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The alcohol-preferring (P) and high-alcohol-drinking (HAD) rats – Animal Models of Alcoholism

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Abstract

The objective of this article is to review the literature on the utility of using the selectively bred alcohol-preferring (P) and high-alcohol-drinking (HAD) lines of rats in studies examining high alcohol drinking in adults and adolescents, craving-like behavior, and the co-abuse of alcohol with other drugs. The P line of rats meets all of the originally proposed criteria for a suitable animal model of alcoholism. In addition, the P rat exhibits high alcohol-seeking behavior, demonstrates an alcohol deprivation effect (ADE) under relapse drinking conditions, consumes amounts of ethanol during adolescence equivalent to those consumed in adulthood, and co-abuses ethanol and nicotine. The P line also exhibits excessive binge-like alcohol drinking, attaining blood alcohol concentrations (BACs) of 200 mg% on a daily basis. The HAD replicate lines of rats have not been as extensively studied as the P rats. The HAD1,2 rats satisfy several of the criteria for an animal model of alcoholism, e.g., these rats will voluntarily consume ethanol in a free-choice situation to produce BACs between 50–200 mg%. The HAD1,2 rats also exhibit an ADE under repeated relapse conditions, and will demonstrate similar levels of ethanol intake during adolescence as seen in adults. Overall, the P and HAD1,2 rats have characteristics attributed to an early onset alcoholic, and can be used to study various aspects of alcohol use disorders.

Keywords

alcohol-preferring (P) rat; high-alcohol-drinking (HAD) rat; animal model of alcoholism; binge drinking; alcohol-seeking behavior

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Introduction

Animal models are very valuable tools for examining normal and abnormal functions of the brain and behavior. Animal models are useful when they reveal some aspect of a complex human condition. The development of an animal model of alcoholism has been difficult because common stock animals do not usually voluntarily consume alcohol under free-choice conditions without experimental manipulations. However, rodents exhibit a wide range of alcohol-drinking preferences (Richter & Campbell, 1940), and this behavior can be genetically influenced (McClearn & Rodgers, 1959). Through selective breeding, several high and low alcohol-consuming rat lines have been developed (Eriksson, 1969; Fadda, Mosca, Colombo, & Gessa, 1989; Mardones & Segovia-Riquelme, 1983), including the alcohol-preferring (P) and high-alcohol-drinking (HAD) lines of rats (Li, Lumeng, & Doolittle, 1993; Li, Lumeng, Doolittle, & Carr, 1991; Li, Lumeng, McBride, & Waller, 1981; Lumeng, Hawkins, & Li, 1977). These lines were developed from different foundation stocks; they exhibit certain similar phenotypes (e.g., high ethanol intakes) and some behavioral and neurobiological differences (reviewed in McBride & Li, 1998; Murphy et al., 2002).

The P and HAD lines of rats have been selected on the basis of their daily free-choice intake of a 10% ethanol solution vs. water, with food always available, and on their preference for the alcohol solution over water. The use of both criteria helps to eliminate rats with high fluid intake. The P and HAD lines were selected on the basis of minimum daily ethanol intakes of 5 g/kg, and a preference ratio of 2:1 of 10% ethanol: water in volume of intake. Ideally, it would be important to also include a 3rd criterion of ethanol intakes producing pharmacologically meaningful blood alcohol concentrations (BACs), i.e., 50 mg% and higher.

BACs are related to the amount and pattern of ethanol intake. Under the 24-h free-choice conditions (10% ethanol vs. water) used for selection, the P rat consumed approximately 70% of its total ethanol intake during the dark cycle (Murphy et al., 1986). The P rats appeared to drink in discrete bouts (average intake of 1.3 ± 0.1 g/kg/episode during dark phase); retro-orbital samples taken at set times in the dark phase (1, 3, 6, and 12 h after lights were turned off) indicated BACs had an average range from 40 to 90 mg% (Murphy et al., 1986). With 4-h scheduled access (10% ethanol vs. water) starting at onset of the dark phase, P rats consumed 2.1 ± 0.2 g/kg/4 h, with ethanol intakes occurring almost exclusively within the first 15 min; BACs peaked at approximately 120 mg% (Murphy et al., 1986). When P rats were given access to 10% ethanol vs. water for four 1-h ethanol access periods across the 12-h dark cycle, ethanol intakes averaged approximately 1 g/kg for each access period; peak BACs at the end of an access period were approximately 75 mg% (Murphy et al., 1986). Overall, these results indicate that the selection process for the P rats also produced animals that drink sufficient ethanol to attain pharmacologically significant BACs. In fact, this early study indicated that binge levels of ethanol intake could be achieved with scheduled access to ethanol during the dark phase.

