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Animal models for medications development targeting alcohol abuse using selectively bred rat lines: Neurobiological and pharmacological validity

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Abstract

The purpose of this review paper is to present evidence that rat animal models of alcoholism provide an ideal platform for developing and screening medications that target alcohol abuse and dependence. The focus is on the 5 oldest international rat lines that have been selectively bred for a high alcohol-consumption phenotype. The behavioral and neurochemical phenotypes of these rat lines are reviewed and placed in the context of the clinical literature. The paper presents behavioral models for assessing the efficacy of pharmaceuticals for the treatment of alcohol abuse and dependence in rodents, with particular emphasis on rats. Drugs that have been tested for their effectiveness in reducing alcohol/ethanol consumption and/or self-administration by these rat lines and their putative site of action are summarized. The paper also presents some current and future directions for developing pharmacological treatments targeting alcohol abuse and dependence.

Keywords

Animal models of alcoholism; Pharmacogenetics; Pharmacogenomics; Selective breeding; Treatment efficacy

1. Prevalence of alcohol abuse and dependence and their impact on society

The cost of alcoholism in the United States approximates \$185 billion each year (Harwood et al., 2000). Over half of adult Americans have a family history of alcoholism or alcohol abuse, and nearly one-third of Americans over 18 years-of-age have a life-time diagnosis of alcohol abuse or dependence (Research Society on Alcoholism, 2009). Previous estimates of

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Conflicts of Interest

None of the authors have real or perceived conflicts of interest.

the ratio of men to women who abuse alcohol has varied between 2:1 and 3:1 (Brienza and Stein, 2002), with this gender gap narrowing in older and younger populations (Brienza and Stein, 2002; Nelson et al., 1998; Wilsnack et al., 1991). The Centers for Disease Control and Prevention (CDC) rank alcohol drinking as the third leading cause of preventable death (Mokdad et al., 2004). For example, the mortality of women with substance use disorders is four times that of breast cancer (Blumenthal, 1997), with a causal relationship delineated between alcohol use and at least 50 different medical conditions (Rehm et al., 2003; also see Reed et al., 1996 for a discussion on the role of genetics).

Today's youth are initiating alcohol use earlier and experiencing more alcohol-related problems (Miller et al., 2001; Winters, 2001), whether they be men or women (Nelson et al., 1998; Kandel et al., 1997). Approximately 80% of high school seniors in the United States have consumed alcohol and half of them initiated drinking before the eighth grade (Johnston et al., 1999). This is significant as early onset of alcohol use is a strong predictor of future alcohol dependence (Grant and Dawson, 1997; Hawkins et al., 1997). Among college students, binge drinking is becoming more prevalent and is also a strong predictor of future alcohol-related problems in men and women from North America (Dawson et al., 2004; Johnston et al., 2008; Presley et al., 1994; Wechsler et al., 2000; White et al., 2006) and Europe (Kuntsche et al., 2004). Pattern of drinking and total volume consumed are important characteristics for evaluating alcohol abuse and its development into alcohol dependence (Heather et al., 1993; Lancaster, 1994). These drinking characteristics have also been used to develop different typologies and/or drinking profiles for alcoholics (Babor et al., 1992; Cloninger, 1987; Conrod et al., 2000; Epstein et al., 1995; Lesch and Walter, 1996; Moss et al., 2007; Prelipceanu and Mihailescu, 2005; Windle and Scheidt, 2004; Zucker, 1987). Importantly, the effectiveness of some treatments appears to depend upon where an individual ranks on the continuum of a respective typology (Cherpitel et al., 2004; Epstein et al., 1995; Dundon et al., 2004; Johnson et al., 2003). Therefore, age-of-onset and pattern of drinking have significant predictive validity for a life-time diagnosis of alcohol abuse or dependence and, in some cases, can predict the effectiveness of treatments targeting these disorders.

2. Alcohol abuse, dependence and the addictive process

In general, alcohol abuse and dependence are parts of a chronic, progressive, relapsing disorder that advances in stages from experimentation to dependence (Heilig and Egli, 2006; Jupp and Lawrence, 2010; Koob, 2009; Koob and Le Moal, 2008; Koob and Volkow, 2010; Spanagel, 2009; Volkow and Li, 2005). In general, the disease progresses from rewarding, euphoric and positive-reinforcement aspects of alcohol intake that drive the disease-process in early stages to the dysphoric and associated negative-reinforcement aspects that drive the process in later stages. Ethanol is positively reinforcing by producing a euphoria/high or a perceived positive sense of well-being (e.g., increases in perceived confidence). Ethanol is negatively reinforcing by removing dysphoria (e.g., anxiety) or a negative sense of well-being (e.g., hangover and physiological withdrawal). Once dependence is acquired, ethanol's negative-reinforcement aspects overshadow ethanol's positive-reinforcement aspects making the disease very difficult to treat. It is noteworthy that progression from experimentation to dependence is not linear in nature, with individuals often returning to earlier stages of the disease process before advancing to final stages of dependence. Therefore, in addition to considering the age-of-onset and pattern of drinking, effective treatment must also take into account the progressive nature of the disease.

3. Criteria for an animal model of alcoholism

Animal models have been successfully used in developing treatments for both medical and psychiatric disorders (Griffin, 2002; McKinney, 2001). An animal model allows an experimenter to control an animal's genetic background, environmental factors and prior drug experience. In addition, it allows for the examination of neurobehavioral, neurochemical and neurophysiological correlates associated with the behavioral, physiological or neurological state that is modeled, in the present case alcohol abuse and dependence. These correlates can, in turn, facilitate the development of pharmacological and/or behavioral treatments for these disorders. There have been reservations as to whether a valid animal model of alcoholism could be developed (Cicero, 1979). These concerns stemmed from the fact that, in general, heterogeneous stock rats consume only modest levels of ethanol, such that blood alcohol concentrations (BACs) achieved are minimal. Thus, experimental manipulations such as fluid deprivation (Sandi et al., 1990), schedule-induced polydipsia (Meisch, 1976), scheduled availability (Holloway et al., 1984), sucrose-fading (Samson, 1986) and forced induction of dependence (Deutsch and Eisner, 1977; Roberts et al., 2000) are generally required to induce appreciable levels of ethanol intake or self-administration which result in pharmacologically relevant BACs in heterogeneous stock rats. This, of course, introduces the influence of other factors (e.g., taste, stress, etc.) which can complicate the interpretation of results. Nevertheless, certain criteria for an animal model of alcoholism have been put forth (Cicero, 1979; Lester and Freed, 1973). Briefly, these criteria are 1) the animal should readily consume ethanol; 2) the amount of ethanol consumed should result in pharmacologically relevant blood ethanol levels; 3) ethanol should be consumed for its post-ingestive pharmacological effects, and not strictly for its caloric value or taste; 4) ethanol should be reinforcing, in other words, the animals must be willing to work for ethanol; 5) chronic ethanol consumption should lead to the expression of metabolic and functional tolerance; and 6) chronic consumption of ethanol should lead to dependence, as indicated by withdrawal symptoms after access to ethanol is terminated. A 7th criterion has been proposed (McBride and Li, 1998), such that an animal model of alcoholism should also display characteristics associated with relapse. One relapse-associated characteristic that should be displayed is a loss of volitional control, often called an alcohol deprivation effect (ADE), when access to alcohol is reinstated following a period of abstinence. The ADE is a transient increase in ethanol consumption, over basal levels, displayed by animals when given free-choice access to ethanol after a period of ethanol deprivation (Sinclair and Senter, 1967). Table 1 illustrates how the ethanol drinking- and self-administration-associated criteria for an animal model of alcoholism (Cicero, 1979; Lester and Freed, 1973; McBride and Li, 1998) relate to the DSM-IV (American Psychiatric Association, 1994) diagnostic criteria for alcohol abuse and dependence.

The observation that people from similar environmental backgrounds often differ considerably in ethanol consumption and the well-documented familial incidence of alcoholism indicate that heredity contributes to alcohol use disorders (AUDs) (Cloninger, 1987; Cotton, 1979; Schuckit, 1986). Similarly, heterogeneous stock rats display a wide-range of ethanol-consumption levels (Richter and Campbell, 1940). In the late 1940's, Williams and associates (Williams et al., 1949) as well as Mardones and Segovia-Riquelme (1983) proposed a genetic influence on ethanol intake in rodents. From their early work and that of three other sites, bidirectional selective breeding has resulted in at least five high alcohol-consuming vs. their respective low alcohol-consuming rat lines. Bidirectional selection, from a heterogeneous foundation stock, is accomplished through systematic mating of animals from the same extreme of the normal distribution (alcohol-preferring on the one hand vs. alcohol-avoiding on the other) over successive generations. This results in divergent lines that exhibit these extreme phenotypes in ethanol preference and alcohol consumption levels that exceed the range displayed by the foundation population. A major

advantage is that this ethanol-drinking phenotype is observed without environmental manipulations. Moreover, these selectively bred rat lines display behavioral and physiological (Table 2) as well as neuro-chemical (Table 3) correlates found in subtypes of alcoholics.

3.1. Neurobehavioral correlates with alcoholism

Clinical and basic research indicate that 1) lower sensitivity to ethanol's effects is positively associated with high ethanol consumption (e.g., Draski and Deitrich, 1996; Schuckit and Gold, 1988); 2) the ability to display greater levels and quicker development of tolerance (a reduction in ethanol's effects after prior treatment with ethanol) to ethanol's effects is associated with excessive ethanol consumption and the development of alcoholism (Lê and Mayer, 1996); 3) the expression of anxiety-like behavior under basal and/or withdrawal conditions has also been associated with excessive ethanol consumption (Heilig et al., 2010a, 2010b; Kirby et al., 2011; Pautassi et al., 2010; Thorsell, 2010); and 4) the expression of low- to moderate-dose ethanol-induced stimulation [which is modeled in rodents by increased motor activity/approach behavior (Chappell and Weiner, 2008; Faria et al., 2008; Wise and Bozarth, 1987), aggression (Chiavegatto et al., 2010), and social facilitation (Varlinskaya and Spear, 2009, 2010)] is associated with an individual's propensity to abuse alcohol. Interestingly, there may be pharmacological validity for this behavioral phenotype, such that the histaminergic (c.f., Panula and Nuutinen, 2011 and references therein) and ghrelin (c.f., Jerlhag et al., 2011b and references therein) systems have been implicated in ethanol-induced motor activation, ethanol-induced conditioned place preference, alcohol-preference and high alcohol consumption behavior. However, the positive relationship between ethanol-induced motor stimulation and high ethanol intake does not always hold. For example, low alcohol-consuming DBA/2J mice display greater acute ethanol-induced motor stimulation than high alcohol-consuming C57BL/6J mice (e.g., Melon and Boehm, 2011). Moreover, there are concerns with establishing consilience and translatability of ethanol-induced stimulation between the rodent and clinical literature (c.f., Crabbe et al., 2010). For instance, rodents can only provide a rudimentary model of the cognitive constructs associated with human approach behavior, aggression and social facilitation. In addition, other than low- to moderate-dose effects on self-report (Morzorati et al., 2002; Viken et al., 2003), heart rate (Finn and Justus, 1997; Peterson et al., 1996), and brain activity (Lukas et al., 1986; Sorbel et al., 1996; Trim et al., 2010) the stimulating effects of ethanol are not as readily seen in humans compared with rodents.

3.2. Neurochemical correlates with alcoholism

Clinical and basic research indicate that alcohol abuse and dependence are related to alterations in acetylcholine (ACh: Chatterjee and Bartlett, 2010; Davis and de Fiebre, 2006; Soderpalm et al., 2000), dopamine (DA: Heinz, 2002), gamma-aminobutyric-acid (GABA: Kumar et al., 2009; Maccioni and Colombo, 2009), glutamate (Davis and Wu, 2001; Gass and Olive, 2008), serotonin (5-HT: Engleman et al., 2008; Lovinger, 1999), opiate (Drews and Zimmer, 1997), neuropeptide-Y (NPY: Heilig and Thorsell, 2002), corticotropin releasing factor (CRF: Koob, 2010), substance P (George et al., 2008), nociceptin/orphanin FQ (NOP, N/OFQ: Economidou et al., 2008); ghrelin (Jerlhag et al., 2009, 2011a, 2011b); neurotrophic factors such as BDNF (Logrip et al., 2009), and hypothalamic-pituitary-adrenal (HPA: Gianoulakis et al., 1995; Keith et al., 1995; Rasmussen et al., 2002; Richardson et al., 2008) systems within the brain. Therefore, innate differences in these neuro-transmitter or neuromodulator systems between the high and low alcohol-consuming lines would suggest a role for these systems in their ethanol-preference phenotypes. Thus, rat animal models displaying these alcohol self-administration phenotypes (Table 2), and neurochemical phenotypes associated with alcohol abuse (Table 3), provide an ideal platform to evaluate

the effectiveness of compounds (Table 4) targeting these neurochemical substrates to treat alcoholism.

3.3. Summary

As described in Section 4 and summarized in Table 2, all of the high alcohol-consuming rat lines, excepting the UChB line in some cases, described herein meet the basic criteria of voluntary ethanol intake (see Section 5 for a discussion of procedures modeling this behavior) and the subsequent development of tolerance and/or dependence, as well as displaying relapse-like behavior and the ability to work/operantly respond for ethanol (see Section 5 for a discussion of procedures modeling these latter two behaviors). When examining other putative animal models of alcoholism, these rudimentary criteria and whether high alcohol consumption will be maintained in the presence of another palatable fluid have been evaluated. Thus, the Fawn-Hooded (FH/WJD: Overstreet et al., 2007) inbred and the Warsaw High-Preferring (WHP: Dyr and Kostowski, 2008) selectively bred rat lines meet these basic criteria but fail to meet the criterion of preferring a sweet solution over ethanol. While there is evidence that the alcohol-preferring P rat line meets the criterion of a preference for ethanol in the presence of another palatable solution (see McMillen and Williams, 1995 for discussion on this latter criterion) and other putative animal models of alcoholism do not meet this criterion, Overstreet et al. (2007) make a cogent argument that the preference for ethanol over a third choice of a palatable solution may be overly simplistic when differentiating animal models of alcoholism. In addition, it has been proposed that an animal model of alcoholism should respond similarly to pharmacological treatments found to effectively reduce ethanol intake in humans and other preclinical models (i.e., predictive validity/pharmacological validation: Dyr and Kostowski, 2008; Overstreet et al., 2007; see Litten et al., 2012 for a discussion on the development of medications and screening models targeting alcoholism). This criterion and these compounds are discussed in Section 5.8.

4. Selectively bred high alcohol-consuming rat lines and their phenotypic characteristics

Selective breeding is a well-established, powerful genetic tool for studying the genetics of many alcohol phenotypes of interest (Crabbe, 2008). Compared to pure association studies such as genome-wide association studies (GWAS) and recombinant inbred lines (RILs) from appropriate crosses, selective breeding from a heterogeneous outbred stock can make low frequency/rare alleles (minor allele frequency <0.05) more common and, thus, be captured within the selected high or low line. The high and low lines will exhibit extreme phenotypes that greatly exceed the range found in the foundation stock. This major advantage is completely missing in GWAS and research using RILs. Additionally, selective breeding for any phenotypes (such as alcohol preference) is hypothesis driven and genetically correlated traits of the primary selected phenotype (presumably due to pleiotropic actions of genes: Crabbe et al., 1990) can be identified and studied. The following subsections describe the five oldest selectively bred high vs. low alcohol-consuming rat lines in the world. The text gives a brief overview of neurobehavioral and neurochemical differences found between the respective lines. The brief overview focuses primarily on observations associated with criteria for an animal model of alcoholism and some neurobehavioral and neuro-chemical correlates associated with alcoholism. Table 3 gives more in-depth information on direct comparisons within the line-pairs and parameters associated with observed neurobiological differences (e.g., brain regions).

4.1. Alko Alcohol and Alko Non-Alcohol rats

These alcohol-preferring [Alko Alcohol (AA)] and alcohol-avoiding [Alko Non-Alcohol (ANA)] rats were developed from a closed-colony of a Wistar–Sprague–Dawley cross foundation stock in Helsinki, Finland (Eriksson, 1968). The lines were revitalized with the Brown-Norway and Lewis lines in the late 1980's and returned to selective breeding (Sommer et al., 2006). As an animal model of alcoholism, AA rats readily consume appreciable levels of ethanol (>5.0 g of ethanol/kg body weight/day), whereas ANA rats avoid ethanol (<1.0 g/kg/day) when food and water are available ad libitum (Ritz et al., 1986). The AA rat will operantly self-administer ethanol, indicating they find ethanol reinforcing and will work for access to ethanol (Files et al., 1997, 1998; Samson et al., 1998). Free access to ethanol results in increased ethanol elimination rate (metabolic tolerance) for AA, but not ANA, rats (Forsander and Sinclair, 1992), and AA rats develop and display greater functional tolerance to the motor-impairing, hypothermic and hypnotic effects of ethanol than ANA rats after repeated ethanol injections (Lê and Kiianmaa, 1988). In addition, the AA rat displays a modest ADE following short deprivation periods (Sinclair and Li, 1989) and display pharmacologically relevant BACs during ethanol self-administration (Aalto, 1986). AA rats are less affected by ethanol than ANA rats as it pertains to ethanol's hypnotic and ataxic effects (Nikander and Pekkanen, 1977; Rusi et al., 1977). Also, AA rats display locomotor activation after limited access to ethanol suggesting AA rats find ethanol rewarding (Paivarinta and Korpi, 1993). In general, the AA line satisfies many of the criteria for an animal model of alcoholism.

Neurochemically, higher levels of 5-HT (Ahtee and Eriksson, 1972, 1973; Korpi et al., 1988) as well as dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) levels, the latter reflecting DA metabolism (Honkanen et al., 1994), were found in certain CNS regions of AA rats compared with ANA rats, suggesting possible genetic subtypes among the selectively bred alcohol-preferring rats. In other work, Katner and Weiss (2001) compared rats from the AA, ANA, and Wistar lines for extracellular concentrations of DA in the nucleus accumbens (Acb) using a no-net-flux microdialysis procedure. Their results indicated that changes in Acb extracellular DA levels predicted high ethanol preference, with rats predisposed to high ethanol intake having a greater DA response to ethanol. These results paralleled other findings from Honkanen and colleagues' study (1994), although differences in Acb extracellular DA levels following ethanol have not always been observed between AA and ANA rats (Kiianmaa et al., 1995). AA rats have lower mRNA levels for the NR1-4 splice variant of the N-methyl-D-aspartate (NMDA) receptor within the hippocampus than the ANA rat, whereas protein levels do not differ (Winkler et al., 1999). Additionally, the AA rat has lower NPY-Y2 receptor mRNA levels within the medial amygdala as well as lower NPY mRNA levels within the hippocampus than their ANA counterparts (Caberlotto et al., 2001). The AA rat has greater or lower mu-opioid receptor levels (depending on the brain region evaluated) in the limbic system, compared with the ANA rat (Soini et al., 1998, 1999). The HPA-system appears to regulate ethanol-intake in the AA, but not the ANA, rat (Fahlke and Eriksson, 2000). These authors reported that adrenalectomy, and corticosterone replacement, altered ethanol intake in AA, but not ANA, rats. Overall, the findings suggest that differences in 5-HT, DA, NMDA, NPY and endogenous opioid systems may contribute to the disparate alcohol drinking behaviors of the AA and ANA rats.

4.2. Alcohol-preferring and alcohol-nonpreferring rats

The alcohol-preferring, P, and alcohol-nonpreferring, NP, rat lines were developed by mass selection from a closed-colony Wistar foundation stock at the Walter Reed Army Hospital and transferred to the Indiana University School of Medicine in Indianapolis, Indiana, USA (Lumeng et al., 1977). Regarding criteria for an animal model of alcoholism, P rats readily

consume greater than 5 g/kg/day of ethanol, whereas NP rats consume less than 1 g/kg/day with food and water available ad libitum (Li et al., 1987). Moreover, P rats attain pharmacologically relevant blood alcohol concentrations (BACs, 50 to 200 mg%: this would approximate .05 to .20 in clinical terms) under 24-h and limited access conditions (Bell et al., 2006, 2008a, 2011; Murphy et al., 1986, 2002; Rodd et al., 2003). Ethanol-drinking in the home-cage also results in intoxication, as measured by motor impairment using an oscillating bar apparatus (Bell et al., 2000, 2001), with the development and expression of tolerance to this effect after chronic drinking (Bell et al., 2011). P rats self-administer ethanol intragastrically for its post-ingestive effects, thus, limiting the role of taste and smell (Murphy et al., 1988; Waller et al., 1984). P rats will operantly self-administer ethanol, which indicates ethanol is reinforcing and these rats will work for access to ethanol (Files et al., 1998; Murphy et al., 1989; Rodd et al., 2003; Rodd-Henricks et al., 2002a, 2002b; Samson et al., 1998; Toalston et al., 2008). Whereas ethanol-naïve P and NP rats display similar levels of ethanol clearance (Li and Lumeng, 1977; Lumeng et al., 1982), P rats, given chronic free-choice access to ethanol, drink sufficient amounts to develop metabolic as well as functional tolerance to the motor impairing and aversive effects of ethanol (Gatto et al., 1987; Lumeng and Li, 1986; Stewart et al., 1991). Moreover, P rats develop dependence with 24-h free-choice ethanol drinking, as indicated by physical signs of withdrawal when access is terminated (Kampov-Polevoy et al., 2000; Waller et al., 1982). In addition, P rats display a robust ADE (Rodd et al., 2003; Rodd-Henricks et al., 2000c, 2001), a characteristic of relapse drinking. With regard to initial sensitivity to ethanol's effects, P rats are less sensitive to the ataxic (Bell et al., 2001) and hypothermic (Stewart et al., 1992) effects of ethanol, compared with NP rats; and develop tolerance quicker than NP rats to the ataxic (Bell et al., 2001) and hypnotic (Kurtz et al., 1996) effects of ethanol as well. The P, but not NP, line display greater acoustic startle reactivity during ethanol-associated withdrawal compared with basal conditions (Chester et al., 2004). P rats display greater locomotor activation after low dose ethanol, compared with NP rats (Rodd et al., 2004a; Waller et al., 1986), and P rats display locomotor activation during ethanol drinking or self-administration (Bell et al., 2002; Melendez et al., 2002). Thus, the P line of rat satisfies the criteria proposed for an animal model of alcoholism.

