Pharmacology, Biochemistry and Behavior 175 (2018) 1–9

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Late aging alters behavioral sensitivity to ethanol in a sex-specific manner in Fischer 344 rats

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ARTICLE INFO

Keywords:
Aging
Alcohol
LORR
Social behavior

ABSTRACT

Responsiveness to ethanol (EtOH) differs as a function of age. Adolescent rodents are less sensitive than adults to the sedative effects of EtOH, whereas they show enhanced sensitivity to EtOH-induced social facilitation. Late aging is associated with a natural decline in social behavior and aging-related peculiarities in sensitivity to EtOH have been largely unexplored. Whether there are sex differences in the behavioral response to EtOH during late aging remains unknown. Thus, behavioral responses to EtOH in male and female Fischer (F) 344 rats aged 4–5 months (adult) and 19–20 months (aging) were examined. First, the effects of saline and EtOH (0.5 and 0.75 g/kg) on social interaction were assessed. Social investigation and contact behavior were lower in aging animals and higher in females. Interestingly, in aged females, social contact behavior was increased following a 0.5 g/kg EtOH dose, whereas the same dose suppressed social contact in aged males. Behavioral sensitivity to the sedative effects of 3.0 and 3.5 g/kg EtOH was assessed with the loss of righting reflex (LORR) test. Although latency to LORR did not differ as a function of age or sex, aged rats showed significantly greater LORR duration and significantly lower blood ethanol concentrations (BECs) at regaining of the righting reflex relative to adults. In addition, females had a lower LORR duration, regardless of age; no sex differences were evident in BECs at awakening. In a second experiment, blood ethanol concentrations (BECs) over time were assessed following 0.75, 1.5, and 3.0 g/kg EtOH in 3-, 12-, and 18-month-old male and female F344 rats. Aged rats had higher peak BECs following 3.0 g/kg EtOH, whereas few age or sex differences were apparent at lower doses. Taken together, these data indicate that late aging is associated with altered sensitivity to the social facilitating effects and sedative effects of EtOH.

1. Introduction

Alcohol use among the elderly is becoming a significant public health concern, with 42.7% of individuals aged 65 and older reporting alcohol use in the past month and 10% of that population exhibiting patterns of alcohol consumption consistent with binge drinking (Substance Abuse and Mental Health Services Administration, 2015). Although there is a large body of literature describing age differences in ethanol (EtOH) sensitivity between adolescents and adults (Spear, 2015; Varlinskaya & Spear, 2015; Varlinskaya et al., 2013, 2014), relatively little is known about responding to alcohol in aged individuals (Squeglia et al., 2014). Given that the size of the elderly population is expanding rapidly, and rates of drinking among the elderly are increasing (Breslow et al., 2017), a better understanding of how late aging affects the behavioral response to alcohol is needed.

When describing the effects of alcohol across the lifespan, it is helpful to define specific ontogenetic periods. Adolescence is often defined as occurring from 12 to 18 years of age in humans, although some researchers extend adolescence into the early-mid 20's (Spear, 2000). In rodents, adolescence can be conservatively defined as occurring from postnatal days (P) 28–42 (Spear, 2000). Adulthood typically begins in the 20's in humans and after P70 in rats. Aging occurs around 18 months in rats, whereas rats of about 24 months of age are often considered “aged”, although what constitutes aging vs. aged is highly strain-dependent.

It has been repeatedly shown that social behavior declines across the lifespan in humans (Lang, 2001; Schiffman, 1997) and in laboratory rodent models (Hunt et al., 2011; Perkins et al., 2016; Salchner et al., 2004; Shoji and Mizoguchi, 2011). Positive social experiences are associated with significant health benefits such as enhanced resilience

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https://doi.org/10.1016/j.pbb.2018.07.012
Received 4 June 2018; Received in revised form 23 July 2018; Accepted 25 July 2018
Available online 29 August 2018
0091-3057/

