Brain, Behavior, and Immunity 24 (2010) 942–951

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

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

Sex-specific social regulation of inflammatory responses and sickness behaviors

Jason R. Yee [a,*], Brian J. Prendergast [b]

[a] Department of Comparative Human Development, University of Chicago, Chicago, IL 60637, USA
[b] Department of Psychology and Committee on Neurobiology, University of Chicago, Chicago, IL 60637, USA

ARTICLE INFO

Article history:
Received 30 September 2009
Received in revised form 3 March 2010
Accepted 13 March 2010
Available online 17 March 2010

Keywords:
Innate immune responses
IL-1β
Corticosterone
Sex differences
Social behavior

ABSTRACT

In many mammals, the availability of familiar conspecifics in the home environment can affect immune function and morbidity. Numerous sex differences exist in immune responses, but whether the social environment impacts the immune system differently in males and females is not fully understood. This study examined behavioral and physiological responses to simulated bacterial infection in adult male and female Wistar rats housed either with three same-sex non-siblings (Group) or alone (Isolate). Rats were injected with bacterial lipopolysaccharide (*Escherichia coli* LPS; 150 μg/kg, i.p.), and behavioral (orectic, locomotor, and social) and physiological (thermoregulatory, cytokine, and corticosterone) inflammatory responses were measured. Among males, LPS-induced fever, suppressed locomotor activity, and inhibited feeding behavior and the magnitude of these responses were greater in Isolate relative to Group housed individuals. In contrast, among females group housing exacerbated behavioral and physiological symptoms of simulated infection. LPS treatments elicited IL-1β production in all groups, but plasma IL-1β concentrations were higher and peaked earlier in Isolate relative to Group males, and in Group relative to Isolate females. Furthermore, plasma concentrations of TNFα and IL-2 were higher in Group relative to Isolate males. Plasma corticosterone concentrations did not vary as a function of social housing conditions. Together, the data indicate that the social environment markedly influences innate immune responses. Group housing exacerbates inflammatory responses and sickness behaviors in females, but attenuates these responses in males. These sex differences are mediated in part by differential effects of the social environment on pro- and anti-inflammatory cytokine production.

1. Introduction

Social isolation is a powerful risk factor for increased morbidity and mortality (Cacioppo et al., 2000; House, 2001; House et al., 1988). The stable presence or absence of familiar conspecifics has long been known to alter immune responsiveness in rodent models, with social isolation in particular generally associated with impaired measures of immune function (Edwards et al., 1980; Plaut et al., 1969; Rabin et al., 1987a; Vessey, 1964). Social isolation impacts diverse aspects of the immune system: individual- relative to group- housing results in decreased mitogen-stimulated lymphocyte proliferation (Bartolomucci et al., 2003; Jessop et al., 1988), decreased antigen-specific IgG production (Demas et al., 2004; Klein et al., 1997; Shanks et al., 1994), delayed wound healing (Detillion et al., 2004), increased parasitic load (Schuster and Schaub, 2001), and increased tumor growth following tumor cell transplantation (Kerr et al., 1997; Kerr et al., 2001; Strange et al., 2000) across different animal models. The role of social organization (i.e., solitary vs. group-living species) on isolation-induced changes in immunity has received limited empirical study (but see, Klein et al., 1997).

Independent of social organization, male mammals are at greater risk than females for broad-based morbidity and mortality. This is especially true for the symptoms of bacterial infection, which are exacerbated in males relative to females (Brabin and Brabin, 1992; Grossman, 1985; Schuster and Schaub, 2001). This sexual diphenism is regulated in part by a higher expression of the LPS-binding Toll-like receptor-4 (TLR4) and CD14 in macrophages of males relative to females (Marriott et al., 2006). In addition, endogenous male sex steroids suppress some aspects of cell-mediated immune function (Gaillard and Spinedi, 1998).