Regarding neurochemical correlates, P rats have lower levels of 5-HT and 5-hydroxy-indole-acetic-acid (5-HIAA) in cortical and limbic regions than their NP counterparts (Murphy et al., 1982, 1987b). Additionally, there are fewer 5-HT immunostained fibers in the anterior frontal cortex, Acb and parts of the ventral hippocampus in P, compared with NP, rats (Zhou et al., 1991a, 1991b), with the dorsal and median raphe of P rats having fewer 5-HT immunostained neurons as well (Zhou et al., 1991c). P rats have lower levels of DA and its metabolites (DOPAC and HVA) in the Acb and anterior striatum, compared with NP rats (Murphy et al., 1982, 1987b). In addition, P rats have decreased numbers of DA neuronal projections from the ventral tegmental area (VTA) to the Acb, relative to NP rats (Zhou et al., 1995). Regarding accumbal DA, operant self-administration of ethanol was found to increase DA overflow above baseline values to a greater extent in the Acb of P rats than in unselected Wistar rats (Weiss et al., 1993). P rats also have reduced numbers of D₂ receptors in the VTA and Acb compared to NP rats (McBride et al., 1993a). There are higher densities of GABAergic terminals found in the Acb of ethanol-naïve P rats, compared with NP rats (Hwang et al., 1990). In addition, P rats have higher densities of mu-opioid receptors in CNS limbic areas, relative to NP, rats, including the Acb shell and core (McBride et al., 1998). Lower levels of NPY are found in the amygdala, hippocampus, and frontal cortex of P, compared with NP, rats (Ehlers et al., 1998). Similarly, lower levels of CRF are found in the amygdala, hypothalamus, prefrontal cortex, and cingulate cortex of P, compared with NP, rats (Ehlers et al., 1992). It is interesting that despite having low CRF levels, at least relative to NP rats, P rats display autonomic reactivity to ethanol consumption and its associated cues (Bell et al., 2002, 2008b) similar to that observed in alcohol-

dependent and -nondependent individuals with a paternal family history of alcoholism (e.g., Brunelle et al., 2007; Conrod et al., 2001; Peterson et al., 1996; also see Section 4.6.). While not tested thus far, these seeming disparate findings (lower CRF in the hypothalamus of P vs. NP rats and ethanol consumption-induced autonomic reactivity in P rats) may be due to increased sensitivity of the HPA-axis to ethanol in P rats. For instance, alcohol-preferring AA rats display greater ethanol-associated increases in Acb β -endorphin levels compared with their ANA counterparts (Lam et al., 2010). Also, clinically, a positive association between ethanol-induced autonomic (heart rate) reactivity and systemic ethanol-induced β -endorphin levels has been reported by Peterson et al. (1996). In conclusion, the differences observed between the P and NP rats suggest that multiple neurotransmitter and neuro-modulatory systems may contribute to the disparate alcohol drinking behaviors displayed by these two rat lines.

4.3. High alcohol-drinking and low alcohol-drinking rats

The high alcohol-drinking, HAD, and low alcohol-drinking, LAD, lines of rats were developed using a within-family selection and rotational breeding design (which decreases the level of inbreeding) from N/NIH heterogeneous stock rats at Indiana University School of Medicine in Indianapolis, Indiana, USA (Li et al., 1993). The N/NIH line of rats was derived from eight inbred strains (ACI, BN, BUF, F344, M520, MR, WKY and WN) at the National Institutes of Health (Hansen and Spuhler, 1984). Two separate colonies were used to breed HAD and LAD lines of rats, such that replicate (HAD1 vs. LAD1 and HAD2 vs. LAD2) lines are available to assess genotypic and phenotypic differences. As a caveat, the selective breeding program of the HAD2-LAD2 line-pair has trailed that of the HAD1-LAD1 line-pair by approximately 1 year (i.e., the HAD2-LAD2 line-pair has trailed the HAD1-LAD1 line-pair by approximately 2 generations of selection). A genotypic or phenotypic trait that is present in both replicate lines would convey greater confidence in the importance of that trait for the development of high or low alcohol drinking behavior than if the trait was identified in only one of the lines. Regarding criteria for an animal model of alcoholism, HAD1 and HAD2 rats readily drink greater than 5 g/kg/day of ethanol, whereas LAD1 and LAD2 rats drink approximately 0.5 g/kg/day (Murphy et al., 2002). HAD1 and HAD2 rats will perform an operant response for access to ethanol indicating ethanol functions as a reinforcer for these rats (Files et al., 1998; Oster et al., 2006; Samson et al., 1998). Moreover, HAD1 and HAD2 rats attain pharmacologically relevant BACs (50 to 150 mg%) during free-choice ethanol drinking or self-administration (Bell et al., 2008a; Murphy et al., 2002; Oster et al., 2006). In addition, HAD1 and HAD2 rats display a robust ADE (Oster et al., 2006; Rodd et al., 2009; Rodd-Henricks et al., 2000b). When the sedative effects of ethanol were examined, HAD1 rats displayed lower sensitivity, compared with LAD1 rats (Froehlich and Wand, 1997). When testing for the development of tolerance, HAD1 rats displayed rapid tolerance to the ataxic effects of ethanol, whereas LAD1 rats do not (Suwaki et al., 2001). A study of HAD1 vs. LAD1 rats revealed that ethanol-associated withdrawal induces greater dysphoria in LAD1 compared with HAD1 rats (Chester et al., 2006). Both HAD1 and HAD2 rats, but not LAD1 and LAD2 rats, display greater acoustic startle reactivity during ethanol-associated withdrawal compared with basal conditions (Chester et al., 2004). Paradoxically, ethanol-associated withdrawal actually decreased, rather than increased, ethanol drinking in HAD2 rats (Chester et al., 2005). HAD1 and HAD2 rats display greater locomotor activation after low- to moderate-dose ethanol compared with their LAD1 and LAD2 counterparts (Krimmer and Schechter, 1991; Rodd et al., 2004a), suggesting HAD rats find low-dose ethanol rewarding. In summary, the HAD replicate lines meet many of the criteria proposed for an animal model of alcoholism.

Regarding neurochemical correlates, HAD1 rats have lower 5-HT and/or 5-HIAA levels in cortical and limbic regions than LAD1 rats (Gongwer et al., 1989). HAD rats have lower

levels of DA and its metabolites (DOPAC and HVA) in the Acb and anterior striatum, compared with LAD rats (Gongwer et al., 1989). Also, Katner and Weiss (2001) compared rats from the HAD1 and LAD1 lines on the extracellular concentrations of DA in the Acb and found that, as with AA vs. ANA rats and P vs. Wistar rats, extracellular DA levels predict high ethanol preference with rats genetically predisposed for high ethanol consumption having a greater DA response following ethanol exposure (Katner and Weiss, 2001; Weiss et al., 1993). Higher densities of GABAergic terminals are found in the Acb of ethanol-naïve HAD rats, compared with their LAD counterparts (Hwang et al., 1990). Similar to P rats, reduced levels of NPY-immunoreactivity in the central amygdala are found in HAD rats, compared with LAD rats (Hwang et al., 1999). Thus, the similar differences observed in the 5-HT, DA, GABA and NPY neuronal systems between HAD vs. LAD and P vs. NP rats suggest that these differences may mediate, at least in part, the high and low ethanol-consuming phenotypes seen in these rat lines.

4.4. Sardinian alcohol-preferring and alcohol-nonpreferring rats

The Sardinian alcohol-preferring, sP, and alcohol-nonpreferring, sNP, rats were developed from a Wistar foundation stock at the University of Cagliari, Italy (Colombo et al., 2006). As an animal model of alcoholism, sP rats readily consume appreciable levels of ethanol (>5.0 g/kg/day ethanol), whereas sNP rats consume <1.0 g/kg/day ethanol (Colombo et al., 2006). The sP rat will operantly self-administer ethanol, indicating ethanol serves as a reinforcer, and they are willing to work for access to ethanol (Colombo et al., 2006; Vacca et al., 2002b). Furthermore, sP rats achieve pharmacologically relevant BACs (> 50 mg%) during free-choice ethanol drinking (Colombo et al., 2006) and display a modest ADE as well (Agabio et al., 2000; Serra et al., 2003). Research on anxiety-like behavior suggests sP rats are innately more anxious than sNP rats, and their higher ethanol intake may be related to ethanol's anxiolytic effects (Colombo et al., 1995; Roman and Colombo, 2009). Additionally, sP, but not sNP, rats find ethanol rewarding as indicated by locomotor activation after limited free-choice access to ethanol (Colombo et al., 1998b) and administration of low doses of ethanol (Agabio et al., 2001). Ethanol-naïve sP and sNP rats display similar levels of ethanol clearance (Quertemont et al., 2000). However, chronic free-choice ethanol drinking by sP rats results in the development of functional tolerance to the motor impairing effects of ethanol (Colombo et al., 2006). At variance with the other lines of alcohol-preferring rats, sP rats are more sensitive to the motor-impairing and sedative/hypnotic effects of ethanol than sNP rats (Colombo et al., 2000b). Additionally, when intermittently exposed to 20% alcohol such that access is given every other day, sP rats display marked escalations in daily alcohol intake (approximately 10 g/kg/day), with signs of alcohol intoxication and behavioral dependence displayed (Loi et al., 2010). Thus, the sP line meets many of the criteria put forth for an animal model of alcoholism.

For neurochemical correlates, whole brain levels of 5-HT and 5-HIAA are higher in sP compared with sNP rats (Bano et al., 1998). However, the sP rat may still display 5-HT deficiencies in discrete brain regions, despite overall increased levels within the brain. Additionally, acute ethanol increases extracellular levels of 5-HT in the frontal cortex of sP, but not sNP, rats (Portas et al., 1994). Compared with the sNP line, the sP line has lower densities of D₂ receptors in subregions of the mesolimbic DA system (Stefanini et al., 1992), a finding similar to that reported in P vs. NP rats (McBride et al., 1993a). Basal DA levels are higher in Acb shell and medial prefrontal cortex of sP than sNP rats (Leggio et al., 2003). With regard to GABA, it appears that (a) a mutation in the GABA-A alpha-6 receptor subunit is evident in the sP rat, relative to the sNP rat (Saba et al., 2001) and (b) GABA-B receptor function is lower in limbic areas of sP than sNP rats (Castelli et al., 2005). The sP rat has lower densities of opiate receptors in the caudate putamen and Acb shell (Fadda et al., 1999), lower basal levels of μ -opioid receptor mRNA and GTP γ S binding in Acb-shell

(Zhou et al., in press), and higher basal proopiomelanocortin mRNA levels in hypothalamus (Zhou et al., in press), compared with their sNP counterparts. Higher density of cannabinoid CB1 receptors and levels of CB1 receptor mRNA, CB1 receptor-mediated G-protein coupling, and endocannabinoids have been found in the cerebral cortex, hippocampus and striatum of alcohol-naïve sP vs. sNP rats (Vinod et al., 2012). Higher levels of serum corticosterone (Bano et al., 1998) and CRF in the central nucleus of amygdala (Richter et al., 2000) have been reported in sP rats, compared with sNP rats, suggesting differences in the HPA-system as well. Finally, higher basal mRNA levels of the stress-responsive, arginine vasopressin (AVP) gene have been observed in the medial and central amygdala as well as the medial hypothalamus of alcohol-naïve sP vs. sNP rats (Zhou et al., 2011). Overall it appears that alterations in the 5-HT, DA, GABA, opioid, cannabinoid, and AVP systems may underlie the different ethanol drinking phenotypes displayed by sP vs. sNP lines.

4.5. University of Chile B and University of Chile A rats

The alcohol-preferring [University of Chile B (UChB)] and alcohol-nonpreferring [University of Chile A (UChA)] lines of rats were developed from a Wistar foundation stock at the University of Chile, Santiago, Chile (Mardones and Segovia-Riquelme, 1983). Regarding criteria for an animal model of alcoholism, UChB rats drink 5 g/kg/day or more of ethanol and achieve BACs observed in humans (c.f., Quintanilla et al., 2006, 2008). In addition, UChB rats display relapse-like behavior as indicated by an ADE upon re-exposure to ethanol access (Tampier and Quintanilla, 2011). On the other hand, UChA rats drink approximately 1 g/kg or less ethanol per day (Mardones and Segovia-Riquelme, 1983) which depends, as reviewed by Quintanilla et al. (2006), upon the aldehyde-dehydrogenase-2 (*Aldh2*, mitochondrial) alleles seen in the respective rat line. These authors indicate that low alcohol-consuming UChA rats have the *Aldh2¹* allele that encodes an enzyme with low affinity for nicotinamide-adenine-dinucleotide (NAD⁺). On the other hand, the high alcohol-consuming UChB rats either have the *Aldh2¹* or the *Aldh2³* alleles which have four- to five-fold higher affinities for NAD⁺. Moreover, the enzyme encoded by *Aldh2¹* has a 33% higher V_{max} than those encoded by *Aldh2²* or *Aldh2³* (Quintanilla et al., 2006).

Behaviorally, UChB rats are less sensitive to the ataxic and hypothermic effects of ethanol, compared with UChA rats, with UChB rats also developing tolerance quicker than UChA rats to these ataxic effects (Tampier and Mardones, 1999; Tampier and Quintanilla, 2002b). In addition, similar to P rats (Stewart et al., 1991) UChB rats are less sensitive to the aversive effects of ethanol than UChA rats as measured by conditioned taste aversion (CTA: Quintanilla et al., 2001) and conditioned place aversion (CPA: Quintanilla and Tampier, 2011). A recent study has shown that chronic ethanol drinking by UChB rats leads to the development of tolerance to its CPA effects (Quintanilla and Tampier, 2011), which is similar to a previous study indicating chronic ethanol intake by UChB rats resulted in tolerance to the aversive effects of disulfiram (Tampier et al., 2008). Similar to P and sP rats, the UChB line of rats displays locomotor activation after low-dose ethanol, whereas the UChA line does not (Quintanilla, 1999). Although there is information on the effects of endogenous levels of, and exogenous treatments affecting, alcohol dehydrogenase, aldehyde dehydrogenase, and acetaldehyde on ethanol intake for these lines (Tampier and Quintanilla, 2002a); there has been very little published on innate neurotransmitter/neuromodulator differences between the UChB and UChA rats. Two studies examining monoamine levels in the Acb shell of UChB vs. UChA rats found that UChB rats had lower basal levels of DA and its metabolites (Quintanilla et al., 2007), but not 5-HT, than UChA rats and moderate-dose ethanol-induced extracellular DA levels were much higher in UChB than in UChA rats (Bustamante et al., 2008). These findings, as it pertains to DA, are similar to those observed in the AA, HAD and P rat lines. In general, it is recognized that elevated levels of

acetaldehyde are aversive. Thus, genetic differences in alcohol dehydrogenase (ADH) and/or ALDH can play a protective or permissive role in the development of alcohol abuse and dependence by increasing or decreasing blood acetaldehyde levels, respectively (Eriksson, 2001; Quintanilla et al., 2006). In summary, while research with the other selectively bred high alcohol-consuming rat lines has focused more on CNS neurobiology, research with the UChB and UChA lines has provided important information on genetic differences in alcohol and/or acetaldehyde metabolism and their role in the development of alcohol abuse and dependence.

4.6. Selectively bred rat lines and some family history positive correlates

The above survey of the literature concerning neurobehavioral (Table 2) and neurobiological (Table 3) phenotypes found in these selectively bred high vs. low alcohol-consuming rat lines indicates that many phenotypes present in alcohol abusing or dependent individuals are also present in these rat lines. For example, similar to the animal literature, clinical studies of human subjects with a family history of alcoholism, suggest that there is an association between a low level of responsivity to ethanol and risk for the development of alcoholism (Crabbe et al., 2010; Schuckit, 1994, 2009). Thus, after an ethanol challenge young adult family history positive (FHP for alcoholism) males (Schuckit, 1985; Schuckit and Gold, 1988) and females (Eng et al., 2005; Lex et al., 1988) display less body sway than family history negative (FHN) controls. An individual's level of response (low vs. high) to ethanol also influences the expression of brain regional activation following an acute ethanol challenge (Trim et al., 2010). Moreover, an individual's level of response to ethanol is directly associated with whether they carry the long- vs. short-allele for the 5-HT transporter (*5htt*, the 5 is used in the present paper to distinguish the gene from Huntingtin, which is *htt*) gene and this association has significant predictive validity for the level of alcohol intake displayed by adolescents (Hinckers et al., 2006). Thus, these animal models of alcoholism can serve as model platforms for screening compounds targeting particular subpopulations of alcoholics when the neurobiological or neurobehavioral phenotypes of the target population overlap with those present in one or more rat line. For instance, it has been shown that both male (Bell et al., 2002) and female (Bell et al., 2008b) P rats display autonomic activation, as indicated by increased heart rate, during ethanol drinking. In addition, this autonomic reactivity could be conditioned to the environment in which ethanol was consumed (Bell et al., 2002, 2008b). These findings parallel the substantial clinical literature on cue-reactivity (autonomic reactivity to alcohol-associated cues) and its association with craving and alcohol abuse (Childress et al., 1993; Drummond et al., 1990; Greeley et al., 1993; Kaplan et al., 1983, 1985; O'Brien et al., 1992; Rajan et al., 1998; Stormark et al., 1998). Thus, monitoring autonomic reactivity in P rats may be an important model system for testing compounds targeting craving, especially in the context of cue-reactivity. None of the other rat lines have been examined for ethanol-induced autonomic reactivity thus far, but this effect is probably present in the other high alcohol-consuming rat lines as well.

As another example, the UChB, and possibly the UChA, rat line would be ideal for assessing manipulations of the *Aldh2* system with compound(s) such as those described by Arolfo et al. (2009) and Rezvani et al. (2012; also see Bell et al., 2012). This stems from the substantial work examining the alcohol and aldehyde dehydrogenase systems of these rat lines, with genetic alterations in the *Aldh2* system playing a prominent role in their divergent ethanol intakes (Quintanilla et al., 2006). In addition, there is an apparent clinical association between an *Aldh2* genotype and alcohol consumption (Hendershot et al., 2009). To facilitate identification of a rat line, or rat lines, with alterations in a particular neurotransmitter, neuromodulator, and/or enzyme system that can be manipulated by a compound targeting that particular system, Table 3 outlines innate differences in

neurotransmitter, neuromodulator and enzyme systems of these rat lines (AA vs. ANA, HAD vs. LAD, P vs. NP and sP vs. sNP) and Table 4 outlines compounds tested thus far in the respective high alcohol-consuming lines.

4.7. Summary

As seen in Table 2, all five of the high alcohol-consuming rat lines consume greater than 5 g/kg/day of ethanol and depending on the specific voluntary drinking protocol produces BACs that range between 50 and 200 mg% (i.e., BACs attainable in humans with AUDs). Similarly, all five of the alcohol-preferring rat lines display relapse behavior, as indicated by an ADE, upon re-exposure to ethanol access (Table 2). In addition, four of the five high alcohol-drinking rat lines have been shown to find ethanol reinforcing, because they operantly self-administer ethanol, and develop tolerance to ethanol-associated effects. However, only three of the rat lines display motor activation associated with ethanol consumption and only two of the rat lines show overt signs of withdrawal during initial abstinence from ethanol. Neurobehaviorally, findings on anxiety-associated differences between high and low ethanol-consuming rats across line-pairs have been mixed. Differences are often contingent upon the experimental or measurement procedure used. For instance, the ability to detect intra-line-pair differences seen in general activity, and other parameters, differs across three test procedures (i.e., Multiple Concentric Square Field, Open Field and Elevated Plus Maze: Roman et al., 2012). For further discussion, see Section 6 which describes published findings on differences between high and low alcohol-consuming rats across four of these line-pairs.

Regarding neurochemical correlates with alcoholism, as far as we can tell all of the studies examining innate neurochemical differences within these rat line-pairs (Table 3) were conducted in male rats. Therefore, sex-differences in these neurochemical substrates have not been examined thus far, which leaves a large gap in the literature. Also, of the four lines described in Table 3, the AA vs. ANA rat line-pair has had the most research conducted on innate neurochemical differences. The P vs. NP line-pair is next in the number of published studies on innate neurochemical differences followed closely by the sP vs. sNP line-pair. Finally, the HAD1 vs. LAD1 and HAD2 vs. LAD2 line-pairs have had relatively little published compared with these other three rat line-pairs. Moreover, at least half of the research published on the HAD vs. LAD rat lines does not explicitly state the replicate line-pair examined, which has forced us to state HAD vs. LAD differences in many instances rather than the preferred HAD1 vs. LAD1 or HAD2 vs. LAD2 distinctions. Also, in general only the DA, NE, 5-HT and opioid systems have been examined in all four lines described in Table 3. Table 3 also makes it clear that different laboratories have focused on different (a) brains regions and/or (b) parameters examined (e.g., findings on protein and mRNA levels are very rarely reported in the same paper). Nevertheless, substantial progress has been made on innate differences in mesolimbic regions (i.e., VTA and Acb) which has been extended to other regions within the mesocorticolimbic and extended amygdala systems (i.e., PFC, CeA and BLA) as well.

