



Chronic social instability increases anxiety-like behavior and ethanol preference in male Long Evans rats



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HIGHLIGHTS

- Chronic stress during adolescence in male rats models addiction vulnerability
- Chronic social instability (CSI) during adolescence was tested in males and females.
- CSI increased anxiety-like behavior and ethanol preference in males.
- CSI did not affect female behavior, CORT, or ethanol intake/preference.

ARTICLE INFO

Article history:

Received 16 November 2016
 Received in revised form 9 February 2017
 Accepted 10 February 2017
 Available online 13 February 2017

Keywords:

Sex differences
 Chronic stress
 Corticosterone
 Adolescence
 Female

ABSTRACT

Chronic stress during adolescence is related to increased prevalence of anxiety disorders and alcohol use disorders in humans. This phenotype has been consistently recapitulated in animal models with male subjects, but models using female subjects are fewer. The aim of these studies was to test the hypothesis that chronic social instability (CSI) during adolescence engenders increased anxiety-like behavior, increased corticosterone, and greater ethanol intake and/or preference than control groups in male and female rats. A chronic social instability (CSI) procedure was conducted in separate cohorts of female and male adolescent Long Evans rats. CSI included daily social isolation for 1 h, and then pair housing with a novel cage mate for 23 h until the next 1 h isolation period from PND 30–46. Control groups included social stability (SS), chronic isolation (ISO), and acute social instability (aSI). At PND 49–50, anxiety-like behavior was assessed on the elevated plus maze, and on PND 51 tails bloods were obtained for determination of corticosterone (CORT) levels. This was followed by 4 weeks of ethanol drinking in a home cage intermittent access ethanol drinking paradigm (PND 55–81 for males, PND 57–83 for females). Planned contrast testing showed that the male CSI group had greater anxiety-like behavior compared controls, but group differences were not apparent for CORT. CSI males had significantly higher levels of ethanol preference during drinking weeks 2–3 compared to all other groups and compared to SS and ISO groups in week 4. For the female cohort, we did not observe consistent group differences in anxiety-like behavior, CORT levels were unexpectedly lower in the ISO group only compared to the other groups, and group differences were not apparent for ethanol intake/preference. In conclusion, chronic stress during adolescence in the form of social instability increases anxiety-like behavior and ethanol preference in male rats, consistent with other models of chronic stress during adolescence. Conversely, and contrary to our hypothesis, female rats' anxiety-like behavior, CORT level, and ethanol intake/preference were not altered by CSI. New paradigms must continue to be explored for study of clinically relevant relationships in female preclinical models.

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1. Introduction

Lifetime prevalence of DSM-5 alcohol use disorders (AUDs) is approximately 36.0% and 22.7% for men and women, respectively. A lifetime AUD diagnosis is significantly related to increased odds for also

having a diagnosis of a mood or anxiety disorder [21], and early life stress is a known vulnerability factor for developing both AUDs and affective disorders [23,27,51,52]. Though AUDs are more prevalent in men, women have higher rates of comorbid anxiety disorders and AUDs following early life stress [20,62]. A preclinical model that imparts behavioral and/or physiological risk factors for increased ethanol intake and/or preference later in life is imperative for understanding underlying neurobiological substrates of these complex disease states and comorbidities [28]. Importantly, there are many instances in which male

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and female humans differ behaviorally, physiologically, and neurobiologically at baseline and/or in response to stress [4,33], with similar sex differences also observed male and female rats [5,17,60]. Thus, the primary goal of these studies was to investigate a model of chronic social instability (CSI) that we hypothesized would engender behavioral and physiological antecedents to enhanced ethanol intake and/or preference in late adolescence/adulthood with inclusion of both males and female rats.

Adolescence is a critical developmental period in humans and rats, during which time stressors are associated with increased vulnerability to AUDs and psychiatric disorders in adulthood, or alcohol (ethanol)-related behaviors and associated affective behaviors in preclinical models [10,12,20,32,64,65]. Here we employed a model of chronic social instability (CSI) during adolescence in separate cohorts of male and female rats, as McCormick [42] suggested the usefulness of CSI during adolescence for studying sex-specific neural substrates of drug use vulnerability. CSI involves pair-housed rats that get 1 h of daily isolation followed by home cage re-pairing with a new, same-sex partner during adolescence. One study of the McCormick et al. research group utilized three groups of adolescent rats: 1) chronic social instability (CSI), 2) stable pair-housed (SS), and 3) acute stress by one day of social instability (aSI) [39]. Another study from this research group using three adolescent rat groups utilized the same CSI and SS groups, but now included an isolation-reared group (ISO) [44]. Thus, we adapted our model to include four groups, with CSI being the group of interest and the other three groups serving as controls for social instability duration and housing condition.

