



SHORT COMMUNICATION

# Behavioral tolerance to endotoxin is enhanced by adaptation to winter photoperiods

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## Summary

Seasonal changes in day length enhance or suppress aspects of immune function in mammals. Following adaptation to short, winter-like short photoperiods, cytokine and behavioral responses to lipopolysaccharide (LPS)-induced simulated infections are attenuated in LPS-naïve Siberian hamsters. This experiment examined whether diminished initial responses to LPS in short days (SDs) are accompanied by decrements in the development of innate immunological memory that leads to endotoxin tolerance. Male hamsters exposed to SDs (9 h-light/day) or kept in their natal long-day (LD) photoperiod (15 h-light/day) for 12–13 weeks were injected with bacterial LPS (625 µg/kg, i.p.) or sterile saline. Ten days later all hamsters were challenged with LPS (625 µg/kg, i.p.), and behavioral sickness responses (anorexia and reductions in nest building) were assessed. In LD hamsters, behavioral responses to the second LPS injection were markedly attenuated but still evident, indicative of partial tolerance. SD hamsters, in contrast, failed to exhibit anorexic or thermoregulatory responses to the second LPS injection, indicative of complete behavioral tolerance to LPS. Thus despite engaging greater naïve responses to LPS, LD hamsters exhibited incomplete LPS tolerance relative to SD hamsters. The expression of behavioral tolerance to endotoxin is relatively diminished during the breeding season, a time of year when naïve responses to endotoxin are at their greatest. During winter, enhancements in behavioral endotoxin tolerance may conserve energy and facilitate survival in the face of energetically challenging conditions.

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## 1. Introduction

Sick animals exhibit profound, transient changes in behavior and motivational state, collectively termed ‘sickness behaviors’ (Hart, 1988). In the case of bacterial infections, sickness behaviors are initiated by the activity of cells in the

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innate immune system, principally macrophages. Following recognition of bacterial cell wall lipopolysaccharide (LPS), macrophages synthesize and secrete pro-(IL-1 $\beta$ , IL-6, and TNF- $\alpha$ ) and anti-(IL-10, IL-1ra) inflammatory cytokines, which act on central and peripheral targets to trigger changes in physiology and behavior (Dantzer, 2001). The ensuing motivational reorganization includes reductions in ingestive, social, and sexual behaviors, induction of an anhedonic state, lethargy, and thermoregulatory changes. Sickness behaviors generated during the acute phase response (APR) to infection forestall bacterial replication, facilitate leukocytogenesis, and are critical to survival (Kluger, 1975; Hart, 1988).

Innate inflammatory responses to microbes are not immovable. Rather, environmental factors can exacerbate or attenuate infection-induced cytokine production and the generation of sickness behaviors (e.g., Aubert et al., 1997). Among the environmental cues capable of robust modulation of the response to LPS are changes in day length (photoperiod). After exposure to short, winter-like photoperiods, male Siberian hamsters challenged with a simulated Gram-negative bacterial infection (systemic LPS) that exhibit lower IL-1 $\beta$ , IL-6, and TNF- $\alpha$  production, and marked decreases in the magnitude and persistence of anorexic and thermoregulatory responses, relative to hamsters exposed to longer, summer-like photoperiods (Bilbo et al., 2002; Prendergast et al., 2003). Several other components of the hamster immune system have also been shown to be enhanced under winter relative to summer photoperiods, including skin inflammatory responses and lymphocyte subsets (Bilbo et al., 2002). These and other data (see Nelson, 2004, for review) have formed the empirical foundations of the 'winter immunoenhancement hypothesis', which proposes that photoperiodic adjustments in immune function may reflect an adaptive reallocation of metabolic resources away from reproductive physiology and towards host defense and survival at times of year when reproduction is unlikely to be successful (Nelson and Demas, 1996). 'Immunoenhancement', here, refers to survival and fitness, and does not imply quantitative increases in all immunological responses following adaptation to short days (SDs). Because acute-phase sickness responses are extremely energetically expensive (Bilbo et al., 2002), the *attenuation* of LPS-induced sickness behaviors during winter accelerates behavioral recovery from severe infections. Earlier termination of fever and resumption of foraging may be adaptive in winter environments where ambient temperatures are relatively lower and food is scarce (Nelson, 2004).