Some of the most common neurochemical findings among the rat lines are alterations in central 5-HT and DA levels, or their metabolites, which is usually manifest as a deficit in the HAD and P rat lines, although both the AA and sP rat lines generally show similar or greater levels of DA and/or metabolites than their low alcohol-consuming counterparts. However, when DA receptors or its transporter were examined high alcohol-consuming rats consistently had similar or less protein or mRNA levels than their low alcohol-consuming counterparts. Similar differences have been reported for the 5-HT system with HAD, P and sP rat lines having lower 5-HT and 5-HIAA levels than LAD, NP and sNP rat lines, respectively. When levels of 5-HT receptors have been examined, the findings have been mixed for all three of these line-pairs. As with the DAergic system, AA rats either had

similar or greater levels of 5-HT, its metabolites and receptors than ANA rats. To a large extent the AA vs. ANA rat line-pair has been the primary focus of research on the endogenous opioid system. While there are reports of AA rats having greater or lesser levels of opioid peptides and their receptors relative to ANA rats, it is surprising that very few studies have reported similar levels between these rat lines. A handful of studies have been published with the P vs. NP and sP vs. sNP rat lines regarding the endogenous opioid system, and the general finding has been that high alcohol-consumers have lower levels of opioid peptides and receptors than low alcohol-consumers. Other than the endogenous opioid system, most of the research on innate differences in neuropeptide systems has been conducted in the P vs. NP line-pair. In general, P rats display deficits in the CRF and tachykinin systems relative to NP rats. Moreover, brain-derived neurotrophic factor (BDNF) and activity-regulated cytoskeleton-associated protein (ARC) have been implicated in excessive ethanol intake as well as its modulation by the NPY system and P rats display deficits in these systems relative to NP rats as well.

It is noteworthy that an early study examined whether an inverse relationship between monoamine levels and excessive alcohol consumption would hold for N-Nih heterogeneous stock rats (Murphy et al., 1987a). These authors found that, after preference testing, the N/Nih rats consuming at least 5 g/kg/day of ethanol had lower levels of 5-HIAA and DA in the hypothalamus and thalamus than rats that consumed less than 0.5 g/kg/day of ethanol. While it is true that ethanol experience may have influenced the findings in the high alcohol-consuming rats, it is doubtful that the miniscule amount of ethanol consumed by the low alcohol-consuming rats would have affected their innate monoamine levels. Moreover, a study in P rats revealed that chronic access to ethanol increased DAergic levels, although 5-HT levels were decreased, in the Acb and the DA levels remained elevated after two weeks of ethanol deprivation (Thielen et al., 2004). It is also noteworthy that a selective breeding program for high alcohol consumption in Wistar rats, Warsaw high-preferring (WHP) vs. Warsaw low-preferring (WLP), has resulted in rat lines with similar phenotypes as those described above (c.f., Dyr and Kostowski, 2008). Note that all of the rat lines discussed herein have a Wistar-associated genetic background, including certain foundation inbred rats of the N/Nih rat line which in turn was the foundation stock for the HAD/LAD lines. For instance, DA, and its metabolites HVA and DOPAC, levels have consistently been found to be lower in the striatum of WHP vs. WLP rats (Dyr et al., 2002). However, lower 5-HT levels in the hippocampus were observed in WHP vs. WLP rats at an early (11th), but not later (21st), generation of selection (Dyr et al., 2002).

5. Procedures for evaluating pharmacological treatments targeting alcohol abuse and dependence

5.1. Using home-cage procedures to evaluate pharmacological treatments targeting alcohol abuse and dependence

The vast majority of experiments assessing the efficacy of compounds targeting alcohol abuse and dependence have done so by testing their ability to reduce home-cage ethanol drinking. A comprehensive review of ligands tested, experimental procedures used and brain regions targeted in high alcohol-consuming rats, for reducing ethanol intake and/or self-administration, is presented in Table 4. A number of reasons support this method of testing compounds not the least of which is simplicity along with lower equipment costs and face validity. Most individuals consume ethanol, including to excess, either in their own home or a similar social venue. Therefore, ethanol consumption by a rat in their home-cage parallels the human condition in many regards. Also, home-cage testing allows the assessment of a compound's effects on water and food intake in the same environment, if these are available ad libitum. Three primary conditions, within the addictive process, can be evaluated in the

home-cage environment. These are (a) the acquisition of ethanol intake, (b) the maintenance of ethanol intake, and (c) relapse-like drinking of ethanol. In turn, each of these three primary conditions can be tested with continuous access (i.e., 24 h/day) or limited access (i.e., a set period of access each test day such as the first hour of the dark cycle) ethanol availability. Note that brief examples are given in the text of Section 5, whereas explicit details of published studies examining the effects of neuropharmacological treatments on ethanol intake in AA, HAD, P and sP rats are described in Table 4. Also, the doses noted in Table 4 are the doses that exerted the significant effects reported in the table (i.e., the doses inducing the drug's noted effect on ethanol intake are the only doses listed).

5.2. Acquisition of ethanol drinking in the home-cage

The acquisition of ethanol intake is tested by either administering a compound concurrently with the initial days/periods of ethanol access, or by pretreating the animal before they receive their initial days/periods of ethanol access. In one such study, Sable et al. (2006) administered naltrexone, a pan-opioid antagonist, subcutaneously daily during the initial 10 days of ethanol access in male and female adolescent and adult P rats. These authors reported a dose-dependent reduction (modest effects at lower doses of 5 or 10 mg/kg and robust effects at higher doses of 20 or 30 mg/kg) in ethanol intake by both sexes and during both stages of development. Moreover, adolescent rats appeared to be more sensitive than their adult counterparts to these effects of naltrexone. Water and food intake as well as body weight were also monitored, with a compensatory increase in water and food intake in those animals showing the greatest reductions in ethanol intake. This latter finding suggests that the adipic effects of naltrexone were specific for ethanol consumption. In another study from our laboratory, the effects of MDL72222, a 5-HT₃ antagonist, were evaluated during the initial 7 days of ethanol access in adolescent male P rats (J.A. Schultz, personal communication). Again, ethanol intake was reduced dose-dependently (1 and 2 mg/kg consistently reduced 24-h intake across the 7 days, but 0.5 mg/kg reduced intake only transiently after the second day of treatment) during the acquisition of ethanol intake by these rats. Unfortunately, in both of these studies ethanol intake increased to control levels shortly after the removal of the drug. Nevertheless, delaying the onset of alcohol abuse in adolescent individuals may reduce the risk of developing alcohol use disorders (AUDs) later in life. This contention stems from research indicating that an early onset of alcohol abuse is associated with a significantly greater risk for developing alcohol dependence during an individual's lifetime (Anthony and Petronis, 1995; Chou and Pickering, 1992; Grant and Dawson, 1997; Hingson et al., 2006).

5.3. Maintenance of ethanol drinking in the home-cage

Assessing the maintenance of ethanol drinking involves the administration of a compound during ongoing drinking behavior. This is often done under limited access conditions to evaluate the acute effects of the compound on ethanol intake. Although, when conducting a study under 24-hour access conditions ethanol intake can be recorded at different time-points during the day allowing the experimenter to measure the effects of the compound under acute, e.g., the first 1 or 4 h post-administration, and more chronic conditions, e.g., 24 hour intake. As an added benefit, 24 hour access allows the effects of the compound to be examined relative to its temporal bioavailability (e.g., absorption, transit across the blood brain barrier, and metabolism) and aftereffects. In a proof-of-concept study, the effects of aripiprazole, a partial D₂ as well as 5-HT_{1A} agonist and 5-HT₂ antagonist (Kenna et al., 2009), were examined during the maintenance of ethanol intake by adult male P and adult male HAD1 rats (first 2 h of the dark cycle). Results indicated that five consecutive days of intraperitoneal injections of a low dose (15 mg/kg), but not higher doses (45 or 90 mg/kg), reduced ethanol drinking on the fourth and fifth days of treatment in P, but not HAD1, rats (K.M. Franklin, personal communication). When the effects of aripiprazole were examined

in AA rats, a dose of 6.0 mg/kg transiently reduced limited access (4 h/day) ethanol intake after chronic systemic treatment (Ingman et al., 2006). In another study from our laboratory, the effects of antalarmin, a CRF1 receptor antagonist, on ethanol drinking were evaluated in adult male and female P rats under limited (first 2 h of the dark cycle) and 24-h access conditions, respectively (Heilig and Egli, 2006; L.G. Carr, personal communication). Findings from this study indicated that 20 mg/kg of antalarmin, administered intraperitoneally, significantly reduced ethanol intake on the 2nd, 4th and 5th of 5 days of treatment in male P rats and the 2nd day of 3 days of treatment in female P rats.

5.4. Relapse of ethanol drinking in the home-cage

Alcohol abuse and dependence are considered chronic relapsing disorders, such that 60–80 percent of abstinent alcoholics will relapse during their lifetime (Barrick and Connors, 2002; Chiauuzzi, 1991; Jaffe, 2002; Weiss et al., 2001). Thus, an animal model of alcoholism ought to demonstrate this feature of the clinical picture as well (McBride and Li, 1998). Although a number of criteria for relapse have been put forth (Barrick and Connors, 2002; Chiauuzzi, 1991; Jaffe, 2002; Weiss et al., 2001), the primary criterion holds that a return to levels of ethanol consumption equal to or greater than that observed prior to abstinence constitutes a relapse. As discussed by Rodd et al. (2004b), the ADE is one and probably the most often used measure of ethanol relapse-drinking behavior in rats. The ADE is defined as a temporary increase in the ratio of alcohol/total fluid intake and/or voluntary intake of ethanol solutions over baseline (prior to the deprivation period) levels when ethanol is reinstated following a period of alcohol deprivation (Sinclair and Senter, 1967). The aripiprazole study, mentioned above, also examined the drug's effects on ethanol relapse drinking, following a 2 week deprivation period. Similar to the findings of the maintenance test, the 15 mg/kg dose of aripiprazole reduced ethanol drinking on the 4th and 5th test days of relapse in P, but not HAD1, rats (K.M. Franklin, personal communication). There is considerable evidence that the alcoholic population is heterogeneous in nature (Babor et al., 1992; Cloninger, 1987; Conrod et al., 2000; Epstein et al., 1995; Lesch and Walter, 1996; Prelipceanu and Mihailescu, 2005; Windle and Scheidt, 2004; Zucker, 1987). Therefore, this latter finding of an effect in P, but not HAD1, rats provides support for testing promising compounds in multiple selectively bred lines, which could serve as models for different subtypes of alcoholics (See Tables 2 through 4; also see Litten et al., 2012). The fact that the AA, P, HAD1, HAD2 and sP rat lines display different levels of an ADE under particular conditions and for different periods of time, indicates that these rat lines can serve as animal models for assessing compounds targeting relapse-like ethanol drinking behavior (e.g., Colombo et al., 2003; Gilpin et al., 2003, 2008b). Also, see the discussion on the operant ADE and its pharmacological manipulation as a measure of relapse behavior described below.

5.5. Using operant procedures to evaluate pharmacological treatments targeting alcohol abuse and dependence

As indicated in the criteria for an animal model of alcoholism (Cicero, 1979; Lester and Freed, 1973), a subject must be willing to work for access to ethanol. Operant procedures allow a researcher to quantify the amount of work a subject will exert in order to obtain access to an ethanol solution. In the present context, work is operationally defined as the amount of lever pressing a subject will display under a fixed-ratio or progressive-ratio schedule greater than 1 (i.e., 1 indicating the subject receives 1 dipper presentation for each lever press). The operant chamber includes a sound-attenuating shell that houses a Plexiglas cage with associated hardware for measuring this work load. The operant test cage [sometimes called a Skinner box after B.F. Skinner who pioneered its use to investigate response contingencies (Skinner, 1971)] generally contains two levers that operate the presentation of a dipper, or sometimes a sipper tube (Cunningham et al., 2000; Epstein et al.,

2006; Leeman et al., 2010; Rodd et al., 2004b; Samson, 2000; Samson and Czachowski, 2003) of ethanol or another palatable fluid (e.g., water, saccharin, etc.). The presentation of the dipper is controlled by a computer program, such that the ratio of lever presses to dipper presentations can be manipulated. Thus, the higher the ratio of lever presses to dipper presentations displayed the greater the amount of work (effort put forth) inferred. Because rats can be trained to press on a lever for access to ethanol, the existing literature using this technique is extensive. This section will provide a brief overview on the use of operant procedures with selectively bred high alcohol-consuming rat lines and general findings on a few compounds targeting alcohol abuse and dependence. Again, a comprehensive summary of ligands, and experimental parameters used in each study, for reducing ethanol intake and/or self-administration by high alcohol-consuming rats is presented in Table 4.

5.6. Maintenance of ethanol drinking in the operant chamber

Similar to home-cage testing, operant procedures allow an investigator to evaluate different phases of the addictive process. Unlike home-cage testing, because an animal must be trained to lever press for ethanol access, operant procedures can not, in general, be used to assess pharmacological manipulation of the acquisition of ethanol self-administration. However, once lever press responding for ethanol has been established, compounds targeting different neurotransmitter/neuromodulator systems can be given prior to operant sessions to examine the effects on maintenance responding for alcohol. For example, the GABA_B receptor agonist, baclofen (Maccioni et al., 2008b), and positive allosteric modulators of the GABA_B receptor, GS39783 (Maccioni et al., 2008b), *rac*-BHFF (Maccioni et al., 2010b) and BHF177 (Maccioni et al., 2009a), reduce the maintenance of ethanol operant self-administration by sP rats, see also Agabio et al. (2012). In AA rats it has been shown that centrally administered SR141716A, a CB₁ cannabinoid receptor antagonist, reduces the maintenance of operant responding for ethanol (Malinen and Hyttia, 2008). And, in inbred P rats, L-152,804, an NPY Y₅ receptor antagonist, reduces the maintenance of operant responding for ethanol as well (Schroeder et al., 2005b).

5.7. Relapse of ethanol drinking in the operant chamber

The effect of forced deprivations on relapse drinking such as the ADE can also be measured using operant procedures. Once maintenance responding for ethanol has been established, a period of forced deprivation can be implemented by keeping the animals in their home cage for a period of weeks or days. Upon their return to the operant chamber, an increase in responding for ethanol above that which was seen prior to the forced deprivation is evidence of an ADE. The cycle of daily operant sessions with periods of forced deprivations can be repeated to examine if the deprivation effect increases in magnitude and/or duration after repeated deprivations. Animals can be pretreated with different pharmacotherapies prior to reintroduction to the operant chamber after forced deprivation in order to examine the ability of these compounds to curb relapse-like self-administration. For example, it has been shown that LY404039, an mGluR_{2/3} agonist (Rodd et al., 2006), and SB-334867, an orexin₁ receptor antagonist (Dhaher et al., 2010), reduce ethanol-seeking and relapse-like (i.e., ADE) operant ethanol responding, respectively, by P rats. In another study with P rats, MPEP, an mGluR₅ antagonist, reduced both the maintenance of operant ethanol responding as well as the expression of an operant ADE (Schroeder et al., 2005a).

5.8. Models of ethanol-craving and -seeking in the operant chamber

One advantage of using operant procedures to measure ethanol self-administration behavior is that the operant environment provides explicit cues signaling ethanol availability. These cues are distinct from those found in the home-cage environment and can be incorporated into experimental procedures to examine ethanol craving behavior. After a substantial number of pairings of the operant cues with ethanol reinforcement/reward, the cues can

elicit lever-pressing behavior even in the absence of ethanol reward (i.e., cue-induced responding). Therefore, it is not surprising that cue-induced reinstatement of responding has been proposed as one measure of craving behavior (Koob, 2000). An example of this is the finding that baclofen reduces cue-induced reinstatement of responding for ethanol in sP rats (Maccioni et al., 2008a), and there is evidence that baclofen reduces craving for alcohol in clinical populations (c.f., Agabio et al., 2012). Two other procedures that use environmental cues associated with operant ethanol self-administration to assess craving/seeking behavior include (a) extinction and (b) Pavlovian Spontaneous Recovery (PSR) of responding paradigms. In both cases, lever-pressing behavior in the absence of ethanol reinforcement is recorded. Despite the absence of reinforcement, it usually takes several sessions after the maintenance of operant responding for ethanol has ended for operant lever pressing to be fully extinguished. Thus, the persistence of responding during extinction (i.e., in the absence of reward) can be considered an indicator of craving as well (Koob, 2000; Littleton, 2000).

5.8.1. Pavlovian Spontaneous Recovery (PSR) of responding—Several weeks to months after the last extinction session, animals can be placed back into the operant chamber to assess PSR of responding. PSR is the spontaneous recovery, of the previously extinguished, lever-pressing behavior due to time spent away from the cues associated with extinction (Rodd et al., 2004b). However, it should be remembered that it is virtually impossible to separate the effect of cue-induced reinstatement of responding (Koob, 2000) from the PSR phenomenon. Similar to extinction, during PSR-testing lever presses are recorded but are not reinforced. As such, like extinction, PSR can measure craving by looking at the persistence of responding in the absence of ethanol reward (Rodd et al., 2004b). Different pharmacotherapies can be used to try to decrease responding indicative of craving during extinction and PSR. Moreover, the differential effects of a compound across different operant parameters can be delineated when assessed within the same animals. For example, in a study examining the maintenance of ethanol responding, ethanol seeking behavior (PSR), and relapse self-administration (ADE), it was found that LY404039, an mGluR_{2/3} agonist, reduced both ethanol-seeking behavior (PSR) and relapse ethanol-responding (ADE) but not the maintenance of ethanol-responding by P rats (Rodd et al., 2006). When evaluating the effects of SB-334867, an orexin₁ receptor antagonist, on operant self-administration of ethanol by P rats, it was found that SB-334867 reduced relapse ethanol-responding (ADE), but not ethanol-seeking (PSR) behavior (Dhaher et al., 2010). These latter findings indicate that results from testing the effectiveness of a compound under one set of ethanol reward or reinforcement conditions do not necessarily reflect the effectiveness of the compound under different conditions. Therefore, just as a compound should be tested in multiple rat lines, with divergent genetic backgrounds, a compound should also be tested under multiple conditions in order to elucidate its efficacy under the myriad of conditions experienced by the alcoholic.

5.9. Summary

In general, the P line has received the most attention when testing compounds for reducing alcohol abuse and dependence (Table 4). The next most commonly tested line is the AA line followed closely by the sP line. As with innate neurobiology, the HAD lines have received the least amount of research regarding compounds to treat alcohol abuse and dependence. In Table 4, 27% (73/266) of the experiments were conducted in female rats, 39% (103/266) of the experiments evaluated the effects of a compound on operant self-administration, and of the home-cage experiments half (84/163) were free-choice continuous access (FCCA) and half (85/163) were free-choice limited access (FCLA). The effects of a compound on (a) acquisition of ethanol intake were examined in 10 studies (4 with P rats and 6 with sP rats), (b) ethanol-seeking were examined in 9 studies (5 with P rats and 4 with AA rats), and (c) relapse to ethanol-drinking behavior were examined in 9 studies (all of these conducted with

P rats). In general, the vast majority of studies were conducted on the maintenance of ethanol drinking or self-administration and in male rats. Thus, more research is needed on possible sex-differences as well as ethanol-seeking and relapse-like drinking (also see Section 8. Future directions).

In general, home-cage ethanol drinking studies offer a rapid, high throughput screening tool for evaluating the efficacy of pharmacological treatments targeting alcohol abuse and dependence. Under these conditions, pharmacological manipulations of the rewarding effects of ethanol can be examined. An added benefit is the assessment of a compound's effects on concurrent food and water intake. However, these latter two measures also introduce a confound such that ethanol absorption is altered (reduced) by gastric contents (i.e., food and water). As noted by Leeman et al. (2010), BAC levels (estimated or actual) are an important parallel measure needed between clinical and animal alcohol research. For instance, the effects of a pharmacological treatment on the latency to drink is an important clinical measure; and, if an animal has food in its stomach, then a BAC reflecting a low pharmacological impact may be present even though the actual amount of ethanol consumed would suggest otherwise. These authors (Leeman et al., 2010) note that the use of a limited access procedure may mitigate some of these effects. In addition, an understanding of a particular rat line's drinking pattern would facilitate developing methodology to reduce the role of dietary confounds. Evaluating the drinking/licking pattern of P and HAD rats (Bell et al., 2006; R. Dhaher personal communication, respectively) confirms the influence of initiating ethanol access at the beginning of the dark cycle. Note that peak ethanol intake in P rats when using a scheduled-access drinking-in-the-dark procedure is the first hour of dark (Bell et al., 2011), whereas peak ethanol intake is three to 4 h into the dark cycle when testing mice (Rhodes et al., 2005; Crabbe et al., 2009). Leeman et al. (2010) also point out that it is becoming increasingly clear that individual differences in a subject's propensity to drink "too much too fast" or "too much too often" need to be factored into individualized treatment strategies and the development of animal models of alcoholism. The drinking-in-the-dark scheduled access (e.g., Bell et al., 2011; Crabbe et al., 2009) and alcohol deprivation effect (c.f., Rodd et al., 2004b) procedures appear to mimic the former and latter respectively. Finally, the relatively crude level of measurement (Heilig and Koob, 2007: g/kg/unit time) and the inability to measure motivation (Tabakoff and Hoffman, 2000) highlight limitations when using home-cage procedures.

Therefore, despite the ease with which home-cage drinking tests can be conducted, the reinforcing effects of ethanol cannot be readily observed under home-cage access conditions. Essentially, an examination of the reinforcing properties of ethanol, and its disruption, requires an evaluation of the amount of effort, or work, a subject is willing to put forth in order to obtain access to ethanol. Operant procedures provide an elegant method to measure this effort and work. Operant testing allows for increased sensitivity of measurement as it pertains to ethanol self-administration and the effects of pharmacological challenges on these measurements. Thus, measurements in latency to drink (lick), changes in response rate across time, and changes in the level of effort exerted to obtain ethanol can be evaluated in the operant setting. In addition, the operant procedure is tailor made to examine cue-induced ethanol-seeking behavior, whereas home-cage procedures do not allow for easy assessment of this behavior. The fact that motor activity and food intake are rarely measured in operant experiments indicates that specificity of drug effects cannot always be determined, although the presence of an alternate reinforcer can give a crude indication of response perseveration, indiscriminate responding or the absence of responding. Due to possible limited resources (e.g., time, equipment, etc.) operant studies on pharmacological treatments have often been acute, rather than chronic, in nature. Acute rather than chronic treatment is a drawback of many pharmacological studies in general (e.g., Leeman et al., 2010). Finally, as noted in the next section, very few studies have been conducted in

multiple rat lines which limit interpretation of the findings, especially as they relate to generalizability across multiple populations.

