



High alcohol intake in female Sardinian alcohol-preferring rats

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ARTICLE INFO

Article history:

Received 7 June 2013

Received in revised form

16 December 2013

Accepted 7 January 2014

Keywords:

Male and female Sardinian alcohol-preferring (sP) rats

Alcohol drinking

Intermittent access to alcohol

ABSTRACT

Sardinian alcohol-preferring (sP) rats have been selectively bred for high alcohol preference and consumption. When exposed to the standard, home cage 2-bottle “alcohol (10%, v/v) vs. water” choice regimen with continuous access, male sP rats consume daily approximately 6 g/kg alcohol. Conversely, when exposed to the intermittent (once every other day) access to 2 bottles containing alcohol (20%, v/v) and water, respectively, male sP rats display marked increases in daily alcohol intake and signs of alcohol intoxication and “behavioral” dependence. The present study was designed to assess alcohol intake in female sP rats exposed, under the 2-bottle choice regimen, to (a) 10% (v/v) alcohol with continuous access (CA10%), (b) 10% (v/v) alcohol with intermittent access (IA10%), (c) 20% (v/v) alcohol with continuous access (CA20%), and (d) 20% (v/v) alcohol with intermittent access (IA20%). Male sP rats (exposed to CA10% and IA20% conditions) were included for comparison. Over 20 daily drinking sessions, daily alcohol intake in female CA10% and IA20% rats averaged 7.0 and 9.6 g/kg, respectively. The rank of alcohol intake was IA20% > IA10% = CA20% > CA10%. Conversely, daily alcohol intake in male CA10% and IA20% rats averaged 6.0 and 8.2 g/kg, respectively. Comparison of female and male rats yielded the following rank of alcohol intake: female IA20% > male IA20% > female CA10% ≥ male CA10%. An additional experiment found that alcohol drinking during the first hour of the drinking session produced mean blood alcohol levels of 35–40 mg% and 85–100 mg% in the CA10% and IA20% rats, respectively. These results (a) extend to female sP rats previous data demonstrating the capacity of the IA20% condition to markedly escalate alcohol drinking, and (b) demonstrate that female sP rats consume more alcohol than male sP rats. This sex difference is more evident under the IA20% condition, suggesting that female sP rats are highly sensitive to the promoting effect of the IA20% condition on alcohol drinking. These data contribute to the characterization of sP rats as a model of excessive alcohol consumption.

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Introduction

The recent “Global Status Report on Alcohol and Health” from the World Health Organization states that alcohol abuse and dependence are responsible for about 2,500,000 deaths per year (WHO, 2011). While the prevalence rate for alcohol consumption and related disorders is widely higher in men than women, adolescent boys and girls do not display large differences in alcohol consumption (Schulte, Ramo, & Brown, 2009). Notably, alcohol abuse and dependence are characterized by sex and gender dimorphisms; these differences involve epidemiology, drinking behavior, amount of alcohol consumed, alcohol metabolism and distribution, and underlying molecular pathomechanisms (Lenz et al., 2012).

Selectively bred, alcohol-preferring rats represent validated animal models of excessive alcohol consumption and have been used in hundreds of studies aimed at investigating the neurobiological bases of alcoholism and identifying potentially effective pharmacotherapies (see Bell et al., 2012). However, relatively few studies have been designed to evaluate sex differences in alcohol-preferring rats (e.g., Bell et al., 2003, 2004, 2008; Bell, Rodd, Sable, et al., 2006; Dhaer, McConnell, Rodd, McBride, & Bell, 2012; Sable, Bell, Rodd, & McBride, 2006; Sarviharju, Jaatinen, Hyytiä, Hervonen, & Kiianmaa, 2001).

Sardinian alcohol-preferring (sP) rats constitute one of these rat lines selectively bred for high alcohol preference and consumption (see Bell et al., 2012; Colombo, Lobina, Carai, & Gessa, 2006). To date, virtually all studies conducted to investigate the alcohol drinking behavior of sP rats have been performed using male rats. These studies have demonstrated that, when exposed to the home cage, 2-bottle “alcohol (10% v/v) vs. water” choice regimen with unlimited access, male sP rats (a) consume daily approximately

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6 g/kg alcohol, (b) display an “alcohol solution vs. water” preference ratio higher than 90%, (c) consume alcohol in 3–4 separate episodes over the dark phase of the daily light/dark cycle, and (d) achieve pharmacologically relevant blood alcohol levels (BALs) (>50 mg%) (see Colombo et al., 2006). Additionally, chronic free-choice alcohol drinking results in the development of functional tolerance to the motor-impairing effects of alcohol (see Colombo et al., 2006).

More recently, alcohol drinking by male sP rats has been tested under a procedure developed and validated by Roy A. Wise in the early 1970s (Wise, 1973), reintroduced a few years ago by Selena E. Bartlett's laboratory (Simms et al., 2008), and known to produce dramatic escalations in alcohol intake in rats (e.g., Bito-Onon, Simms, Chatterjee, Holgate, & Bartlett, 2011; Carnicella, Amamoto, & Ron, 2009; Carnicella, Yowell, & Ron, 2011; Chatterjee et al., 2011; George et al., 2012; Hopf et al., 2011; Landgren et al., 2012; Li, Bian, Dave, & Ye, 2011; Li et al., 2010; Stuber et al., 2008) and mice (e.g., Crabbe, Harkness, Spence, Huang, & Metten, 2012; Hwa et al., 2011; Melendez, 2011; Rosenwasser, Fixaris, Crabbe, Brooks, & Ascheid, 2013). This procedure is based on the exposure to intermittent (once every other day) access to a 20% (v/v) alcohol solution (in free choice with water); on the intervening days, water is the sole fluid available. In male sP rats exposed to this procedure, daily alcohol intake escalated to approximately 9 g/kg and was associated with the onset of signs of behavioral dependence [rats consumed alcohol despite (a) quinine adulteration of the alcohol solution or (b) concurrent availability of an alternative, highly palatable saccharin solution] and intoxication (reduced performance at the Rota-Rod task) (Loi et al., 2010).

