examined free-choice drinking of 10% ethanol vs. water using a 4 h/day access protocol. These authors reported that ethanol intakes of adult male P rats approximated 2 g/kg/session. However, most of the ethanol was consumed within the first 15 min, which resulted in average peak BELs reaching 120 mg% (Table 3). Similar to male P rats, adult female P rats consume 2–3 g/kg/4-h of 10% ethanol (vs. water) under limited-access home-cage conditions (McKinzie et al., 1998a).

Other work has shown that both male P and male HAD rats will consume 2–3 g/kg of 10% ethanol during a 4-h access period in their home cages, even when 0.0125% saccharin is concurrently available (Russell, McBride, Lumeng, Li, & Murphy, 1996). Again, both rat lines consumed the majority of the 10% ethanol solution within the first 15 min, whereas most of the saccharin intake occurred after the first hour of access. These results indicate that both P and HAD rats will exhibit binge-like alcohol intakes even when a highly palatable solution is concurrently available. In addition, these rat lines appear to consume ethanol for its CNS pharmacological effects because the pattern of drinking produced BELs exceeding binge criterion levels (i.e., 80 mg%) within the first hour. However, a study about this time indicated that a 30-min/day operant access protocol (10% ethanol vs. water) produced meaningful ethanol intakes in HAD2, but not P or HAD1, lines (Files, Samson, Denning, & Marvin, 1998). The low intakes in this study (Files, Samson, Denning, & Marvin, 1998) could be a result of experiments being conducted during the light cycle. A subsequent study examining both home-cage and operant procedures, with 2-h/day access sessions, reported ethanol intakes ~2 g/kg/2-h by female P rats under either condition (Nowak, McKinzie, McBride, & Murphy, 1999).

Most operant ethanol self-administration studies are undertaken using fixed-schedule access conditions. Such operant studies would qualify as models of binge-like drinking if the self-

administration results in BELs of 80 mg% or higher (NIAAA, 2004). More recent operant studies have examined ethanol intake when access is limited to a single 1 h/day session. When examining ethanol (15% v/v) intake using a standard 2-lever operant procedure with schedules of reinforcement being ethanol = fixed ration 5 (FR5) and water = fixed ratio 1 (FR1), male P rats consumed ~1.3 g/kg/h (Rodd et al., 2003), male HAD1 rats consumed ~1.2 g/kg/h (Oster et al., 2006) and male HAD2 rats consumed ~1.6 g/kg/h (Oster et al., 2006). A study examining the effect of changing the 2nd lever from water to 0.0125% saccharin (FR1) revealed male P rats still consumed ~1.3 g/kg/h (Toalston et al., 2008). Similar to the Russell et al. (1996) study, this last finding indicates P rats will continue to self-administer significant amounts of ethanol in the presence of a highly palatable alternative solution.

Subcutaneous (s.c.) ethanol levels have also been examined under limited (1 h/day) access conditions (Engleman et al., 2008). These authors reported that adult P rats consumed ~1 g/kg/1-h session and s.c. ethanol levels paralleled, albeit at significantly lower levels, BELs. In agreement with previous work, P rats drank the majority of ethanol in the first 5 min of the session. BELs increased steadily across the 1-h access session and peaked at approximately 50 mg% at the end of the session. Ethanol levels decreased gradually over the following 3 h, indicating an extended time course of measurable systemic ethanol levels. In addition, the operant technique has been adapted to study the co-abuse of ethanol and nicotine using 1-h/day access to mimic binge-like drinking and smoking conditions (Hauser et al., 2012). Concurrent access to multiple concentrations of ethanol (10, 20, and 30%) was used because this results in higher ethanol intakes than when a single ethanol concentration is presented (e.g., Bell et al., 2003, 2004). Each ethanol solution also contained 0.14 mg/mL nicotine. This study used a 3-lever operant chamber (each lever allowed the presentation of its respective solution on an FR5 schedule), with water available *ad libitum* via a water bottle. Under these conditions, adult female P rats consumed ~2 g/kg/session ethanol and ~2 mg/kg/session nicotine to produce BELs approximating 80 mg% and blood nicotine levels (BNLs) approximating 50 ng/mL. These BELs and BNLs represent values regularly achieved by binge drinkers and chronic smokers.

In summary, these results with scheduled access drinking illustrate the utility of using P and HAD rats to study binge-like alcohol drinking, under both home-cage and operant conditions. In addition, the results further illustrate that ethanol is more rewarding than saccharin, and that these selectively bred rats can be used to study the co-abuse of ethanol and nicotine.