Subsequent studies indicated that the availability of higher concentrations of ethanol (10 vs. 15%) and the availability of multiple concentrations (15% vs. 10, 20, and 30%) resulted in

higher ethanol intakes and BACs (McBride et al., 2013; Rodd-Henricks et al., 2001). Under certain drinking conditions, BACs exceeding 150 mg% and reaching 200 mg% can be attained by P rats (McBride et al., 2013; Rodd-Henricks et al., 2001); these BACs readily produce motor impairment and sedation (Lumeng, Waller, McBride, & Li, 1982). Ethanol intakes that produce BACs approaching 200 mg% have been termed ‘loss-of-control’ drinking (McBride et al., 2013).

Even though the P and HAD lines meet the selection criteria, it is important to establish these lines as suitable animal models to provide a better understanding of the neurobiological bases underlying alcohol use disorders (AUDs). The closer the animal model is to the human condition, the greater is the potential for understanding the biology of the condition. However, it is only possible for an animal to exhibit certain characteristics of the broad spectrum of features associated with the human alcoholic conditions.

Criteria for an animal model of alcoholism

The criteria of an animal model of alcoholism have been proposed (Cicero, 1979; Lester & Freed, 1973). These criteria were proposed for application to animal studies and were not proposed to address diagnostic criteria. The proposed criteria were designed to indicate the main features that could be applied to animals that would address many of the features applied to humans, except those features that are unique to humans. The original 6 criteria are summarized in Table 1 along with studies with the P and HAD rats that attempted to satisfy these criteria. The animal should orally self-administer alcohol under free-choice conditions, and the amount of alcohol ingested should produce pharmacologically relevant BACs. If social drinking is being studied, then BACs well below 50 mg% and closer to 10 mg% would be adequate. However, alcoholics are likely to consume amounts of alcohol sufficient to approach or exceed intoxicating BAC levels, which would be greater than 50 mg%. In the case of binge drinking, BACs would have to reach 80 mg%, according to the National Institute on Alcohol Abuse and Alcoholism (NIAAA) standards (2004).

The general effects of alcohol in rodents are similar to the general effects in humans. Low blood concentrations (10–25 mg%) are stimulating, concentrations of 50–100 mg% produce motor impairing effects, concentrations of 150–200 mg% are sedative, and concentrations in the range of 300–400 mg% can be toxic. Under 24-h free-choice conditions, the P rat will voluntarily consume 5–8 g/kg/day and produce BACs in the range of 50–200 mg% (Li, Lumeng, McBride, & Waller, 1979; Lumeng & Li, 1986; Murphy et al., 1986). Under scheduled access conditions, P and HAD rats will consume 2–3 g/kg ethanol within a 1- or 2-h session to produce BACs that reach 80–100 mg% on a daily basis (Bell, Rodd, Lumeng, Murphy, & McBride, 2006; Murphy et al., 1986; Oster et al., 2006; Rodd et al., 2003).

Additional criteria are a) alcohol should produce positive reinforcing effects, and b) the animals should be consuming the alcohol for its pharmacological effects and not solely for its caloric value, taste, or smell. Also, the animals should be willing to work to obtain the alcohol. Several studies demonstrated that P rats will operant respond even with high workload (fixed-ratio) requirements (Ciccioppo, Angeletti, & Weiss, 2001; Czachowski & Samson, 2002; Files, Samson, Denning, & Marvin, 1998; Murphy, Gatto, McBride,

Lumeng, & Li, 1989; Rodd et al., 2003; Samson, Files, Denning, & Marvin, 1998), achieving estimated BACs in excess of 80 mg% (Rodd et al., 2003). Moreover, recently it has been demonstrated that P rats will exhibit 'loss-of-control' binge-like alcohol drinking and attain BACs of 200 mg% on a daily basis (McBride et al., 2013).

