Sex differences in photoperiodic and stress-induced enhancement of immune function in Siberian hamsters

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Abstract

Siberian hamsters breed during the long days of spring and summer when environmental conditions (e.g., ambient temperatures, food availability) are favorable for reproduction. Environmental conditions may also influence the onset and severity of infection and disease, and photoperiodic alterations in immune function may comprise part of a repertoire of seasonal adaptations to help survive winter. In order to test the hypothesis that animals use day length to anticipate seasonal stressors and adjust immune function, we measured antigen-specific delayed-type-hypersensitivity (DTH) responses in the skin of male and female hamsters during long, “summer-like,” or short, “winter-like” days, at baseline and following acute restraint stress. Sex steroid hormones were lower, and cortisol was higher, in males and females during short days. Baseline DTH was enhanced in short-compared to long-day males, and acute stress augmented this effect. In contrast, photoperiod alone did not influence the DTH response in females. As predicted, female hamsters exhibited significantly higher DTH responses than males during long days, but not during short days. However, this enhancement was observed in acutely stressed females only. Cortisol concentrations were significantly higher at baseline in females, and increased more in response to stress, compared to males in both photoperiods. These results suggest that photoperiod provides a useful cue by which stressors in the environment may be anticipated in order to adjust immune function. Furthermore, interactions among reproductive status and stress responses appear to mediate the expression of sex differences in immune responses in hamsters.

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1. Introduction

Environmental conditions, such as temperature, and the availability of food, water, and shelter, often vary on a seasonal basis. These conditions may influence the onset and severity of infection and disease; for instance, challenging conditions during winter may weaken immune function and compromise survival via hypothermia, starvation, or shock (Afoke et al., 1993; Lack, 1954; Ross et al., 1989). High thermoregulatory demands for small mammals, in particular, during the relatively cold winter months typically coincide with low food availability. The energetic bottleneck faced by animals during winter has led to the evolution of specific adaptations that allow these animals to conserve energy and cope with winter successfully (Heideman and Bronson, 1990; Nelson et al., 1998). One of these adaptations involves the cessation of reproduction: Siberian hamsters (Phodopus sungorus) stop breeding during the winter by responding to day length (photoperiod) cues that allow individuals to anticipate challenging conditions, and prepare accordingly for them (Bartness et al., 1993).
Photoperiodic alterations in immune function may also comprise part of a repertoire of seasonal adaptations to winter (Nelson et al., 2002). Immune function is compromised in many species during the winter in the wild, but is enhanced in the laboratory during short-day conditions when all other factors, such as food and temperature, are held constant (Demas and Nelson, 1996, 1998; Nelson et al., 1998). Because the onset of winter conditions is predictable, Siberian hamsters appear to use day length to anticipate their onset and adjust immune function. Male hamsters increase glucocorticoid concentrations and the number of blood leukocytes during short, winter-like days in the laboratory compared to hamsters housed in long, summer-like days (Bilbo et al., 2002). Short-day hamsters also traffic immune cells out of the blood more quickly in response to acute restraint stress, and exhibit enhanced delayed-type-hypersensitivity (DTH) responses in the skin compared to long-day animals, both at baseline and following restraint (Bilbo et al., 2002).

DTH reactions are antigen-specific, T cell-mediated immune responses. Following antigenic challenge, the DTH immune reaction is characterized by inflammation at the site of challenge by an infiltration of monocytes and lymphocytes into the skin, and the physiological role of this system is to provide front-line defense against pathogens (Meltzer and Nacy, 1989; Wachsman et al., 1992). Stress often suppresses immune function and increases susceptibility to infection and disease (Cohen et al., 1991; Fox, 1981). However, in contrast to chronic stress, which is often immunosuppressive (Dhabhar and McEwen, 1997), acute stress in rats, mice, and hamsters appears to enhance skin immune function at a time when injury is likely. Primary immune defense areas, such as the skin, lymph nodes, lungs, and gastrointestinal tract, represent the first line of bodily defense, and infection or injury is most likely to occur first in these peripheral areas (Sprent and Tough, 1994). Glucocorticoids mediate the trafficking of leukocytes out of the blood and among tissues during stress, whereas adrenalectomy prevents stress-induced trafficking and enhancement of DTH reactions (Dhabhar, 2000; Dhabhar et al., 1996). Thus, acute (~2 h) restraint stress significantly enhances DTH responses in rodents by inducing a rapid redeployment of immune cells out of the blood and into the skin in preparation for impending challenge (Dhabhar, 2000; Dhabhar and McEwen, 1999).