A number of recent reviews (e.g., Leeman et al., 2010; Litten et al., 2012; Stephens et al., 2010) discuss the need to examine the effects of compounds under more than one self-administration procedure. This allows for greater pharmacological differentiation in treatment effectiveness. For instance, naltrexone's ability to reduce acute ethanol reinforcement/reward would appear to target "too much too fast" ethanol intake (c.f., O'Malley and Froehlich, 2003) and acamprosate's effectiveness in severely dependent subjects, as well as its ability to interfere with excessive but not moderate consumption by rats (Rimondini et al., 2002), would appear to target "too much too often" ethanol intake (c.f., DeWitte et al., 2005). Refining the level of measurement (e.g., licking rate) may also facilitate medications development and the translatability of findings to the clinical condition (Leeman et al., 2010; Litten et al., 2012; Stephens et al., 2010). For example, it has been shown that allopregnanolone, while not altering the overall amount of ethanol consumed, at moderate to high doses reduced licking frequency and high doses reduced bout sizes in mice (Ford et al., 2008). Several of the examples in the text of Section 5 highlight differences in pharmacological efficacy across self-administration procedures (i.e., acquisition vs. maintenance vs. relapse of self-administration behavior) highlighting that very few studies have examined differences in treatment efficacy within the same subject (Table 4). A recent study not only examined pharmacological efficacy across high alcohol-consuming rat lines and test procedures but also employed multiple high resolution behavioral endpoints (Maccioni et al., in press). As noted in Section 6.4. below, this study (Maccioni et al., in press) found that GS39783, and to some extent baclofen, differentially affected – from almost no effect to virtually complete suppression – lever-responding for alcohol in P, sP, and AA rats (Maccioni et al., in press). These latter findings provide support for (a) heterogeneity in the efficacy of pharmacological manipulations on alcohol self-administration by different alcohol-preferring rat lines, (b) the hypothesis that these rat lines may represent models of different subtypes of alcoholics, and (c) the need for testing promising compounds in more than one line of alcohol-preferring rats and with more than one ethanol self-administration procedure.

Despite heterogeneity among animal models of alcoholism, it has been argued that pharmacological treatments evaluated in the clinical setting should also be assessed in the different animal models to test for pharmacological validity/generalizability (c.f., Litten et al., 2012). Therefore, it should be highlighted that naltrexone, and naloxone, consistently reduce ethanol intake in all of the lines in Table 4, as well as the UChB (Quintanilla and Tampier, 2000), FH/Wjd (Overstreet et al., 2007), and WHP (Dyr and Kostowski, 2008) rat lines. Results with acamprosate have been equivocal in Table 4, but are more promising in the FH/Wjd line (Overstreet et al., 2007). However, topiramate does reduce ethanol intake in P (Table 4) as well as HAD1 (KM Franklin, personal communication) rats but still needs to be tested in the other lines. Prazosin, an adrenergic α_1 antagonist, consistently reduces ethanol intake in P rats (Table 4) but needs to be tested in the other lines as well. Baclofen reduces ethanol self-administration under operant conditions in AA, P and sP rats (Table 4), although it has very modest effects in HAD1 and P rats under home-cage access conditions (KM Franklin, personal communication; but see Quintanilla et al., 2008 regarding positive findings in UChB rats under home-cage access conditions). Gabapentin increases ethanol intake in P and Wistar rats while inducing a very modest decrease in ethanol intake by HAD1 rats (KM Franklin, personal communication), but still needs to be tested in other rat lines. Amperozide, a 5HT_{2A} antagonist, reduces ethanol intake in AA, HAD and P (Table 4) as well as FH/Wjd (Overstreet et al., 2007) rats. Findings with 5HT₃ antagonists have shown promise in P and sP rats (Table 4), although unpublished work from our laboratory suggests this does not hold true for ondansetron itself (but see Overstreet et al., 2007 regarding

positive findings in FH/Wjd rats). Inhibitors of the serotonin transporter decrease ethanol intake in HAD and P (Table 4) as well as UChB (Alvarado et al., 1990) and FH/Wjd (Overstreet et al., 2007) rats. Finally, antalarmin, a CRF₁ antagonist, reduces ethanol intake in P (Table 4) as well as FH/Wjd rats (Overstreet et al., 2007). Other CRF₁ antagonists have shown no effect on, or possible increases in, ethanol intake by sP rats (Table 4).

6. Comparisons of the selectively bred rat lines

As described above, multiple selective breeding programs have been developed for rat line-pairs differing in alcohol-preference scores. The development of multiple line-pairs was implicitly based on the hypothesis that if a characteristic associated with high, or low, alcohol consumption was observed in more than one line-pair then the probability of this characteristic being associated (positively or negatively) with a genetic predisposition for alcohol abuse is heightened. The development of the replicate pair of HAD vs. LAD rat lines was based explicitly on this hypothesis. The rat line-pairs discussed herein were developed in the 60's, 70's, and early- to mid-80's. Since then, it has become increasingly clear that alcoholism is a heterogeneous disorder with multiple possible antecedents and trajectories. Thus, experiments directly comparing multiple rat line-pairs are relatively recent and very few. These studies are important because they may delineate multiple typologies within this collection of animal models for alcoholism, and this would provide some face validity for the line-pairs regarding the clinical picture.

6.1. Neurobehavioral differences

In an early study, Salimov (1999) examined the AA vs. ANA, P vs. NP, HAD1 vs. LAD1 and HAD2 vs. LAD2 rat line-pairs, as well as several mouse lines with differences in ethanol intake, for anxiety-like behaviors (several measures with the elevated cross-maze and inescapable slip funnel tests). A factor analysis was conducted to see where the respective lines scored on the dimension/factors generated. Although a factor analysis increases the complexity of interpretation, since interpretation is not based on the raw data itself; it is instructive that the HAD1 and HAD2 lines had significant separation in factor scores from the LAD1 and LAD2 lines for factor 1, whereas the AA and P lines had significant separation from the ANA and NP lines, respectively, for factor 2. Thus, the HAD1 and HAD2 line-scores clustered together on factor 1, and the AA and P line-scores formed a separate cluster on factor 2. Given that the HAD-LAD replicate pairs were generated from the same N/Nih foundation stock and the AA-ANA as well as P-NP lines had Wistar lines as their foundation stock, this is not entirely surprising. In another study, Overstreet et al. (1997a) reported that whereas HAD's differed significantly from LAD's (the replicate pair was not identified) on open field rearing, this measure did not differentiate P's from NP's nor did it differentiate AA's from ANA's. In another study examining anxiety-like behavior (Knapp et al., 1997), it was reported that total ultrasonic vocalizations (USVs) differentiated P from NP and AA from ANA rats. However, these authors (Knapp et al., 1997) also reported that time spent vocalizing differentiated P from NP, but not AA from ANA, rats. Contrarily, latency to emit USVs, after an air puff, differentiated AA from ANA, but not P from NP, rats.

In a recent study (Roman et al., 2012), the Multiple Concentric Square Field (MCSF), Open Field (OF) and Elevated Plus Maze (EPM) tests were used to examine a number of anxiety-, impulsivity- and risk taking-like behaviors between the AA vs. ANA, HAD1 vs. LAD1, HAD2 vs. LAD2, P vs. NP as well as sP vs. sNP rat lines. The use of multiple behavioral measures, especially within one test session/apparatus, has been proposed to increase the reliability and comprehensiveness of the constructs measured (c.f., Meyerson et al., 2006; Ramos, 2008), which supports the utility and complexity (71 behavioral parameters were recorded) of the Roman and colleagues study (2012). In summary, the authors (Roman et al.,

2012) noted that the sP line showed greater anxiety-related behaviors than the sNP line and the AA, and to a lesser extent the P, line(s) displayed higher risk-taking behavior than their low alcohol-consuming counterparts. These authors reported that the HAD1 and HAD2 lines could not be differentiated from the LAD1 and LAD2 lines on these two behavioral dimensions. This study (Roman et al., 2012) also revealed that no single parameter within the MCSF, OF and EPM tests revealed a significant difference between high and low alcohol-consuming rats across all five line-pairs. In fact, only three (4%) of the parameters differentiated high from low alcohol-consuming rats across four of the line-pairs and 28 (41%) of the parameters differentiated high vs. low alcohol-consuming rats for only one line-pair. In addition, these tests were most sensitive in measuring differences within the sP vs. sNP and AA vs. ANA line-pairs and were relatively insensitive in detecting differences within the P vs. NP line-pair.

When examining ethanol-induced tolerance, it has been reported that with a high dose of ethanol (2.5 g/kg) rapid tolerance is observed in P and HAD1 rats but not in NP and LAD1 rats, whereas HAD2 and LAD2 rats did not differ in the development and expression of tolerance to the motor impairing effects of ethanol (Suwaki et al., 2001). Similar findings were found when rapid tolerance to moderate-dose ethanol-induced motor impairment was examined (Suwaki et al., 2001). One of the few studies that has examined nonethanol-associated consummatory behavior (Overstreet et al., 1997a) reported that food intake did not differentiate HAD's, P's and AA's from their low alcohol-consuming counterparts, whereas water intake differentiated P's from NP's but did not differentiate HAD's and AA's from their low alcohol-consuming counterparts (also see Files et al., 1998; Samson et al., 1998). In the late 90's, two studies were conducted that examined operant self-administration of ethanol by AA, HAD1, HAD2 and P rats, as well as their low alcohol-consuming counterparts (Files et al., 1998; Samson et al., 1998). We will only discuss the findings from the high alcohol-consuming rat lines here. One study examined operant self-administration of ethanol under continuous (24-h) access conditions (Files et al., 1998). In this study (Files et al., 1998), the order of magnitude for ethanol responses per day was $HAD2 > HAD1 = P > AA$; the order of magnitude for ethanol bouts per day was $HAD2 > AA = P > HAD1$; the order of magnitude for ethanol g/kg/day was $HAD2 > HAD1 > AA = P$; and the order of magnitude for ethanol dipper presentations per bout was $HAD1 > P > HAD2 > AA$. These authors noted that their findings indicate that even though these rat lines may drink similar amounts of ethanol per day under home-cage access conditions; there are significant differences in the reinforcing properties of ethanol as measured by operant response number, ethanol bouts per day, total ethanol consumed and dipper presentations per bout. The second study examined continuous access home-cage drinking and operant self-administration of ethanol under limited (30-min) access conditions (Samson et al., 1998). These authors reported that during initiation of ethanol drinking in the home-cage the order of magnitude for ethanol intake was $AA \sim HAD1 = HAD2 > P$; after employing a sucrose-fading procedure the order of magnitude for ethanol intake was $P \sim HAD1 > HAD2 \sim AA$; and the order of magnitude for ethanol self-administration under fixed-ratio four (FR-4) limited access operant conditions was $HAD1 > P = HAD2 > AA$. Again, these findings indicate some significant differences in the reinforcing effects of ethanol under limited access conditions.

6.2. Genetic differences

In an early transcriptome and RT-PCR confirmatory analysis of the frontal cortex between AA vs. ANA and P vs. NP rats (Worst et al., 2005), it was found that whereas the AA and ANA rats differed in the expression of 6 genes (Munc18, Stx1a, Stx1b, Cacna2d1, Vamp2 and mGluR₃) the P and NP rats differed only in the expression of Vamp2. When examining quantitative trait loci (QTL's) for alcohol preference of high and low alcohol-consuming rat

lines, it was found that the QTL's mediating differences between P and NP rats were located on chromosomes 3, 4 and 8 (Bice et al., 1998; Carr et al., 1998); whereas QTL's mediating differences between HAD1 and LAD1 rats were located on chromosomes 1, 5, 10, 12 and 16 (Foroud et al., 2000). An initial follow-up study revealed QTLs on chromosomes 5, 10 and 16, but not 12, mediated alcohol preference differences between HAD2 and LAD2 rats (Foroud et al., 2003). A subsequent study revealed that QTLs on chromosomes 10 and 16, but not 5 and 12, mediated alcohol preference differences between HAD2 and LAD2 rats (Carr et al., 2003). Thus, differences in QTLs mediating alcohol preference exist even between replicate line-pairs (HAD1-LAD1 vs. HAD2-LAD2) selectively bred from the same foundational rat line (N/Nih).

A recent study has also examined innate differences in gene expression within the VTA across the AA vs. ANA, HAD1 vs. LAD1, HAD2 vs. LAD2, P vs. NP and sP vs. sNP rat line-pairs (McBride et al., 2012). This study was based on three premises (McBride et al., 2012). First, that many genes not related to alcohol abuse and dependence have been fixed during the selective breeding programs discussed above. By extension, if multiple rat line-pairs that have been subjected to the same selection criteria are studied under the same methodological conditions, then the detection of significant differences in gene expression that are not directly associated with the phenotype should be minimized. Second, any common genes that are identified across the rat line-pairs should have a high probability of mediating the high, or low, alcohol consumption phenotype. Finally, the fact that there are genotypic and phenotypic differences between the line-pairs suggests that common gene networks/pathways may be identified across the line-pairs rather than common individual genes. The study revealed that no single gene was significant across all five line-pairs, although 22 genes differed significantly in the same direction across three or four of the line-pairs. Moreover, analyses using Gene Ontology and Ingenuity Pathway information revealed significant categories and networks for up to three, but not more, of the line-pairs. In general, the biological systems identified included transcription, synaptic function, intracellular signaling and protection against oxidative stress with the dopamine and glutamate neurotransmitter systems implicated as well (McBride et al., 2012).

6.3. Neurochemical differences

A study examining innate differences in central urocortin 1 (Ucn1) levels has been conducted between the AA vs. ANA, HAD1 vs. LAD1, HAD2 vs. LAD2 and inbred P (iP) vs. inbred NP (iNP) rat line-pairs (Turek et al., 2005). The Addiction Research Foundation high and low alcohol-consuming (HARF and LARF) rat lines were compared as well, but will not be discussed here. The neuropeptide Ucn1 is related to CRF and binds to both the CRF1 and CRF2 receptors (Bale and Vale, 2004). When the number of Ucn1-positive cells in the Edinger-Westphal nucleus (EWN) was examined, HAD2 rats had greater levels than LAD2 rats, iP rats had lower levels than iNP rats but AA and HAD1 rats did not differ from their low alcohol-consuming counterparts. These differences were confirmed when optical density of Ucn1 immunoreactivity in the EWN was the dependent variable. When the number of Ucn1-positive fibers in the lateral septum was assessed, HAD2 rats had greater levels than LAD2 rats, AA rats had greater levels than ANA rats but HAD1 and iP rats did not differ from their low alcohol-consuming counterparts. When comparing the average number of Ucn1-positive cells in the (EWN) of the high alcohol-consuming rat lines the order of magnitude was HAD2>HAD1>iP>AA. When comparing the average number of Ucn1-positive fibers in the lateral septum of the high alcohol-consuming rat lines the order of magnitude was HAD2>HAD1~iP>AA. In general, this study revealed multiple significant differences in the Ucn1 system between and within these rat line-pairs.

6.4. Differences in pharmacological efficacy

Differences between the rat lines have also been found when assessing the efficacy of pharmacological treatments to reduce ethanol intake. Maccioni et al. (in press) conducted an in-depth study examining baclofen, a GABA-B agonist, and GS39783, a positive allosteric modulator of the GABA-B receptor, on ethanol self-administration across three of the high alcohol-consuming rat lines (AA, P and sP). The first observation was that operant self-administration of ethanol differed among the lines, such that the order of magnitude was $P > sP > AA$. Moreover, the order of breakpoint for ethanol self-administration among the rat lines was also $P > sP > AA$. Baclofen's efficacy in decreasing ethanol intake differed across the rat lines, when the rats were placed on a fixed-ratio operant schedule; such that 1.7 and 3 mg/kg doses were effective in P rats, whereas only the 3 mg/kg dose was effective in sP and AA rats. In addition, baclofen's efficacy in decreasing ethanol intake differed across the rat lines, when the rats were placed on a progressive-ratio operant schedule; such that 1.7 and 3 mg/kg doses were effective in P and sP rats, whereas only the 3 mg/kg dose was effective in AA rats. Interestingly, the 3 mg/kg dose of baclofen increased the latency to respond under the fixed-ratio schedule in all three lines, but the 3 mg/kg dose of baclofen increased the latency to respond under the progressive-ratio schedule in the P and AA rat lines only. Similarly, GS39783's efficacy in decreasing ethanol intake differed across the rat lines, when the rats were placed on a fixed-ratio operant schedule; such that the 25, 50 and 100 mg/kg doses were effective in P and sP rats, whereas only the 50 and 100 mg/kg doses were effective in AA rats. As with baclofen, GS39783's efficacy in decreasing ethanol intake differed across the rat lines, when the rats were placed on a progressive-ratio operant schedule as well; such that the 25, 50 and 100 mg/kg doses were effective in P and sP rats, but none of the doses were effective in AA rats. Regarding latency to respond, the 100 mg/kg dose of GS39783 increased the latency to respond under the fixed-ratio schedule in the P and AA, but not sP, rat lines. However, none of the GS39783 doses affected latency to respond under the progressive-ratio condition. It should be noted that baclofen continues to be examined in clinical trials (Litten et al., 2012).

6.5. Summary

The findings discussed in Section 6 highlight some of the heterogeneity in genotypic and phenotypic characteristics found in animal models of high alcohol consumption. As discussed by Begleiter and Porjesz (1995), alcoholism, as a complex disorder with significant heterogeneity, shares characteristics commonly found in other complex neuropsychiatric diseases/disorders. These characteristics include (1) clinical heterogeneity; (2) polygenic inheritance, such that multiple genes are involved; (3) genetic heterogeneity, such that different polymorphisms/post-translational modifications of a certain gene/gene product may yield similar symptomology; (4) reduced genetic penetrance, such that not all individuals with particular genes or specific variations in a gene develop the disorder; (5) epistatic effects, such that the disorder results from interactions with alleles at different loci; and (6) phenocopies, such that the alcoholism phenotype can be expressed despite lack of a clear genetic predisposition. We propose that the selectively bred, high alcohol-consuming rats discussed herein are excellent platforms to evaluate endophenotypes associated with AUDs and the efficacy of compounds targeting alcohol abuse and dependence. We also propose that the expanded use of multiple selectively bred, high alcohol-consuming rat lines will result in (a) observations of other endophenotypic or pharmacological efficacy differences across these rat lines or, conversely, (b) increased generalizability/homogeneity of findings on endophenotypes or efficacy in pharmacological interventions targeting AUDs.

Thus far, only a handful of studies have actually examined more than one or two of these rat lines to determine whether the findings are generalizable or not. Nevertheless, findings from these few studies support the hypothesis that these animal models, as a group, display some

of alcoholism's clinical-like heterogeneity. One clear distinction can be made between the genotypes of P vs. NP and HAD vs. LAD line-pairs, such that QTLs associated with alcohol preference are on chromosomes 3, 4 and 8 for the P vs. NP line-pair, whereas the QTLs are located on chromosomes 5, 10, 12 and 16 for the HAD1 vs. LAD1 and chromosomes 10 and 16 for the HAD2 vs. LAD2 line-pairs. Understandably, candidate genes associated with the alcohol preference phenotype also differ between these line-pairs, with NPY, alpha synuclein (Snca) and the CRF₂ receptor (Liang et al., 2003; Spence et al., 2009) as well as preproNPY (c.f., Koob and Le Moal, 2006) on chromosome 4 for the P vs. NP line-pair and CREB binding protein (Crebbp) and a MAP kinase (Mapk8ip3) on chromosome 10 (Bice et al., 2010) as well as proenkephalin on chromosome 5 and neuronal nitric oxide synthase-1 on chromosome 12 (c.f., Koob and Le Moal, 2006) for the HAD vs. LAD line-pairs.

7. Overall summary

Alcoholism remains a significant public health concern, both in terms of societal cost and as a contributing factor in medical diseases and death. Alcohol exposure at an early age and binge-type drinking have been demonstrated to be predictive of alcohol abuse or alcohol dependence later in life and different drinking patterns have been used to classify individuals into different typologies and/or drinking profiles. Research indicates that the effectiveness of certain pharmacotherapies is influenced by where an individual falls on these classification continuums. Thus, in order to effectively evaluate pharmacotherapies in an animal model, the proposed model should allow for evaluating the effects of (a) early alcohol exposure and (b) different drinking patterns or endpoints including continuous access, limited access, binge-like drinking and relapse.

The progressive nature of alcohol abuse and dependence must also be considered when attempting to determine an effective treatment. Progression from alcohol experimentation to dependence is not always linear in nature, with individuals often returning to earlier stages of the disease process before advancing to the final stages of dependence. The positive-reinforcement aspects of alcohol (e.g., euphoria) that drive the disease early on, are usually replaced by negative-reinforcement aspects (e.g., removal of anxiety or withdrawal) in the later stages of the addiction cycle. This makes alcohol dependence very difficult to treat. An effective animal model of alcoholism should display both the positive-and negative-reinforcement aspects of the disease so that the effectiveness of different compounds can be evaluated for each aspect.

Animal models allow experimenters to control for differences in the subject's (a) genetic background, (b) exposure to environmental factors, and (c) prior drug experience. Animal models of alcoholism have allowed the neurobehavioral, neurochemical and neurophysiological correlates associated with the behavioral, physiological and/or neurological states associated with alcohol abuse and dependence to be examined. Criteria for an animal model of alcoholism have been put forth that relate to the DSM-IV (American Psychiatric Association, 1994) diagnostic criteria for alcohol abuse and dependence. In addition, the familial incidence of alcoholism has been well established and a genetic influence on ethanol intake in rodents has been incorporated into bidirectional selective breeding programs for ethanol preference and alcohol consumption. As such, the translational value of selectively bred high alcohol-consuming rat lines is a real benefit over other models that use environmental manipulations (e.g., ethanol inhalation chambers, schedule-induced polydipsia, sucrose fading, etc.) to promote excessive alcohol intake.