P rats consume alcohol for its pharmacological effects and not solely for its caloric value, taste, or smell, as indicated by the findings that P and non-preferring (NP) rats react to the taste and smell of ethanol similarly (Bice & Kiefer, 1990); the P rat will self-administer high quantities of ethanol intra-gastrically (Murphy et al., 1988; Waller, McBride, Gatto, Lumeng, & Li, 1984), and will continue to consume high amounts of alcohol in the presence of other highly palatable solutions and caloric sources (Lankford, Roscoe, Pennington, & Myers, 1991; Lumeng, Hawkins, & Li, 1977; Nowak, McKinzie, McBride, & Murphy, 1999; Russell, McBride, Lumeng, Li, & Murphy, 1996; Toalston et al., 2008). In these latter cases, the ethanol and sweet solutions are concurrently available and the rat has free-choice between the two solutions. In the case of intra-gastric self-administration, BACs of 115–300 mg% were readily reached (Waller, McBride, Gatto, Lumeng, & Li, 1984).

Other criteria that are needed to establish an animal model of alcoholism are that both metabolic and functional tolerance should develop after a period of free-choice alcohol consumption. The P rat has been shown to develop metabolic tolerance (Lumeng & Li, 1986) following chronic free-choice drinking. Tolerance to the motor-impairing (Gatto et al., 1987) and aversive (Stewart, McBride, Lumeng, Li, & Murphy, 1991) effects of alcohol following chronic free-choice drinking demonstrated the development of functional tolerance.

A final criterion (Cicero, 1979; Lester & Freed, 1973) to satisfy is that physical signs of dependence should develop when alcohol is withdrawn after a period of chronic consumption. The P rat developed dependence following chronic free-choice drinking as indicated by physical signs of withdrawal when ethanol was removed (Kampov-Polevoy, Matthews, Gause, Morrow, & Overstreet, 2000; Waller, McBride, Lumeng, & Li, 1982).

Thus, the P rat satisfies all the original criteria (Table 1) proposed for a suitable animal model of alcoholism. Although not studied as extensively as the P rat, the HAD replicate lines of rats satisfy several of the criteria for an animal model of alcoholism (Table 1). The P and HAD rats are good animal models for studying a) genetic factors that contribute to vulnerability to high alcohol drinking behavior, b) mechanisms underlying the CNS rewarding effects of ethanol and mediating high alcohol-drinking behavior, c) long-range consequences of alcohol drinking, and d) factors contributing to the development of excessive (dangerous) levels of alcohol intake.

Other important characteristics of an animal model of alcoholism

The original criteria proposed by Lester & Freed (1973) and Cicero (1979) for characterizing an animal model of alcoholism did not incorporate relapse drinking. Alcoholism is a chronically relapsing disorder. Repeated episodes of relapse drinking are common among alcoholics (Lim & Keefe, 2004; Malcolm, Herron, Anton, Roberts, & Moore, 2000a; Malcolm, Roberts, Wang, Myrick, & Anton, 2000b; McKay, Franklin,

Patapis, & Lynch, 2006). Therefore, another criterion (proposed by McBride & Li, 1998) should be that the animal model readily demonstrates relapse drinking after a prolonged period of abstinence.

Relapse drinking

Relapse drinking is defined as a return to a high level of intake that is equal to or greater than the amount of ethanol intake prior to the period of abstinence, and produces pharmacologically relevant BACs. Both the P and HAD rats demonstrate relapse drinking under both free-choice drinking and operant conditions; moreover, these lines have significantly higher ethanol intakes following a prolonged period of abstinence (at least 2 weeks), which progressively increases with repeated cycles of drinking and abstinence (Oster et al., 2006; Rodd et al., 2003; Rodd-Henricks et al., 2000a, b). The temporary increase in the intake of ethanol over baseline conditions when ethanol is reinstated after a prolonged abstinence period is termed the Alcohol Deprivation Effect (ADE).

