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Effects of ethanol on startle responding in alcohol-preferring and -non-preferring rats

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Abstract

The objectives of the present study were to determine (a) if differences exist between the selectively bred alcohol-preferring (P) and -non-preferring (NP) lines of rats in the acoustic startle response (ASR) and prepulse inhibition (PPI), and (b) the effects of ethanol on these measures. Alcohol-naïve adult female P and NP rats received a single i.p. injection of saline or ethanol (0.25, 0.5, 1.0, or 1.5 g/kg) and were placed in the startle apparatus 10 min later. After a 5-min acclimation period, rats received five alternating trials of a startle stimulus alone (SSA) (115-dB white noise) or a PPI trial (90-dB white noise preceding a 115-dB white noise). Analysis of the ASR revealed that P rats exhibited higher startle amplitudes than did NP rats with saline injections. The 0.5-g/kg ethanol dose reduced the startle amplitude in P, but not NP, rats. The 1.0- and 1.5-g/kg ethanol doses nearly abolished the ASR in the NP line, whereas only the highest ethanol dose had this effect in the P line. Vehicle-treated P and NP rats exhibited comparable PPI levels, but only P rats showed a significant disruption (30%) at the 0.50-g/kg ethanol dose. Neither P nor NP rats were affected by ethanol treatment at the 0.25-g/kg dose. Overall, the results suggest that: (a) the difference in baseline ASR may indicate line differences in the neurocircuitry mediating this response, possibly reflecting higher innate levels of emotional reactivity in the P line; (b) the P line may be more sensitive than the NP line to the effects of ethanol in reducing emotional reactivity; and (c) low-dose ethanol may have a greater disruptive effect on sensorimotor gating mechanisms in the P than NP rat.

Keywords: Acoustic startle response; Prepulse inhibition; Alcohol-preferring P rats; Alcohol-non-preferring NP rats; Anxiety; Sensorimotor gating

Alcoholism is often observed in the presence of other psychiatric illnesses, with as many as two-thirds of all alcoholics meeting the criteria for at least one other mental disorder [13,16,21,32,38,50]. However, it is unclear whether psychiatric deficits predate alcohol abuse, or come as a direct consequence of excessive alcohol consumption. One hypothesis that has been proposed to explain the high comorbidity between alcoholism and psychiatric disorders is a genetic linkage between the proclivity to abuse alcohol and the expression of certain psychiatric symptoms [44]. Efforts to identify psychopathological traits as potential vulnerability factors for alcohol abuse have lead researchers to identify several neuropsychiatric deficits that may be associated with alcoholism (cf. Ref. [43]). For example, impairments in attentional processing have been associated with a familial pattern of alcohol abuse [12,33,36,44]. In addition, anxiety disorders are among the most common syndromes found comorbid with alcoholism [21]. For example, children of alcoholics often exhibit heightened emotional reactivity [14], and individuals with a family history positive for alcoholism are more reactive to both

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aversive and non-aversive stimuli compared to individuals with a negative family history of alcohol abuse [8,9].

Animals selectively bred for ethanol preference and non-preference provide a useful model to study behavioral phenotypes that may be associated with alcohol abuse. One such model is the alcohol-preferring (P) and -non-preferring (NP) lines of rats, which were selectively bred for their respective voluntary preference and non-preference for 10% ethanol [24]. Thus far, only the P line of rats satisfies the proposed criteria [6] for an animal model of alcoholism [24,29]. P rats voluntarily consume between 5 and 8 g ethanol/kg body weight/day, attaining BAC between 50–200 mg%, whereas the NP line consumes less than 1 g/kg/day [23,24]. P rats drink ethanol for its reinforcing, pharmacological properties and not solely for its taste or caloric properties, as evidenced by studies that demonstrated that they will self-administer ethanol directly into the stomach [46] or ventral tegmental area [10]. Additionally, it has been demonstrated that the P rats will develop both metabolic [25] and functional tolerance [11] as well as physical dependence [47] with chronic free-choice drinking. P and NP line differences in measures of anxiety have been reported in several tests, suggesting that P rats have higher levels of anxiety than NP rats [37,39]. In addition, the P line appeared to be more sensitive than NP rats to the anxiolytic effects of alcohol [39], although in the anti-conflict test, the reverse was found [1].