DTH responses in female Siberian hamsters have not yet been tested. Females do not exhibit photoperiodic alterations in leukocyte numbers, suggesting that DTH responses may not differ according to day length (Bilbo et al., in press). However, females exhibit higher numbers of total white blood cells, total lymphocytes, T cells, and B cells in the blood compared to males during long days, but not short days (Bilbo et al., in press), suggesting that DTH responses may be elevated in females compared to males during long days as well. Sex differences in immune function are well established. Females of many species generally exhibit enhanced immune responses compared to males (Gaillard and Spinedi, 1998; Klein, 2000; Schuurs and Verheul, 1990). Enhanced DTH responses are reported in female mice (Matarese et al., 2001; Ptak et al., 1988), rats (Elliot et al., 2002), and humans (Rees et al., 1989), compared to males. Depressed DTH responses have also been reported in females following lead exposure in rats (Bunn et al., 2001a,b), and burn injury in mice (Gregory et al., 2000a). Contradicting reports in females may depend in part on high or low concentrations of circulating sex steroid hormones. In general, exogenous estradiol has immuno-enhancing effects on humoral immunity (McCrudden and Stimson, 1991; Seaman and Gindhart, 1979), but may either enhance or suppress cell-mediated immunity depending on low or high doses, respectively (Kovacs et al., 2002). Exogenous testosterone generally depresses both humoral and cell-mediated immunity, and increases susceptibility to bacterial and viral infections (Schuurs and Verheul, 1990; Viselli et al., 1995).

Few studies have investigated the expression of sex differences in vertebrates under naturally occurring alterations in reproductive status. Gonadectomy and hormone replacement paradigms fail to mimic conditions that occur within the animal (i.e., the total absence or presence of the hormone versus cyclical secretion patterns). Sex steroid concentrations increase in response to long days, and decrease in response to short days, in this species (Bartness, 1996). Glucocorticoids fluctuate on a seasonal basis as well; cortisol concentrations are higher in short days in males (Bilbo et al., 2002). Importantly, photoperiodic alterations in sex- and stress-steroid hormones may contribute to the expression of sex differences in immune function in this species. Thus, the goal of this study was twofold: (1) to determine whether female Siberian hamsters alter immune responses during short days in preparation for winter conditions similar to males, and (2) to determine whether photoperiod influences the expression of sex differences in DTH in hamsters. We measured antigen-specific DTH responses in male and female hamsters during long or short days, at baseline and following acute (2 h) restraint, and measured circulating testosterone, estradiol, and cortisol concentrations in males and females within each condition.

2. Materials and methods

2.1. Animals

Adult (4–6 months of age) male and female Siberian hamsters (Phodopus sungorus) from our breeding colony.
were used in this study, originally established from a wild-bred stock obtained from Dr. K. Wynne-Edwards, Queen’s University. Animals were housed from weaning in same-sexed sibling pairs in polypolypropylene cages (27.8 x 7.5 x 13 cm) in colony rooms with constant temperature and humidity of 21 ± 4°C and 50 ± 10%, respectively, and had constant access to food (Harlan Teklad 8640 Rodent Diet, Indianapolis, IN) and filtered tap water. On week zero, 16 male and 16 female hamsters were housed in long-day conditions with a reverse 16:8 light:dark cycle (lights on 24:00 h EST), and 25 male and 25 female hamsters were housed in short-day conditions with a reverse 8:16 light:dark cycle (lights on 06:00 h EST).

2.2. Reproductive measures

On week 8, all male hamsters were lightly anesthetized with isoflurane vapors, and assessed for reproductive response to photoperiod via external testis measurements using electronic digital calipers (MAX-Series). The length and width of the left testis was measured (±0.1 mm). The product of testis width squared times testis length provides a measure of estimated testis volume (ETV) that is highly correlated with testis weight (Gorman and Zucker, 1995). Males from the short-day conditions with ETVs ≥ 2 standard deviations below the long-day mean were considered reproductive responders to short days. Females and males were assessed for reproductive response to short days based on changes in body mass and winter-typical changes in pelage, using a scale of 1–4 as described by Duncan and Goldman (1984) (1, dark “summer” fur; 4, white “winter” fur). Sixteen males and 16 females were considered reproductive responders to short days and used in subsequent procedures.

