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Ovariectomy results in inbred strain-specific increases in anxiety-like behavior in mice

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ABSTRACT

Women are at an increased risk for developing affective disorders during times of hormonal flux, including menopause when the ovaries cease production of estrogen. However, while all women undergo menopause, not all develop an affective disorder. Increased vulnerability can result from genetic predisposition, environmental factors and gene by environment interactions.

In order to investigate interactions between genetic background and estrogen depletion, we performed bilateral ovariectomy, a surgical procedure that results in estrogen depletion and is thought to model the post-menopausal state, in a genetically defined panel of 37 inbred mouse strains. Seventeen days post-ovariectomy, we assessed behavior in two standard rodent assays of anxiety- and depressive-like behavior, the open field and forced swim tests.

We detected a significant interaction between ovariectomy and genetic background on anxiety-like behavior in the open field. No strain specific effects of ovariectomy were observed in the forced swim assay. However, we did observe significant strain effects for all behaviors in both the open field and forced swim tests.

This study is the largest to date to look at the effects of ovariectomy on behavior and provides evidence that ovariectomy interacts with genetic background to alter anxiety-like behavior in an animal model of menopause.

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1. Introduction

The lifetime prevalence of having at least one major depressive episode for women is 22%; almost twice the incidence observed in men [1]. Women are also at a significantly increased lifetime risk for developing generalized anxiety disorders compared to men [1]. Furthermore, it has been shown that women, in particular, are at an elevated risk for affective disorders such as depression and anxiety during stages of life marked by drastic fluctuations in endogenous estrogen levels – at the onset of menses, during the perinatal and postpartum period and at menopause [2,3].

During menopause, the ovaries stop production of estrogen, resulting in a decline in circulating estrogen levels [4]. While all women undergo menopause, not all will experience changes in mood. The risk of experiencing disturbances in mood during menopause has been estimated to be as high as 47% for natural menopause and 38% for surgical menopause [5]. Many factors lead to increased vulnerability during this sensitive time including genetic predisposition, environmental factors and complex interactions between the two. Disentangling the effects of genetics and the environment on increased risk for mood disorders in the human population has been hampered by the complexity of human neuropsychiatric diseases, considerable environmental variability, lack of access to relevant (brain) tissue and ethical barriers inherent in human studies. Therefore, a tractable experimental model is necessary to move this research forward.

Inbred mice have been used for many years to model complex human diseases [6]. As an experimental population, inbred mouse strains offer many advantages: 1) fixed homozygosity resulting in a stable genetic reference population; 2) availability of full sequence data for many inbred strains; 3) substantial genetic and phenotypic variation across strains; and 4) the ability to control or manipulate environmental

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variables on a fixed genetic background to study challenges such as ovariectomy (OVX) [7].

One commonly used rodent model of estrogen depletion includes bilateral removal of the ovaries, or OVX, resulting in a decline in circulating estrogen levels mimicking human menopause and postmenopausal periods [8,9]. Previous studies have shown that OVX in rodents results in increased anxiety [9,10] and depressive-like behavior [8,9,11–14] and that estrogen replacement reverses these effects [8,12,14–16]. Strain-specific differences in OVX-induced behavioral changes in animal models of anxiety and depression have also been observed [11], highlighting the usefulness of examining differences across inbred strains to assess the effects of genetic background on behavioral responses to OVX.

Inbred strain surveys are a useful first step toward understanding the genetic architecture of complex traits and determining the extent to which genetic background contributes to phenotypic variance. We assessed the effect of OVX on anxiety- and depressive-like behaviors in 37 genetically diverse inbred mouse strains. We identified significant strain effects for all behaviors, and effects of OVX on locomotion, exploratory and anxiety-like behavior in the open field and percent immobility in the forced swim test. This is the largest study to date that assesses the effects of OVX on anxiety- and depressive-like behavior in a wide range of inbred mouse strains. It is also the largest reported strain survey of depressive-like behavior in the forced swim test. These data provide evidence that the effects of OVX on anxiety-like behavior are modulated by genetic background. As such, they provide a starting point for studies into genetic influences on vulnerability to develop an affective disorder during the postmenopausal period, and more generally on the underlying genetics of both depression- and anxiety-related behaviors in a rodent model.