Although rats are a canonical model organism for the study of psychoneuroimmunological mechanisms, interactions between sex and social organization are seldom considered in studies of immune function. We hypothesized that the social environment would alter immunological and behavioral responses to a simulated bacterial infection in a sex-specific manner. To test this hypothesis, male and female Wistar rats that had been raised in social isolation or in social groups were treated with LPS; over the days that followed, body temperature, locomotion, food intake, and social behavior were quantified. To identify immunological and neuroendocrine mechanisms that mediate social and sex

* Correspondence to: Jason R. Yee, Brain-Body Center, University of Illinois at Chicago, 1601, W. Taylor St., M/C 912, Chicago, IL 60612, USA. Fax: +1 312 996 7658.
E-mail address: jyee@psych.uic.edu (J.R. Yee).

0889-1591/$ - see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.bbi.2010.03.006

differences in LPS-elicited innate immune responses, blood cytokine and corticosterone concentrations were determined during the hours before and after LPS treatment.

2. Materials and methods

2.1. Animals and photoperiod treatments

Male and female Wistar rats (HsdRccHan:WIST) ($n = 75$) were bred at the University of Chicago from stock purchased from Harlan (Indianapolis, IN, USA). Pups were weaned at 21–25 days of age and housed with same-sex non-siblings in groups of 3/cage (Group) or 1/cage (Isolate). Final sample sizes are indicated in Fig. 1. In the Group condition, only one (focal) animal received the injection (LPS or saline) on any given experimental run. Otherwise, Group and Isolate animals were treated and handled in an identical manner. At all times, rats were housed in in polypropylene cages ($25.9 \times 47.6 \times 20.9$ cm) at 22 ± 1 °C and 50 ± 5% humidity and had *ad libitum* access to food (Teklad 8640; Harlan, Indianapolis, IN, USA) and filtered tap water. Rats were housed under a light–dark cycle that provided 14 h of light and 10 h of darkness per day (onset of darkness: 12:00 h C.S.T.). This light cycle was chosen to mimic summer daylengths in which rodents are capable of producing robust immune responses. A dim (<0.1 lux) red light remained on at all times to facilitate behavioral observations during the scotophase. Experiments began when rats were 90–150 days of age. All procedures conformed to guidelines of "Principles of Laboratory Animal Care" (NIH publication No. 86-23, revised 1985) and the USDA Guidelines for the Care and Use of Laboratory Animals, and were pre-approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Chicago.

2.2. Body temperature and activity telemetry

Body temperature (T_b) and locomotor activity were recorded telemetrically from rats ($n = 39$) bearing temperature-sensitive radiotransmitters (G2 E-mitter; Respironics Inc.; Bend, OR) which were implanted i.p. under deep surgical anesthesia (sodium pentobarbital,100 mg/kg, i.p.) according to methods described in detail elsewhere (Prendergast et al., 2002). After recovery from surgery, rats were returned to their home cages and received buprenorphine (0.5 mg/kg, s.c.) as an analgesic at 12 h intervals for 48 h. One week later, Isolate and Group cages, each containing one radiotransmitter-bearing animal (i.e., the focal animal), were placed on receiver boards (ER-4000; Respironics Inc.); T_b data were collected every 5 min and transmitted to a PC using VitalView software (Respironics Inc.).

2.3. Injection treatments

After ⩾2 days of baseline data collection, rats received an i.p. injection of either 150 μg/kg of *Escherichia coli* lipopolysaccharide (LPS; serotype 0127:B8; Sigma) or 0.9% sterile physiological saline (SAL) 10–30 min before the onset of darkness in a counterbalanced, blocked design, with all focal animals receiving both LPS and SAL treatments in random order. In the Group condition, only one animal received the injection on any given experimental run. Injection volumes ranged from 0.1–0.4 ml. Successive injections were separated by 7 days. LPS is the biologically-active fragment of endotoxin from gram-negative bacteria; it is non-replicating. This dose and strain of LPS was used because it reliably elicits physiological and behavioral symptoms of infection in Wistar rats (Bluthe et al., 2001; Dogan et al., 2000; Dogan et al., 2002).