2.3. Induction of DTH

On week 10, DTH was induced by application of the antigen, 2,4-dinitro-1-flourobenzene (DNFB; Sigma), to the pinnae of hamsters following initial immunization to the dorsum. On day 1, all hamsters were taken in pairs into the surgery room, anesthetized at ~09:00 h EST with isoflurane vapors, and rapidly (<1 min) bled from the retro-orbital sinus (0.2 ml) for later determination of serum cortisol, estradiol (females), and testosterone (males), and received 0.5 ml saline injections. Next, 20 μl of DNFB [0.2% (wt/vol) in 4:1, acetone:olive oil vehicle] was applied to the shaved skin of the right pinna. Left pinnae were treated with vehicle, and animals were returned to their home cages. Pinna thickness was measured every 24 h for the next 6 days at 10:00 h EST, and all measurements were made on the same relative region of the pinna.

2.5. RIA procedures

Blood samples were centrifuged at 4°C for 30 min at 2500 rpm, and the supernatant was collected and frozen at −70°C until assayed for cortisol, estradiol, and testosterone concentrations. Cortisol represents the primary glucocorticoid in this species (Reburn and Wynne-Edwards, 1999), and concentrations were determined in duplicate in a single assay using a Diagnostic Products Corporation 125I double antibody kit (Los Angeles, CA). Serum testosterone and estradiol concentrations were determined in duplicate in single assays using Diagnostic Systems Laboratories 125I double antibody kits for testosterone and estradiol, respectively (Webster, TX). These kits have previously been validated for use in Siberian hamsters (Bilbo et al., in press; Jasnow et al., 2000; Reburn and Wynne-Edwards, 1999). The high and
low limits of detectability of the testosterone assay were 25 and 0.1 ng/ml, respectively. The high and low limits of detectability of the estradiol assay were 4000 and 5 pg/ml, respectively. The high and low limits of detectability of the cortisol assay were 530 and 5 ng/ml, respectively. The intra-assay coefficients of variation were <10% in all cases.

2.6. Data analysis and statistics

Body mass, ETV (males), and pelage score data were analyzed between photoperiod groups within each sex using two-tailed t tests. Sex steroid hormone concentrations were analyzed between groups within each sex using two-tailed t tests (baseline), and as a function of manipulation (baseline vs stress or control) using repeated measures analyses of variance (ANOVA). Non-detectable low testosterone samples were assigned a value of 0.09 ng/ml, and non-detectable high samples were assigned a value of 25.1 ng/ml, for the purpose of statistical analyses. Non-detectable low estradiol samples were assigned a value of 0.09 ng/ml, and non-detectable high samples were assigned a value of 4.9 ng/ml. No samples fell beyond the high limit in the estradiol assay. Baseline cortisol concentrations (day of sensitization) and post-manipulation cortisol concentrations (day of challenge) were each analyzed among groups in separate one-way ANOVAs. Cortisol concentrations on the day of sensitization and the day of challenge were compared to one another among groups using a repeated measures ANOVA. Non-detectable high cortisol samples were assigned a value of 531 ng/ml for the purpose of statistical analyses. No samples fell below the low limit in this assay. DTH reactions were analyzed as percent increases in pinna thickness over baseline for each animal, and compared between groups using repeated measures. DTH reactions (days 1–6) in females from each photoperiod and stress group were correlated to circulating estradiol concentrations, on the days of sensitization and challenge, using Pearson Product Moment Correlations. Post hoc (Tukey’s Honestly Significant Difference) tests were performed to further distinguish among groups, and all differences were considered statistically significant if p < .05. All statistics were performed using SigmaStat Statistical Software (SPSS, Chicago, IL).