The ADE phenomenon has been observed in the P rat under a variety of experimental designs (McKinzie et al., 1998; Rodd-Henricks et al., 2000b; Sinclair & Li, 1989). Furthermore, with concurrent availability of 10, 20, and 30% ethanol under 24-h free-choice drinking conditions, following either a 2- or 8-week abstinence period, P rats will increase their intakes from ~6 g/kg/day to ~11 g/kg/day (Rodd-Henricks et al., 2001). More importantly, during the first 2 h of access, the P rats consume ~4 g/kg ethanol. With repeated deprivations, the 24-h intakes reached ~16 g/kg/day with ~6 g/kg consumed in the first 2 h. Trunk blood BACs ranged from 160 to 205 mg% when measured 3 h into the dark cycle after the ethanol solutions were returned (Rodd-Henricks et al., 2001).

P rats also demonstrate an ADE under operant conditions (conducted during the dark phase) with only a single ethanol concentration (15%) vs. water (Rodd et al., 2003). P rats showed an ADE following a 2- or 5-week abstinence period. Estimated intakes during the 1-h operant session increased from ~1.3 g/kg at baseline (before deprivation) to ~3.8 g/kg when access to ethanol was returned following a 3rd prolonged deprivation period; this relapse level of intake would produce BACs exceeding 150 mg%.

The HAD replicate lines demonstrate an ADE under 24-h free-choice (Rodd-Henricks et al., 2000a), but only after a 2nd deprivation. Similarly, with an abbreviated relapse protocol, HAD rats from both replicate lines displayed an ADE, achieving BACs of 70–100 mg% (Bell et al., 2008). Under operant conditions (1-h sessions with 15% ethanol vs. water) during the dark cycle, HAD rats showed a reliable ADE after the 3rd deprivation (Oster et al., 2006). The estimated ethanol intakes (3.0–3.5 g/kg/session) on the 1st reacquisition day would be sufficient to produce BACs over 150 mg%. Overall, the P and HAD rats appear to be excellent animal models for studying relapse under binge drinking conditions.

Alcohol-seeking behavior

Craving, or a strong desire to use alcohol, is one of the DSM-V criteria for diagnosing AUDs (Table 2). Many individuals who are dependent on alcohol experience craving (De Bruijn, Korxec, Koerselman, & van Den Brink, 2004). A recent study suggested that alcohol craving may be a predictor of relapse (Schneekloth et al., 2012). Because of the subjective

measure of craving, it is difficult to assess and quantify in humans. The expression of an ADE and/or ethanol-seeking behavior may be animal measures of 'craving-like' behavior. The P and HAD1,2 rats express a robust ADE following prolonged abstinence (Oster et al., 2006; Rodd et al., 2003; Rodd-Henricks et al., 2000a, 2001). Similarly, P rats express robust ethanol-seeking behavior after a prolonged alcohol-free period following extinction training (Hauser et al., 2011, 2012a; Rodd et al., 2006; Rodd-Henricks et al., 2002a, b).

Drug-seeking behavior can be induced by distinct cues associated with drug self-administration, priming with low doses of the drug, and stress (e.g., foot shocks). Most studies to date use these experimental approaches to study drug reinstatement responding, including alcohol (reviewed in Rodd, Bell, Sable, Murphy, & McBride, 2004b). The Pavlovian Spontaneous Recovery (PSR) procedure has been employed to study alcohol-seeking behavior (Rodd et al., 2006; Rodd-Henricks et al., 2002a, b). The PSR procedure tests the responses on the ethanol lever vs. the water lever in the absence of any reinforcer. In this procedure, the P rat first undergoes 6–8 weeks of daily operant ethanol self-administration, followed by 7–9 extinction sessions (1-h operant sessions without any fluids present). After the extinction sessions, the P rats are placed in their home cages for 2–8 weeks without ethanol or any additional operant experience. Without any priming doses, discrete cues (other than the contextual cues of the operant chamber), or stress, the animals are returned to the operant chamber without ethanol or water present and allowed to respond. Under these conditions, the P rats spontaneously respond on the ethanol lever several-fold higher than on the water lever (Rodd et al., 2006; Rodd-Henricks et al., 2002a, b). This procedure parallels the human alcoholic who goes through detoxification and is alcohol-free for a prolonged period.