Effects of early life stress on anxiety-like behavior, ethanol-related behaviors, and neurobiology have been successfully modeled in male rats [10]. A similar model in female rats has yet to be firmly established [9,10,37], but some behavioral and physiological consequences of CSI have been investigated in both male and female rats [38,42,47]. Therefore, for CSI female rats, we hypothesized greater anxiety-like behavior on the elevated plus maze (EPM) compared to the other three groups based on previous data in females tested immediately or 25 days after the housing procedure [47], and we hypothesized hypothalamic-pituitary adrenal (HPA) axis dysfunction reflected by increased baseline CORT levels in females based on previous studies showing group differences in baseline or stress-evoked levels of plasma CORT [25,29,39]. We also hypothesized that female CSI rats would show greater ethanol intake and/or preference, as CSI engendered greater locomotor sensitization in response to nicotine and amphetamine in female rats (an indicator of addiction vulnerability for stimulant drugs), and CSI female rats showed significant place preference for drug (amphetamine) compared to non-stressed controls [38,46], thus suggesting the potential utility of CSI as a model of addiction vulnerability for females [45]. In males, we hypothesized that CSI male rats, relative to the other three groups, would show greater anxiety-like behavior on the EPM, HPA axis dysfunction as reflected by increased baseline CORT levels in CSI rats, and greater ethanol intake/preference in a home cage drinking paradigm, based on robust and long-lasting effects of chronic stress during adolescence in the CSI model and other models with male rats [10,43,46].

2. Materials and methods

2.1. Subjects

Experiments were conducted in two separate cohorts of Long Evans rats. The first cohort included 24 male rats ($n = 6/\text{group}$) and the second cohort included 32 female rats ($n = 8/\text{group}$), both arriving in the laboratory at postnatal day (PND) 21 (Envigo, Indianapolis, IN, USA). Upon arrival, rats were weighed and housed in pairs of two. Rats were housed in a vivarium maintained on a 12 h light/dark cycle (lights on from 7:00 to 19:00) with the temperature set at approximately 20–22 °C. Food and water were available ad libitum throughout the

study, except during 1 h isolation periods. It should be noted that male and female studies were conducted at different times, thus not allowing direct statistical comparison of males and females. All animal care procedures were in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by the University of Dayton Institutional Animal Care and Use Committee.

2.2. Chronic social instability procedure

The CSI procedure began on PND 30 and continued as described below until PND 46 (modeled after [39,47]). Four housing groups were created with the CSI group being the group of greatest interest: 1. Chronic social instability (CSI): from PND 30–45 rats were pair housed in their home cage but socially isolated daily for 1 h in a clean, standard lab cage; then, each CSI rat was pair housed with a new cage mate from the CSI group for 23 h until the next 1 h isolation period. Due to cohort sizes, the new cage mate was repeated every 5 days for males and 7 days for females; 2. Social stability (SS): from PND 30–45 rats were pair housed in their home cage but were socially isolated daily for 1 h in a clean, standard lab cage; then, each SS rat was returned to the home cage with the original cage mate; 3. Chronic isolation (ISO): from PND 30–45 rats were single housed and handled for standard bedding changes and weighing; 4. Acute social instability (aSI): from PND 30–45 rats were pair housed in their home cage with the same cage mate and handled for standard bedding changes and weighing, but on PND 45 rats were socially isolated for 1 h in a clean, standard lab cage; then, each aSI rat was pair housed with a new cage mate from the aSI group for 24 h. Cage mates were always same sex. At PND 46, all rats were single housed for the remainder of the study.

2.3. Anxiety-like behavior: elevated plus maze

The elevated plus maze (EPM) was conducted as a measure of anxiety-like behavior on PND 49–50. The EPM was conducted a few days after cessation of the CSI procedure because we predicted that if increased anxiety-like behavior was present in a clinically significant way in CSI rats, then it would be present for a protracted period of time. Each rat was run once on the EPM (half on PND 49 and half on PND 50), properly counterbalanced for equal representation of each group on each of those two days. The maze was standard setup and size, with two open arms, two closed arms, and a central junction (each arm approximately 50 cm long; 10 cm × 10 cm junction; 49.5 cm high from floor). The test was conducted in low light with illumination focused on the open arms. Consistent illumination on each arm was verified with a light meter. Rats were allowed 10 min to acclimate to the procedure room before testing. Each trial was videotaped using EthoVision XT 11.5 software (Noldus Information Technology, Inc., Leesburg, VA, USA). Our measure of anxiety-like behavior was time spent on the open arms (seconds), with number of closed arm entries used as a measure of general locomotor activity [16,24]. Rat behavior was tracked using 3-point detection (nose, center, tail-base) and center-point data are described herein. Each trial lasted 5 min (300 s).

2.4. Tail bloods & corticosterone measurements

Tail bloods were taken on PND 51 for evaluation of plasma CORT level (beginning at 10 a.m.). With the same rationale as the experimental timing of the EPM, bloods were taken a few days after cessation of the CSI procedure because we predicted that if an alteration in CORT was present in a clinically significant way in CSI rats, then group differences would be present for a protracted period of time. Samples were centrifuged for 10 min and plasma was stored at –80 °C until analysis of CORT levels. CORT was measured using a competitive enzyme immunoassay containing a polyclonal CORT antibody (Immunodiagnostic Systems, Scottsdale, AZ, USA). Briefly, CORT from the samples and

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