Free-choice multiple-scheduled-access ethanol drinking by P and HAD rats

Thus far, limited-access and 24-h access procedures have provided some information on the acute pharmacological interference of ethanol drinking (see Bell et al., 2012 for a comprehensive review of studies conducted in alcohol-preferring rat lines). However, it is our contention that rat protocols employing a single limited access session per day do not validly address human binge-drinking. This stems from the facts that a) human binge drinking occurs primarily during adolescence and early adulthood, b) human binge drinking is a repetitive phenomenon, such that this type of drinking is engaged in several, or more,

times a month, and c), as noted in Table 1, in the strictest sense the developmental windows for rat adolescence and peri-adolescence are only 2 weeks each. Further complicating the development of an animal model of binge-like drinking is the fact that a generally accepted clinical definition of this phenomenon (NIAAA, 2004) is a relatively recent occurrence. For instance, the NIAAA definition (2004) of binge drinking (a time frame of 2 h) differentiates it from bender-like drinking (a time frame of 2 or more days). Earlier clinical definitions did not always make this distinction, with the number of these instances increasing as one retrospectively examines the literature (c.f., Plant & Plant, 2006). In addition, despite its general acceptance, there is still some controversy over the 4/5 rule of the NIAAA definition (2004; for some pros and cons see Goldman, 2006; Wechsler & Nelson, 2006; White, Kraus, & Swartzwelder, 2006).

On the other hand, as reviewed by Bell and colleagues (2013), a generally accepted basic research definition of binge drinking is still lacking. This lack of consensus stems from the three points about binge drinking research mentioned above and the fact that most rats, as discussed below, do not readily consume sufficient ethanol to achieve pharmacologically relevant BELs, which means they certainly do not achieve binge-associated BELs (i.e., ≥ 80 mg%). Therefore, our laboratory has sought to examine binge-like drinking using a) selectively bred alcohol-preferring rats, b) a multiple, rather than a single, scheduled-access procedure, c) concurrently available multiple ethanol concentrations, and d) ethanol presentation during the dark phase. The use of selectively bred alcohol-preferring rats (P and HAD) capitalizes on their innate proclivity to consume large amounts of ethanol. The use of multiple scheduled-access sessions allows a researcher to capitalize on repeated discrete bouts of ethanol-drinking per day. And, the use of concurrently available multiple ethanol concentrations as well as access during the dark phase capitalizes on significant increases in intake induced by these procedural manipulations. We believe that the combination of these four factors results in an animal model of binge-like drinking with construct and face validity relative to the human condition. Regarding the repetitive nature of binge drinking, it is noteworthy that other animal models of binge-like drinking, which use forced ethanol exposure, also incorporate multiple exposures per day (e.g., Zahr et al., 2013). In general, the findings described below indicate that exposure of high alcohol-consuming rats to multiple free-choice, scheduled-access sessions across the dark cycle results in daily ethanol intake levels approximating, and sometimes exceeding, that seen when these rats are given 24-h free-choice access, producing BELs ≥ 80 mg%.

A study examining the effect of two 1-h ethanol (15 and 30% available concurrently) access periods during the dark cycle (5 days/week) on intake by adult male P rats revealed average intakes of 2.5 g/kg/h and average BELs of 120 mg% at the end of the 1-h session, which would not represent peak BELs (Bell, Rodd, Lumeng, Murphy, & McBride, 2006a). Moreover, ~60% of the ethanol was consumed in the first 6 min with ~95% of the ethanol consumed within the first 12 min. In a parallel study (Bell et al., 2006c), adult female inbred P (iP) rats were given four 1-h free-choice ethanol (15 and 30%) access periods across the dark cycle. This study (Bell et al., 2006c) revealed that four 1-h access periods yielded greater initial ethanol intake by the binge-like access group compared with a continuous access (24 h/7 days/week) group (peak intakes were 8 g/kg/day and 6 g/kg/day, respectively). Results from these studies indicated that whereas multiple 1–h access periods

across the dark cycle result in ethanol intakes of 1.5 g/kg/h or higher, with peak BELs regularly exceeding 100 mg%, there is a point of diminishing returns, such that more access periods are not always better (Table 4).

Another study (Bell, Rodd, Lumeng, Murphy, & McBride, 2006a) indicated that three 1-h ethanol access periods, each separated by 2 h, may maximize ethanol intake in adult male P rats. Thus, our laboratory set out to characterize binge-like ethanol drinking by peri-adolescent and adult, male and female P rats using a multiple-scheduled-access procedure that involved three 1-h access periods across the dark cycle (Bell et al., 2011). Using this procedure it was found that, during a 1-h access period, ethanol intake by adolescent [postnatal day (PND) 45 or 47] male P rats climbed from 1.7 g/kg at 15 min to 2.7 g/kg at 60 min, with BELs climbing from ~60 mg% at 15 min to 100 mg% at 30 and 60 min (Bell et al., 2011). In addition, intoxication was evaluated, with an oscillating bar task (c.f., Bell et al., 2000, 2001), in adult female P rats. Binge-drinking rats displayed significantly shorter latencies to fall during the 4th, but not 1st, week of ethanol access compared with water controls, despite no difference in latency to fall between the 1st- and 4th-week binge drinkers. Moreover, ethanol intake increased from ~1.5 to ~2.25 g/kg/h and BELs increased from ~35 to ~75 mg% across weeks. These latter results suggest the development of tolerance across the 4 weeks of multiple-scheduled-access to ethanol. The intoxicating effects of binge-like drinking by peri-adolescent female P rats were also examined, again using latency to fall in the oscillating bar task (Bell et al., 2011). Binge-drinking rats displayed significantly shorter latencies to fall vs. same-aged water controls (~80 sec vs. 120 sec, respectively). In addition, average ethanol intake by the binge-drinkers was ~3 g/kg/30-min with ~90 mg% average BELs detected after the test for intoxication.