Adolescent alcohol drinking

Alcohol use often begins in the second decade of life, with the first use of alcohol typically occurring in early adolescence (13–14 years of age; Faden, 2006). Results from the National Longitudinal Alcohol Epidemiological Survey indicated that individuals initiating alcohol use before 14 years old had a 4-fold higher rate of lifetime alcohol dependence than individuals that initiated use after the age of 20 (Grant & Dawson, 1997). The importance of the first episode of alcohol intoxication occurring during the mid-teens is included in the DSM-V section on addictive behaviors (Table 3). Therefore, another important feature to be considered in an animal model is that significant ethanol intakes producing pharmacologically relevant BACs are demonstrated under free-choice conditions during adolescence. The adolescent window in rats is narrow (28–42 days of age) and does not allow sufficient time for inducing non-selectively bred rats to voluntarily consume alcohol to produce significant BACs. Both the P (Bell, Rodd, Lumeng, Murphy, & McBride, 2006; Bell et al., 2003; McBride et al., 2005) and HAD replicate (Bell et al., 2004) rats fit the criteria proposed by Cloninger (1987) for the early onset alcoholic, i.e., the selectively bred rats exhibit high alcohol drinking behavior during adolescence that is similar to adult ethanol intakes (Bell et al., 2011). These findings are important since it is possible to use these lines of rats to study mechanisms underlying the development of adolescent alcohol drinking, and, as well, to study the long-range consequences of adolescent alcohol drinking.

The utility of P and HAD rats for studying co-abuse of alcohol with other drugs

Good animal models of high alcohol drinking behavior offer excellent experimental approaches toward studying mechanisms underlying the co-abuse of alcohol with other drugs. Whereas common stock strains of rats will self-administer most drugs of abuse, e.g., cocaine, these stock rats will not usually drink sufficient alcohol to attain abuse levels, i.e., intoxication.

Alcohol and nicotine are the two most frequently used drugs in the world and are often used together (Kandel, Chen, Warner, Kessler, & Grant, 1997). In individuals diagnosed with alcohol dependency, the rate of smoking is estimated to be between 80 and 97% (Gulliver et al., 1995; Hughes, 1995, 1996; Hurt et al., 1994; John, Hill, Rumpf, Hapke, & Meyer, 2003a; John et al., 2003b). Epidemiological studies of U.S. populations indicate that, for individuals with cannabis use disorders, there is a 45–80% lifetime prevalence of developing a co-morbid alcohol use disorder (Agosti, Nunes, & Levin, 2002; Regier et al., 1990; Stinson, Ruan, Pickering, & Grant, 2006). Cocaine is another drug that is often co-abused with alcohol. A majority of individuals dependent on cocaine can also be diagnosed as alcohol dependent (Carroll, Rounsaville, & Bryant, 1993; Miller, Millman, & Keskinen, 1989). Alcoholics are more likely to use cocaine, and cocaine use can increase alcohol consumption (Heil, Badger, & Higgins, 2001; Staines, Magura, Foote, Deluca, & Kosanke, 2001). Therefore, there is an important need to understand the brain mechanisms contributing to the co-abuse of alcohol with other drugs of abuse.

Despite the high importance of studying the co-abuse of alcohol with other drugs of abuse, there have been relatively few animal models developed to address this issue. Lê et al. (2010) used male Wistar rats and developed an operant procedure for intravenous (i.v.) nicotine and oral ethanol self-administration in the same session. Hauser et al. (2012b) developed an oral operant co-abuse model for concurrent ethanol and nicotine self-administration by P rats. With the latter procedure, P rats reached BACs that were at binge drinking levels (100 mg%) and also produced blood nicotine levels (25 ng/mL) that were comparable to human nicotine levels attained following smoking.

Another reason for using the selectively bred P rat to study the use and co-use of drugs of abuse is that selective breeding for high alcohol consumption also appears to be associated with increased sensitivity to the reinforcing effects of various drugs of abuse. Compared to alcohol-non-preferring (NP) rats, the P rat appears to be more sensitive to the i.v. self-administration of nicotine (Lê et al., 2006). In support of this conclusion, a more recent study (Hauser et al., 2013) indicated that the P rats were more sensitive than Wistar rats to the reinforcing effects of nicotine in the posterior VTA. Another study (Katner et al., 2011) indicated that P rats were more sensitive than Wistar rats to the reinforcing effects of cocaine in the nucleus accumbens shell. These results with nicotine and cocaine are consistent with previous studies indicating that the pVTA (Gatto, McBride, Murphy, Lumeng, & Li, 1994; Rodd et al., 2004a) and nucleus accumbens shell (Engleman et al., 2009) of P rats are more sensitive than Wistar or NP rats to the reinforcing effects of ethanol. Moreover, chronic alcohol drinking by P rats increases the sensitivity of the posterior VTA to the reinforcing effects of ethanol (Rodd et al., 2005a, b). Overall, these studies support the idea that there is an association between selective breeding for high