The present study was designed to examine differences between the P and NP lines in the acoustic startle response (ASR) and in the reduction of this response with prepulse inhibition (PPI). The startle reflex response is modulated by emotional states and has been used to investigate individual differences in emotional reactivity in both people and animals [3,34]. PPI of the ASR refers to the ability of a weak prestimulus to inhibit the response to a startle-eliciting stimulus. PPI has been described as an experimental measure of sensorimotor gating, and is believed to be an important mechanism for screening irrelevant stimuli [4,5]. PPI deficits are seen in individuals with psychiatric disorders that are associated with attentional impairments [4,5,33,40], and in children with a positive family history of alcoholism [14]. The loss of PPI in rats, as a result of lesions or pharmacological manipulation, has been used as an animal model of attentional impairment [41]. Several key limbic regions (e.g., nucleus accumbens, ventral tegmental area, raphe nuclei, amygdala, hippocampus, etc.) have been implicated in mediating PPI of the ASR [20]. Both dopamine (DA) and serotonin (5-HT) appear to be involved in modulating the startle response [7], and both DA and 5-HT neurotransmission within the mesolimbic system appear to be involved in modulating PPI [20]. Neurobiological studies indicated differences in the DA innervation and dopamine D_2 receptor densities in the nucleus accumbens and ventral tegmental area, and widespread differences in 5-HT innervation and receptor densities in the limbic system and other CNS regions between the P and NP lines [29]. These latter results suggest that there may be differences between the P and NP lines in the neurocircuitry mediating the ASR and PPI.

The first hypothesis to be tested in the present study was that there would be innate differences in the ASR and PPI between P and NP rats, because of the innate differences in DA and 5-HT systems and potential differences in levels of anxiety between the lines. The effects of ethanol on these measures were studied, as well, because P rats appear to be more sensitive than NP rats to the anxiolytic effects of ethanol [39] and these lines exhibit different sensitivities to low [48] and high [26] ethanol doses in measures of motor activity. In addition, ethanol has been shown to alter the ASR in rats [35] and humans [15], alter PPI at a low dose in humans [17], and reduce stress reactivity and disrupt attention [2]. The second hypothesis to be tested was that ethanol would have different effects on the ASR and PPI inhibition between the P and NP rats.

1. Method

1.1. Animals

Subjects were 109 ethanol-naïve, female rats (weight-matched; 284 ± 2 g) from the S 39–40 generations of the P and NP lines. Animals were pair-housed in $18 \times 24 \times 45$ cm plastic tubs with wire grid tops and maintained on a 12/12-light/dark cycle (lights on at 0700 h) in a temperature- (21°C) and humidity- (50%) controlled vivarium. Harlan rat chow (Teklad Diet #7001, Harlan Industries, Indianapolis, IN) and water were available ad libitum. All experiments were conducted during the light portion of the light cycle between 0900 and 1400 h. Animals used in this experiment were maintained in facilities accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC). All research protocols were approved by the institutional animal care and use committee, in accordance with the guidelines of the *Institutional Care and Use Committee of the National Institute on Drug Abuse, NIH*, and the *Guide for the Care and Use of Laboratory Animals* (National Research Council 1996).

Female rats were chosen to be used in the current study mainly because of availability. Female P and NP rats also maintain their body weights better than males which minimizes weight-related effects on the startle measurements. Both male and female rats have been used in ASR studies with gender differences appearing in one study [22] but not in the other [19]. Additionally, in the study in which gender effects were observed in the ASR [22], PPI was comparable across gender with male and female Wistar rats showing approximately a 10% difference in the level of PPI. Estrous cycle effects on PPI have been reported for female Sprague–Dawley rats, with lower values observed during proestrous compared to either diestrous or estrous [19]. While not monitored, however, any fluctuations in behavior due to the stage of the estrous cycle should be randomized across

treatment groups. If there are effects of the estrous cycle on increasing the variance of the PPI data, these effects must be relatively small because of the low variance in the PPI data (see Results section).

1.2. Apparatus

Testing was conducted in a commercial startle reflex system (S-R lab; San Diego Instruments, CA) equipped with an internal light and sound source. The chamber was sound-attenuated and ventilated with an exhaust fan, and contained a stabilimeter comprised of an 8.2-cm diameter Plexiglas rodent cylinder resting on a Plexiglas platform. Startle responses were transduced by a piezoelectric accelerometer located beneath the platform and were converted into arbitrary units based on calculations from force and latency of startle. Data were sampled at 1 KHz for 150 ms and stored as the average of 150 one-millisecond readings, starting at the onset of each startle stimulus.