These results support the contention that the multiple-scheduled-access procedure can be used to model binge-like drinking. For instance, this type of drinking results in the regular occurrence of 80 mg% [the threshold BEL in NIAAA's (2004) definition for binge drinking] and motor impairment as a measure of intoxication (Bell et al., 2006a, 2011). These benchmarks were achieved in both peri-adolescent and adult P rats of both sexes. Moreover, the findings (Bell et al., 2011) provide some "face" validity for this developmental binge-drinking model, such that peri-adolescent rats consumed more alcohol than their adult counterparts both in terms of total consumption per day and consumption per 1-h access period. Also, whereas adult P rats given continuous access consumed more alcohol than those given binge-like access, the reverse was true for peri-adolescent P rats, with binge-like access animals consuming significantly more ethanol each day than their continuous access counterparts.

The multiple-scheduled-access procedure can also be used with operant protocols (e.g., McBride et al., 2013a; Warnock et al., 2012). For instance, using a 3-lever operant procedure with concurrent access to 10, 20, and 30% ethanol and four 1-h daily access sessions, it has been shown that adult female P rats self-administer 1.2 to 1.7 g/kg/1-h session and attain BELs greater than 200 mg% (McBride et al., 2013a). Such high BELs are associated with profound intoxication, are dangerous, and suggest that this procedure can induce loss-of-control drinking. Therefore, this procedure offers a model for determining alterations in neurocircuitry responsible for the loss of an ability to control/limit a person's

drinking. Additionally, the multiple-scheduled-access procedure produces ethanol intakes and BELs that reliably exceed binge levels on a daily basis in both adult and peri-adolescent P rats.

Ethanol-drinking behavior of other rat lines

There are several other selectively bred, alcohol-preferring rat lines in the world, which meet the general criteria of consuming at least 5 g/kg/day of ethanol and exhibiting a clear preference for 10% ethanol over water. The ALKO Accepting/alcohol-preferring AA rat line was developed from a closed colony of Wistar-Sprague-Dawley cross foundation stock in Helsinki, Finland (Eriksson, 1968). The Sardinian alcohol-preferring sP rats were developed from a local Wistar foundation stock at the University of Cagliari, Italy (Colombo, Lobina, Carai, & Gessa, 2006). The alcohol-preferring University of Chile B UChB line of rat was developed from a local Wistar foundation stock at the University of Chile, Santiago, Chile (Mardones & Segovia-Riquelme, 1983). And, more recently, the alcohol-preferring Warsaw High Preferring WHP line was developed from a local Wistar foundation stock at the Institute of Psychiatry and Neurology in Warsaw, Poland (Bisaga & Kostowski, 1993). In addition, the High 'Addiction Research Foundation' HARF rat was selectively bred at the Center for Addiction and Mental Health in Toronto, Ontario, Canada, to consume considerable amounts of ethanol when given 20 min of access per day (≥ 1 g/kg/20-min, > 6 g/kg/day; Lê, Israel, Juzytsch, Quan, & Harding, 2001). The HAD replicate and HARF rat lines were selectively bred from the N/NIH foundation stock (a cross of 8 inbred rat strains with varying levels of ethanol intake; Hansen & Spuhler, 1984). Of the international selectively bred alcohol-preferring rat lines, the majority of the pharmacology and neurobiology of alcohol preference/consumption research has been conducted in the AA, HAD replicate, P, sP, and UChB lines (see Bell et al., 2012; also see Sommer, Hyytiä, Kiianmaa, 2006; Colombo, Lobina, Carai, & Gessa, 2006; Quintanilla, Israel, Sapag, & Tampier, 2006 for earlier reviews on the AA, sP, and UChB lines, respectively). Table 5 outlines the 24-h ethanol-drinking levels displayed by these and other rat lines and experimental manipulations used to achieve these levels of intake (e.g., intermittent access where the rats are given 24-h, free-choice access to 20% ethanol vs. water Monday, Wednesday, and Friday of each week). Table 6 outlines the levels of limited access ethanol consumption displayed by these and other rat lines along with associated experimental manipulations (e.g., the limited access session is presented during the dark/nocturnal/active cycle for rats).

Still, other rat lines have also been used to examine the pharmacology and neurobiology of ethanol drinking and self-administration (see Tables 5 and 6). Three such rat lines are derivatives of previously selected rat lines, such that the High Ethanol Preferring (HEP) line was derived from the P line (Myers, Robinson, West, Biggs, & McMillen, 1998), the Cologne AA (cAA) line was derived from the AA line (Maurel, De Vry, De Beun, & Schreiber, 1999), and the Marchigian sP (msP) was derived from the sP line (Ciccocioppo et al., 2006). These lines like their progenitors consume > 5 g/kg/day of ethanol and display a clear ethanol (11% or 10%) preference over water. The inbred Fawn Hooded rat, whether from a vendor in the United States or France, consumes ~4 g/kg/day of ethanol with a modest preference for 10% ethanol over water (Overstreet, Rezvani, Cowen, Chen, &