The selectively bred high alcohol-consuming rat lines meet many, and in some cases all, of the proposed criteria for an animal model of alcoholism. Many of the neurobehavioral and neurobiological phenotypes present in alcohol abusing or dependent individuals are also

present in the high alcohol-consuming lines. However, in spite of similar selection criteria for the alcohol-drinking phenotypes, the correlated behavioral traits and neurochemical and gene expression profiles may differ among the rat lines, suggesting that the high alcohol-drinking phenotype can be mediated by disparate signaling pathways in the CNS. This variability in neurobehavioral and neurobiological responses could be an ideal platform for screening compounds targeting particular subpopulations of alcoholics. This is especially true when the neurobiological or neurobehavioral phenotypes of the target population overlap with those present in one or more of the high alcohol-drinking rat lines.

Ethanol consumption by a rat in their home-cage can be used to model the type of excessive alcohol consumption that occurs in humans. Home-cage testing allows a researcher to determine how well a therapeutic agent can curb ethanol intake when water and food are also available as is typical in the clinical condition. The ability of a compound to prevent or moderate the acquisition of ethanol intake can be examined in high-alcohol drinking rats who are alcohol naïve at the start of home-cage testing. The ability to delay the onset of alcohol abuse may ultimately reduce the severity of alcohol dependence later in life. In addition, the ability of the compound to both reduce ethanol intake once home-cage drinking has been acquired (i.e., maintenance drinking) as well as prevent relapse drinking after a period of abstinence can also be examined. This ability to evaluate a compound during these different drinking phases is a significant benefit of home-cage drinking procedures. It is important to consider, however, that it is very difficult to differentiate nonspecific effects (taste aversion, sedation, motor impairment, interactions with general feeding behavior, etc.) from reward- and reinforcement-related effects when measuring ethanol consumption in the home cage, especially when continuous ethanol access is used.

Because an animal must be trained to lever press for ethanol, operant testing procedures cannot typically be used to assess how well a pharmacotherapy can prevent the acquisition of ethanol-associated responding. Similar to home cage drinking procedures, operant procedures can be used to examine how well a compound reduces the maintenance of responding for alcohol, as well as relapse-like behavior (i.e., an ADE). Because the animal must lever press for alcohol access, operant procedures also allow a researcher to evaluate how a given compound alters responding in the absence of an ethanol reward (i.e., seeking or craving behavior), as is typical during extinction and Pavlovian Spontaneous Recovery. As there are cues unique to the operant testing environment that are not present in the home cage, operant testing offers the distinct advantage of investigating cue-induced responding (i.e., seeking or craving behavior in the absence of ethanol reinforcement) and how well a given pharmacotherapy prevents this behavior.

With the background on these rat animal models of alcoholism and techniques to assess different stages in the addiction cycle laid out, a comprehensive list of ligands tested in these rat animal models was presented in Table 4. The purpose of the table is to give researchers, both clinical and preclinical, a primary resource to examine previous work aimed at manipulating particular neurotransmitter/neuromodulator systems within the milieu of genetic selection. Today, there is greater recognition that, in order to be effective, treatments will have to be tailored to an individual's genetic and behavioral make-up, including co-morbid psychiatric conditions. The neurotransmitter/neuromodulator systems mediating these co-morbid conditions often overlap with the systems mediating alcohol abuse and dependence (Table 3). Tables 3 and 4 will allow investigators of these co-morbid conditions to recognize compounds or neurobiological systems that are effective in ameliorating or mediating disorders in their area of expertise. Thus, compounds approved to treat these co-morbid conditions may be successfully repurposed to treat alcohol abuse and dependence as well.

8. Future directions

The selective breeding programs described herein have led to the creation of several invaluable and irreplaceable alcohol-preferring rat lines that play a critical role in advancing our knowledge of the factors that mediate the development of alcoholism. Moreover, these high alcohol-consuming rat lines have provided important information for medication development to curtail alcohol abuse and dependence (Tables 3 and 4). Thus, we believe that the future of medication development targeting alcohol abuse and dependence will be advanced by the continued use of these animal models and should involve a multidimensional and multipronged strategy:

1. One strategy is to use next-generation DNA sequencing technologies to delineate the genomic signatures of selection in the multiple pairs of high/low alcohol-consuming rat lines and next-generation RNA seq methodologies to analyze allele-specific expression of genes in F1 crosses from high×low lines. These high throughput technologies should help move the field from QTL analyses (e.g., Ehlers et al., 2010) to quantitative trait nucleotide [QTN; i.e., single nucleotide polymorphisms (SNPs)] and quantitative trait gene (QTG; e.g., Milner and Buck, 2010) analyses. By doing so, the level of genomic resolution and the power of these analyses can be exponentially enhanced resulting in a greater proportion of genetic variation associated with alcohol preference in these rat models being revealed. By localizing the genetic variation to genes and SNPs, research on the potential importance of the epigenomics/epigenetics (e.g., Moonat et al., 2010; Renthal and Nestler, 2009) in alcohol preference can also be advanced. These developments will allow an investigator to combine traditional hypothesis-generating research based on deductive reasoning with unprejudiced genome association studies across the five alcohol-preferring rat lines. Research findings from this approach will further delineate neuropathways mediating the rewarding and reinforcing effects of ethanol. In turn, new drugable targets can be examined to prevent and/or treat alcohol abuse and dependence.
2. Another direction is the continued use of emerging and evolving neuroscience methodologies to examine the role of second messenger systems, protein-protein interactions, and synaptic plasticity (e.g., Gorini et al., 2010; Newton and Messing, 2006; Russo et al., 2010; Szumlinski et al., 2008; Tabakoff et al., 2001). These methodologies would include high throughput gene and/or protein expression techniques and their synthesis (e.g., Gorini et al., 2011; Kerns and Miles, 2008; Neuhold et al., 2004; Treadwell, 2006). Presently, this synthesis has started to reveal the complex neurobiology of alcoholism and the role of genetics in its development through functional and genetical genomics (e.g., Farris et al., 2010; Rodd et al., 2007; Tabakoff et al., 2009). Nevertheless, it is believed that with the continued development of these more advanced bioinformatic strategies, the findings generated by functional and genetical genomics will increase our knowledge on the neurobiology of AUDs many-fold.
3. Alcoholism (alcohol dependence) is a chronically relapsing disorder conceptualized to cycle between impulsive drinking leading to alcohol binge intake and intoxication and compulsive drinking mediated by physical and motivational withdrawal from alcohol in its absence including preoccupation with and anticipation of alcohol consumption (Koob, 2003). The former (impulsive drinking) is associated with positive reinforcement, whereas the latter (compulsive drinking) is associated with negative reinforcement (Koob and Le Moal, 2006). These cycles are repeated spirally and they become more exaggerated over time. Additionally, when these repeated cycles are coupled with the development of tolerance, the level

of alcohol intake increases and signs/symptoms of alcohol withdrawal worsen. To date, the testing of antidipsic medications in alcohol-preferring rats, and rodents in general for that matter, has primarily been limited to the setting of impulsive drinking/positive reinforcement (Koob et al., 2003). In the future, proprietary and nonproprietary molecules should also be tested for their ability to reduce alcohol drinking in alcohol-preferring rats made alcohol-dependent by chronic intermittent alcohol vapor exposure (e.g., Gilpin et al., 2008a).

4. After delineating top candidate genes, as has been done in the P and HAD1-2 selected lines, future studies should use reverse genetic tools such as zinc-finger nucleases (ZNFs) and truncated transcription activator-like effector nucleases (TALENs) to induce double-strand breaks at targeted loci to produce KO rats using selectively bred rats as the background stock (e.g., Wood et al., 2011). These new targeted genome editing tools can specifically convert alcohol-preferring rats to become more alcohol-nonpreferring and vice versa; thereby the roles of these manipulated genes in alcohol preference and excessive alcohol intake can be better defined.
5. Presently, researchers are actively testing a series of marketed and unmarketed new proprietary molecules that are supplied by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) via a Health and Human Services (HHSN) Medication Development Contract (also see Litten et al., 2012 for discussions on this and other medication development programs undertaken by NIAAA of the National Institutes of Health). Thus far, nine marketed medications (some of these findings have been incorporated into the text via personal communications from KM Frankin) and seven new proprietary molecules have been evaluated for their effects on the maintenance of ethanol drinking as well as relapse-like behavior. These evaluations have been conducted under double-blind conditions such that only the Project Officer at NIAAA is aware of the doses and the compound characteristics (i.e., the mechanism of action for the proprietary compounds is not known by the investigators). The results thus far have provided new information on comparisons of drug efficacy between adult male P vs. HAD1 rats. This parallels the work by Maccioni et al. (in press) described in Section 6.4. When taken together, the findings from these studies support the notion that the availability of multiple selectively bred high alcohol-consuming rat lines should provide an important platform for evaluating treatment compounds in the context of clinical heterogeneity.
6. Given the preclinical data indicating dopamine and serotonin mediate, at least in part, the rewarding and reinforcing effects of ethanol (and other drugs of abuse), it is surprising that clinical trials with compounds targeting these systems have not been as effective as expected (e.g., Edens et al., 2010). However, as noted by Johnson (2005, 2010) and Litten et al. (2012), complex neuropsychiatric disorders generally require a polypharmacy approach in treatment and there is no reason to expect alcoholism, or drug addiction, to be any different. As a caveat, this conjecture is borne out by the fact that over 75% of the patents granted, between 2000 and 2010, for the treatment of alcoholism world-wide include compounds targeting multiple neurotransmitter, neurohormonal, neuromodulator or enzymatic systems (Bell et al., 2012). It is noteworthy that Rezvani et al. (2000)) have conducted a study examining the effects of an intraperitoneally administered cocktail containing naltrexone (6 mg/kg), fluoxetine (3 mg/kg) and a TRH analog (TA-0910, 0.6 mg/kg) on ethanol intake in P, HAD (replicate line not stated) and Fawn Hooded rats. Whereas only fluoxetine alone induced a modest reduction in P rats, the cocktail treatment resulted in a robust decrease in alcohol intake by all

three rat lines (reductions ranged from 40% in HAD rats to 70% in P rats). In addition, Table 4 identifies compounds with multiple neurochemical targets. Overall, it is clear that more research with polypharmacy treatments needs to be done.

Given the above, pharmacogenetic/pharmacogenomic strategies for the treatment of alcohol abuse and dependence are evolving (Haile et al., 2008; Johnson et al., 2011; Kranzler and Edenberg, 2010; Ray et al., 2009, 2010; Sher et al., 2010; Shields and Lerman, 2008; Wong et al., 2008). However, these approaches need further development. Future work will need to examine genotypic and phenotypic associations both in clinical and preclinical (i.e., rodent) populations. On a parallel track, compounds targeting neuronal systems implicated by certain genotypic-phenotypic associations will need to be evaluated in both the preclinical and clinical settings. As noted by Litten et al. (2012), these compounds, especially those being investigated for repurposing, may be assessed in clinical-like laboratory settings before undergoing FDA-associated clinical trials. Some of this will be trial-and-error, but when appropriate animal models are used, relatively high throughput screening can be undertaken. While an animal model that expresses the desired phenotype is a good starting point, an animal model that expresses both genotypic and phenotypic characteristics of the disorder is preferred. Thus, selectively bred high alcohol-consuming rat lines are ideally suited for this work. Similarly, greater use of genetic screening via blood samples will provide important information about the effects of off-the-shelf compounds that have been approved for other disorders when treated in alcohol abusing or dependent individuals. Finally, the continued use, and development, of advanced neuroimaging techniques will also provide vital information on brain regions of interest as putative sites of action for different compounds when evaluated in alcoholics, polysubstance abusers, healthy controls, and individuals suffering from dual, or multiple, psychiatric disorders. In summary, progress has been made in developing treatments for alcohol abuse and dependence; however, continued biochemical, genetic, and behavioral research is required to further develop pharmacotherapies tailored to an individual's genetic, neurochemical, physiological and psychological make-up.

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Table 1

How the criteria for an animal model of alcoholism (Cicero, 1979; Lester and Freed, 1973; McBride and Li, 1998) relate to diagnostic criteria, for alcohol abuse and dependence, as outlined in the DSM-IV (American Psychiatric Association, 1994).

DSM-IV	Animal model
Expression of tolerance by either <ul style="list-style-type: none"> a. increased amounts needed to achieve desired effect, or b. diminished effect with continued level of use 	Chronic alcohol consumption leads to tolerance to the appetitive and/or aversive effects of alcohol with greater amounts consumed over time.
Alcohol is consumed to either <ul style="list-style-type: none"> a. avoid expression of withdrawal symptoms, or b. to relieve withdrawal symptoms 	Chronic alcohol consumption results in withdrawal signs and alcohol intake is increased during and/or after withdrawal of alcohol access (the alcohol deprivation effect, ADE, a model of relapse behavior can also be considered a model of this).
Alcohol is consumed either <ul style="list-style-type: none"> a. in greater quantities, or b. over a longer period than desired 	Chronic drinking leads to increased amounts consumed over time (the ADE can also be considered a model of this).
Inability to control alcohol use	Reinstatement/relapse of alcohol consumption and the ADE.
Excessive amount of time is spent in <ul style="list-style-type: none"> a. obtaining, b. using, or c. recovering from the effects of alcohol 	Will operantly respond for alcohol, even with high workload (fixed-ratio) requirements.
Alcohol use leads to forsaking important <ul style="list-style-type: none"> a. social, b. occupational, and/or c. recreational activities 	Will consume and self-administer alcohol until impaired/intoxicated.
Alcohol use is continued despite knowledge of persisting problems associated with alcohol use	Has not been tested

Table 2
Criteria for an animal model of alcoholism that each of the high alcohol-consuming selected lines successfully meets.

Criteria	Rat line				
	AA	P	HAD	sP	UChB
1) Ethanol is orally self-administered under free-choice conditions	>5 g EtOH/kg body weight consumed per day ¹	>5 g EtOH/kg body weight consumed per day ⁷	>5 g EtOH/kg body weight consumed per day ¹⁶	>5 g EtOH/kg body weight consumed per day ²⁰	>5 g EtOH/kg body weight consumed per day ²⁷
2) Pharmacologically relevant BACs achieved with self-administration	BACs seen in humans achieved ²	BACs seen in humans achieved ⁸	BACs seen in humans achieved ¹⁷	BACs seen in humans achieved ²¹	BACs seen in humans achieved ²⁸
3a) Ethanol consumed for its post-ingestive effects and not for taste or calories only	Not tested	EtOH is self-administered intra-gastrically ⁹	Not tested	Not tested	Not tested
3b) Ethanol is rewarding as indicated by drinking-induced locomotor activation	EtOH consumption leads to motor activation ³	EtOH consumption leads to motor activation ¹⁰	Not tested	EtOH consumption leads to motor activation ²²	Not tested
4) Ethanol is positively reinforcing (<i>i.e.</i> , the animal works for access)	EtOH is operantly self-administered ⁴	EtOH is operantly self-administered ¹¹	EtOH is operantly self-administered ¹⁸	EtOH is operantly self-administered ²³	Not tested
5) Chronic consumption leads to metabolic and functional tolerance	Metabolic ⁵ tolerance expressed	Metabolic ¹² and functional ¹³ tolerance expressed	Not tested	Functional tolerance expressed ²⁴	Functional tolerance expressed ²⁹
6) Chronic consumption leads to dependence (<i>i.e.</i> , withdrawal-like signs are seen)	Not tested	Chronic consumption leads to dependence ¹⁴	Not tested	Chronic consumption leads to dependence ²⁵	Not tested
7) Relapse-like behavior is displayed	Display an ADE ⁶	Display an ADE ¹⁵	Display an ADE ¹⁹	Display an ADE ²⁶	Display an ADE ³⁰

¹ Ritz et al., 1986.

² Aalto, 1986.

³ Patvarinta and Korpi, 1993.

⁴ Files et al., 1998; Samson et al., 1998.

⁵ Forsander and Sinclair, 1992.

⁶ Sinclair and Li, 1989.

- ⁷Li et al., 1987.
- ⁸Bell et al., 2006, 2008a, 2011; Murphy et al., 1986, 2002; Rodd et al., 2003.
- ⁹Murphy et al., 1988; Waller et al., 1984.
- ¹⁰Bell et al., 2002; Melendez et al., 2002.
- ¹¹Files et al., 1998; Murphy et al., 1989; Rodd et al., 2003; Rodd-Henricks et al., 2000a, 2000b; Samson et al., 1998; Toalston et al., 2008.
- ¹²Lumeng and Li, 1986.
- ¹³Gatto et al., 1987; Stewart et al., 1991.
- ¹⁴Kampov-Polevoy et al., 2000; Waller et al., 1982.
- ¹⁵Rodd et al., 2003; Rodd-Henricks et al., 2000a, 2000c, 2001.
- ¹⁶Rodd-Henricks et al., 2000a.
- ¹⁷Bell et al., 2008a; Murphy et al., 2002; Oster et al., 2006.
- ¹⁸Files et al., 1998; Oster et al., 2006; Samson et al., 1998.
- ¹⁹Oster et al., 2006; Rodd et al., 2009; Rodd-Henricks et al., 2000b.
- ²⁰Agabio et al., 1998.
- ²¹Colombo et al., 2006.
- ²²Colombo et al., 1998b.
- ²³Vacca et al., 2002b.
- ²⁴Colombo et al., 2006.
- ²⁵Loi et al., 2010.
- ²⁶Agabio et al., 2000; Serra et al., 2003.
- ²⁷Mardones and Segovia-Riquelme, 1983; Quintanilla et al., 2006.
- ²⁸Quintanilla et al., 2008.
- ²⁹Quintanilla and Tampier, 2011; Tampier et al., 2008.
- ³⁰Tampier and Quintanilla, 2011.

Table 3

Innate differences in neurotransmitter systems between high and low alcohol-consuming rats within the respective line-pairs.

	AA vs. ANA	H1 vs. L1	H2 vs. L2	P vs. NP	sP vs. sNP	Brain regions	Reference
<i>Dopamine (DA) system</i>							
DA content							
	AA=ANA	-	-	-	-	Acb EtOH-induced	Kiianmaa et al., 1995
	AA>ANA	-	-	-	-	Acb EtOH-induced	Tuomainen et al., 2003
	AA>ANA	-	-	-	-	Whole Brain?	Ahtee and Eriksson, 1975
	-	H1>L1	-	-	-	Acb EtOH-induced	Kaner and Weiss, 2001
	-	H<L	-	-	-	Acb, CPU	Gongwer et al., 1989
	-	-	-	P<NP	-	Acb	Murphy et al., 1987b
	-	-	-	-	sP>sNP	mPFC; AcbSh	Leggio et al., 2003
	-	-	-	-	sP=sNP	Acb, Hyp	Devoto et al., 1998
DOPAC content	AA=ANA	-	-	-	-	Acb EtOH-induced	Kiianmaa et al., 1995
	AA>ANA	-	-	-	-	Acb, CPU	Honkanen et al., 1994
	-	H<L	-	-	-	Acb, CPU	Gongwer et al., 1989
	-	-	-	P<NP	-	Acb	Murphy et al., 1987b
	-	-	-	-	sP=sNP	Acb, Hyp	Devoto et al., 1998
HVA content	AA=ANA	-	-	-	-	Acb	Kiianmaa et al., 1995
	AA>ANA	-	-	-	-	Acb, CPU	Honkanen et al., 1994
	-	H<L	-	-	-	Acb, CPU	Gongwer et al., 1989
	-	-	-	P<NP	-	Acb	Murphy et al., 1987b
	-	-	-	-	sP=sNP	Acb, Hyp	Devoto et al., 1998
L-DOPA content	AA<ANA	-	-	P<NP	-	Acb, CPU	Murphy et al., 1987b
	-	-	-	-	sP=sNP	Acb, Hyp	Devoto et al., 1998
	AA<ANA	-	-	-	-	PVN	Korpi et al., 1991
Tyrosine hydroxylase	AA>ANA	-	-	-	-	Whole Brain	Pispa et al., 1986
DA-beta-hydroxylase	-	-	-	-	sP<sNP	Cg	Casu et al., 2002
D ₁ receptor	-	-	-	-	-	-	-
Innate level	-	-	-	-	sP=sNP	AcbSh, LC	Casu et al., 2002
	AA=ANA	-	-	-	-	Acb, CPU	Syvalahti et al., 1994
	-	-	H2=L2	-	-	PFC, Ach, OFT, VTA, VP, CPU, GP, SN	McBride et al., 1997a
	-	-	-	P=NP	-	PFC, Ach, OFT, VTA, VP, CPU, SN	McBride et al., 1997b
	-	-	-	-	sP<sNP	Pooled Limbic Regions	De Montis et al., 1993

	AA vs. ANA	H1 vs. L1	H2 vs. L2	P vs. NP	sP vs. sNP	Brain regions	Reference
D ₂ receptor							
Innate level	AA=ANA	-	-	-	-	Acb, CPU	Syvalahti et al., 1994
	AA<ANA	-	-	-	-	CPU	Korpi et al., 1987
	-	-	H2=L2	-	-	Acb, OFT, CPU, VTA, SN	McBride et al., 1997a
	-	-	-	P<NP	-	Acb, CPU, VTA	McBride et al., 1993a
mRNA	-	-	-	-	sP<NP	Acb, OFT, CPU	Stefanini et al., 1992
D ₃ receptor	AA=ANA	-	-	-	-	Acb, CPU	Syvalahti et al., 1994
Innate level	-	-	H2=L2	-	-	Acb, OFT	McBride et al., 1997a
	-	-	-	P=NP	-	Acb, OFT	McBride et al., 1997b
Dopamine Transporter (DAT)							
Innate level	-	-	-	-	sP<NP	AcbSh, Cg	Casu et al., 2002
Function	AA<ANA	-	-	-	-	AcbCo	Pelkonen et al., 2010
α -synuclein _{DA-associated}							
Innate level	-	-	-	P>NP	-	CPU, Hipp	Liang et al., 2003
mRNA	-	-	-	P>NP	-	Hipp	Liang et al., 2003
MFB-stimulated activity	AA>ANA	-	-	-	-	AcbCo	Pelkonen et al., 2010
DA-stimulated adenyly cyclase	-	-	-	-	sP<NP	Pooled Limbic Regions	De Montis et al., 1993
<i>Endocannabinoid system</i>							
Fatty Acid Amidohydrolase (FAAH)	AA<ANA	-	-	-	-	PFC	Hansson et al., 2007
Anandamide content	AA=ANA	-	-	-	-	PFC	Hansson et al., 2007
	-	-	-	-	sP>sNP	CPU, Hipp	Vinod et al., 2012
Arachidonoylglycerol-1	AA>ANA	-	-	-	-	PFC	Hansson et al., 2007
Arachidonoylglycerol-2	AA>ANA	-	-	-	-	PFC	Hansson et al., 2007
	-	-	-	-	sP>sNP	Ctx, CPU	Vinod et al., 2012
CB1 receptor							
Innate level	AA<ANA	-	-	-	-	PFC	Hansson et al., 2007
	-	-	-	-	sP>sNP	Ctx, CPU, Hipp	Vinod et al., 2012
mRNA	-	-	-	-	sP>sNP	Ctx, CPU, Hipp	Vinod et al., 2012
Function	-	-	-	-	sP<sNP	VTA	Melis et al., 2009
<i>Gamma-Aminobutyric Acid (GABA) system</i>							