1.3. Test procedure

Experimentally naïve P and NP rats ($N = 9–14$/line/group) first received single, i.p. saline injections for four consecutive days in order to habituate them to the injection procedure. On day five, rats were assigned to either saline or ethanol groups. Ethanol doses were 0.25, 0.5, 1.0, or 1.5 g/kg (i.p.) in a 15% v/v saline solution. The volume administered to the saline controls matched that of the 1.5-g/kg ethanol group. Ten minutes following the injection, rats were placed in the startle chamber. Testing began following a 5-min acclimation period. During this time, and throughout the session, a 70-dB background noise was present. The test session consisted of five alternating trials of a startle stimulus alone (SSA) and a prepulse (PP) trial. SSA trials consisted of a 115-dB white noise burst that had a duration of 750 ms. On PP trials, a 100-ms 90-dB white noise immediately preceded the 115-dB stimulus. Trials occurred on a fixed 90-s intertrial interval. Preliminary studies in our laboratory determined that the 90-dB acoustic stimulus had no startle-eliciting properties itself.

1.4. Data analysis

Startle amplitude was calculated by taking the mean of the five SSA responses for each animal. To assess possible line differences in baseline startle responding, a Student's *t*-test was performed on the startle amplitude of saline control groups for P and NP rats. Because baseline differences were seen between the lines, separate ANOVAs were subsequently performed on the startle amplitudes for each line as a function of ethanol dose. In the presence of a significant ANOVA, group differences were determined with the protected least significant difference test (Fisher test) [18]. PPI was calculated as $[(SSA - PP)/SSA] \times 100$. PPI in the 1.0- and 1.5-g/kg dose groups was not included in the analysis, because motor functioning may have been impaired in the NP line in the 1.0-g/kg group, and in both lines in the 1.5-g/kg group [48]. PPI data were analyzed using a two-factor ANOVA and post-hoc Fisher test.

2. Results

Fig. 1 illustrates mean startle amplitudes in female P and NP rats following vehicle or ethanol administration. Analysis of the data indicated line differences in baseline startle responses, with saline-treated P rats exhibiting startle values