Lawrence, 2006; Femenia, García-Gutiérrez, & Manzanares, 2010, respectively). In addition, some rat lines selectively bred for a different behavioral phenotype display modest to relatively high ethanol intakes per day. For instance, Maudsley Reactive (MR/Har) rats consume close to 4 g/kg/day of ethanol with a 60% preference for 10% ethanol over water (Adams, Mitchell, Campbell, & Samson, 2002). Unlike the alcohol-preferring vs. alcohol-nonpreferring rat lines, their Maudsley Non-Reactive (MNR/Har) counterparts consume close to the same amounts of ethanol, ~3.5 g/kg/day and a 50% preference for ethanol over water (Adams, Mitchell, Campbell, & Samson, 2002). Another example is the Taste Aversion Resistant (TAR) rat line, which consumes > 5 g/kg/day of ethanol (Orr, Whitford-Stoddard, & Elkins, 2004). Similar to selectively bred alcohol-nonpreferring rats, Taste Aversion Prone (TAP) rats (the TAR counterpart), consume very little ethanol (Orr, Whitford-Stoddard, & Elkins, 2004).

Finally, outbred rat lines have also been used to investigate the pharmacology and neurobiology of ethanol reward and reinforcement (see Tables 5 and 6). The 2 primary outbred rat lines displaying appreciable levels of ethanol intake, although they require experimental manipulations to achieve the levels described above, are the Wistar and Long-Evans Hooded lines. Note that Wistar lineage is found in all of the selectively bred rat lines achieving pharmacologically relevant BECs. The Sprague-Dawley rat line has been used, but in general this line displays significantly lower ethanol intakes than the Wistar and Long-Evans Hooded lines. Only a few examples are presented in Tables 5 and 6 and these studies included experimental manipulations (described therein) that resulted in ethanol intakes significantly greater than levels seen in experimentally naïve rats of these same lines. For instance, when employing an alcohol deprivation effect protocol, Wistar rats can consume close to 4.5 g/kg/day of ethanol (Sinclair & Li, 1989). Other work has demonstrated that when giving Wistar and Long-Evans Hooded rats intermittent (Monday, Wednesday, and Friday) 24-h, free-choice access to 20% ethanol, these lines will consume ≥ 5 g/kg/day achieving 50 to 60 mg% BEC levels 45 min into the dark cycle (Simms et al., 2008). When given limited access, outbred rats rarely display ethanol intakes approaching 1 g/kg/h. However, experimental manipulations including fading or adaptation procedures (e.g., Czachowski, Santini, Legg, & Samson, 2002) have resulted in Wistar rats consuming greater than 1.5 g/kg/2-h (Bono, Balducci, Richelmi, Koob, & Pulvirenti, 1996) and Long-Evans Hooded rats consuming ~0.7 g/kg/20-min and achieving ~65 mg% BELs (Czachowski, Santini, Legg, & Samson, 2002). Interestingly, using the same procedures of Czachowski et al. (2002), Czachowski and Samson (2002) reported that P, HAD1, and HAD2 rats consume between 1 and 1.5 g/kg/20-min, with no significant line differences in intake.

Conclusion

In summary, these findings indicate that the selectively bred P, HAD1, and HAD2 rat lines display a pattern of higher ethanol intakes and bouts of drinking during the dark period of the light-dark cycle. Even under 24-h free-choice drinking conditions, these rat lines regularly consume sufficient amounts of ethanol to produce pharmacologically relevant BELs. Furthermore, under scheduled access (binge-like) conditions during the dark phase, P and HAD rats consistently drink enough ethanol to meet criteria for binge drinking, such as

BELs greater than 80 mg% and the expression of intoxication. In addition, these rat lines will continue to engage in binge-like drinking even when a highly palatable alternative solution is present. The scheduled-access procedure can also be used to study the co-abuse of ethanol and other addictive compounds. For instance, this procedure results in binge-like BELs concurrently with blood nicotine levels equivalent to those seen in chronic smokers. When the scheduled-access procedure is modified to include multiple access periods across the dark cycle and the concurrent presentation of multiple ethanol concentrations, BELs 2–3 times the binge criterion threshold can be achieved, suggesting the presence of loss-of-control drinking. To provide some context for these findings from the P and HAD replicate lines, a limited number of ethanol drinking studies using other lines of rats were also presented.

These studies, on rat lines besides the P and HAD replicate lines, indicate that selective breeding for alcohol-preference results in rat lines that readily consume ethanol to the point of intoxication. Selective breeding for other behavioral phenotypes may also result in appreciable levels of ethanol intake, but these intakes rarely result in BELs that meet the standard definition of binge-like drinking (i.e., ≥ 80 mg%). Similarly, inbred rat lines may display modest-to-high (~4 g/kg/day) levels of ethanol intake but, once again, these intakes seldom result in BELs ascribed to binge-like drinking. Finally, without experimental manipulations, outbred rats rarely display ethanol intakes that approach half (i.e., 2.5 g/kg/day) of the ethanol intake criterion used to selectively breed for an alcohol preference. However, this review highlighted some experimental manipulations (e.g., access during the dark phase, intermittent access, multiple-scheduled-access) that will significantly increase ethanol consumption by all of these selectively bred, inbred, and outbred rat lines. Moreover, these experimental procedures can be successfully conducted in water-satiated rats providing multiple genetic platforms to examine the neurobiology and pharmacology of alcohol dependence.

