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Sex differences in sleep, anhedonia, and HPA axis activity in a rat model of chronic social defeat

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ABSTRACT

Repeated bouts of a major stressor such as social defeat are well known to induce a depression phenotype in male rats. Despite strong evidence and acknowledgement that women have a two-fold lifetime greater risk of developing major depression compared to men, the inclusion of female rats in studies employing social defeat are very rare; their absence is attributed to less aggressive interactions. This study sought to compare in male and female rats the impact of repeated social defeat, three times per week for four weeks, on the development of changes in sleep architecture and continuity, sucrose preference as a measure of anhedonia, changes in body weight, and basal plasma corticosterone levels. We found significant reductions in rapid eye movement sleep (REMS) during the light phase in both females and males, and significant increases in numbers of vigilance state transitions during the early dark phase in females but not in males. Additionally, females exhibited significantly greater reductions in sucrose intake than males. On the other hand, no sex differences in significantly elevated basal corticosterone levels were evident, and only the males exhibited changes in body weight. Taken together these findings suggest that the inclusion of female rats in studies of social defeat may offer greater insights in studies of stress and depression.

1. Introduction

"The most common stressors in humans are of a psychological or social nature" (Hollis et al., 2011), and severe life events often precede onset of depression (Bangasser and Valentino, 2014; Hollis and Kabbaj, 2014; Stroud et al., 2008). Vulnerability to depression may be increased in situations reflective of loss of power or social standing as well as from an experience of defeat (Carvalho et al., 2013). Although stress in rats can in no way fully depict the human biobehavioral phenomenon of depression, social defeat has been useful for studying individual stress responsiveness and is cautiously acknowledged as a valid model for human depression (Chaouloff, 2013; Hollis and Kabbaj, 2014; Koolhaas et al., 2013). Biobehavioral commonalities between melancholic or endogenous depression in humans and social defeat in rats include anhedonia, operationalized as a reduced preference for sucrose water; alterations in sleep architecture or continuity; changes in weight, and hypothalamic-pituitary-adrenal (HPA) axis dysregulation (American Psychiatric Association, 2013; Becker et al., 2008; Kamphuis et al., 2015; Patki et al., 2013; Razzoli et al., 2007; Rygula et al., 2006; Stetler and Miller, 2011). The administration of an antidepressant has been shown to significantly reduce the social defeat-induced anhedonia (Becker et al., 2008; Rygula et al., 2006) and HPA axis changes (Becker et al., 2008). More recent studies have shown social defeat to result in a negative cognitive processing bias, pessimism (Papciak et al., 2013) and greater sensitivity to pain resulting from hind paw formalin injection (Rivat et al., 2010).

A major limitation of the rodent social defeat literature is our lack of knowledge of sex differences in responses to this stressor given the vast majority of studies are undertaken in male rats because females exhibit a reduced level of aggression (Chaouloff, 2013; Hollis and Kabbaj, 2014). Yet women have a two-fold lifetime greater risk of developing major depression compared to men (Altemus et al., 2014; Ferrari et al., 2013; Kessler and Bromet, 2013); thus, the omission of social defeat studies in female rats is a scientific gap. Furthermore, a limited number of papers report the impact of social defeat on sleep architecture or continuity; no

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studies including females were evident. Poor sleep may be antecedent to depression or co-morbid with depression (Gold et al., 2015; Palagini et al., 2013; Pillai et al., 2011). This study sought to determine whether the consequences of social defeat observed in male rats are also evident in females, particularly with regard to changes in sleep architecture and continuity, anhedonia, changes in body weight and basal levels of plasma corticosterone.

2. Materials and methods

2.1. Experimental design

A 2 × 2 factorial design was employed to accomplish the objectives of this study: male versus female and intruder versus home cage control. Fig. 1 depicts the procedural time course for this study.

2.2. Animals

Fischer 344 rats from Harlan Laboratories (Indianapolis, IN) were purchased to maintain a breeding colony for the F344 rats used as intruders in this study. Cohorts of age-matched mature offspring were entered into study at 4–12 months at the time of the first social defeat encounter; age was included as a covariate in the analyses. Three cohorts were specifically bred for random distribution into the four groups comprising this 2 × 2 design. Nine additional cohorts were accrued from the unperturbed control group of a larger study seeking to learn whether early pain affects behavioral responses to social defeat and pain at maturity. The timing of perturbations was consistent across studies. Table 1 includes the numbers of animals employed for each outcome included in this report.

