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Research report

Dissociation between the aversive and pharmacokinetic effects of ethanol in female Fischer and Lewis rats

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Abstract

In humans and laboratory animal models, vulnerability to alcohol abuse is influenced by endogenous factors such as genotype. Using the inbred Fischer and Lewis rat strains, we previously reported stronger conditioned taste aversions (CTA) in male Fischer rats that could not be predicted by genotypic differences in alcohol absorption [Roma PG, Flint WW, Higley JD, Riley AL. Assessment of the aversive and rewarding effects of alcohol in Fischer and Lewis rats. Psychopharmacology (Berl) 2006;189:187–99]. The present study made similar assessments in Fischer and Lewis females via four-trial CTA induced by 1 or 1.5 g/kg intraperitoneal (IP) ethanol ($n = 10$–12/strain/dose) as well as measures of blood alcohol concentrations (BAC) at 15, 60 and 180 min post-injection with 1.5 g/kg IP ethanol or saline ($n = 7$–8/strain/dose). Dose-dependent CTAs were produced, but the strains did not differ from each other in these measures; however, BACs in the Lewis females were significantly higher than Fischer at all three time points. As with males of the Fischer and Lewis genotypes, a dissociation between BACs and the aversive effects of alcohol was observed. These data are the first assessments of these particular phenotypes in Fischer and Lewis females, and when considered with the historical data, suggest a Genotype × Sex interaction in the centrally mediated sensitivity to alcohol's aversive effects.
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1. Introduction

Alcohol is one of the most widely abused drugs in the world, as well as the most prevalent topic of the substance dependence disorders [19,21]. As with other drugs of abuse, the development of alcohol abuse and dependence are influenced by a number of biological factors, including genetics. Human epidemiological research consistently reveals significant heritability of alcohol abuse and alcoholism [11], and recent advances in molecular biology have enabled the search for molecular genetic risk factors in humans and in non-human primate models [1,2,30]. In addition to these correlational approaches, laboratory researchers also utilize a variety of experimental methodologies to better understand genetic contributions to addiction. A particularly useful tool in this regard is the study of selectively bred lines and inbred strains of rodents [7], and the systematic comparison between the inbred Fischer (F344) and Lewis (LEW) rat strains is emerging as a valid approach for exploring genetic influences on drug abuse vulnerability.

Fischer and Lewis rats sometimes exhibit markedly divergent biobehavioral profiles in response to drugs of abuse, including alcohol [22,32]. At the behavioral level, Suzuki et al. [40] reported significantly greater alcohol consumption by body weight in Lewis rats across a range of concentrations within an operant oral self-administration preparation. However, Taylor et al. [42] reported greater intake in Fischer rats during the second week of a 5% ethanol-only diet, but this strain effect was only evident among the males. Taylor et al. also identified a number of differences in withdrawal-induced body temperature regulation and spontaneous locomotor activity, but as with the ethanol consumption, these effects were both strain- and sex-dependent. It is interesting to note that the interactions revealed by Taylor et al. [42] could not be predicted given the virtually exclusive study of male Fischer and Lewis responses to alcohol (also see Refs. [4,29,37]). Although their report focused on dependence

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and withdrawal after forced access (which may account for the discrepancy between their findings and the free operant work of Suzuki et al. [40], also see Ref. [41]), their data still underscore the importance of both genotype and biological sex in animal models of alcohol abuse (cf. [5,24]).

In addition to the self-administration work described above, our laboratory recently reported an assessment of several motivational and physiological responses to alcohol in male Fischer and Lewis rats [34]. Although no significant place conditioning effects emerged in either strain (as is common with rats, see Ref. [12]), the Fischer animals were more sensitive than Lewis subjects to the aversive effects of 1.25 and 1.5 g/kg IP ethanol within a conditioned taste aversion design (CTA; see Refs. [6,14,35]). Despite these effects of genotype on CTA, the strains did not differ in peak blood alcohol concentrations following a 1 or 1.5 g/kg injection, while neither strain exhibited a significant hypothermic response to a 1.5 g/kg ethanol challenge.

The pattern of male Lewis rats showing stronger alcohol-seeking behavior and weaker CTA is consistent with other work showing an inverse relationship between ethanol's aversive and reinforcing effects in various alcohol preferring and non-preferring rodents [32], and implies a centrally mediated, genetically influenced dissociation between the physiological and aversive effects of alcohol in the Fischer and Lewis rat strains. However, aside from the work of Taylor et al. [42], we are not aware of any direct comparisons of alcohol-induced phenotypes in females of these strains. Given the increasing emphasis on the biological bases of drug abuse in females [20,25–27,43], the purpose of the present study was to contribute relevant data on alcohol in Fischer and Lewis rats. Specifically, adult female animals of both strains were tested under the same CTA design at doses previously reported in males [34], where consumption of a novel saccharin solution was immediately followed by IP injection of 1 or 1.5 g/kg ethanol over multiple conditioning trials. Additional females were administered a 1.5 g/kg dose with blood samples taken at multiple points thereafter. Together, these assessments provide novel parametric data on the aversive and pharmacokinetic effects of alcohol within the Fischer–Lewis model.