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Table 1

Estimated parallel ages* between the rat, associated developmental stage, and the human equivalent (Adapted from Bell et al., 2013)

Rat Ages [Post-Natal Days (PNDs)]								
PNDs 1–7	**PNDs 8–21**	**PND 21**	**PNDs 22–27**	**PNDs 28–42**	**PNDs 43–60**	**PNDs 61–75**	**PNDs 76–90**	**PNDs 90–**
Male 6–15 g	16–40 g	40 g	40–70 g	70–155 g	155–260 g	260–335 g	335–390 g	390–
Female 6–15 g	16–38 g	38 g	38–65 g	65–130 g	130–180 g	180–210 g	210–250 g	250–
Human Ages								
Neonate	**Prejuvenile**	**Weaning**	**Juvenile**	**Adolescent**	**Peri-Adolescent**	**Early Young Adult**	**Young Adult**	**Adult**
−3 to 0 Months	0–6 Years	6 Years	7–12 Years	13–18 Years	18–21 Years	21–24 Years	25–28 Years	28 Years–

*Because most rat studies do not list age but many do provide body weights, estimated rat body weights (average estimates for Wistar, Long-Evans Hooded and Sprague-Dawley rats) are included here.

Table 2

Ethanol intakes of adult and peri-adolescent P, HAD1, and HAD2 rats under 24-h free-choice access conditions

Conditions	Ethanol Intakes and Blood Ethanol Levels (BELs)	Reference
Adult male P rats; 10% ethanol vs. water; monitored pattern of ethanol intake	~7 g ethanol/kg/day; multiple bout drinking of 1–1.5 g/h; ~70% ethanol intake in dark phase; BELs averaged 45–90 mg% during dark phase	Murphy et al., 1986
Adult male P rats; 24-h operant with escalating 2% to 30%; ethanol (FR5) vs. water	Greatest intake at 15%, ~8 g/kg/day; average intake ~6 g/kg/day	Murphy et al., 1989
Adult male P rats; male HAD1 rats; male HAD2 rats; 10% ethanol vs. water	~6 g/kg/day for P and HAD1 rats; ~5 g/kg/day for HAD2 rats	Samson et al., 1998
Adult male P rats; male HAD1 rats; male HAD2 rats; 24-h 2-lever operant; 10% ethanol (FR1) vs. water (FR1)	~3.5 g/kg/day for P rats; ~4.5 g/kg/day for HAD1 rats; ~6.5 g/kg/day for HAD2 rats; ~11 ethanol bouts/day for HAD1 rats; ~16 ethanol bouts/day for P rats; ~22 ethanol bouts/day for HAD2 rats	Files et al., 1998
Male & female peri-adolescent P rats; 15% ethanol vs. water; concurrent 10, 20, & 30% ethanol vs. water	With single ethanol concentration ~6 g/kg/day; with multiple ethanol concentrations ~10 g/kg/day	Bell et al., 2003
Male & female peri-adolescent HAD1 & HAD2 rats; 15% ethanol vs. water; concurrent 10, 20, & 30% ethanol vs. water	With single ethanol concentration ~5 g/kg/day; with multiple ethanol concentrations ~7 g/kg/day; no significant sex or line differences	Bell et al., 2004
Male & female adult & peri- adolescent P rats; 15% ethanol vs. water; monitored pattern of drinking	Adult & peri-adolescent intakes 6–8 g/kg/day; majority occurred during dark phase; BELs at end of dark phase were 40–60 mg%	Bell et al., 2006b
Adult male P rats; 20% ethanol vs. water; intermittent access (MWF)	Peak at ~6.5 g/kg/day; ~40 mg% at 45 min into dark phase	Simms et al., 2008
Male & female adult & peri- adolescent HAD1 & HAD2 rats; 15% ethanol vs. water; monitored pattern of drinking	Adult & peri-adolescent HAD1 intakes 6–8 g/kg/day; HAD2 intakes ~6 g/kg/day except for male adolescent HAD2 intakes ~9 g/kg/day; most ethanol drinking occurred during the dark phase	Dhaher et al., 2012