alcohol drinking behavior and sensitivity to the reinforcing effects of nicotine and cocaine, as well as ethanol, and that chronic drinking can increase the CNS rewarding effects of ethanol. Thus far, sensitivity to the rewarding effects of other drugs of abuse has not been tested in the P rat.

Conclusions

The characteristics of P and HAD rats make these animals very useful for studying the many complex mechanisms involved with regulating high alcohol drinking behavior and the development of alcohol addiction and AUDs. Table 1 lists the original critical criteria proposed to establish a suitable animal model to study alcoholism. These criteria focused on making a strong animal model and did not include criteria that were unique to humans (Table 2). The P rat satisfies all of the original criteria and the HAD1,2 rat satisfies 4 of the 6 original criteria. The development of tolerance and physical signs of withdrawal following chronic drinking were not examined in the HAD1,2 rats. Most of the diagnostic criteria stated in DSM-IV for evaluating AUDs are also stated in DSM-V. Table 2 compares the characteristics of P and HAD1,2 rats with some of the diagnostic criteria given in DSM-IV and DSM-V. The P rat (and to some degree the HAD1,2 rat) expresses characteristics that could satisfy diagnostic criteria for defining an individual with an AUD. Table 3 summarizes some additional important features of AUDs that also can be studied with the P and HAD1,2 rats. The P and HAD rats are excellent animal models for studying brain mechanisms involved in the voluntary intake of alcohol under 24-h free-choice, oral scheduled access or operant limited-access conditions. Under the latter 2 conditions (conducted during the dark phase), these rats will consume sufficient ethanol to reach and exceed binge levels (80 mg%). The P rat spontaneously exhibits robust alcohol-seeking behavior without priming, discrete cues, or stress, after a period of prolonged abstinence. In addition, these rats can exhibit loss-of-control drinking (BACs of 200 mg%). Both P and HAD rats demonstrate a robust ADE under relapse conditions, and both exhibit early-onset alcoholic characteristics, in that, during adolescence, these lines have alcohol intakes that are comparable to adult levels. Finally, the P and HAD rats offer the potential of being useful animal models for studying the co-abuse of alcohol with other drugs.

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Table 1

Criteria proposed for a suitable animal model of alcoholism (Cicero, 1979; Lester & Freed, 1973) and characteristics demonstrated by P and HAD1,2 rats

Animal model criteria	Characteristics of the P and HAD1,2 rats
The animal should orally self-administer ethanol under free-choice conditions.	P and HAD1,2 rats voluntarily consume alcohol orally under free-choice conditions. Ethanol intakes of 5–8 g/kg/day are readily attained (reviewed in McBride & Li, 1998; Murphy et al., 2002).
Ethanol self-administration should lead to pharmacologically relevant BACs.	Highly relevant BACs of 50–200 mg% ethanol can be reached with voluntary ethanol drinking under 24-h or scheduled access conditions by P and HAD1,2 rats (reviewed in McBride & Li, 1998; Murphy et al., 2002).
Ethanol should be consumed primarily for its post-ingestive pharmacological effects and not solely for its caloric value, taste, or smell.	It has been shown that taste and smell reactivity is similar for P and NP rats (Bice & Kiefer, 1990). P rats will self-administer ethanol directly into the stomach to produce intoxicating BACs (Waller et al., 1984), and P and HAD1 rats will maintain high ethanol intakes even in the presence of highly palatable solutions (Lankford et al., 1991; Russell et al., 1996; Toalston et al., 2008).
Ethanol should be positively reinforcing, and the animals should work to obtain ethanol.	P and HAD1,2 rats will operant respond for ethanol in sufficient amounts to produce BACs that exceed 80 mg% (equivalent to human binge drinking) when food and water are available. P rats have a very high breakpoint for ethanol (Czachowski & Samson, 2002; Oster et al., 2006; Rodd et al., 2003).
Chronic ethanol consumption should lead to metabolic and functional tolerance.	P rats develop metabolic tolerance (Lumeng & Li, 1986), and functional tolerance to the motor impairing and aversive effects of ethanol (Gatto et al., 1987; Stewart et al., 1991) following chronic free-choice drinking.
Physical signs of withdrawal should develop following ethanol withdrawal after a period of chronic consumption.	P rats develop physical signs of dependence following withdrawal of ethanol after a prolonged period of chronic free-choice alcohol drinking (Kampov-Polevoy et al., 2000; Waller et al., 1982).