Table 1
Mean (±SEM) body mass (g), estimated testis volumes (mg; males), and pelage scores (1, brown; 4, white), in male and female hamsters housed in long or short days for 8 weeks; *Significantly different from long day (within sex), p < .05

<table>
<thead>
<tr>
<th></th>
<th>Males (n = 16)</th>
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<th>Females (n = 16)</th>
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<tr>
<td></td>
<td>Long day</td>
<td>Short day</td>
<td>Long day</td>
<td>Short day</td>
</tr>
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<td>Body mass</td>
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<td>28.1 ± 0.7*</td>
<td>32.5 ± 1.2</td>
<td>24.6 ± 1.3*</td>
</tr>
<tr>
<td>ETV</td>
<td>812 ± 38</td>
<td>281 ± 46*</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pelage score</td>
<td>1.0 ± 0.0</td>
<td>3.0 ± 0.13*</td>
<td>1.0 ± 0.0</td>
<td>2.7 ± 0.1*</td>
</tr>
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3. Results

3.1. Reproductive measures

After 10 weeks of photoperiodic treatment, male short-day hamsters weighed significantly less, and had significantly smaller testes and whiter pelages compared to male long-day hamsters (p < .05, for all; Table 1). Female short-day hamsters had significantly whiter pelages and weighed significantly less compared to female long-day hamsters (p < .05, for both). Long-day females weighed significantly less than long-day males (p < .05).

3.2. Hormones

Baseline serum testosterone and estradiol concentrations were significantly lower in short-day males and females, respectively, than in long-day hamsters of each sex (p < .05, for both; Figs. 1A and B). Baseline serum cortisol concentrations were higher in both short-day males and females compared to long-day hamsters of each sex (p < .05, for both; Figs. 1C and D). Cortisol concentrations were higher in all females (Fig. 1D) compared to all males (Fig. 1C), in both long days and short days (p < .05, for both).

3.3. Restraint-induced changes in hormones

Two hours of restraint stress significantly increased testosterone concentrations in long-day males, but not short-day males (p < .05; Fig. 2A). Restraint did not significantly influence estradiol concentrations in females compared to non-stressed controls (p > .05; Fig. 2B). Restraint significantly increased cortisol concentrations in all animals compared to non-stressed controls (p < .05, for all; Fig. 3). Short-day exposure resulted in significantly greater increases in cortisol in response to restraint in both males and females, compared to long-day animals (p < .05, for all). Non-stressed females exhibited significantly higher cortisol than non-stressed males in both long and short days, and stressed females exhibited significantly higher cortisol than stressed males in both photoperiods (p < .05, for
Furthermore, the restraint-induced increase in cortisol (compared to baseline) was greater in females than males in both photoperiods (\( p < .05 \), for both).

### 3.4. DTH

**Photoperiod differences.** Non-stressed short-day males exhibited an enhanced DTH response compared to non-stressed long-day males (\( p < .05 \); Fig. 4A). Similarly, stressed short-day males exhibited an enhanced DTH response compared to stressed long-day males (\( p < .05 \)). Restraint stress significantly increased the inflammatory response during days 3–4 post-DNFB challenge compared to non-stressed animals in short-day males only (\( p < .05 \)). Photoperiod alone did not influence the DTH response in females within either non-stress or stress conditions (\( p > .05 \); Fig. 4B). Stress enhanced the DTH response in long-day females compared to all non-stressed females on day 2 post-DNFB challenge, and compared to non-stressed long-day females on days 3–4 post-DNFB. Stressed long-day females had a higher DTH response than all other females on day 6 post-DNFB (\( p < .05 \), for all).

**Sex differences.** Long-day stressed females exhibited a significantly higher DTH response than all long-day males on days 2–6 post-DNFB challenge (\( p < .01 \), for all; Fig. 5A). There were no significant differences in DTH responses between male and female non-stressed hamsters in long days. During short days, there were no significant sex differences in DTH (\( p > .05 \); Fig. 5B).
3.5. DTH–estradiol correlations

Variances in DTH values were numerically higher in females than males, which may have resulted from fluctuations in estradiol concentrations, particularly in short-day females, because estradiol concentrations did not decrease several-fold in short-day females as testosterone did in short-day males. Furthermore, we did not control for estrus cycle in females; therefore alterations in estradiol either on the day of sensitization or challenge could have influenced the DTH response in females. However, there were no significant correlations between estradiol (sensitization or challenge) and DTH responses on any day in any group (stress and non-stressed) of females when analyzed either across photoperiods or separately for each photoperiod ($p >.05$, for all; data not shown).