Table 3

Ethanol intakes of adult P, HAD1 and HAD2 rats under scheduled access conditions

Conditions	Ethanol intakes and BELs	Reference
Adult male P rats; 4h access; dark phase; 10% ethanol vs. water; time-course BELs	~2 g/kg/session with most consumed within first 15-min; BELs peaked at ~120 mg % 1h into the session	Murphy et al., 1986
Adult male P & HAD rats; 4h access; dark phase; 10% ethanol vs. 0.0125% saccharin	~2 g/kg/session for P rats & ~3 g/kg/session for HAD rats; major bout of ethanol drinking for both lines occurred within first 15-min; majority of saccharin intake occurred after 1st h	Russell et al., 1996
Adult female P rats; 4h access; dark phase; 10% ethanol vs. water	2–3 g/kg/session	McKinzie et al., 1998a
Adult male P rats; 4h access; dark phase; 2-lever operant; 15% ethanol (FR5) vs. water (FR1)	~2 g/kg/session most consumed in 1st 30-min	McKinzie et al., 1998b
Adult male P rats; male HAD1 rats; male HAD2 rats; 30-min access; 2-lever operant; 10% ethanol (FR1) vs. water (FR1)	~0.25 g/kg/30-min for P rats; ~0.65 g/kg/30-min for HAD1 rats; ~0.25 g/kg/30-min for HAD2 rats	Files et al., 1998
Adult female P rats; 2h access; dark phase; 10% ethanol vs. water; 2h operant, 10% ethanol (FR1) & 0.0125% saccharin (FR1)	~2 g/kg/session most consumed in 1st 15-min; ~17 ml saccharin/session most consumed after 30-min; ~120 ethanol responses/session most in 1st 20-min; ~110 saccharin responses/session most in 1st 40-min	Nowak et al., 1999
Adult male P, adult male HAD1, adult male HAD2; 20-min appetitive & 20-min consummatory sessions; 10% ethanol; light phase	1 to 1.5 g/kg/20-min with no line differences in intake	Czachowski & Samson, 2002
Adult male P rats; 1h access; dark phase; 2-lever operant; 15% ethanol (FR5) vs. water (FR1)	~1.3 g/kg/session	Rodd et al., 2003
Adult male HAD1 & HAD2 rats; 1h access; dark phase; 2-lever operant; 15% ethanol (FR5) vs. water (FR1)	HAD1 intakes ~1.2 g/kg/session; HAD2 intakes ~1.6 g/kg/session	Oster et al., 2006
Adult male P rats; 1h access; dark phase; 2-lever operant; 15% ethanol (FR5) vs. 0.0125% saccharin (FR1)	~1.2 to 1.4 g/kg/session; ~300 ethanol responses/session; ~20 saccharin responses/session	Toalston et al., 2008
Adult female P rats; 1h access; dark phase; 3-lever operant; concurrent 10, 20 & 30% ethanol each containing 0.14 mg/ml nicotine (FR5) with water freely available	~2 g/kg/session & 2 mg nicotine/kg/session; ~80 mg% BELs & ~50 ng/ml blood nicotine levels	Hauser et al., 2012

Table 4

Ethanol intakes and BELs of P rats under multiple scheduled access conditions

Conditions	Ethanol intakes and BELs	Reference
Adult male P rats; 4 × 1-h access across dark phase; 1 × 4-h access during early dark phase; 10% ethanol vs. water	~1 g/kg/1-h session; average BELs ~40 to 80 mg% (range 0 to 152 mg%) at the end of each session; ~2 g/kg/4-h session most of it in the 1st 15 min; average BEL at 1 h ~120 mg% (range 42 to 178 mg%) at 3.5 h ~50 mg%	Murphy et al., 1986
Adult male P rats; 3 × 1-h access across dark phase; concurrent 15 & 30% ethanol vs. water	~2 g/kg/session; BELs ~80 mg%	Bell et al., 2006a
Male & female adult & peri- adolescent P rats; 3 × 1-h access across dark phase; concurrent 15 & 30% ethanol vs. water	Peri-adolescent female intakes ~10 g/kg/d, adult female intakes ~7 g/kg/d, adolescent male intakes ~6 g/kg/d, and adult male intakes ~5 g/kg/d; adolescent male BEL levels ~60 mg% at 15 min, ~100 mg% at 30 min, ~80 mg% at 45 min and ~100 mg% at 60 min; adult female BEL ~75 mg% at 60 min; peri-adolescent female BEL ~90 mg% at 30 min	Bell et al., 2011
Adult female P rats; 4 × 1-h access across dark phase; 3-lever operant; concurrent 10, 20, & 30% ethanol (FR5) with *ad libitum* water	Ethanol intakes were 1.2–1.7 g/kg/session; BELs ~125 mg% after 1st session; ~175 mg% after 2nd session; ~130 mg% before 3rd session; ~235 mg% after 4th session	McBride et al., 2013a

Table 5

Ethanol intakes of other adult and peri-adolescent rats under 24-h free-choice access conditions