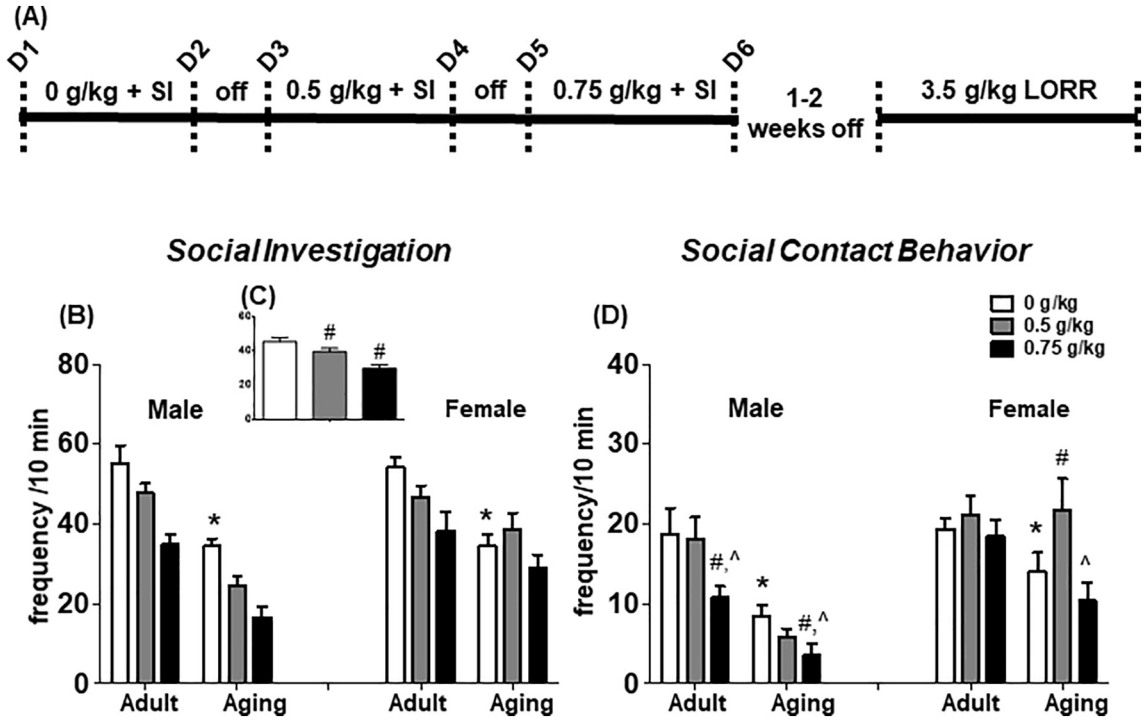

Fig. 1. (A) Timeline for Experiment 1 assessing social behavior and sedation following EtOH. (B) Frequency of social investigation for all groups and collapsed across age and sex (insert; C) and (D) frequency of contact behavior in a 10-min social interaction test with a sex-matched adult conspecific. All data expressed as mean ± SEM. (*) $p < 0.05$ vs. adult saline-injected rats; (#) $p < 0.05$ vs. saline-injected vehicle; (^) $p < 0.05$ vs. 0.5 g/kg EtOH.

(Charuvastra and Cloitre, 2008) and better recovery from illness or trauma (DeVries et al., 2007; Norman et al., 2010), and perceived social isolation and social stress are strong predictors of morbidity and mortality (Bisschop et al., 2003; House et al., 1988; Seeman, 2000). Given relatively high alcohol use among the elderly associated with age-related declines in social behavior, it is critical to understand the relationship between social behavior and alcohol during late aging.

In rats, age-related differences have been observed in the effects of EtOH on social behavior. Specifically, in adult Sprague-Dawley rats, low to moderate doses of EtOH (0.75–1.0 g/kg) produced social inhibition, whereas adolescent Sprague-Dawley rats were not sensitive to these socially suppressing effects of EtOH (Varlinskaya and Spear, 2012). In contrast, adolescent Sprague-Dawley rats demonstrated social facilitation at low EtOH doses, indexed via increases in social behavior, an effect of EtOH not evident in adults under normal conditions (Varlinskaya and Spear, 2002). As mentioned previously, social behavior is suppressed in 18–24 month old F344 rats (Perkins et al., 2016), although whether aged rats are more sensitive to the socially suppressing effects of low-dose EtOH relative to their younger adult counterparts remains to be investigated.

High doses of EtOH produce substantial motor impairment and sedation. Aged Sprague-Dawley rats (18-month-old) are more sensitive to the motor impairing effects of EtOH relative to adolescent and adult Sprague-Dawley rats (Novier et al., 2013; Ornelas et al., 2015), an effect that may be associated with alterations in cerebellar expression of PKCγ (Van Skike et al., 2010). In addition, 18 month old Sprague-Dawley rats are sensitive to acute EtOH-induced cognitive deficits, evidenced by impaired performance on the water maze (Novier et al., 2013). Altered behavior in response to EtOH in late aging could be due simply to age differences in EtOH pharmacokinetics and/or EtOH absorption and distribution. Indeed, there are some studies demonstrating impaired clearance of high doses of EtOH (3.0 g/kg) in 18-month-old Sprague-Dawley rats (Ornelas et al., 2015), although others have shown no age differences in BECs following acute administration of lower doses of EtOH (1.5–2.5 g/kg) (Matthews and Mittleman, 2017; Novier et al., 2016). All the aforementioned studies were performed exclusively in males. Whether aged female rats show altered EtOH pharmacokinetics remains to be determined. The goals of the current study were to: (1) assess behavioral sensitivity to EtOH across a wide range of doses in aged rats, (2) explore age and/or sex differences in the behavioral response (LORR) and physiological response (BEC and CORT) to EtOH, and (3) examine changes in BECs over time following low, moderate, and high doses of EtOH.

2. Material and methods

2.1. Subjects

Experiment 1 tested 3- and 18-month-old (at arrival; 4–5 and 19–20 months at testing-referred to as adult and aging, respectively) male and female F344 rats (n = 11–14/group). Experiment 2 tested 3-, 12-, and 18-month-old (at arrival; 4–5, 13–14, and 19–20 months at testing, referred to as adult, middle-aged, and aging, respectively) male and female F344 rats (n = 7–10/group). All animals were obtained from the National Institute of Aging (NIA) colony maintained by Charles River Laboratories. Subjects were given at least 2 weeks to acclimate to the colony before experiments began. Social partners were young adult sex-matched F344 rats obtained from Charles River Laboratories. Colony was maintained at 22 ± 1 °C with 12:12 light:-dark cycle (lights on 0700). All rats were pair-housed and provided ad libitum access to food and water. On each of two days prior to the onset of behavioral testing, experimental subjects and partners were handled for 3 min. For social interaction testing, subjects were marked on the day prior to testing with a non-toxic permanent marker to allow the experimenter to distinguish subjects from partners. At all times, rats were maintained and treated in accordance with the guidelines set forth by the Institute of Laboratory Rat Resources (2011) and in accordance with the protocol approved by the IACUC at Binghamton University.