4. Discussion

These results confirm and extend previous results (Bilbo et al., 2002); baseline DTH responses were enhanced in short-day compared to long-day males. Furthermore, acute stress significantly augmented DTH compared to non-stressed hamsters in short-day males only. In contrast to males, photoperiod alone did not influence the DTH response in females. As predicted, female hamsters exhibited significantly higher DTH...
responses than males during long days, but not during short days. However, this enhancement was observed in acutely stressed females only. Cortisol concentrations were significantly higher at baseline in females, and increased more in response to stress, compared to males in both photoperiods. Sex steroid hormones were lower, and cortisol was higher, in both sexes in short days than long days.

We hypothesized that photoperiod may provide a useful cue by which stressors in the environment may be anticipated. Augmentation of immune function in short-day hamsters may occur in preparation for seasonal stressors such as low temperatures and reduced food availability, which would otherwise increase susceptibility to infection. Cortisol concentrations were higher in both males and females during short days than long days. Elevated corticosterone concentrations have been reported during short days in male prairie voles (*Microtus ochrogaster*) (Nelson et al., 1996) and white-footed mice (*Peromyscus leucopus*) (Ransone and Bradley, 1992), and may reflect changes in metabolism. Contrary to the idea that glucocorticoids necessarily suppress immune function, increased cortisol concentrations during short days appear to mobilize the usage of energy stores throughout the body and allocate appropriate energy to immune function.

However, in contrast to males, photoperiod did not influence DTH in females. Similarly, blood leukocyte numbers and secondary antibody responses to an antigen do not vary by day length in females, whereas leukocyte numbers increase, and antibody production decreases, in short-day compared to long-day males (Bilbo et al., in press; Hadley et al., 2002). Estradiol concentrations did not decrease to the same extent in short-day females as did testosterone in short-day males. If short-day alterations in DTH are sex-steroid hormone mediated, then one would not expect dramatic photoperiodic alterations in DTH in females. However, estradiol concentrations were not significantly related to DTH responses in any group of females, making this explanation unlikely. A second possibility is that short-day *enhancement* of immune function may be a relative term; DTH data in long-day males may represent a decrease in immune function compared to a higher baseline observed in short-day males and females. A decrease in DTH in long-day males may be a consequence of the immunosuppressive influences of testosterone, the energetic burden of reproductive investment, or both. Reproduction is energetically expensive. If metabolic demands exceed caloric input, then trade-offs and energy shortages necessarily occur among various energetic demands (Bronson, 1989; Wade and Schneider, 1992). Thus, individuals likely maintain the highest degree of immune function that is possible within a constrained energetic budget without evoking autoimmunity (Klein and Nelson, 1999). Reproduction is typically more energetically expensive for females than males (Avitsur and Yirmiya, 1999; Thompson and Ni- coll, 1986; Wade and Schneider, 1992). However, the majority of energetic investment occurs during pregnancy and lactation in females, rather than prior to conception as in males (Bronson, 1989; Wade and Schneider, 1992). Thus, one could argue that assessment of immune function in long-day males and non-pregnant/non-lactating long-day females is not a direct comparison. Photoperiodic alterations in DTH in females may be observed if pregnant or lactating long-day females are included, and this possibility remains to be investigated.

Sex differences in immune function in vertebrates are well documented. Females of many species generally exhibit enhanced immune responses and increased...
resistance to disease and infection than males. These sex differences have been attributed, in part, to the direct and indirect immuno-modulatory actions of sex steroid hormones (Alexander and Stimson, 1988; Gaillard and Spinedi, 1998; Grossman, 1989; Grossman, 1985; Olsen and Kovacs, 1996). The results of this experiment both confirm and contradict these findings. Males and females exhibited reduced testosterone and estradiol concentrations, respectively, during short compared to long days. As predicted, sex differences in DTH were observed during long days when sex steroids were high, but not during short days when sex steroids were low. However, enhanced DTH responses in long-day females compared to males occurred following acute restraint stress only. Our results are similar to reports in mice, in which baseline responses do not differ, but females exhibit enhanced initial DTH responses following burn injury compared to males (Gregory et al., 2000a,b). However, others report sex differences under non-stress, baseline conditions in rats and mice (Matarese et al., 2001; Ptak et al., 1988).