Conditions	Ethanol Intakes and Blood Ethanol Levels (BELs)	Reference
Adult male ALKO Alcohol- Accepting (AA) rats; 10% ethanol vs. water; daily drinking patterns	~5.3 g/kg/day; periodic binges primarily during the dark phase; peak BEL ~25 mg%	Aalto, 1986
Adult male AA rats; 24-h operant; 10% ethanol *ad libitum* water and food	~5 g/kg/day	Hyytiä & Sinclair, 1989
Adult male AA rats; 10% ethanol vs. water	~7 g/kg/day to ~7 g/kg/day; testing for alcohol deprivation effect	Sinclair & Li, 1989
Adult male Sardinian alcohol- preferring (sP) rats; 10% ethanol vs. water	~7 g/kg/day to ~7 g/kg/day; 1st hr of re-exposure ~0.7 g/kg/h to ~1.1 g/kg/h; testing for alcohol deprivation effect	Agabio et al., 2000
Adult male and female sP rats; 10% ethanol vs. water	~6.5 g/kg/day; periodic binges primarily during the dark phase; peak BEL ~110 mg%	Colombo et al., 2006
Adult male sP rats; 10% or 20% ethanol vs. water; intermittent (MWF) access or continuous (7 days/week) access	~9 g/kg/day for 20% intermittent access; ~7.5 g/kg/day for 20% continuous access; ~7.5 g/kg/day for 10% intermittent access; ~6.5 g/kg/day for 10% continuous access	Loi et al., 2010
Adult female University of Chile B (UChB) alcohol- preferring rats, concurrent 10% and 20% ethanol vs. water	~7.3 g/kg/day to ~12 g/kg/day; testing for alcohol deprivation effect	Tampier & Quintanilla, 2011
Adult female Warsaw alcohol High-Preferring (WHP) rats; 10% ethanol vs. water	6–8 g/kg/day; ~80% ethanol preference; primarily during dark phase	Dyr & Kostowski, 2008; Zalewska- Kaszubska et al., 2008
Adult male and female High 'Addiction Research Foundation' (HARF) rats; 10% ethanol vs. water	~6.5 g/kg/day; ~75% ethanol preference	Lê et al., 2001
Adult male and female high ethanol-preferring (HEP) rats; 11% ethanol vs. water	~6 g/kg/day for females; ~5 g/kg/day for males	Myers et al., 1998
Adult Marchigian sP (msP) rats; 10% ethanol vs. water;	~7 g/kg/day; periodic binges primarily during the dark phase; 80% of ethanol consumed during dark phase, 1st bout within 1 h of dark onset; BELs ~75 mg% after a bout	Ciccocioppo et al., 2006
Adult Fawn Hooded (FH/Wjd) rats; 10% ethanol vs. water	~4 g/kg/day; ~90% ethanol preference	Overstreet et al., 2006
Adult male Fawn Hooded rats [Janvier (France)]; 10% ethanol vs. water	~4.1 g/kg/day considered high preferring; ~3.5 g/kg/day considered low preferring	Femenia et al., 2010
Adult male Maudsley Reactive (MR/Har) vs. Maudsley Nonreactive (MNRA/Har) rats; 10% ethanol vs. water	Before adaptation procedures, ~1.5 g/kg/day for MR/Har and ~1.7 g/kg/day for MNRA/Har; after adaptation procedures, ~3.8 g/kg/day for MR/Har and ~3.3 g/kg/day for MNRA/Har; ~60% ethanol preference for MR/Har and ~50% ethanol preference for MNRA/Har	Adams et al., 2002
Adult male and female Taste- Aversion-Resistant (TAR) rats; 10% ethanol vs. water	~5.5 g/kg/day	Orr et al., 2004
Adult male Wistar rats; 10% ethanol vs. water	~2.6 g/kg/day to ~4.4 g/kg/day; testing for alcohol deprivation effect	Sinclair & Li, 1989
Young adult male Lewis, Wistar and Wistar-Kyoto rats; 10% ethanol vs. water	~0.6 g/kg/day for Lewis rats; ~2.6 g/kg/day for Wistar rats; ~0.9 g/kg/day for Wistar-Kyoto rats	Goodwin et al., 2000
Adult male Wistar rats; 20% ethanol vs. water; intermittent access (MWF)	Peak at ~6 g/kg/day; ~60 mg% at 45 min into dark phase	Simms et al., 2008
Adult male Long-Evans rats; 20% ethanol vs. water; intermittent access (MWF)	Peak at ~5 g/kg/day; ~50% ethanol preference; ~60 mg% at 45 min into dark phase	Simms et al., 2008

Conditions	Ethanol Intakes and Blood Ethanol Levels (BELs)	Reference
Adult male Long-Evans rats; 20% ethanol vs. water; intermittent access (MWF)	~5 g/kg/day	Nielsen et al., 2012
Adult male Sprague-Dawley rats; 20% ethanol vs. water; intermittent access (MWF)	Peak at ~4.8 g/kg/day; ~50 mg% BEL at 30 min of access	Bito-Onon et al., 2011
Adult male Sprague-Dawley rats; 10% ethanol vs. water; continuous access	Peak at ~1.8 g/kg/day; ~25 mg% BEL at 30 min of access	Bito-Onon et al., 2011