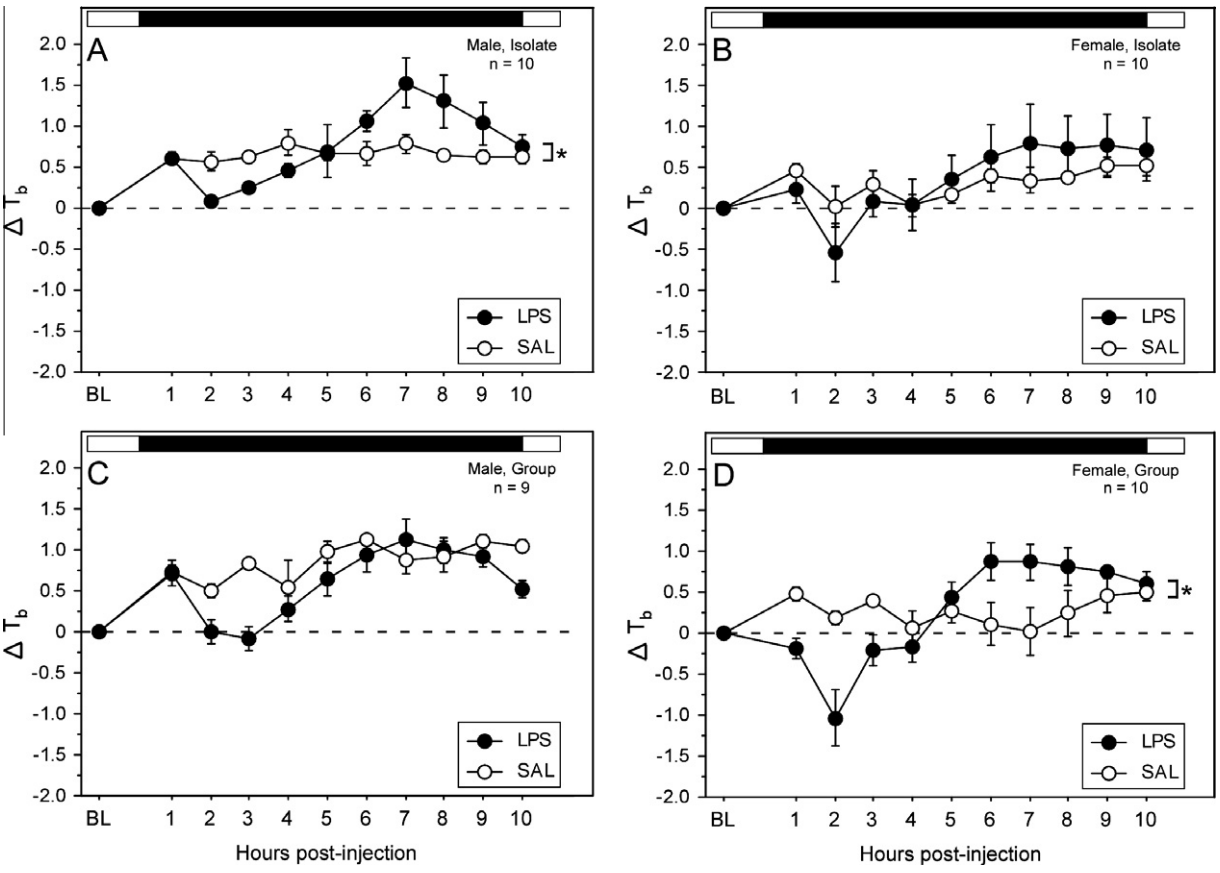

Fig. 1. Mean (±SEM) hourly change in body temperature of male (A and C) and female (B and D) Wistar rats housed 1/cage (Isolate; panels A and B) or 3/cage (Group; panels C and D) prior to and following treatment with lipopolysaccharide (150 μg/kg, i.p.; LPS) or saline (at time 0). Open:filled bars above each plot indicate the daily light:dark cycle. Within each panel: $^*p < 0.05$ vs. saline.