	AA vs. ANA	H1 vs. L1	H2 vs. L2	P vs. NP	sP vs. sNP	Brain regions	Reference
GABA function	AA<ANA	—	—	—	—	VP EIOH-induced ↓	Kempainen et al., 2010
GABA _A receptor							
Innate level	AA<ANA	—	—	—	—	Ctx, Hipp, LH	Wong et al., 1996
	—	H>L	—	—	—	Acb	Hwang et al., 1990
	—	—	—	P>NP	—	Acb	Hwang et al., 1990
<i>Benzodiazepine (BNZ) site</i>							
Response to BNZ	AA>ANA	—	—	—	—	Across Regions Tested	Wong et al., 1996
	—	—	—	P>NP	—	PFC, Cg, AcbSh, CPU, DLS	Thielen et al., 1997
<i>Glutamate (Glu) System</i>							
NMDA Receptor 1 (NR1)							
mRNA NR1-4	AA<ANA	—	—	—	—	Hipp	Winkler et al., 1999
<i>Glycine (Gly) system</i>							
Receptor Subunit Expression							
Innate level							
GlyRa1	AA=ANA	—	—	—	—	Cg, Acb, Amyg, AH, PH, CPU, VTA	Jonsson et al., 2009
GlyRa2	AA>ANA	—	—	—	—	PFC	Jonsson et al., 2009
GlyRa3	AA>ANA	—	—	—	—	VTA	Jonsson et al., 2009
GlyRβ	AA=ANA	—	—	—	—	Cg, Acb, Amyg, AH, PH, CPU, VTA	Jonsson et al., 2009
<i>Histamine system</i>							
Histamine							
Content	AA>ANA	—	—	—	—	FC, Sep, Hyp, Hipp, MB	Lintunen et al., 2001
<i>te/e-methylhistamine</i>							
Content	AA>ANA	—	—	—	—	FC, Hyp, Hipp	Lintunen et al., 2001
L-histidine decarboxylase							
Content	AA=ANA	—	—	—	—	Hyp	Lintunen et al., 2001
H1 receptor							
Innate level	AA<ANA	—	—	—	—	MC, Hipp	Lintunen et al., 2001
mRNA	AA<ANA	—	—	—	—	MC, LS, Hipp	Lintunen et al., 2001
H2 receptor							
Innate level							
mRNA	AA=ANA	—	—	—	—	MC, LS, Hyp, Hipp	Lintunen et al., 2001

	AA vs. ANA	H1 vs. L1	H2 vs. L2	P vs. NP	sP vs. sNP	Brain regions	Reference
H3 receptor							
Innate level	AA<ANA	-	-	-	-	MC, Acb, Hipp	Lintunen et al., 2001
<i>Norepinephrine (NE) system</i>							
NE Content	AA=ANA	-	-	-	-	Whole Brain?	Ahtee and Eriksson, 1975
DA-beta-hydroxylase	-	-	-	-	sP<sNP	Cg	Casu et al., 2002
	-	-	-	-	sP=sNP	AcbSh, LC	Casu et al., 2002
NE Transporter (NET)							
NET content (LC)	-	H<L	-	-	-	LC	Hwang et al., 2000
	-	-	-	P<NP	-	LC	Hwang et al., 2000
<i>Opioid system</i>							
β -Endorphin content	AA<ANA	-	-	-	-	Hyp	DeWaele et al., 1994
	AA<ANA	-	-	-	-	Amyg, PAG	Gianoulakis et al., 1992
	AA>ANA	-	-	-	-	Sep	Gianoulakis et al., 1992
	AA=ANA	-	-	-	-	Ctx, Acb, CPU, Hipp	Gianoulakis et al., 1992
β -Endorphin release	AA>ANA	-	-	-	-	Acb EtOH-induced	Lam et al., 2010
Proopiomelanocortin mRNA	AA>ANA	-	-	-	-	Arcuate	Lindblom et al., 2002
	AA>ANA	-	-	-	-	Hyp, Pituitary	Gianoulakis et al., 1992
	AA>ANA	-	-	-	-	Arcuate	Marinelli et al., 2000
(Pro)enkephalin mRNA	-	-	-	-	sP>sNP	Hyp	Zhou et al., in press
	AA<ANA	-	-	-	-	Acb, Pituitary	Nyländer et al., 1994
	AA>ANA	-	-	-	-	PFC	Marinelli et al., 2000
	-	-	-	P=NP	-	AS, MS, PS, Amyg, MH	Li et al., 1998
	-	-	-	P<NP	-	AH	Li et al., 1998
Enkephalin	-	-	-	-	sP=sNP	AcbSh, AcbCo	Fadda et al., 1999
	-	-	-	-	sP<sNP	CPU	Fadda et al., 1999
	-	-	-	-	sP>sNP	Cg, FC, PC	Fadda et al., 1999
(Pro)dynorphin mRNA	AA>ANA	-	-	-	-	MDTN	Marinelli et al., 2000
Dynorphin-A	AA<ANA	-	-	-	-	CPU, Pituitary	Nyländer et al., 1994
Dynorphin-B	AA<ANA	-	-	-	-	Acb, Pituitary	Nyländer et al., 1994
Pan-opioid receptors							

	AA vs. ANA	H1 vs. L1	H2 vs. L2	P vs. NP	sP vs. sNP	Brain regions	Reference
Innate level	—	—	—	—	sP<sNP	AcbSh, CPU	Fadda et al., 1999
μ receptor Innate level	AA<ANA	—	—	—	—	Hipp	Soini et al., 1998
	AA>ANA	—	—	—	—	SN, SC	Soini et al., 1998
	AA>ANA	—	—	—	—	BLA, GP, MPOA, SN	Soini et al., 1999
	AA>ANA	—	—	—	—	CPU, SN	Soini et al., 2002
	AA>ANA	—	—	—	—	PFC, AcbSh	Marinelli et al., 2000
mRNA	—	H1<L1	—	—	—	Amyg	Learn et al., 2001
	—	—	—	P>NP	—	OFT, AcbSh, AcbCo, BLA	McBride et al., 1998
	—	—	—	P<NP	—	PostMedCtx	McBride et al., 1998
	—	—	—	—	sP<sNP	CPU	Fadda et al., 1999
	—	H=L	—	—	—	FC, Acb, CPU, Hyp, Hipp	Gong et al., 1997
	—	H>L	—	—	—	IC	Gong et al., 1997
	—	—	—	—	sP<sNP	AcbSh, AcbCo, CPU, Cg	Zhou et al., in press
	AA>ANA	—	—	—	—	Ctx, Acb, CPU, Thal	DeWaele et al., 1995
	AA<ANA	—	—	—	—	Cg, BLA, Hipp, Thal, MB	Soini et al., 1998
	—	—	—	P<NP	—	BLA, HippCA2	Strother et al., 2001
δ receptor Innate level	—	—	—	—	sP<sNP	CPU	Fadda et al., 1999
	AA>ANA	—	—	—	—	OlfCtx, Cg, BLA, CPU, GP, SC, CeGr	Soini et al., 1999
	AA>ANA	—	—	—	—	CPU, SN	Soini et al., 2002
	AA<ANA	—	—	—	—	VMH	Marinelli et al., 2000
<i>Serotonin (5-HT) system</i>							
5-HT	AA>ANA	—	—	—	—	Hyp, Hipp	Korpi et al., 1988
	AA>ANA	—	—	—	—	Whole Brain?	Ahtee and Eriksson, 1972, 1973
	—	H<L	—	—	—	FC, CPU, Hipp, Hyp	Gongwer et al., 1989
	—	—	—	P<NP	—	FC, Acb, CPU	Murphy et al., 1987b
5-HIAA	—	—	—	—	sP<sNP	FC	Devoto et al., 1998
	—	—	—	—	sP<sNP	PFC Sugar-induced	De Montis et al., 2004
	AA=ANA	—	—	—	—	Acb	Kiianmaa et al., 1995

	AA vs. ANA	H1 vs. L1	H2 vs. L2	P vs. NP	sP vs. sNP	Brain regions	Reference
Tryptophan hydroxylase	AA=ANA	-	-	-	-	FC, CPU, Hipp, Hyp	Korpi et al., 1988
	AA>ANA	-	-	-	-	Whole Brain	Ahtee and Eriksson, 1972
	-	H<L	-	-	-	PC, CPU, Ach, Sept	Gongwer et al., 1989
	-	H<L	-	-	-	Hipp, Hyp	Gongwer et al., 1989
Immunoreactivity	-	-	-	P<NP	-	FC	Murphy et al., 1987b
	-	-	-	-	sP<NP	FC	Devoto et al., 1998
	-	-	-	-	sP<NP	DR	Casu et al., 2004
	-	-	-	-	sP=sNP	MR	Casu et al., 2004
5-HT _{1A} receptor							
Innate level	AA=ANA	-	-	-	-	FC, Hipp, Hyp	Korpi et al., 1992
	-	H<L	-	-	-	pHipp	McBride et al., 1997a
	-	-	-	P>NP	-	mPFC, mAcb, vHipp, DR	McBride et al., 1994
5-HT _{1B} receptor							
Innate level	-	-	-	P<NP	-	Cg, Sept, LA	McBride et al., 1997b
5-HT ₂ receptor							
Innate level	AA=ANA	-	-	-	-	FC, Hipp, Hyp, BS	Korpi et al., 1992
	-	H=L	-	-	-	Ctx, Ach, CPU, Of	McBride et al., 1997a
	-	-	-	P<NP	-	mPFC, Cg, FC, PC, TC	McBride et al., 1993b
	-	-	-	-	sP<NP	mPFC, PFC, Cg	Ciccocioppo et al., 1999
5-HT _{2C} receptor							
Innate level	-	-	-	P>NP	-	Hipp, Amyg	Pandey et al., 1996
5-HT ₃ receptor							
Innate level	AA=ANA	-	-	-	-	FC, Ach, Hipp, Amyg	Korpi et al., 1992
	AA=ANA	-	-	-	-	Ctx, Hipp, Amyg	Ciccocioppo et al., 1998
	-	-	-	P=NP	-	Ctx, Ach, CPU, Hipp, Amyg	McBride et al., 1997b
	-	-	-	P<NP	-	Amyg	Ciccocioppo et al., 1998
Serotonin							
Transporter (SERT)							
Innate level	-	-	-	-	sP<NP	Cg, AchSh	Casu et al., 2004
	-	-	-	-	sP=sNP	Hipp, CPU	Casu et al., 2004

	AA vs. ANA	H1 vs. L1	H2 vs. L2	P vs. NP	sP vs. sNP	Brain regions	Reference
<i>Neuropeptides</i>							
AVP content							
mRNA	-	H>L	-	-	-	PVN	Hwang et al., 1998
	-	-	-	P>NP	-	PVN	Hwang et al., 1998
	-	H=L	-	-	-	SON (p~0.05)	Hwang et al., 1998
	-	-	-	P=NP	-	SON (p~0.05)	Hwang et al., 1998
CGRP content							
	-	H=L	-	-	-	mPFC, Acb, CeA, CPU, BLA	Hwang et al., 1995
	-	-	-	P=NP	-	mPFC, Acb, CeA, BLA	Hwang et al., 1995
CGRP receptor levels (CeA)							
	-	H<L	-	-	-	CeA	Hwang et al., 1995
	-	-	-	P<NP	-	CeA, CPU	Hwang et al., 1995
CRF content							
	-	H=L	-	-	-	CeA, PVN	Hwang et al., 2004a
	-	-	-	P=NP	-	PVN	Hwang et al., 2004a
	-	-	-	P<NP	-	PFC, Pir Ctx, Hyp, Amyg	Ehlers et al., 1992
	-	-	-	P<NP	-	CeA	Hwang et al., 2004a
mRNA	-	-	-	P<NP	-	CeA	Hwang et al., 2004a
<i>Degradation enzymes</i>							
ACE							
mRNA	AA>ANA	-	-	-	-	Striatum, SC, IC	Winkler et al., 1998
NEP							
mRNA	AA>ANA	-	-	-	-	Striatum, SC, IC	Winkler et al., 1998
Melanocortin (alpha-MSH)							
MC receptor							
Antagonist _(nonselective)							
Agouti protein level _(endogenous)							
mRNA	AA<ANA	-	-	-	-	Arcuate	Lindblom et al., 2002
MC3 receptor							
	AA>ANA	-	-	-	-	Arcuate, PVN, VMH	Lindblom et al., 2002
	AA<ANA	-	-	-	-	AcbSh	Lindblom et al., 2002
MC4 receptor							
	AA>ANA	-	-	-	-	VMH	Lindblom et al., 2002
NPY content							
	-	H1<L1	-	-	-	CeA, Arcuate, PVN	Hwang et al., 1999
	-	H1=L1	-	-	-	mPFC, Cg	Hwang et al., 1999
	-	-	-	P<NP	-	CeA	Hwang et al., 1999

	AA vs. ANA	H1 vs. L1	H2 vs. L2	P vs. NP	sP vs. sNP	Brain regions	Reference
mRNA	-	-	-	P>NP	-	Cg, Arcuate, PVN	Hwang et al., 1999
	-	-	-	P=NP	-	AcbSh	Hwang et al., 1999
	-	-	-	P<NP	-	FC, Hipp, Amyg	Ehlers et al., 1998
	-	-	-	P=NP	-	CPU, Hyp	Ehlers et al., 1998
	-	-	-	P<NP	-	CeA, MeA	Pandey et al., 2005
	-	-	-	P=NP	-	BLA	Pandey et al., 2005
	AA<ANA	-	-	-	-	Hipp	Caberlotti et al., 2001
	AA=ANA	-	-	-	-	Cg, MeA, PVN, Arcuate	Caberlotti et al., 2001
	-	-	-	P<NP	-	CeA, MeA	Pandey et al., 2005
	-	-	-	P=NP	-	BLA	Pandey et al., 2005
Y1 receptor Innate level	-	-	-	P<NP	-	CeA, RTN	Suzuki et al., 2004
	-	-	-	P=NP	-	Pir Ctx, BLA, MeA	Suzuki et al., 2004
	-	-	-	P<NP	-	DG	Hwang et al., 2004b
	-	-	-	P=NP	-	FC, PC, PRh Ctx	Hwang et al., 2004b
mRNA	AA=ANA	-	-	-	-	Cg, Hipp, Amyg, Arcuate, PVN	Caberlotti et al., 2001
	AA<ANA	-	-	-	-	MeA	Caberlotti et al., 2001
	AA=ANA	-	-	-	-	Cg, BA, Arcuate	Caberlotti et al., 2001
Tachykinins Substance P content	-	-	-	P<NP	-	CeA, IPAC	Yang et al., 2009
	-	-	-	P>NP	-	mHA	Yang et al., 2009
	-	-	-	P<NP	-	FC	Slawecki et al., 2001
	-	-	-	P<NP	-	FC, Hyp	Slawecki et al., 2001
	-	-	-	P<NP	-	MS, LS	Morzorati and Kubek, 1993
Neurokinin (NK) content TRH content	AA=ANA	-	-	-	-	EWN	Turek et al., 2005
	AA>ANA	-	-	-	-	LS	Turek et al., 2005
	-	H1=L1	-	-	-	EWN, LS	Turek et al., 2005
Urocortin 1 content	-	-	-	-	-	-	-
	-	-	-	-	-	-	-
	-	-	-	-	-	-	-
	-	-	-	-	-	-	-
	-	-	-	-	-	-	-
	-	-	-	-	-	-	-
	-	-	-	-	-	-	-
	-	-	-	-	-	-	-
	-	-	-	-	-	-	-
	-	-	-	-	-	-	-

	AA vs. ANA	H1 vs. L1	H2 vs. L2	P vs. NP	sP vs. sNP	Brain regions	Reference
<i>Neurotrophins</i>							
BDNF content	–	–	H2>L2	–	–	EWN, LS	Turek et al., 2005
	–	–	–	P<NP	–	EWN	Turek et al., 2005
	–	–	–	P=NP	–	LS	Turek et al., 2005
	–	–	–	–	–	–	–
	–	–	–	P<NP	–	CeA, MeA	Prakash et al., 2008
	–	–	–	P=NP	–	BLA	Prakash et al., 2008
	–	–	–	P<NP	–	Acb	Yan et al., 2005
	–	–	–	P=NP	–	Ctx, Hipp, CPU	Yan et al., 2005
	–	–	–	P<NP	–	CeA, MeA	Moonat et al., 2011
	–	–	–	P=NP	–	BLA	Moonat et al., 2011
	–	–	–	P<NP	–	CeA, MeA	Prakash et al., 2008
	–	–	–	P=NP	–	BLA	Prakash et al., 2008
	–	–	–	P<NP	–	CeA, MeA	Moonat et al., 2011
	–	–	–	P=NP	–	BLA	Moonat et al., 2011
<i>Activity-regulated cytoskeleton-associated protein (Arc)</i>							
Innate level	–	–	–	P<NP	–	CeA, MeA	Moonat et al., 2011
	–	–	–	P=NP	–	BLA	Moonat et al., 2011
mRNA	–	–	–	P<NP	–	CeA, MeA	Moonat et al., 2011
	–	–	–	P=NP	–	BLA	Moonat et al., 2011
<i>G protein-coupled receptor components</i>							
β-arrestin 2 content							
Innate level	AA>ANA	–	–	–	–	Acb, Hipp, CPU	Bjork et al., 2008
mRNA	AA>ANA	–	–	–	–	Acb, Hipp, CPU	Bjork et al., 2008
	AA=ANA	–	–	–	–	Cg, CeA, BLA, DG	Bjork et al., 2008

AA=Alko Alcohol; ANA=Alko Non-Alcohol; H1=High alcohol-drinking replicate 1; L1=Low alcohol-drinking replicate 1; H2=High alcohol-drinking replicate 2; L2=Low alcohol-drinking replicate 2; P=Alcohol-preferring; NP=Alcohol-nonpreferring; sP=Sardinian alcohol-preferring; sNP=Sardinian alcohol-nonpreferring; –=Not tested; EtOH=ethanol; ACE=Angiotensin-Converting Enzyme; NEP=Neutral Endopeptidase; NPY=Neuropeptide Y; AVP=Arginine Vasopressin; CGRP=Calcitonin Gene-Related Peptide; CRF=Corticotropin Releasing Factor; MSH=Melanocortin Stimulating Hormone; TRH=Thyrotropin Releasing Hormone; BDNF=Brain Derived Neurotrophic Factor; Acb=Nucleus Accumbens; AcbCo=Acb Core; AcbSh=Acb Shell; AH=Anterior Hypothalamus; Amyg=Amygdala; AS=Anterior Septum; BA=Basal Amygdala; BLA=Basal Lateral Amygdala; CeA=Central Amygdala; CeGr=Central Gray; Cg=Cingulate Cortex; CPU=Caudate Putamen; Ctx=Cortex; DG=Dentate Gyrus; DLS=Dorsal Lateral Septum; DR=Dorsal Raphe; EWN=Edinger-Westphal Nuclei; FC=Frontal Cortex; GP=Globus Pallidum; Hipp=Hippocampus; Hyp=Hypothalamus; IC=Inferior Colliculus; IPAC=Interstitial Nucleus of the Posterior Limb of Anterior Commissure; LA=Lateral Amygdala; LC=Locus Coeruleus; LH=Lateral Hypothalamus; LS=Lateral Septum; mAcb=Medial Acb; MB=Medial Forebrain Bundle; MC=Motor Cortex; MDTN=Medial Dorsal Thalamic Nucleus; MeA=Medial Amygdala; MH=Medial Hypothalamus; mHA=Medial Habenular Nucleus; mPFC=Medial Prefrontal Cortex; MPOA=Medial Preoptic Area; MR=Medial Raphe; MS=Medial Septum; OlfCtx=Olfactory Tubercle; PAG=Periaqueductal Gray; PC=Parietal Cortex; PFC=Prefrontal Cortex; PH=Posterior Hypothalamus; pHipp=Posterior Hipp; Pir Ctx=Piriform Cortex; PostMedCtx=Posterior Medial Cortex; PRh Ctx=PeriRhinal Cortex; PS=Posterior Septum;

PVN=PeriVentricular Nucleus; RTN=Reticular Thalamic Nucleus; SC=Superior Colliculus; Sep=Septum; SN=Substantia Nigra; SON=SupraOptic Nucleus; TC=Temporal Cortex; Thal=Thalamus; vHipp=Ventral Hipp; VMH=Ventral Medial Hypothalamus; VP=Ventral Pallidum; VTA=Ventral Tegmental Area.

CNS pharmacological targets shown to influence alcohol intake and/or self-administration in rat lines bred for high alcohol preference/consumption.