If engaged repeatedly or sustained for prolonged intervals, inflammatory responses can lead to any of several pathophysiological conditions, including metabolic syndrome, somatic wasting, and septic shock (Nathan, 2002). Constraints on the extent of LPS-induced inflammation are afforded by cellular negative-feedback mechanisms that are engaged in parallel with the initial inflammatory response to LPS (Sly et al., 2004; Foster et al., 2007). This negative regulation induces a state of 'LPS tolerance', characterized by organismal and macrophage hyporesponsiveness to restimulation by LPS, thereby decreasing the likelihood of sepsis. Following an initial (naive) treatment with LPS, subsequent LPS treatments elicit attenuated cytokine and

behavioral (fever, food intake) responses in tolerant animals (Langhans et al., 1991; Nava and Carta, 2000). The degree of tolerance varies in a dose-dependent manner with the amount of the initial LPS treatment (Beeson, 1947; Labeta et al., 1993). In addition to protecting against sepsis, LPS tolerance also substantially decreases the energetic consequences of reexposure to LPS (e.g., diminished anorexia and fever). Once instated, LPS tolerance can endure for weeks, reflecting a form of short-term memory in the innate immune system (Valles et al., 2005; Gantner and Singh, 2007).

Whether photoperiod affects the development of LPS tolerance remains unresolved. On one hand, the relatively greater proinflammatory response to LPS under long, relative to SDs may be accompanied by a relatively greater concurrent activation of negative regulators of inflammation (i.e., mechanisms that induce tolerance), and therefore greater behavioral tolerance might be predicted in long days (LDs). Alternatively, however, if winter adaptations in the immune system are also manifest in mechanisms that control the development of LPS tolerance, then one would predict LPS tolerance to be facilitated in hamsters adapted to short photoperiods, consistent with the winter immunoenhancement hypothesis. A modest attenuation of LPS tolerance under long, relative to short, days has been reported in a population of female meadow voles (Engeland et al., 2003); however, asymmetries in the proportion of voles that were concurrently pregnant in LDs (40%) versus SDs (0%) preclude a definitive interpretation of the data. Moreover, in meadow voles photoperiod does not affect the magnitude of the initial, acute response to LPS (Engeland et al., 2003). To directly address this issue, this experiment tested whether adaptation to a short photoperiod facilitates or impairs the development of behavioral tolerance to LPS. LPS-induced anorexia and suppression of nest building behavior were measured, as these are the two most robustly photoperiodic sickness behaviors yet described in rodents (Wen et al., 2007), and each bears critically on winter energy balance.

## 2. Methods

### 2.1. Animals and photoperiod manipulations

Procedures in this experiment conformed to the NIH Guidelines for the Care and Use of Laboratory Animals and were approved by the University of Chicago Institutional Animal Care and Use Committee. Siberian hamsters (*Phodopus sungorus*;  $n = 45$ ) from our laboratory breeding colony were raised 2–4 per cage ( $28 \times 17 \times 12 \text{ cm}^3$ ) under a 15L:9D photoperiod (LD; lights-off: 18:00 h) with *ad libitum* access to food and filtered water. Ambient temperature was  $20 \pm 0.5^\circ \text{C}$  and relative humidity was  $53 \pm 2\%$  throughout the experiment. At 3–4 months of age (*week 0*), hamsters were either transferred into 9L:15D (SD; lights-off: 18:00 h;  $n = 25$ ) or remained in LD ( $n = 20$ ). On *weeks 0* and *12*, testis volumes were determined under light isoflurane anesthesia to assess gonadal responses to the photoperiod manipulations. SD hamsters that failed to exhibit  $>40\%$  decrease in testis size by *week 12* ( $n = 4$ ) were regarded as

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