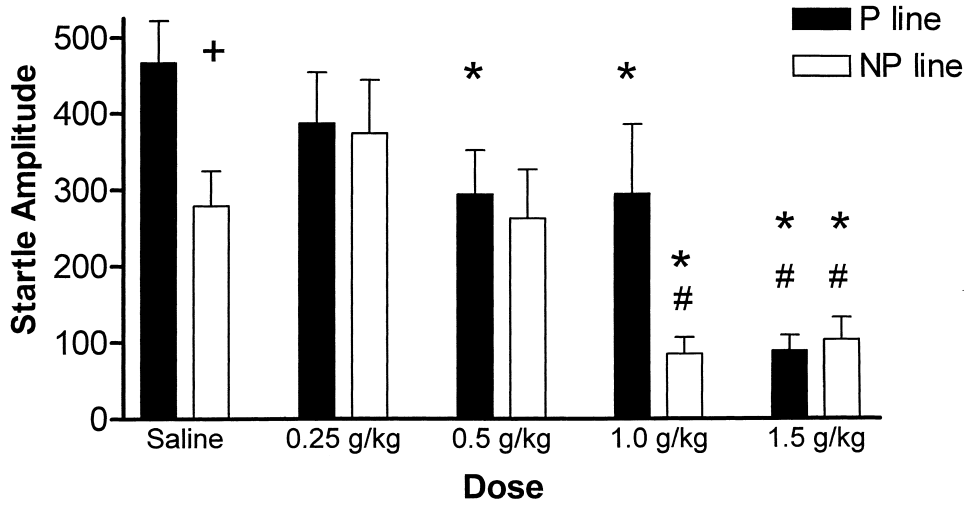

Fig. 1. Startle amplitude of female P and NP rats ($N = 9–14$/line/treatment) in response to a 115-dB stimulus after treatment with saline or ethanol (0.25, 0.5, 1.0, 1.5 g/kg). Data are mean startle amplitudes of the five trials ± SEM. Baseline startle responding differed significantly between P and NP lines of rats, with P rats displaying 40% higher startle amplitude than NP rats ($^{+}p < 0.02$). Startle amplitude in P rats was decreased significantly following 0.5, 1.0, and 1.5 g/kg, with motor impairing effects seen at the 1.5-g/kg dose only ($^{*}p < 0.05$ vs. saline for P line; $^{\#}p < 0.05$ vs. all other doses for P line). In NP rats, startle responding was significantly impaired following the 1.0- and 1.5-g/kg doses ($^{*}p < 0.05$ vs. saline for NP line; $^{\#}p < 0.05$ vs. 0.25 and 0.50 g/kg for NP line).

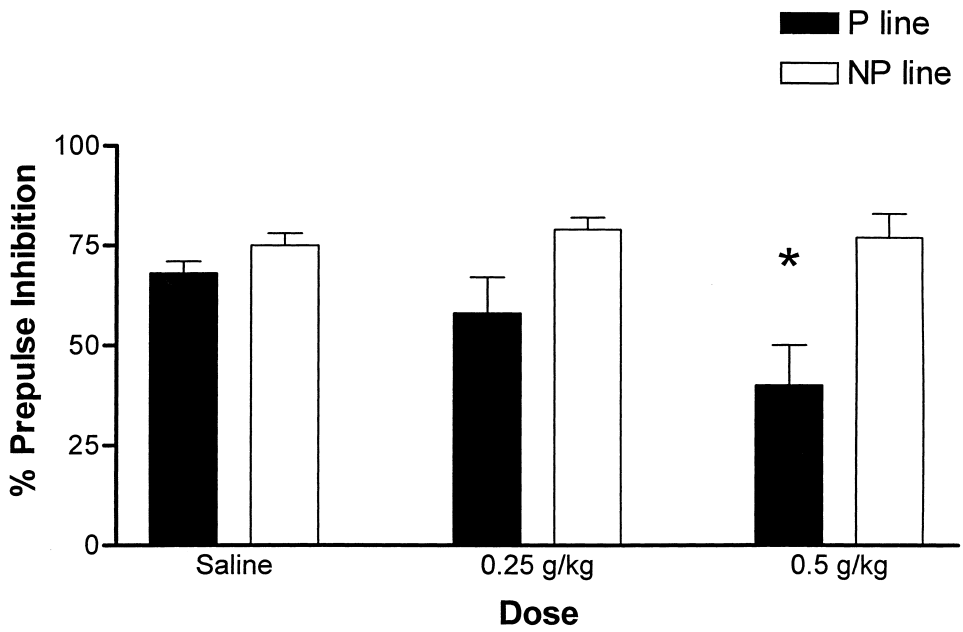

Fig. 2. Effect of ethanol on PPI of acoustic startle in female P and NP rats. Both P and NP rats exhibited similar baseline levels of PPI. Ethanol had no effect on PPI in NP rats; however, PPI was significantly disrupted in P rats following 0.5 g/kg ethanol ($*p<0.05$ vs. saline).

40% higher than values for NP rats, $t(21)=2.55$, $p<0.02$. One-way ANOVA performed on startle amplitude in P rats indicated a main effect of dose, $F(4,50)=6.31$, $p<0.001$. Follow-up analysis revealed a significant decrease in startle amplitude following 0.5, 1.0, and 1.5 g/kg ethanol. Additionally, the 1.5-g/kg dose produced significantly less startle than the 0.25-, 0.5-, and the 1.0-g/kg doses (all p values <0.05) for the P rats.

One-way ANOVA performed on the startle amplitude in NP rats also indicated a main effect of dose, $F(4,49)=5.17$, $p<0.001$. Post-hoc analysis revealed a significant decrease in startle amplitude in the 1.0- and 1.5-g/kg ethanol dose groups compared to the saline, 0.25-, and 0.5-g/kg dose groups. Neither the 0.25- nor 0.5-g/kg ethanol dose altered startle levels in NP rats compared to their vehicle controls.