TABLE 2

DSM-IV & DSM-V criteria for alcohol use disorders and characteristics of these criteria exhibited by P and HAD1,2 rats

DSM-IV	Animal model	DSM-V
Need for markedly increased amounts of alcohol to achieve intoxication or desired effect	Chronic drinking by P rats produces tolerance to aversive effects and increases alcohol intake (Gatto et al., 1987; Stewart et al., 1991).	Need for markedly increased amounts of alcohol to achieve intoxication or desired effect
Alcohol is taken to relieve or avoid withdrawal symptoms.	Not tested in P or HAD rats, although P rats will readily drink to intoxication (BACs > 80–100 mg%) on a daily basis (McBride et al., 2013).	Alcohol is taken to relieve or avoid withdrawal symptoms.
Unsuccessful efforts to control alcohol use	P and HAD1,2 rats readily demonstrate an alcohol deprivation effect after a prolonged alcohol-free period and can attain BACs that approach 200 mg% (Oster et al., 2006; Rodd et al., 2003; Rodd-Henricks et al., 2000a, 2001).	Unsuccessful efforts to control alcohol use
Important social, occupational, or recreational activities affected because of alcohol abuse.	Unique to human condition	Important social, occupational, or recreational activities are given up or reduced because of alcohol use.
A great deal of time is spent in activities necessary to obtain alcohol or recover from its effects.	P rats will achieve binge levels of drinking (and higher) under conditions in which access to ethanol is scheduled for 3–4 1-h sessions each day (Bell et al., 2009, 2011; McBride et al., 2013).	A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.
Continued alcohol use despite knowledge of having a persistent problem that is likely to be a result of or exacerbated by alcohol drinking	Unique to human condition	Continued alcohol use despite knowledge of having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol
	P rats demonstrate robust alcohol-seeking behavior in the environment previously associated with ethanol self-administration after a prolonged ‘rest’ period which followed extinction training (Hauser et al., 2011, 2012a; Rodd et al., 2006; Rodd-Henricks et al., 2002a, b).	Craving, or a strong desire to use alcohol
	P rats develop physical signs of dependence in 8–24 h following withdrawal of ethanol after a prolonged period of chronic free-choice alcohol drinking (Kampov-Polevoy et al., 2000; Waller et al., 1982).	Physical signs of withdrawal that occur within several hours or a few days

Table 3

Additional features in DSM-V and characteristics of P and HAD1,2 rats

DSM-V Additional features	Characteristics of P and HAD1,2 rats
Use of heavy doses of alcohol with resulting repeated and significant distress or impaired function	P rats will consume high amounts of alcohol to produce BACs > 150 mg% and exhibit motor impairment and sedation (McBride et al., 2013; Rodd-Henricks et al., 2000a, 2001).
First episode of alcohol intoxication is likely to occur during mid-teens.	P and HAD1,2 rats demonstrate levels of alcohol drinking during adolescence that are comparable to adult intakes (Bell et al., 2003, 2004, 2006).
Not mentioned in DSM-V is the high prevalence of smoking in alcohol-dependent individuals (John et al., 2003a, b).	P rats may be good animal models for co-abuse because a) they are more sensitive than low alcohol-consuming rats to reinforcing effects of nicotine and cocaine, and b) under binge-like conditions these rats will concurrently consume ethanol and nicotine to attain high BACs of 80 mg% and significant nicotine blood levels of 25 ng/mL (Hauser et al., 2012b, 2013; Katner et al., 2011).