Table 6

Ethanol intakes of other adult rats under scheduled access conditions

Conditions	Ethanol intakes and BELs	Reference
Adult male ALKO alcohol- accepting (AA) rats; 1 h or 4 h; light phase; 10% ethanol vs. water	~0.8 g/kg/1-h; ~1.3 g/kg/4-h	Ingman et al., 2003
Adult male AA rats; 90 min; dark phase; 10% ethanol vs. water	~0.65 g/kg/90 min	Landgren et al., 2011a, b
Adult male Sardinian alcohol- preferring (sP) rats; 15 min/day; dark-phase; 10% ethanol vs. water	1.2 g/kg/15-min; ~96% ethanol preference; ~45 mg% BEL	Colombo et al., 1998
Adult male AA, P and sP rats; 30-min operant; dark phase; 15% ethanol vs. water	~0.8 g/kg/30-min session for AA rats; ~1.3 g/kg/30-min session for P rats; ~1.0 g/kg/30-min session for sP rats; operant self-administration followed a 10-day 24-h free- choice adaptation phase	Maccioni et al., 2012
Adult male Warsaw alcohol High- Preferring (WHP) rats; 4 day access; dark phase; 10% ethanol vs. water	~4 g/kg/4h; ~1 g/kg/each hour of access	Dyr & Kostowski, 2008
Adult male and female High 'Addiction Research Foundation' (HARF) rats; 20 min/day access; light phase; 12% ethanol vs. water	~1.4 g/kg/20-min for females; ~1 g/kg/20-min for males; ethanol intake took place in test cages	Lê et al., 2001
Adult male and female high ethanol-preferring (HEP) rats; 2 h/day access; dark phase; ~15% ethanol vs. water; restricted access	~2.7 g/kg/2-h for females; ~1.7 g/kg/2-h for males; ethanol concentration determined by individual rat preference; ~90 mg% BEL for females; ~85 mg% BEL for males	Myers et al., 1998
Adult male and female HEP rats; 2 h/day access; dark phase; 10% ethanol vs. water; restricted access	~3.5 g/kg/2-h for female rats; ~2.8 g/kg/2-h for male rats; most ethanol consumed during the 1st 15 min	West et al., 1998, 1999
Adult male and female Cologne ALKO alcohol-accepting (cAA) rats; 12h/day; 10% ethanol vs. water; restricted access	~6.5 g/kg/12-h; ~80% ethanol preference	Maurel et al., 1999
Adult Marchigian sP (msP) rats; 2 h/day; beginning of dark phase; 10% ethanol vs. water	~1 g/kg/2-h	Ciccocioppo et al., 2007
Adult male Maudsley Reactive (MR/Har) vs. Maudsley Nonreactive (MNRA/Har) rats; 30-min operant; light phase; 10% ethanol	At FR1, ~0.4 g/kg/30-min for MNRA and ~0.2 g/kg/30-min for MR; at FR2, ~3.5 g/kg/30-min for MNRA and ~0.1 g/kg/30-min for MR; at FR4, ~0.15 g/kg/30-min for MNRA and ~0 g/kg/30-min for MR	Adams et al., 2002
Adult male and female Taste- Aversion-Prone (TAP) and TA- Resistant (TAR) rats; 2 h/day; 10% ethanol vs. water	~0.5 g/kg/2-h and ~1 mg% at the end of the session for TAP rats; ~2.0 g/kg/2-h and ~16 mg% at the end of the session for TAR rats	Orr et al., 2004
Adult male Wistar rats; 2 h/day; light phase; 10% ethanol vs. water	~1.7 g/kg/2-h; following fading procedures in conjunction with fluid restriction	Bono et al., 1996
Adult male Wistar rats; dark phase; 6% ethanol vs. water; ethanol and water restricted	~1 g/kg/h; *Wistar rats were screened for preference greater than 50%*; revealed periodic bout-like drinking	Ericson et al., 1998
Adult male Wistar rats; dark phase; 6% ethanol vs. water; ethanol and water restricted	~0.7 g/kg/h	Stromberg et al., 2001
Adult male Wistar rats; 3h/day (MWF); last 3 h of light phase; 20% ethanol vs. water	6 weeks of intermittent (MWF) 24-h access to 20% ethanol vs. water; followed by 6 weeks of 3 h/day (MWF); ~1.5 g/kg/3-h; ~1.25 g/kg in 1st of 3 h; rats with continuous access to 20% ethanol vs. water drank ~0.5 g/kg/last 3 h of light phase	Hopf et al., 2011
Adult male Long-Evans Hooded rats; 20-min operant sipper-tube model; light-phase; 10% ethanol	~0.7 g/kg/20-min; ~65 mg% BEL; operant ethanol self- administration initiated by sucrose-fade procedures	Czachowski et al., 2002
Adult male Long-Evans Hooded rats; 30-min operant; light phase; 10% ethanol vs. water	0.5 to 0.6 g/kg/30-min	Janak & Gill, 2003

Conditions	Ethanol intakes and BELs	Reference
Adult male Long-Evans Hooded rats; 30-min operant access; light phase; 10% ethanol	~0.7 g/kg/30-min	Landgren et al., 2011a, 2011b
Adult male Sprague-Dawley rats; 3 h/day; dark phase; 10% ethanol vs. water	~2 g/kg/3-h	Mhatre & Holloway, 2003
Adult male Sprague-Dawley rats; 30-min operant access; dark phase; 20% ethanol	Previously had 8 weeks of intermittent (MWF) 24-h access to 20% ethanol vs. water; ~1 g/kg/30-min session; ~20 mg% BEL	Bito-Onon et al., 2011
Adult male Sprague-Dawley rats; 30-min operant access; dark phase; 10% ethanol	Previously had 8 weeks of continuous 24-h access to 10% ethanol vs. water; ~0.4 g/kg/30-min session; ~7 mg% BEL	Bito-Onon et al., 2011