Animals had free access to food and water except only water was available for the 4 h before surgery. The vivarium was maintained at 22 ± 1 °C on a 12/12 light–dark cycle such that all testing, surgery and manipulations were accomplished during the dark phase. Long Evans Outbred rats were purchased from Harlan Laboratories to be used as residents for the social defeat paradigm. All animals were weighed weekly to monitor general health. All experimental protocols were approved by the Johns Hopkins University Institutional Animal and Care and Use Committee.

2.3. Surgery

Implantation of telemetric transmitters for electroencephalogram (EEG) and electromyogram (EMG) recording was accomplished under isoflurane anesthesia. After shave and betadine preparation, animals were injected with 50 mg/kg ampicillin subcutaneously. A small incision through the skin and abdominal musculature on the right side just below the thorax was made and the transmitter unit inserted (Model TL11M2-F40-EET, Data Sciences International, St. Paul, MN). After immobilization in a stereotaxic frame, an incision was made through the scalp and neck and the skull was cleared of tissue using 2% hydrogen peroxide and dehydrated using 70% ethyl alcohol. The tunneled electrodes were attached to steel screws threaded into the skull at coordinates 2.0 mm lateral to the central suture and 2.0 mm anterior to both lambda and bregma, and stabilized with dental acrylic. EMG wires were inserted and anchored at the dorsal nuchal muscle. The abdominal skin and muscle layers were sutured with 5-0 monofilament wire and the scalp and neck incision with 3-0 Braunamid polyamide thread. Before the discontinuation of isoflurane, animals were injected subcutaneously with 1.5 mg/kg meloxicam and 10 mg/kg morphine in a slow release suspension (SRS) in separate injections, and 2% lidocaine ointment was applied to both suture lines. Animals recovered for 4 weeks before entering into the protocol. The SRS is comprised of mannide monooleate (Arlacel A, Sigma, St. Louis, MO), light mineral oil and normal saline (6.7%, 40% and 53.3% by volume, respectively) (Page et al., 1993).

Each female Long Evans resident for the social defeat paradigm underwent surgery to separate the ovary from the uterine horn bilaterally, rendering them sterile but preserving normal hormonal cycling. Under isoflurane anesthesia, the abdomen was shaved and prepared with betadine, and ampicillin, 50 mg/kg was administered subcutaneously. A 2 cm midline incision was made through the skin and muscle layer, and both uterine horns were ligated with 3-0 Braunamid polyamide thread just below the ovary and the separated ovary remained in the abdomen. The abdomen was irrigated and the skin and muscle layers sutured with 5-0 monofilament wire. Before discontinuing the isoflurane, animals were injected subcutaneously with 1.5 mg/kg meloxicam and 10 mg/kg morphine SRS in separate injections. Sutures were removed 10–12 days later, after which each female was introduced into the cage of a single male Long Evans retired breeder for a minimum of 4 weeks before being used in the social defeat paradigm.

Table 1
Numbers of animals included in each outcome.

Outcome	Males		Females	
	Intruder	Home	Intruder	Home
Sleep – EEG instrumented	8	4	7	8
Sucrose preference	10	10	11	12
Body weight	15	12	16	17
Corticosterone	8	5	6	6

Note: vertical columns are not additive as any single animal contributes data to more than one outcome.

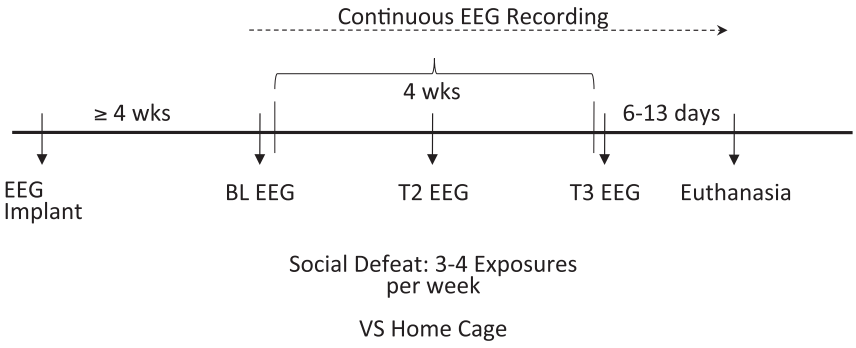

Fig. 1. Time course of study procedures.