2. Method

2.1. Subjects and housing

A total of 76 alcohol-naïve adult female rats served as subjects; 38 were of the Fischer strain (F344/SsNHsd) and 38 were of the Lewis strain (LEW/NH). The strains' respective weights (mean ± S.D.) at the start of the study were 189 ± 16 and 217 ± 14 g. All animals were individually housed in hanging wire-mesh cages (24 cm × 19 cm × 18 cm) and had ad libitum access to food and water in the home cage; fluid access for animals involved in the CTA experiment is described in detail below. Animal housing rooms operated on a 12-h light/12-h dark schedule (lights on at 08:00 h) and were maintained at an ambient temperature of 23 °C. Estrous cycles were not actively monitored; however, all subjects from each experiment were housed within the same room to promote estrous synchrony through olfactory and pheromonal cues ([28], but see Ref. [36]). All procedures were conducted between 10:00 and 16:00 h and were in compliance with the US Animal Welfare Act and National Research Council guidelines as well as standards established by the Animal Care and Use Committee at American University.

2.2. Drugs and solutions

Ethanol stock and sodium saccharin were both obtained from Sigma (St. Louis, MO). Ethanol was combined with saline into a 15% solution (v/v) and administered via IP injection at doses of 0, 1 or 1.5 g/kg, depending on the experiment. All non-drug saline injections were also administered IP and were equivolume to the respective ethanol dose. Saccharin was prepared as a 1 g/l (.1 %) solution in tap water.

2.3. Alcohol-induced CTA

2.3.1. Habituation

Subjects involved in the CTA experiment were given 20-min access to water daily until fluid consumption and weights stabilized. During all CTA-related procedures, fluid was presented in inverted 50 ml graduated Nalgene tubes sealed by rubber stoppers fitted with stainless steel spouts; individual consumption was measured to the nearest 0.5 ml.

2.3.2. Conditioning

On Day 1, subjects were given 20-min access to the saccharin solution instead of water. Immediately after this period, each rat was individually transported to a nearby room and injected with its randomly assigned dose of 1 or 1.5 g/kg IP ethanol (n = 11–12 per combination of strain and dose). On Day 2, the animals were given access to water for the 20-min period, followed immediately by a saline injection equivolume to their respective ethanol dose. This pattern of 20-min saccharin access followed by ethanol injection on Day 1 followed by 20-min water access and saline injection on Day 2 constituted one conditioning cycle. The CTA procedure was carried out for three consecutive cycles over 6 days, with a fourth saccharin exposure on Day 7 as a final test of alcohol-induced CTA.

Previous CTA work from our laboratory with female Fischer and Lewis rats has consistently shown equivalent and stable saccharin consumption across trials in exclusively vehicle-treated control groups [13,15,23]. Therefore, in order to maximize sample size of the alcohol-treated groups, vehicle controls were not included in the present study. The effect of dose was still amenable to between-groups comparisons, but given ethanol's well-documented aversive effects [8], CTA within any given group was defined as the significant decrease in mean saccharin consumption relative to the first saccharin exposure. The high 1.5 g/kg dose was chosen for the present study based on its previously reported ability to differentiate males of these strains in an identical CTA paradigm [34], whereas the low 1 g/kg dose that did not differentiate the males was used to allow a unique sensitivity to the aversive effects of alcohol in female Fischer or Lewis animals to emerge.

2.4. Blood alcohol assessment

Following the CTA experiment, additional female Fischer and Lewis rats were randomly assigned to receive IP injections of 1.5 g/kg ethanol (n = 8 per strain) or equivolume saline (n = 7 per strain). Tail blood samples were obtained at 15, 60 and 180 min post-injection. Before the 15-min sampling, each rat's tail was soaked in warm water for 60–75 s and wiped dry with a paper towel. The rat was then held in an oversized restraint tube (Plas-Labs, Lansing, MI) while approximately 1 mm of the tip of the tail was cut with surgical scissors. For subsequent samplings, the tail was re-soaked and dried, but no further incisions were made and the restraint tube was employed on an as-needed basis. For all samplings, approximately 40–90 μl of whole blood were collected in heparinized capillary tubes (Drummond Scientific, Broomall, PA) and the contents immediately transferred to microcentrifuge vials. Each sample was centrifuged at 3000 rpm for 20 min; the plasma was then transferred via micropipette to new vials and kept frozen until ready for assay. Undiluted plasma was assayed using the HP 6890 Series headspace gas chromatography/mass spectrometry system (Hewlett-Packard, Palo Alto, CA) based on protocols developed in-house by the Laboratory of Clinical and Translational Studies at the National Institute on Alcohol Abuse and Alcoholism.

2.5. Data presentation and analysis

Data for the CTA experiment were excluded from one Fischer animal in the 1.5 g/kg group that died during the experiment. For the CTA analyses, the groups

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