Thus, interactions between reproductive condition and stress responses appear to mediate immune responses in female hamsters. Females generally exhibit higher adrenocorticotrophic hormone (ACTH) responses to stress, and increased baseline and stress-induced glucocorticoid release compared to males (Handa et al., 1994; Rivier and Rivest, 1991; Shanks et al., 1994). Female hamsters had higher cortisol concentrations at baseline, and increased cortisol more in response to stress, than males in both long and short days. Glucocorticoids released during acute stress mediate leukocyte trafficking and increase DTH responses in rats and mice (Dhabhar, 2000). However, acute stress augmented DTH only during long days in female hamsters. Similarly, acute stress enhanced DTH in short-day males, but not long-day males. Testosterone concentrations increased dramatically following acute stress in long-day males, which likely accounts for the lack of a significant stress-enhancement in these males. Chronic stress typically decreases testosterone concentrations (Knol, 1991; Tsuchiya and Horii, 1995b). However, transient increases in testosterone following stress have also been reported in several species (Gomez et al., 2002; Gregory and Schmid, 2001; Heiblum et al., 2000; Tsuchiya and Horii, 1995a). In rats, stress-induced changes in testosterone appear to be biphasic; acute stress (1–90 min) increases testosterone whereas chronic stress (3–48 h) suppresses testosterone (Feek et al., 1989). Sapolsky (1986) has reported that socially high-ranking baboons show transient increases in testosterone in response to stress, in contrast to immediate decreases observed in subordinant animals. This difference occurs despite a similar suppression of luteinizing hormone (LH) in both groups. Similar results have been reported in rodents (Albeck et al., 1997; Knol, 1991), and reptiles (Gregory and Schmid, 2001). Importantly, short-day males did not exhibit an increase in testosterone in response to stress; this likely was not possible due to altered negative feedback mechanisms during short days in this species, which prevent the release of gonadotrophins (i.e., GnRH, LH, FSH) necessary to stimulate the release of testosterone. Thus, stress-induced cortisol release likely increased DTH responses in both long- and short-day males, and the lack of an increase in testosterone in short-day males may have prevented a subsequent suppression of DTH.

Acute stress persistently increases estradiol release in female rats (Shors et al., 1999). However, there are several additional reports of stress- or cortisol-induced suppression of GnRH, LH, and estradiol in females (Debus et al., 2002; Kam et al., 2000; Servatius et al., 2001, 2000). Conflicting reports may be due to the relative timing of the stress procedure in relation to the production or pulsatile release of gonadotrophins or subsequent estradiol release. Stress did not significantly influence estradiol concentrations in female hamsters in either photoperiod; however, the lack of a clear effect of stress on estradiol may also be due to estrus cycle variation among animals. Regardless, estradiol concentrations were not significantly correlated to DTH in females under any condition, suggesting that restraint stress influenced DTH in females independent of estradiol.

In sum, neither estradiol nor cortisol concentrations alone predicted immune responses in females, and DTH did not vary according to stress condition or photoperiod alone. Enhanced immune function in long-day females may also be attributed to a lack of the immunosuppressive effects of androgens, the organizational influences of sex steroids during development, or both. In males, DTH responses were high coincident with low testosterone in short days, and vice versa in long days. However, it remains to be determined whether photoperiodic changes in DTH are testosterone-mediated, and studies are currently underway in our laboratory. Additional mechanisms underlying photoperiodic changes in DTH should also be considered. The pineal hormone, melatonin, encodes day length information, and appears to be the primary hormone mediating seasonal changes in reproduction and physiology in mammals (Bartness et al., 1993). Melatonin receptors have been localized on lymphocytes and monocytes, as well as within the thymus and lymphoid tissue throughout the body (Barjavel et al., 1998; Calvo et al., 1995; Cardinali et al., 1997; Maestroni, 1995). The role of melatonin as part of an integrative system to coordinate reproductive and other physiological processes makes it a likely candidate for the seasonal mediation of immune function in hamsters.

Taken together, environmental and reproductive influences on immune surveillance and function are likely profound, and numerous future investigations remain. We suggest that circulating stress- and sex-steroid
hormones are neither universally immuno-suppressive, nor enhancing. Rather, their effects are likely context dependent. Future research in this area may benefit greatly from the inclusion of females in more studies of immune function and stress in a variety of species, in order to gain insight into diverse mechanisms.

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References