Table 4

Neurotransmitter system/receptor	AA	H1	H2	P	sP	Sex	EtOH access	Dose	Reference
<i>Cholinergic (ACh) system</i>									
ACh esterase inhibitor									
Desoxyphenazine									
Systemic	↓	-	-	-	-	F	FCLA	10–30 mg/kg	Doetkotte et al., 2005
Galanthamine									
Systemic	↓	-	-	-	-	F	FCLA	2.5 mg/kg	Doetkotte et al., 2005
Nicotinic receptor (nAChR)									
Agonist									
Sazetidine-A _{Partial}									
Systemic	↓	-	-	-	-	M	Oper	3 mg/kg	Rezvani et al., 2010
Cytisine _{Partial}									
Systemic	-	-	↓	-	-	M	FCCA	0.5, 1.5 mg/kg	Bell et al., 2009
Antagonist									
Lobeline									
Systemic	-	-	↓	-	-	M	FCCA	1, 5 mg/kg	Bell et al., 2009
Muscarinic receptor (mAChR)									
Agonist									
Carbachol									
Microinjection	-	-	-	↓	-	F	FCCA	1–4 µg (ppN)	Katner et al., 1997
Microinjection	-	-	-	↓	-	F	FCCA	1, 2 µg (VTA)	Katner et al., 1997
Antagonist									
Scopolamine									
Systemic	-	-	-	↓	-	M	FCCA	0.5, 2 mg/kg	Rezvani et al., 1990
Microinjection	-	-	-	↓	-	F	FCCA	5–15 µg (ppN)	Katner et al., 1997
Methylscopolamine									
Systemic	-	-	-	↓	-	M	FCCA	0.5, 2 mg/kg	Rezvani et al., 1990
Microinjection	-	-	-	↓	-	F	FCCA	5, 10 µg (VTA)	Katner et al., 1997
<i>Dopamine (DA) system</i>									

Neurotransmitter system/receptor	AA	H1	H2	P	sP	Sex	EtOH access	Dose	Reference
DA system stimulant									
Ibogaïne	↓	-	-	↓	-	M	FCCA	10–60 mg/kg	Rezvani et al., 1995
Systemic									
D ₁ receptor									
Level	↑	-	-	-	-	M	FCCA	AcbCo	Sari et al., 2006
	-	-	-	↑	-	M	FCIA	AcbCo, LA, IA	Sari et al., 2006
Agonist									
SKF 38393									
Systemic	-	↓	-	-	-	F	FCLA	2–6 mg/kg	Dyr et al., 1993
Antagonist									
SCH 23390									
Systemic	-	↓	-	-	-	F	FCLA	3–30 mg/kg	Dyr et al., 1993
Systemic	-	-	-	↓	-	M	FCCA	0.1–0.5 mg/kg	Mason et al., 1997
Microinjection	-	-	-	↓	-	M & F	Oper	0.5–20 µg (BNST)	Eiler et al., 2003
SCH 39166									
Systemic	-	-	-	-	↓	M	FCCA	1, 5 mg/kg	Panocka et al., 1995a
D ₂ receptor									
Level	-	-	-	↑	-	M	FCCA	AcbSh, AcbCo	Sari et al., 2006
	-	-	-	↑	-	M	FCIA	AcbSh, AcbCo, CPU	Sari et al., 2006
Agonist									
Quinpirole									
Systemic	-	↓	-	-	-	F	FCLA	0.04–2 mg/kg	Dyr et al., 1993
Microinjection	-	-	-	↓	-	F	FCLA	2–4 µg (VTA)	Nowak et al., 2000
Microinjection	-	-	-	↓	-	F	Oper	0.1–0.3 µg (VTA)	Hauser et al., 2011
Quinelorane									
Microinjection	-	-	-	↓	-	F	FCLA	2–4 µg (VTA)	Nowak et al., 2000
Bromocriptine									
Systemic	-	-	-	↓	-	M	Oper	1–4 mg/kg	Weiss et al., 1990
Systemic	-	-	-	↓	-	?	FCLA	1 mg/kg	McBride et al., 1990
Systemic	-	-	-	↓	-	M	FCCA	0.5 mg/kg	Mason et al., 1994
Antagonist									

Neurotransmitter system/receptor	AA	H1	H2	P	sP	Sex	EtOH access	Dose	Reference
Spiroperone									
Systemic	-	↓	-	-	-	F	FCLA	30 µg/kg	Dyr et al., 1993
Sulpiride									
Microinjection	-	-	-	↓	-	F	FCLA	2-4 µg (VTA)	Nowak et al., 2000
Microinjection	-	-	-	↓	-	F	FCLA	0.1-2 µg (Acb)	Levy et al., 1991
Microinjection	-	-	-	↓	-	F	FCLA	0.25-2 µg (VP)	Melendez et al., 2005
Clozapine									
Systemic	↔	-	-	-	-	M	FCLA	0.3-5 mg/kg	Ingman and Korpi, 2006
Olanzapine									
Systemic	↓	-	-	-	-	M	FCLA	0.1-1.25 mg/kg	Ingman and Korpi, 2006
Eticlopride									
Systemic	-	-	-	↓	-	M	FCCA	0.01, 0.05 mg/kg	Mason et al., 1997
Microinjection	-	-	-	↔	-	M & F	Oper	0.5-20 µg (BNST)	Eiler et al., 2003
Microinjection	-	-	-	↓	-	M & F	Oper	20, 40 µg (VTA)	Eiler et al., 2003
Mixed									
Partial agonist/antagonist									
Aripiprazole									
Systemic acute	↔	-	-	-	-	M	FCLA	0.3-3 mg/kg	Ingman et al., 2006
Systemic chronic	↓	-	-	-	-	M	FCLA	6 mg/kg	Ingman et al., 2006
D₃ receptor									
Agonist									
7-OH-DPAT									
Systemic	-	-	-	↓	-	M	FCCA	0.075-0.3 mg/kg	Mason et al., 1997
Antagonist									
SB-277011-A									
Systemic	-	-	-	↓	-	M	Oper	10, 30 mg/kg	Thanos et al., 2005
Dopamine Transporter (DAT)									
Function	-	↑	-	-	-	F	FCCA _(Adult)	Acb	Carroll et al., 2006
Inhibitor									
GBR12909	-	-	-	↑	-	M	FCCA _(Adult)	Acb	Sahr et al., 2004

Neurotransmitter system/receptor	AA	H1	H2	P	sP	Sex	EtOH access	Dose	Reference
Systemic	-	-	-	↓	-	?	FCLA	20 mg/kg	McBride et al., 1990
DOV 102,677 (also inhibits NET & SERT)									
Systemic	-	-	-	↓	-	M	Oper	6.25–50 mg/kg	Yang et al., 2012
Reverse Transporter									
Amphetamine									
Systemic	-	-	-	↓	-	?	FCLA	1 mg/kg	McBride et al., 1990
Endocannabinoid system									
CB1 receptor									
Agonist									
WIN55,212-2									
Systemic	↑	-	-	-	-	M	Oper	0.5, 1 mg/kg	Malinen and Hyttia, 2008
Microinjection	↔	-	-	-	-	M	Oper	1–5 µg (Acb, VTA)	Malinen and Hyttia, 2008
Systemic	-	-	-	-	↑	M	FCCA	0.5–20 mg/kg	Colombo et al., 2002b
CP 55,940									
Systemic	-	-	-	↑	-	F	Oper	1, 2 mg/kg	Getachew et al., 2011
Systemic	-	-	-	-	↑	M	FCCA	3–30 mg/kg	Colombo et al., 2002b
Antagonist									
Rimonabant (SR141716)									
Systemic	↓	-	-	-	-	M	Oper	3, 10 mg/kg	Hansson et al., 2007
Systemic	↓	-	-	-	-	M	Oper	1–10 mg/kg	Malinen and Hyttia, 2008
Systemic	-	-	-	-	↓	M	FCCA	1, 3 mg/kg	Vinod et al., 2012
Systemic	-	-	-	↓	-	F	Oper	1, 2 mg/kg	Getachew et al., 2011
Systemic	-	-	-	↓	-	?	Oper	0.3–1 mg/kg	Adams et al., 2010
Systemic	-	-	-	-	↓	M	FCLA	2.5–10 mg/kg	Colombo et al., 1998a
Systemic	-	-	-	-	↓	M	FCCA _{Acquisition}	0.3–3 mg/kg	Serra et al., 2001
Systemic	-	-	-	-	↓	M	Oper	0.3–3 mg/kg	Maccioni et al., 2009b
Microinjection	↓	-	-	-	-	M	Oper	1, 3 µg (Acb, VTA)	Malinen and Hyttia, 2008
Microinjection	↓	-	-	-	-	M	Oper	3, 6 µg (PFC)	Hansson et al., 2007
SR147778									

Neurotransmitter system/receptor	AA	H1	H2	P	sP	Sex	EtOH access	Dose	Reference
Systemic	-	-	-	-	↓	M	FCCA _{Acquisition}	0.3–3 mg/kg	Gessa et al., 2005
<i>Gamma-Aminobutyric Acid (GABA) system</i>									
GABA transaminase inhibitor									
Gamma-vinyl GABA									
Systemic	↓	-	-	-	-	?	FCCA	100–500 mg/kg	Wegelius et al., 1993
GABA _A receptor									
Agonist									
Muscimol									
Microinjection	-	-	-	↔	-	F	FCLA	0.05, 0.1 μg (VTA)	Nowak et al., 1998
Acamprosate [*]									
(also NMDA antagonist)									
Systemic	↑	-	-	↑	-	M	Oper	200 mg/kg	Cowen et al., 2005a
Topiramate [*]									
(also AMPA/kainate antagonist)									
Systemic	-	-	-	↓	-	?	FCCA	10 mg/kg	Breslin et al., 2010
Systemic	-	-	-	↓	-	M	FCCA	10 mg/kg	Lynch et al., 2011
Antagonist									
Bicuculline									
Microinjection	-	-	-	↓	-	F	FCLA	0.05, 0.1 μg (VTA)	Nowak et al., 1998
Picrotoxin									
Microinjection	-	-	-	↓	-	F	FCLA	0.05, 0.1 μg (VTA)	Nowak et al., 1998
SR95531									
Microinjection	-	-	-	↓	-	M & F	Oper	32 ng (VTA)	Eiler and June, 2007
GABA _A -α2									
shRNAi	-	-	-	↓	-	?	Oper	CeA(S) Acb & VP (NS)	Liu et al., 2011
Toll-like receptor 4 _{GABA-A-α2-associated}									
shRNAi	-	-	-	↓	-	?	Oper	CeA(S) Acb & VP (NS)	Liu et al., 2011

Benzodiazepine (BNZ) site

Agonists

Positive Modulators

Midazolam_{Full}

Neurotransmitter system/receptor	AA	H1	H2	P	sP	Sex	EtOH access	Dose	Reference
Systemic	↑	-	-	-	-	M	FCLA	0.3-10 mg/kg	Wegelius et al., 1994
Systemic	↓	-	-	-	-	M	FCLA	0.1-10 mg/kg	Ingman et al., 2004
Abecarnil _{Partial}									
Systemic	↔	-	-	-	-	M	FCLA	0.1-10 mg/kg	Wegelius et al., 1994
ZK 91296 _{Partial}									
Systemic	↑	-	-	-	-	M	FCLA	3-30 mg/kg	Wegelius et al., 1994
Bretazenil _{Partial}									
Systemic	↑	-	-	-	-	M	FCLA	0.1-10 mg/kg	Wegelius et al., 1994
CGS 9895 _{Partial}									
Systemic	↓	-	-	-	-	M	FCLA	0.3-30 mg/kg	Wegelius et al., 1994
Negative Modulators									
Ro 15-4513 _{Inverse agonist}									
Systemic	↓	-	-	-	-	M	FCLA	1-10 mg/kg	Wegelius et al., 1994
Systemic	-	-	-	↓	-	M	FCLA	2 mg/kg	McBride et al., 1988
Ro 19-4603 _{Inverse agonist}									
Systemic	↓	-	-	-	-	M	FCLA	0.3-3 mg/kg	Wegelius et al., 1994
Systemic	-	-	-	↓	-	F	FCCA	0.3 mg/kg×2	June et al., 1994
Systemic	-	-	-	↓	-	F	FCLA	0.005-0.3 mg/kg	June et al., 1996
Systemic	-	-	-	↓	-	M & F	Oper	0.0045-0.3 mg/kg	June et al., 1998d
Systemic	-	-	-	-	↓	M	FCLA	1 mg/kg×3/day	Balakleevsky et al., 1990
Microinjection	-	-	-	↓	-	M & F	Oper	2-100 ng (Ach)	June et al., 1998a
Ru 34000									
Systemic	-	-	-	↓	-	M	Oper	1-5 mg/kg	June et al., 1998b
Microinjection	-	-	-	↓	-	M	Oper	50-200 ng (VTA)	June et al., 1998b
Ro 15-1788									
Systemic	-	-	-	↓	-	M	Oper	8, 16 mg/kg	June et al., 1994
Systemic	-	-	-	↓	-	M	FCLA	40 mg/kg	June et al., 1998d
CGS 8216									
Systemic	-	-	-	↓	-	M	FCLA	15-20 mg/kg	June et al., 1998a
Systemic	-	-	-	↓	-	M	Oper	15-20 mg/kg	June et al., 1998a

Neurotransmitter system/receptor	AA	H1	H2	P	sP	Sex	EtOH access	Dose	Reference
Systemic	-	-	-	↓	-	M	FCLA	40 mg/kg	June et al., 1998e
ZK 93426									
Systemic	-	-	-	↓	-	M	FCLA	30, 50 mg/kg	June et al., 1998a
Systemic	-	-	-	↓	-	M	Oper	30, 50 mg/kg	June et al., 1998a
Systemic	-	-	↓	-	-	M	FCLA	40 mg/kg	June et al., 1998e
Mixed									
Partial agonist/antagonist									
βCC _{GABA-Aα1} selectivity									
Microinjection	-	↓	-	-	-	M & F	Oper	20–60 μg (C _{6A})	Foster et al., 2004
Microinjection	-	-	-	↓	-	M & F	Oper	10–40 μg (C _{6A})	Foster et al., 2004
Systemic	-	↓	-	-	-	F	Oper	1–10 mg/kg	June et al., 2003
Systemic	-	-	-	↓	-	F	Oper	5–40 mg/kg	June et al., 2003
Microinjection	-	↓	-	-	-	F	Oper	2.5–7.5 μg (VP)	June et al., 2003
Microinjection	-	-	-	↓	-	F	Oper	5–40 μg (VP)	June et al., 2003
GABA _B receptor									
Agonist									
Baclofen *									
Systemic	-	-	-	↓	-	M	Oper	3 mg/kg	Liang et al., 2006
Systemic	-	-	-	-	↓	M	Oper	3 mg/kg	Maccioni et al., 2005
Systemic	-	-	-	-	↓	M	FCCA _{Acquisition}	3 mg/kg	Colombo et al., 2002a
Systemic	-	-	-	-	↓	M	FCCA	5, 10 mg/kg	Colombo et al., 2000a
Systemic	-	-	-	-	↓	M	Oper	1, 3 mg/kg	Maccioni et al., 2008b
Systemic	↓	-	-	↓	↓	M	Oper	3 mg/kg	Maccioni et al., in press
CGP44532									
Systemic	-	-	-	-	↓	M	FCCA _{Acquisition}	0.3, 1 mg/kg	Colombo et al., 2002a
Positive Modulators									
GHB									
Systemic	-	-	-	↓	-	?	FCLA	50–300 mg/kg	June et al., 1995
Systemic	-	-	-	-	↓	M	FCCA	300, 400 mg/kg	Agabio et al., 1998
Systemic	-	-	-	-	↓	?	FCLA	200, 300 mg/kg	Gessa et al., 2000

Neurotransmitter system/receptor	AA	H1	H2	P	sP	Sex	EtOH access	Dose	Reference
Systemic	-	-	-	-	↓	M	Oper	25–100 mg/kg	Maccioni et al., 2008c
CGP7930									
Systemic	-	-	-	↓	-	M	Oper	20 mg/kg	Liang et al., 2006
Systemic	-	-	-	-	↓	M	FCCA _{Acquisition}	25–100 mg/kg	Orrù et al., 2005
Systemic	-	-	-	-	↓	M	FCCA _{Maintenance}	25–100 mg/kg	Orrù et al., 2005
GS39783									
Systemic	-	-	-	-	↓	M	Oper	25–100 mg/kg	Maccioni et al., 2008b
Systemic	-	-	-	-	↓	M	FCCA _{Acquisition}	6.25–25 mg/kg	Orrù et al., 2005
Systemic	-	-	-	-	↓	M	FCCA _{Maintenance}	100 mg/kg	Orrù et al., 2005
Systemic	-	-	-	-	↓	M	Oper	25–100 mg/kg	Maccioni et al., 2007
Systemic	-	-	-	-	↓	M	Oper	25–100 mg/kg	Maccioni et al., 2010a
Systemic	↓	-	-	↓	↓	M	Oper	50, 100 mg/kg	Maccioni et al., in press
BHF177									
Systemic	-	-	-	-	↓	M	Oper	25, 50 mg/kg	Maccioni et al., 2009a
rac-BHFF									
Systemic	-	-	-	-	↓	M	Oper	50–200 mg/kg	Maccioni et al., 2010b
Glutamate (Glu) system									
mGluR1 receptor									
Level	-	-	-	↑	-	M	FCCA	AcbCo, CeA	Obara et al., 2009
Antagonist	-	-	-	↑	-	M	FCIA	AcCo, CeA	Obara et al., 2009
CPCCOEt									
Systemic	-	-	-	↔	-	M	Oper	3, 10 mg/kg	Schroeder et al., 2005a
JNJ 16259685									
Systemic	-	-	-	↓	-	M	Oper	0.1–1 mg/kg	Besheer et al., 2008a
Systemic	-	-	-	↓	-	M	Oper	0.3, 1 mg/kg	Besheer et al., 2008b
mGluR2/3 receptor									
Agonist									
LY379268									
Systemic	↓	-	-	-	-	M	Oper	5 mg/kg	Backstrom and Hyytia, 2005

Neurotransmitter system/receptor	AA	H1	H2	P	sP	Sex	EtOH access	Dose	Reference
Systemic	↓	-	-	-	-	M	Oper _{EtOH Seeking}	5 mg/kg	Backstrom and Hyytia, 2005
Microinjection	-	-	-	↓	-	M	Oper	0.17 µg (Acb)	Besheer et al., 2010
Antagonist									
LY341495	-	-	-	-	↔	M	Oper	10 mg/kg-sig	Schroeder et al., 2005a
Systemic	-	-	-	-	↓	F	Oper _{EtOH Seeking}	3, 5 mg/kg	Rodd et al., 2006
LY404039	-	-	-	-	↓	F	Oper _{Relapse}	3, 5 mg/kg	Rodd et al., 2006
Systemic	-	-	-	-	↔	F	Oper _{Maintenance}	3, 5 mg/kg	Rodd et al., 2006
mGluR5 receptor	-	-	-	-	↑	M	FCCA	AcbCo	Obara et al., 2009
Level	-	-	-	↑	-	M	FCIA	AcbCo, CeA	Obara et al., 2009
Antagonist									
MPEP	-	-	-	↓	-	M	Oper	3, 10 mg/kg	Schroeder et al., 2005a
Systemic	-	-	-	↓	-	M	Ope _{ICP & PFC NS}	10 µg (Acb=S)	Besheer et al., 2010
Microinjection	-	-	-	↓	-	M	Oper	2 mg/kg	Cowen et al., 2005b
MTEP	-	-	-	↓	-	M	Oper	2 mg/kg	Cowen et al., 2005b
Systemic	-	-	-	↓	-	M	Oper	15 mg/kg	Backstrom and Hyytia, 2005
mGluR8 receptor	↓	-	-	-	-	M	Oper _{EtOH Seeking}	10, 15 mg/kg	Backstrom and Hyytia, 2005
Agonist									
(S)-3,4-DCPG	↓	-	-	-	-	M	Oper	15 mg/kg	Backstrom and Hyytia, 2005
Systemic	↓	-	-	-	-	M	Oper _{EtOH Seeking}	10, 15 mg/kg	Backstrom and Hyytia, 2005
Systemic	↓	-	-	-	-	M	Oper _{EtOH Seeking}	10, 15 mg/kg	Backstrom and Hyytia, 2005
NMDA receptor									
NR2a	-	-	-	↑	-	M	FCCA	AcbCo, CeA	Obara et al., 2009
Level	-	-	-	↑	-	M	FCIA	AcbSh, AcbCo, CeA	Obara et al., 2009
NR2b	-	-	-	↑	-	M	FCCA	AcbCo, CeA	Obara et al., 2009
Level	-	-	-	↑	-	M	FCCA	AcbCo, CeA	Obara et al., 2009

Neurotransmitter system/receptor	AA	H1	H2	P	sP	Sex	EtOH access	Dose	Reference
NMDA Antagonist									
L-701,324 (also glycine antagonist)	↓	—	—	—	—	M	Oper _{EtOH} Seeking	4 mg/kg	Backstrom and Hyytia, 2004
Systemic									
AMPA/Kainate receptor Antagonist									
CNQX									
Systemic	↓	—	—	—	—	M	Oper _{EtOH} Seeking	1.5 mg/kg	Backstrom and Hyytia, 2004
Homer2a/b									
Level	—	—	—	↑	—	M	FCCA	AcbCo, CeA	Obara et al., 2009
Histamine system									
H1 receptor	—	—	—	↑	—	M	FCCA	AcbCo, CeA	Obara et al., 2009
Antagonist	—	—	—	↑	—	M	FCIA	AcbCo, CeA	Obara et al., 2009
Mepyramine									
Systemic	↔	—	—	—	—	M	Oper	1–10 mg/kg	Lintunen et al., 2001
H3 receptor									
Agonist									
R-α-methylhistamine									
Systemic	↔	—	—	—	—	M	Oper	1–10 mg/kg	Lintunen et al., 2001
Antagonist									
Thioperamide									
Systemic	↓	—	—	—	—	M	Oper	3, 10 mg/kg	Lintunen et al., 2001
Clobenpropit									
Systemic	↓	—	—	—	—	M	Oper	10 mg/kg	Lintunen et al., 2001
Norepinephrine (NE) system									
NE Transporter (NET)									
Inhibitor									