The present study was designed to conduct an initial characterization of the alcohol drinking behavior of female sP rats. To date, their daily alcohol intake has been assessed for the sole purpose of selecting individuals for mating in the early stages of the breeding program; this test has always been performed using the standard, home cage 2-bottle “alcohol (10% v/v) vs. water” choice regimen with unlimited access, i.e., the procedure under which sP rats have been selectively bred (see Colombo et al., 2006). In Experiment 1 of the present study, different groups of female and male rats were used and exposed to the following conditions: (a) 10% (v/v) alcohol with continuous access (CA10%; the “standard” condition, as used in the selective breeding), (b) 10% (v/v) alcohol with intermittent access (once every other day) (IA10%), (c) 20% (v/v) alcohol with continuous access (CA20%), and/or (d) 20% (v/v) alcohol with intermittent access (once every other day) (IA20%). This design allowed the following two research questions to be addressed: (1) Is intermittent access to 20% alcohol a powerful procedure in inducing escalation in alcohol drinking also in female sP rats? (2) Does alcohol consumption, under multiple conditions, differ between female and male sP rats? Additionally, Experiment 2 assessed BALs resulting from alcohol drinking in CA10% and IA20% female and male sP rats.

Materials and methods

All experimental procedures employed in the present study were in accordance with the European Communities Council Directive (86/609/EEC) and the subsequent Italian Law on the “Protection of animals used for experimental and other scientific reasons.”

Animals

Female and male sP rats, from the 77th (Experiment 1) and 85th (Experiment 2) generation and approximately 75-days-old at the start of the study, were used. Rats were individually housed in standard plastic cages with woodchip bedding. Single-cage housing started 15 days before the start of exposure to alcohol (see below). Female and male rats were housed in separate rooms (this allowed conduction of the experiment with the 2 sexes concurrently). The

animal facility was under an inverted 12 h light/12 h dark cycle (lights on at 9:30 p.m.), at a constant temperature of 22 ± 2 °C and relative humidity of approximately 60%. Food pellets (Mucedola, Settimo Milanese, MI, Italy) were always available.

Experimental procedures

Experiment 1: alcohol drinking under CA10%, IA10%, CA20%, and IA20% conditions

Female rats ($n = 32$) were divided into 4 groups ($n = 8$), matched for body weight, and exposed to the home cage, 2-bottle “alcohol vs. water” choice regimen under the following 4 conditions: CA10% [10% (v/v) alcohol with continuous access (24 h/day, 7 days/week)]; IA10% [10% (v/v) alcohol with intermittent alcohol access (three 24 h drinking sessions per week on Monday, Wednesday, and Friday; 2 water bottles for the remaining 4 days)]; CA20% [20% (v/v) alcohol with continuous access (24 h/day, 7 days/week)]; IA20% [20% (v/v) alcohol and water with intermittent alcohol access (three 24 h drinking sessions per week on Monday, Wednesday, and Friday; 2 water bottles for the remaining 4 days)]. Male rats ($n = 16$) were divided into 2 groups ($n = 8$), matched for body weight, and exposed to the home cage, 2-bottle “alcohol vs. water” choice regimen under CA10% and IA20% conditions, respectively.

Bottles (120 mL total volume plus metal cap with 0.8 mm [diameter] hole [Tecniplast, Buguggiate, VA, Italy]) were refilled every day with 100 mL of fresh solution and their left-right positions interchanged daily in the continuous-access rat groups and at every drinking session in the intermittent-access rat groups to avoid development of position preference. Bottles were presented at lights-off. Alcohol and water intake was recorded 1 h after lights-off (T1) and the day after immediately before lights-off (T24). Intake was monitored by weighing the bottles (0.01 g accuracy). Possible fluid spillage was calculated by using multiple bottles filled with the water and the 2 alcohol concentrations (10% and 20%) positioned in empty cages interspersed in the cage racks; mean spilt volumes were subtracted before data analysis. Exposure to alcohol and water lasted for 45 days in the continuous-access rat groups and 20 drinking sessions in the intermittent-access rat groups.

Experiment 2: blood alcohol levels

Female ($n = 15$) and male ($n = 15$) rats were divided into 2 groups ($n = 7$ – 8), matched for body weight, and exposed to the home cage, 2-bottle “alcohol vs. water” choice regimen under the CA10% and IA20% conditions (identical to those described above), respectively. Bottle management and fluid-intake recording were identical to those performed in Experiment 1. Exposure to alcohol and water lasted for 7 days in the continuous-access rat groups and 4 drinking sessions in the intermittent-access rat groups. At T1 of drinking session 4, blood samples (50 μ L) were collected from the tip of the tail of each rat for BAL determination. This time period of blood sampling was chosen as drinking session 4 has often resulted as being one of the drinking sessions with the highest alcohol intake in sP rats (Loi et al., 2010; Experiment 1 of the present study). Blood samples were analyzed by means of an enzymatic system [GL5 Analyzer (Analox Instruments, London, UK)] based on measurement of oxygen consumption in the alcohol–acetaldehyde reaction.

Statistical analysis

Experiment 1: alcohol drinking under CA10%, IA10%, CA20%, and IA20% conditions

Data on alcohol and water intake were expressed in g/kg and mL/kg, respectively. Only the data collected in the 20 sessions of alcohol exposure of the intermittent-access rat groups underwent statistical analysis.

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