2. Methods and materials

2.1. Animals

Female mice from 37 inbred strains were purchased from The Jackson Laboratory (Bar Harbor, Maine) and transported to the University of North Carolina (UNC) at 5–7 weeks of age. Mice were housed 3–5 to a cage by strain and maintained on a 12-hour light-dark cycle (lights on at 7:00 A.M.). Food (Pico rodent chow 20; Purina, St. Louis, MO, USA) and water were provided ad libitum. Mice were allowed to acclimate to the facility for at least one week prior to surgery.

All procedures were approved by the UNC Institutional Animal Care and Use Committee and followed the guidelines set forth by the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals.

2.2. Ovariectomy and sham surgeries

Animals were anesthetized with a 1.2% solution of tribromoethanol (Sigma-Aldrich, St. Louis, MO) administered by intraperitoneal injection at a dose of 125–250 mg/kg. A dorsal midline incision was made in the skin caudal to the posterior border of the ribs. An incision was made in the muscle and the fat pad located just beneath the muscles was pulled out to expose the ovary. The fallopian tube was clamped off, the ovary removed and muscle and skin were sutured (Med Rep Express, Prescott, AZ). This process was performed bilaterally. Buprenorphine HCl (Patterson Veterinary, Devens, MA) was administered subcutaneously at a dose of 0.05 mg/kg of body weight after surgery and as needed during the recovery period. Animals recovered for 17 days prior to behavioral testing. Verification of a complete bilateral OVX was performed at the conclusion of the study by dissection. The procedure for the sham surgery mice (SHAM) was identical to OVX excluding clamping and tying off the fallopian tube and removal of the ovary.

2.3. Behavioral study design

Behavioral testing occurred 17 days after OVX surgery based on evidence from the literature showing behavioral effects in inbred mice at this post-surgical interval [11]. Mice were a mean age of 78 days (± 7 days standard deviation) at the onset of testing. All behavioral testing was performed during the light part of the light/dark cycle between 8:00 A.M. and 12:00 P.M. The open field assay was performed first, followed two days later by the forced swim test. Mice were tested in 46 different batches over 2 years. Each batch contained multiple strains and no single strain was tested in only one batch. The average number of mice tested per strain in the open field was 9 (range 5–20) for both SHAM and OVX mice. The average number of mice tested per strain in the forced swim test was 8 (range 5–17) for both SHAM and OVX. Numbers of mice tested individually by strain are listed in Supplemental Tables 1–2 for open field and forced swim respectively. C57BL/6J mice are overrepresented as they served as an ongoing control group across the entirety of the experiment. Other strains varied in number due to their availability from the Jackson Laboratory within the timeframe of the project.

2.4. Behavioral testing

2.4.1. Open field

The open field (Versamax Animal Activity Monitoring System, AccuScan Instruments Inc., Columbus, OH, USA) was 42 × 42 × 30 cm consisting of a white Plexiglas floor and clear Plexiglas walls. There were 16 photocells on each side of the arena that allowed for tracking of both horizontal and vertical (rearing) activity. The arena was in a sound-attenuating chamber to control ambient noise and light within the apparatus. Mice were placed in the open field arena for 10 min and a number of behavioral measures were recorded and analyzed in five 2-minute bins using the Versamax activity monitor and analyzer software system. These behavioral measures included locomotor behaviors measured as total distance traveled (cm), time spent in movement (seconds), center distance (cm), margin distance (cm), exploratory behavior (vertical movements or rearing) and anxiety-like behavior (percent time spent in the 9 square inch central zone of the arena).

2.4.2. Forced swim test

The forced swim test is a commonly used measure of depression-like behavior in rodents. Mice were placed for 6 min into a 25 cm high glass-polycarbonate cylinder that was 17 cm in diameter (Noldus, Wageningen, The Netherlands) and filled halfway with water maintained at room temperature (26–28 °C). Test sessions were video recorded and analyzed using Noldus Ethovision 7.0 software. Immobility, defined as no movements other than those required for staying afloat, was scored for the entire 6 min test period, similar to previously published studies [17–19]. Mice from the C58/J strain were not tested in the forced swim test due to their inability to remain above water.

2.5. Statistical analysis

2.5.1. Correlation of Behaviors

Correlational analysis on the 6 variables measured in the open field and percent immobility in the forced swim test was conducted within each of the two treatments groups to determine the relationship among behaviors, within treatment. To account for multiple tests (21 within each treatment), a Bonferroni adjusted α-threshold of .0024 was used to test for significance.

2.5.2. Analysis of OVX and strain

Three types of effect were studied: the effect of strain on behavior in SHAM mice, the effect of OVX on behavior across all strains, and the

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