Neurotransmitter system/receptor	AA	H1	H2	P	sP	Sex	EtOH access	Dose	Reference
Desipramine									
Systemic	-	-	-	↓	-	M	FCCA	5 mg/kg	Murphy et al., 1985
DOV 102,677 ^(also inhibits SERT & DAT)									
Systemic	-	-	-	↓	-	M	Oper	6.25–50 mg/kg	Yang et al., 2012
α_1 receptor									
Antagonist									
Prazosin [*]									
Systemic	-	-	-	↓	-	M	FCLA	0.5–2 mg/kg	Rasmussen et al., 2009
Systemic	-	-	-	↓	-	M	Oper ^{Maintenance}	1.5 mg/kg	Verplaetse et al., 2012
Systemic	-	-	-	↓	-	M	Oper ^{EtOH Seeking}	0.5–1.5 mg/kg	Verplaetse et al., 2012
α_2 receptor									
Agonist									
Medetomidine									
Systemic	↔	-	-	-	-	M	FCCA	3 µg/kg/h	Korpi, 1990
Antagonist									
Atipamezole									
Systemic	↑	-	-	-	-	M	FCCA	30 µg/kg/h	Korpi, 1990
<i>Opioid system</i>									
μ receptor									
Agonist									
14-methoxymetopon									
Systemic	-	-	-	-	↑	M	FCLA	12.25 µg (60 min)	Sabino et al., 2007
Systemic	-	-	-	-	↑	M	FCLA	30 µg (240 min)	Sabino et al., 2007
Systemic	-	-	-	-	↓	M	FCLA	30 µg (30 min)	Sabino et al., 2007
Microinjection	-	-	-	-	↑	M	FCLA	10 pg (ICV; 30 min)	Sabino et al., 2007
Microinjection	-	-	-	-	↓	M	FCLA	100 ng (ICV; 30 min)	Sabino et al., 2007
Microinjection	-	-	-	-	↑	M	FCLA	100 ng (ICV; 240 min)	Sabino et al., 2007
Morphine ^(also δ & κ agonist)									
Systemic	-	-	-	-	↑	M	FCCA	1 mg/kg	Vacca et al., 2002a
Systemic	-	-	-	-	↓	M	FCCA	10 mg/kg	Vacca et al., 2002a

Neurotransmitter system/receptor	AA	H1	H2	P	sP	Sex	EtOH access	Dose	Reference
Antagonist									
Naltrexone[*] (also δ & κ antagonist)									
Systemic	↓	-	-	-	-	?	FCCA	3, 7.5 mg/kg	Coonfield et al., 2004
Systemic	-	-	-	↓	-	?	FCCA	3, 7.5 mg/kg	Coonfield et al., 2004
Systemic	↓	-	-	-	-	M	FCCA	1 mg/kg×2	Parkes and Sinclair, 2000
Systemic	↓	-	-	-	-	M	FCLA	0.1–3 mg/kg	Koistinen et al., 2001
Systemic	-	↓	-	-	-	M	FCCA	2.5, 5 mg/kg	Myers and Lankford, 1996
Microinjection	-	-	-	↓	-	M & F	Oper	0.5–5 μ g (CeA)	Foster et al., 2004
Systemic	-	-	-	↓	-	M & F	Oper	0.01–8 mg/kg	June et al., 1998c
Systemic	-	-	-	↓	-	M & F	FCCA _{Acquisition}	5–30 mg/kg (Adol)	Sable et al., 2006
Systemic	-	-	-	↓	-	M & F	FCCA _{Acquisition}	20, 30 mg/kg (Adult)	Sable et al., 2006
Systemic	-	-	-	-	↓	F	Oper _{EtOH Seeking}	1–10 mg/kg	Dhaher et al., 2012
Systemic	-	-	-	↓	-	F	Oper _{Relapse}	1–10 mg/kg	Dhaher et al., 2012
Systemic	-	-	-	-	↓	M	Oper	50–450 μ g/kg	Sabino et al., 2006
Naloxone[*] (also δ & κ antagonist)									
Systemic	↓	-	-	-	-	M	Oper	1, 2.5 mg/kg	Hyttia and Sinclair, 1993
Systemic	↓	-	-	-	-	M	Oper	0.3, 1 mg/kg	Hyttia and Kianmaa, 2001
Microinjection	↓	-	-	-	-	M	Oper	10, 30 μ g (ICV)	Hyttia and Kianmaa, 2001
Systemic	-	↓	-	-	-	M	FCLA	0.075–18 mg/kg	Froehlich et al., 1990
Systemic	-	↓	-	-	-	M	FCLA	0.5–3 mg/kg	Froehlich et al., 1991
Systemic	-	-	-	↓	-	F	Oper	0.003–0.75 mg/kg	June et al., 1999
Systemic	-	-	-	↓	-	M	FCLA	2.5–10 mg/kg	Badia-Elder et al., 1999
Systemic	-	-	-	-	↓	M	Oper	1, 3 mg/kg	Maccioni et al., 2005
Nalmefene[*] (also δ & κ antagonist)									
Systemic	-	-	-	↓	-	M & F	Oper	.001–5 mg/kg	June et al., 1998c
Microinjection	-	-	-	↓	-	F	Oper	1–20 μ g (Hipp)	June et al., 2004
Microinjection	-	-	-	↓	-	F	Oper	0.5–60 μ g (Acb)	June et al., 2004

Neurotransmitter system/receptor	AA	H1	H2	P	sP	Sex	EtOH access	Dose	Reference
Naloxonazine									
Systemic	↓	-	-	-	-	M	FCLA	15 mg/kg	Honkanen et al., 1996
CTOP									
Microinjection	↓	-	-	-	-	M	Oper	3 µg (icv)	Hyytiä and Kianmaa, 2001
Microinjection	↓	-	-	-	-	M & F	FCLA	1 µg (icv)	Hyytiä, 1993
Beta-FNA									
Systemic	-	↓	-	-	-	M	FCLA	10–20 mg/kg	Krishnan-Sarin et al., 1995c
Antagonist									
LY255582									
Systemic	-	-	-	↓	-	F	Oper _{EtOH Seeking}	0.1–1 mg/kg	Daher et al., 2012
Systemic	-	-	-	↓	-	F	Oper _{Relapse}	0.03–1 mg/kg	Daher et al., 2012
Systemic	-	-	-	↓	-	F	Oper _{Maintenance}	0.1–1 mg/kg	Daher et al., 2012
δ receptor									
Agonist activity									
Enkephalinase inhibitor									
Thiorphan									
Systemic	-	↑	-	-	-	M	FCLA	30 mg/kg	Froehlich et al., 1991
Hydrocinnamic acid									
Systemic	-	↔	-	-	-	M	FCLA	125, 250 mg/kg	Froehlich et al., 1991
Antagonist									
Naltrindole									
Systemic	↔	-	-	-	-	M	FCLA	1, 15 mg/kg	Honkanen et al., 1996
Systemic	-	-	-	↓	-	M	FCLA	7.5–20 mg/kg	Krishnan-Sarin et al., 1995b
Microinjection	↓	-	-	-	-	M	Oper	10, 30 µg (icv)	Hyytiä and Kianmaa, 2001
Naltriben									
Systemic	-	-	-	↓	-	F	Oper	0.9–4 mg/kg	June et al., 1999
Systemic	-	-	-	↓	-	M	FCLA	3 mg/kg×2	Krishnan-Sarin et al., 1995b
ICI 174,864									

Neurotransmitter system/receptor	AA	H1	H2	P	sP	Sex	EtOH access	Dose	Reference
Systemic	-	↓	-	-	-	M	FCLA	1, 3 mg/kg	Froehlich et al., 1991
Systemic	-	-	-	↓	-	M	FCLA	3-8 mg/kg	Krishnan-Sarin et al., 1995a
Microinjection	↔	-	-	-	-	M & F	FCLA	3 µg (icv)	Hyytiä, 1993
Me(2)-Dmt-Tic-OH	↔	-	-	-	-	M	FCLA	10, 30 mg/kg	Ingman et al., 2003b
Systemic	↔	-	-	-	-	M	FCLA	10, 30 mg/kg	Ingman et al., 2003b
<i>Sigma-receptor (Opioid & PCP binding?)</i>									
σ ₁ Antagonist									
NE-100									
Systemic	-	-	-	-	↓	M	FCCA	17.8, 30 mg/kg	Sabino et al., 2009b
BD-1063									
Systemic	-	-	-	-	↓	M	Oper	4.4-11 mg/kg	Sabino et al., 2009a
<i>Serotonin (5-HT) system</i>									
Precursor									
D ₁ L-5-HTP									
Systemic	-	-	-	↓	-	?	FCLA	40 mg/kg	McBride et al., 1990
5-HT ₁ receptor									
Agonist									
TFMPP									
Systemic	-	-	-	↓	-	?	FCLA	1 mg/kg	McBride et al., 1990
5-HT _{1A} receptor									
Agonist									
8-OH-DPAT									
Systemic	-	-	-	↓	-	?	FCLA	1 mg/kg	McBride et al., 1990
Antagonist									
WAY 100,635									
Systemic	-	-	-	↓	-	F	FCCA	0.1, 0.5 mg/kg	Zhou et al., 1998
5-HT ₂ receptor									
Agonist									
DOI									
Systemic	-	-	-	↓	-	?	FCLA	1 mg/kg	McBride et al., 1990

Neurotransmitter system/receptor	AA	H1	H2	P	sP	Sex	EtOH access	Dose	Reference
Antagonist									
Amperozide (FG 5606)									
Systemic	↓	-	-	-	-	?	FCCA	5, 10 mg/kg	Overstreet et al., 1997b
Systemic	-	↓	-	-	-	M	FCCA	2 mg/kg	Lankford and Myers, 1996
Systemic	-	-	-	↓	-	?	FCCA	2.5–10 mg/kg	Overstreet et al., 1997b
Systemic	-	-	-	↓	-	M	FCCA	2, 5 mg/kg	Lankford et al., 1996
Deramciclane									
Systemic	↔	-	-	-	-	F?	FCLA	3, 10 mg/kg	Ingman et al., 2004
FG 5974 (also 5-HT1A agonist)									
Systemic	↔	-	-	-	-	?	FCCA	1–10 mg/kg	Overstreet et al., 1997b
Systemic	-	-	-	↓	-	?	FCCA	10, 30 mg/kg	Overstreet et al., 1997b
Systemic	-	-	-	↓	-	M	FCCA	2.5–10 mg/kg	Piercy et al., 1996
Systemic	-	-	-	↓	-	M	FCCA	2, 5 mg/kg	Lankford et al., 1996
FG5893 (also 5-HT1A agonist)									
Systemic	-	-	-	↔	-	M	FCCA	2, 5 mg/kg	Lankford et al., 1996
FG5865 (also 5-HT1A agonist)									
Systemic	-	↓	-	-	-	M	FCCA	1, 2.5 mg/kg	Long et al., 1996
Ritanserin (also 5-HT1C antagonist)									
Systemic	-	-	-	-	↔	M	FCCA	1, 10 mg/kg	Panocka et al., 1993
Risperidone (also D2 antagonist)									
Systemic	↓	-	-	-	-	M	FCLA	0.1, 1.0 mg/kg	Ingman et al., 2003a
Systemic	-	-	-	-	↓	M	FCCA	10 mg/kg	Panocka et al., 1993
Aripiprazole (also D2 and 5-HT1A agonist)									
Systemic	↓	-	-	-	-	M	FCLA	6 mg/kg	Ingman et al., 2006
5-HT₃ receptor									
Antagonist									
MDL 72222									
Systemic	-	-	-	↓	-	M	FCCA _{Acquisition}	1 mg/kg	Rodd-Henricks et al., 2000a
Systemic	-	-	-	↓	-	M	FCCA _{Maintenance}	1 mg/kg	Rodd-Henricks et al., 2000a

Neurotransmitter system/receptor	AA	H1	H2	P	sP	Sex	EtOH access	Dose	Reference
Systemic	-	-	-	↓	-	M	FCCA _{Relapse}	3 mg/kg	Rodd-Henricks et al., 2000a
Systemic	-	-	-	↔	-	M	FCCA _{Relapse}	1, 7 mg/kg	Rodd-Henricks et al., 2000a
Systemic	-	-	-	-	↓	M	FCLA	3-7 mg/kg×3	Fadda et al., 1991
ICS 205-930									
Systemic	-	-	-	↓	-	M	FCCA _{Acquisition}	1, 5 mg/kg	Rodd-Henricks et al., 2000a
Systemic	-	-	-	↓	-	M	FCCA _{Maintenance}	1, 5 mg/kg	Rodd-Henricks et al., 2000a
Systemic	-	-	-	↓	-	M	FCCA _{Relapse}	5 mg/kg	Rodd-Henricks et al., 2000a
Microinjection	-	-	-	↓	-	F	Oper _{Acquisition}	0.125-1.25 µg (pVTA)	Rodd et al., 2010
Systemic	-	-	-	↑	-	F	Oper _{Maintenance}	0.75, 1.25 µg (pVTA)	Rodd et al., 2010
5-HT ₄ receptor									
Antagonist									
GR113808									
Systemic	-	-	-	↓	-	M	FCLA	1-10 mg/kg	Panocka et al., 1995b
Serotonin Transporter (SERT)									
Reverse Transporter									
Fenfluramine									
Systemic	-	-	-	↓	-	?	FCLA	3 mg/kg	McBride et al., 1990
Inhibitor									
Fluoxetine									
Systemic	-	↓	-	-	-	?	FCLA	3 mg/kg	Rezvani et al., 2000
Systemic	-	-	-	↓	-	F	FCCA	1 mg/kg	Zhou et al., 1998
Systemic	-	-	-	↓	-	M	FCCA	5, 10 mg/kg	Murphy et al., 1985
Systemic	-	-	-	↓	-	M	FCLA	10 mg/kg	Murphy et al., 1985
Systemic	-	-	-	↓	-	M	Oper IG	10 mg/kg	Murphy et al., 1988
Systemic	-	-	-	↓	-	?	FCCA	1 mg/kg	Rezvani et al., 2000
Clomipramine _(also inhibits NET & DAT)	↑	-	-	-	-	M	FCCA	25 mg/k	Hilakivi and Sinclair, 1986
Systemic									^g Neonate Xment Adult Test

Neurotransmitter system/receptor	AA	H1	H2	P	sP	Sex	EtOH access	Dose	Reference
Fluvoxamine									
Systemic	-	-	-	↓	-	M	FCCA	10 mg/kg	Murphy et al., 1985
Systemic	-	-	-	↓	-	M	FCLA	10 mg/kg	Murphy et al., 1985
DOV 102,677_(also inhibits NET & DAT)									
Systemic	-	-	-	↓	-	M	Oper	6.25–50 mg/kg	Yang et al., 2012
Neuropeptides									
AVP									
V1b receptor									
Antagonist									
SSR149415									
Systemic	-	-	-	-	↓	M	FCCA	30 mg/kg	Zhou et al., 2011
CRF									
CRF(1) receptor									
Antagonist									
LWH-63									
Systemic	-	-	-	-	↔	M	Oper	10 mg/kg	Sabino et al., 2006
Systemic	-	-	-	-	↑	M	FCLA	10, 20 mg/kg	Sabino et al., 2006
MJL-1-109-2									
Systemic	-	-	-	-	↔	M	FCLA	10 mg/kg	Sabino et al., 2006
R121919									
Systemic	-	-	-	-	↔	M	FCLA	5–20 mg/kg	Sabino et al., 2006
MPZP									
Systemic	-	-	-	↓	-	M	Oper	5–20 mg/kg	Gilpin et al., 2008a
Antalarmin[*]									
Systemic	-	-	-	↓	-	M & F	FCCA	20 mg/kg	Heilig and Egli, 2006
Melanocortin (alpha-MSH)									
MC receptor									
Agonist_(nonselective)									
MTII									
Microinjection	↓	-	-	-	-	F	FCCA	1 nmol (ICV)	Ploj et al., 2002
MC4 receptor									

Neurotransmitter system/receptor	AA	H1	H2	P	sP	Sex	EtOH access	Dose	Reference
Antagonist									
HS014	↔	-	-	-	-	F	FCCA	1 nmol (ICV)	Ploj et al., 2002
NPY									
NPY treatment									
Microinjection	-	↑	-	-	-	F	SBLA	5, 10 µg (ICV)	Badia-Elder et al., 2003
Microinjection	-	↑	-	-	-	F	FCCA	0.5 µg (PVN)	Gilpin et al., 2004
Microinjection	-	↓	-	-	-	F	FCCA	1 µg (PVN)	Gilpin et al., 2004
Microinjection	-	-	-	↓	-	M	FCCA	100 pmol (CeA)	Pandey et al., 2005
Microinjection	-	-	-	↓	-	F	FCCA _{Relapse}	1 µg (CeA)	Gilpin et al., 2008b
Microinjection	-	-	-	↓	-	F	FCCA	10 µg (ICV)	Gilpin et al., 2003
Microinjection	-	-	-	↓	-	M	FCCA	5, 10 µg (ICV)	Badia-Elder et al., 2001
Microinjection	-	-	-	↓	-	F	FCCA _{Relapse}	5 µg (ICV)	Bertholomey et al., 2011
Microinjection	-	-	-	↓	-	M	FCCA	100 pmol (CeA)	Zhang et al., 2010
Y2 receptor									
Antagonist									
JNJ-31020028	-	-	-	↔	-	M	Oper	15–40 mg/kg	Cippitelli et al., 2011
Systemic	-	-	-	↔	-	M	Oper	0.3, 1 nmol (ICV)	Cippitelli et al., 2011
BH0246									
Microinjection	-	-	-	↓	-	M	Oper	1 nmol (ICV)	Cippitelli et al., 2011
Y5 receptor									
Antagonist									
L152804	-	-	-	↓	-	M	FCCA	3 mg/kg	Schroeder et al., 2005b
Systemic	-	-	-	↓	-	M	Oper	10, 20 mg/kg	Schroeder et al., 2005b
NPS									
NPS treatment									
Microinjection	-	-	-	↓	-	F	FCCA	1.2 nmol (ICV)	Badia-Elder et al., 2008
Microinjection	-	-	-	↓	-	F	FCLA	0.075–1.2 nmol (ICV)	Badia-Elder et al., 2008

Neurotransmitter system/receptor	AA	H1	H2	P	sP	Sex	EtoH access	Dose	Reference
<i>Orexin</i>									
Orexin-1 receptor									
Antagonist									
SB-334867									
Systemic	-	-	-	↓	-	F	OperRelapse	10, 20 mg/kg	Dhafer et al., 2010
Systemic	-	-	-	↓	-	F	OperEtoH Seeking	10, 20 mg/kg	Dhafer et al., 2010
<i>Tachykinins</i>									
Neurokinin (NK)									
NK1 receptor									
Agonist									
[Sar9, Met(O2)11]substance P									
Microinjection	-	-	-	-	↔	M	FCLA	31.2–250 ng (icv)	Ciccocioppo et al., 1994
NK2 receptor									
Agonists									
GR 64349									
Microinjection	-	-	-	-	↔	M	FCLA	125–1000 ng (icv)	Ciccocioppo et al., 1994
NK3 receptor									
Agonists									
[Asp5,6, MePhe8]substance P ₍₅₋₁₁₎									
Microinjection	-	-	-	-	↓	M	FCLA	31.2–500 ng (icv)	Ciccocioppo et al., 1994
Suc[Asp6, MePhe8]substance P ₍₆₋₁₁₎									
Microinjection	-	-	-	-	↓	M	FCLA	31.2–500 ng (icv)	Ciccocioppo et al., 1994
[MePhe7]neurokinin B									
Microinjection	-	-	-	-	↓	M	FCLA	500–1000 ng (icv)	Ciccocioppo et al., 1994
<i>TRH content</i>									
TRH Analog									
TA-0910									
Systemic	-	-	-	-	↓	M	FCCA	0.75 mg/kg	Mason et al., 1994
TA-0910									
Systemic	-	-	-	-	↓	M	FCCA	0.75 mg/kg	Mason et al., 1997
TA-0910									

Neurotransmitter system/receptor	AA	H1	H2	P	sP	Sex	EtOH access	Dose	Reference
Systemic	–	–	–	–	↓	M	FCCA	0.25, 0.75 mg/kg	Rezvani et al., 1992

AA=Alko Alcohol; H1=High alcohol-drinking replicate 1; H2=High alcohol-drinking replicate 2; P=Alcohol-preferring; sP=Sardinian alcohol-preferring; –=Not tested;

↓=Decreased ethanol intake or self-administration; ↑=Increased ethanol intake or self-administration; ↔=No effect on ethanol intake or self-administration; ↓=Mixed effects on ethanol intake or self-administration; FCCA=Free-choice continuous access; FCLA=Free-choice limited access; FCLA=Free-choice limited access; Oper=Operant; SBLA=Single-bottle limited access; Acb=Nucleus accumbens; AcbCo=Nucleus accumbens core; AcbSh=Nucleus accumbens shell; BNST=Bed nucleus of stria terminalis; CeA=Central amygdala; IA=Intercalated amygdaloid nuclei; LA=Lateral amygdala; CPU=Caudate putamen; Hipp=Hippocampus; ICV=Intracerebroventricular; PFC=Prefrontal cortex; PPN=Pedunculopontine nucleus; PVN=Paraventricular nucleus; VP=Ventral pallidum; VTA=Ventral tegmental area; pVTA=Posterior ventral tegmental area; S=Significant; NS=Nonsignificant; Xment=Treatment; ×2=2 treatments per day; ×3=3 treatments per day; Adol=Tested during adolescence; Adult=Tested during adulthood; GHB=Gamma hydroxybutyric acid; AVP=Arginine vasopressin; CRF=Corticotropin releasing factor; MSH=Melanocyte stimulating hormone; NPY=Neuropeptide Y; NPS=Neuropeptide S; TRH=Thyrotropin releasing hormone.

* indicates compounds undergoing clinical trials (Litten et al., 2012).