The effects of ethanol on PPI are seen in Fig. 2. A two-factor line × dose ANOVA conducted on PPI indicated a main effect of line, $F(1,61)=20.68$, $p<0.001$, and a significant line × dose interaction, $F(2,61)=3.22$, $p<0.05$. Whereas saline-treated P and NP rats exhibited similar levels of PPI (68% and 75%, respectively), line differences emerged following ethanol administration. Although ethanol did not affect PPI in NP rats at either ethanol dose, P rats exhibited a significant disruption in PPI following 0.5 g/kg ethanol.

3. Discussion

Female P and NP rats were tested for differences in startle reactivity and PPI following saline or ethanol pretreatment. Under vehicle conditions, P rats exhibited an increased ASR relative to NP rats, suggesting greater levels of emotional reactivity [45] in the P line. Our findings are in agreement with other reports of increased "anxiety" in P rats relative to NP rats using other animal tests of anxiety [39], but such differences were not observed in all studies [1,31]. Additionally, recent studies from our laboratory with male P and NP rats, using a fear-potentiated startle paradigm, support the conclusion of higher levels of emotional reactivity exhibited by P rats [30]. In this study, startle responding was consistently greater in P than NP rats following fear conditioning, although baseline levels of acoustic startle responding were similar for P and NP rats in that study. Several methodological differences may have contributed to the alternative finding on baseline differences; there were parametric differences in the startle sessions, and different genders of animals were used as well.

Following treatment with low to moderate doses of ethanol, within the range of 0.5–1.0 g/kg, P rats showed moderate, but significant reductions in startle amplitude. Only P rats in the 1.5-g/kg dose group showed a marked decrease in their startle response levels. NP rats, on the other hand, did not show moderate reductions in startle amplitude with the 0.5-g/kg dose, but displayed a dramatic decrease in the ASR following both 1.0 and 1.5 g/kg ethanol. The marked reduction by the NP line at the two highest doses, and by the P line at the 1.5-g/kg dose is likely a result of motor impairment. Previous studies have indicated that, in this ethanol dose range, NP rats are more sensitive than P rats to the reduction in locomotor activity [48] and motor impairment [26] produced by ethanol. The greater sensitivity

of the NP line to the 1.0-g/kg dose of ethanol, observed in the present study, is in agreement with these reports.

The results suggest that P rats may be more sensitive than NP rats to the anxiolytic effects of ethanol, as indicated by the reduction in startle amplitude in the P line at the 0.5-g/kg dose (Fig. 1). These results support previous findings in P and NP rats that were examined in three different behavioral tests of anxiety, an approach-avoidance conflict test, the elevated-plus maze test, and a passive avoidance test [39]. These investigators found higher innate anxiety levels in the P rats relative to NP rats and that low-dose ethanol (0.5–1.0 g/kg) administration produced anxiolytic-like effects only in the P line.

The primary pathway that has been proposed to mediate the ASR includes, for the most part, the auditory nerve, the ventral cochlear nucleus, the dorsal nucleus of the lateral lemniscus, the caudal pontine reticular nucleus, spinal interneurons, and spinal motor neurons (see Ref. [19]). Pharmacological depletion of 5-HT or electrolytic lesions of the dorsal and median raphe nuclei results in an increased startle response (see Ref. [7]). The P line of rats has fewer 5-HT neurons in the raphe [53] and reduced innervation to several forebrain regions [51,52] compared to the NP line. Although hind brain regions have not been studied, these latter findings suggest that reduced 5-HT innervation of the neurocircuit mediating the ASR may contribute to the higher response in the P than NP rat.

PPI was only examined in the 0.25- and 0.5-g/kg dose groups for both lines, because of the motor impairing effects of ethanol in the NP rats at doses of 1.0 g/kg and greater. There were no differences in PPI between the two lines under vehicle conditions; however, 0.5 g/kg ethanol disrupted PPI in the P but not the NP line. PPI is a measure of sensorimotor gating and is believed to be important for attentional processes. In animals, PPI is impaired by a variety of compounds such as amphetamine and other dopaminergic-like agonists [27,42]. In the present study (Fig. 2), a dose of ethanol that is known to be stimulatory in the P line of rats [48] disrupted this measure of sensorimotor gating. It is interesting that only the P line of rats showed evidence of disruption of PPI at low doses of ethanol, suggesting a possible genetic link between alcohol preference and ethanol sensitivity of the acoustic sensorimotor gating mechanisms.

The nucleus accumbens is an important site for the convergence of mesolimbic neurotransmitter systems regulating PPI (see Ref. [20]). PPI can be disrupted with systemic or intra-accumbal injections of a DA D2 agonist and that this effect can be reversed with a D2 antagonist [49] (also see Ref. [20]). The P line of rat has reduced DA innervation to the nucleus accumbens [54] and lower densities of D2 receptors [28] than NP rats. However, there is no difference in PPI between the P and NP lines (Fig. 2). With these differences in the DA system between the lines, the NP line might have been expected to demonstrate greater PPI than the P line. It is possible that the line differences seen in these DA parameters may be too small to impact on PPI. Because these DA differences are genetically influenced, it is also possible the other mechanisms developed to compensate for the reduction in DA function within the limbic system.

Overall, these results suggest that the female P rats may be more reactive to startle-evoking stimuli than are female NP rats, suggesting greater levels of ‘‘anxiety’’ in these animals. Moreover, our findings suggest that P and NP lines show different sensitivity to the anxiolytic effects of low doses of ethanol, lending support to an association between the ‘‘stress-response dampening’’ effects of alcohol and ethanol preference. Basal levels of PPI were similar between the P and NP rats; however, following ethanol administration PPI was disrupted in the P rats, but not the NP animals. The disruption of the sensorimotor gating mechanisms observed at the low ethanol dose may be related to the general motor stimulating properties of ethanol in P rats.

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References

[1] Baldwin HA, Wall TL, Schuckit MA, Koob GF. Differential effects of ethanol on punished responding in the P and NP rats. Alcohol Clin Exp Res 1991;15:700–4.
[2] Begleiter H, Porjesz B. Neurophysiological phenotypic factors in the development of alcoholism. In: Begleiter H, Kissin B, editors. The genetics of alcoholism. New York: Oxford Press, 1995. pp. 294–326.
[3] Bradley MM, Cuthbert BN, Lang PJ. Startle reflex modification: emotion or attention? Psychophysiology 1990;27:513–22.
[4] Braff DL, Geyer MA. Sensorimotor gating and schizophrenia. Human and animal model studies. Arch Gen Psychiatry 1990;47:181–8.
[5] Castellanos FX, Fine EJ, Kaysen D, Marsh WL, Rapoport JL, Hallett M. Sensorimotor gating in boys with Tourette’s syndrome and ADHD: preliminary results. Biol Psychiatry 1996;39:33–41.
[6] Cicero TJ. A critique of animal analogues of alcoholism. In: Majchrowicz E, Noble EP, editors. Biochemistry and pharmacology of alcohol. New York: Plenum, 1979. pp. 533–60.
[7] Davis M. The mammalian startle response. In: Eaton RC, editor. Neural mechanisms of startle behavior. New York: Plenum, 1984. pp. 287–351.
[8] Finn PR, Pihl RO. Risk for alcoholism: a comparison between two different groups of sons of alcoholics on cardiovascular reactivity and sensitivity to alcohol. Alcohol Clin Exp Res 1988;12:742–7.
[9] Finn PR, Zeitouni NC, Pihl RO. Effects of alcohol on psychophysiological hyperreactivity to nonaversive and aversive stimuli in men at high risk for alcoholism. J Abnorm Psychol 1990;99:79–85.
[10] Gatto GJ, McBride WJ, Murphy JM, Lumeng L, Li T-K. Ethanol self-infusion into the ventral tegmental area by alcohol-preferring rats. Alcohol 1994;11:557–64.
[11] Gatto GJ, Murphy JM, Waller MB, McBride WJ, Lumeng L, Li T-K. Chronic ethanol tolerance through free-choice drinking in the P line of alcohol-preferring rats. Pharmacol Biochem Behav 1987;28:111–5.

[12] Gorenstein EE. Cognitive–perceptual deficit in an alcoholism spectrum disorder. J Stud Alcohol 1987;48:310–8.
[13] Grant BF, Dawson DA. Age at onset of alcohol use and its association with DSM-IV alcohol abuse and dependence: results from the national longitudinal alcohol epidemiologic survey. J Subst Abuse 1997;9:103–10.
[14] Grillon C, Dierker L, Merikangas KR. Startle modulation in children at risk for anxiety disorders and/or alcoholism. J Am Acad Child Adolesc Psychiatry 1997;36:925–32.
[15] Grillon C, Sinha R, O'Malley SS. Effects of ethanol on the acoustic startle reflex in humans. Psychopharmacology 1994;114:167–71.
[16] Helzer JE, Pryzbeck TR. The co-occurrence of alcoholism with other psychiatric disorders in the general population and its impact on treatment. J Stud Alcohol 1988;49:219–24.
[17] Hutchison KE, Rohsenow D, Monti P, Palfai T, Swift R. Prepulse inhibition of the startle reflex: preliminary study of the effects of a low dose of alcohol in humans. Alcohol Clin Exp Res 1997;21:1312–9.
[18] Keppel G. Design and analysis: a researcher's handbook. Englewood Cliffs, NJ: Prentice-Hall, 1982.
[19] Koch M. Sensorimotor gating changes across the estrous cycle in female rats. Physiol Behav 1998;64:625–8.
[20] Koch M. The neurobiology of startle. Prog Neurobiol 1999;59:107–28.
[21] Kushner MG, Sher KJ, Beitman BD. The relation between alcohol problems and the anxiety disorders. Am J Psychiatry 1990;147:685–95.
[22] Lehman J, Pryce CR, Feldon J. Sex differences in the acoustic startle response and prepulse inhibition in Wistar rats. Behav Brain Res 1999;104:113–7.
[23] Li T-K, Lumeng L, McBride WJ, Waller MB. Progress toward a voluntary oral consumption model of alcoholism. Drug Alcohol Depend 1979;4:45–60.
[24] Li T-K, McBride WJ. Pharmacogenetic models of alcoholism. Clin Neurosci 1995;3:182–8.
[25] Lumeng L, Li T-K. The development of metabolic tolerance in the alcohol-preferring P rat: comparison of forced and free-choice drinking of ethanol. Pharmacol Biochem Behav 1986;25:1013–20.
[26] Lumeng L, Waller MB, McBride WJ, Li T-K. Different sensitivities to ethanol in alcohol-preferring and -nonpreferring rats. Pharmacol Biochem Behav 1982;16:125–30.
[27] Mansbach RS, Geyer MA, Braff DL. Dopaminergic stimulation disrupts sensorimotor gating in the rat. Psychopharmacology 1988;94:507–14.
[28] McBride WJ, Chernet E, Dyr W, Lumeng L, Li T-K. Densities of dopamine D2 receptors are reduced in CNS regions of alcohol-preferring P rats. Alcohol 1993;10:387–90.
[29] McBride WJ, Li T-K. Animal models of alcoholism: neurobiology of high alcohol drinking behavior in rodents. Crit Rev Neurobiol 1998;12:339–69.
[30] McKinzie DL, Sajdyk TJ, McBride WJ, Murphy JM, Lumeng L, Li T-K, Shekhar A. Acoustic startle and fear-potentiated startle in alcohol-preferring (P) and -nonpreferring (NP) lines of rats. Pharmacol Biochem Behav 2000;65:691–6.
[31] McMillen BA, Means LW, Matthews JN. Comparison of the alcohol-preferring P rat to the Wistar rat in behavioral tests of impulsivity and anxiety. Physiol Behav 1998;63:371–5.
[32] Penick EC, Powell BJ, Nickel EJ, Bingham SF, Riesenmy KD, Read MR, Campbell J. Co-morbidity of lifetime psychiatric disorder among male alcoholic patients. Alcohol Clin Exp Res 1994;18:1289–93.
[33] Pihl RO, Peterson J, Finn P. Inherited predisposition to alcoholism: characteristics of sons of male alcoholics. J Abnorm Psychol 1990; 99:291–301.
[34] Plappert CF, Pilz PK, Schnitzler HU. Acoustic startle response and habituation in freezing and nonfreezing rats. Behav Neurosci 1993;107:981–7.
[35] Pohorecky LA, Cagan M, Brick J, Jaffe LS. The startle response in rats: effect of ethanol. Pharmacol Biochem Behav 1976;4:311–6.
[36] Porjesz B, Begleiter H, Reich T, van Engeland H, Edenberg HJ, Foroud T, Goate A, Litke A, Chorlian DB, Stimus RD, Rice J, Blangero J, Almasy L, Bauer LO, Kuperman S, O'Connor S, Rohrbaugh J. Amplitude of visual P3 event-related potential as a phenotypic marker for a predisposition to alcoholism: preliminary results from the COGA project. Alcohol Clin Exp Res 1998;22:1317–23.
[37] Salimov RM, McBride WJ, Sinclair JD, Lumeng L, Li T-K. Performance in the cross-maze and slip funnel tests of four pairs of rat lines selectively bred for divergent alcohol drinking behavior. Addict Biol 1996;1:273–80.
[38] Schuckit MA, Tipp JE, Bucholz KK, Nurnberger JI Jr., Hesselbrock RR, Crowe RR, Kramer J. The life-time rates of three major mood disorders and four major anxiety disorders in alcoholics and controls. Addiction 1997;92:1289–304.
[39] Stewart RB, Gatto GJ, Lumeng L, Li T-K, Murphy JM. Comparison of alcohol-preferring (P) and nonpreferring (NP) rats on tests of anxiety and for the anxiolytic effects of ethanol. Alcohol 1993;10:1–10.
[40] Swerdlow NR, Benbow CH, Zisook S, Geyer MA, Braff DL. A preliminary assessment of sensorimotor gating in patients with obsessive compulsive disorder. Biol Psychiatry 1993;33:298–301.
[41] Swerdlow NR, Braff D, Taaid N, Geyer M. Assessing the validity of an animal model of deficient sensorimotor gating in schizophrenic patients. Arch Gen Psychiatry 1994;51:139–50.
[42] Swerdlow NR, Mansbach RS, Geyer MA, Pulvirenti L, Koob GF, Braff DL. Amphetamine disruption of prepulse inhibition of acoustic startle is reversed by depletion of mesolimbic dopamine. Psychopharmacology 1990;100:413–6.
[43] Tarter RE, Alterman AI, Edwards KL. Vulnerability to alcoholism in men: a behavioral–genetic perspective. J Stud Alcohol 1985; 46:329–56.
[44] Tarter RE, Hegedus AM, Goldstein G, Shelly C, Alterman AI. Adolescent sons of alcoholics: neuropsychological and personality characteristics. Alcohol Clin Exp Res 1984;8:216–22.
[45] Walker DL, Davis M. Double dissociation between the involvement of the bed nucleus of the stria terminalis and the central nucleus of the amygdala in startle increases produced by conditioned versus unconditioned fear. J Neurosci 1997;17:9375–83.
[46] Waller MB, McBride WJ, Gatto GJ, Lumeng L, Li T-K. Intragastric self-infusion of ethanol by the P and the NP (alcohol-preferring and -nonpreferring) lines of rats. Science 1984;225:78–80.
[47] Waller MB, McBride WJ, Lumeng L, Li T-K. Induction of dependence on ethanol by free-choice drinking in alcohol-preferring rats. Pharmacol Biochem Behav 1982;16:501–7.
[48] Waller MB, Murphy JM, McBride WJ, Lumeng L, Li T-K. Effect of low dose ethanol on spontaneous motor activity in alcohol-preferring and -nonpreferring lines of rats. Pharmacol Biochem Behav 1986; 24:617–23.
[49] Wan F-J, Taaid N, Swerdlow NR. Do D1/D2 interactions regulate prepulse inhibition in rats? Neuropsychopharmacology 1996;14:265–74.
[50] Weissman MM, Myers J, Harding PS. Prevalence and psychiatric heterogeneity of alcoholism in a United States urban community. J Stud Alcohol 1980;41:672–81.
[51] Zhou FC, Bledsoe S, Lumeng L, Li T-K. Immunostained serotonergic fibers are decreased in selected brain regions of alcohol-preferring rats. Alcohol 1991;8:425–31.
[52] Zhou FC, Bledsoe S, Lumeng L, Li T-K. Reduced serotonergic immunoreactive fibers in the forebrain of alcohol-preferring rats. Alcohol Clin Exp Res 1994;18:571–9.
[53] Zhou FC, Pu CF, Lumeng L, Li T-K. Serotonergic neurons in alcohol-preferring rats. Alcohol 1994;11:397–403.
[54] Zhou FC, Zhang JK, Lumeng L, Li T-K. Mesolimbic dopaminergic system in alcohol preferring rats. Alcohol 1995;12:403–12.