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Perinatal photoperiod organizes adult immune responses in Siberian hamsters (*Phodopus sungorus*)

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Weil, Zachary M., Leah M. Pyter, Lynn B. Martin II, and Randy J. Nelson. Perinatal photoperiod organizes adult immune responses in Siberian hamsters (*Phodopus sungorus*). *Am J Physiol Regul Integr Comp Physiol* 290: R1714–R1719, 2006. First published January 12, 2006; doi:10.1152/ajpregu.00869.2005.—Individuals of many nontropical rodent species display reproductive, immunological, and somatic responses to day length. In general, short day (SD) lengths inhibit reproduction and enhance immune function in the laboratory when all other conditions are held constant. Most studies to date have focused on seasonal variation in immune function in adulthood. However, perinatal photoperiods also communicate critical day length information and serve to establish a developmental trajectory appropriate for the time of year. Nontropical rodents born early in the breeding season undergo rapid reproductive development, presumably to promote mating success during their first reproductive season. Rodents born late in the breeding season suspend somatic growth and puberty until the following vernal breeding season. We tested the hypothesis that perinatal day lengths have similar enduring effects on the immune system of rodents. Siberian hamsters (*Phodopus sungorus*) were maintained prenatally and until weaning (21 days) in either SDs (8 h light:16 h dark) or long days (LD) (16 h light:8 h dark), then they were weaned into either the opposite photoperiod or maintained in their natal photoperiod, forming four groups (LD-LD, LD-SD, SD-LD, and SD-SD). After 8-wk in these conditions, cell-mediated immune activity was compared among groups. SD-SD hamsters of both sexes enhanced immune function relative to all other groups. The reproductive effects of perinatal photoperiod were not evident by the end of the experiment; circulating testosterone and cortisol sampled at the end of the experiment reflected the postweaning, but not the perinatal photoperiod. This experiment demonstrates long-lasting organizational effects of perinatal photoperiod on the rodent immune system and indicates that photoperiod-induced changes in the immune system are dissociable from changes in the reproductive system.

photoperiodism; seasonality; melatonin; delayed-type hypersensitivity

MANY NONTROPICAL ANIMALS DISPLAY annual variation in reproductive and immune activity. Winter represents an energetic bottleneck, wherein increased thermoregulatory requirements coincide with reduced energy availability (7). Therefore, during the spring and summer, which encompasses much of the breeding season for small, nontropical vertebrates, investments are biased toward reproductive activities; however, during late autumn and winter, resources are diverted to traits promoting over-winter survival. In the laboratory, many seasonal physiological and behavioral responses can be induced by manipulating day length (photoperiod) (21). Photoperiod information is transduced into a physiological signal via nocturnal secretion of pineal melatonin (11). Short day (SD) lengths (<12.5 h light/day) inhibit reproductive function, but enhance several aspects of immune function (21).

Adult Siberian hamsters (*Phodopus sungorus*) housed in SD lengths enhance delayed-type hypersensitivity (DTH; an index of cell-mediated immune activity) responses (2). The majority of research on seasonality of immune function has focused on photoperiod-induced differences in adult animals born and raised in long days (LDs) (but see Refs. 23 and 27) that experience photoperiod manipulation in adulthood. Early-life photoperiods are also important sources of seasonal information and can establish an individual's developmental trajectory by regulating somatic and reproductive development (6). Because the adaptations associated with investing in reproduction or survival mechanisms are generally mutually exclusive, it is useful for small animals to follow the appropriate seasonal developmental trajectory soon after birth. Siberian hamsters born late in the breeding season delay puberty until the following spring, whereas hamsters born early in the season undergo rapid reproductive development, presumably to have the opportunity to mate before autumn (12). Photoperiod information is communicated in utero to Siberian hamster pups (15) via the maternal melatonin rhythm. In addition to regulation of developmental processes, early-life photoperiod also affects reproductive (15) and affective (28) responses to day lengths later in life. Intermediate day lengths (e.g., 14 h) occur at both the beginning and the end of the breeding season; thus the same day lengths forecast very different environmental conditions. Photoperiodic rodents solve this problem by comparing ambient day length to a reference day length that is encoded prenatally via a mechanism termed photoperiod history (15, 25, 31). Thus for the reproductive system of seasonally breeding rodents, the direction of photoperiodic change is more important than the absolute day length (24).

The present study was designed to examine the enduring effects of perinatal (the period from conception to weaning) photoperiod on cell-mediated immune function in adulthood. Animals were born in either SD or LD and maintained in their natal photoperiod until weaning, at which time they were either left in their birth photoperiod or they were transferred to the opposite lighting condition. The hamsters were housed in the adult photoperiod for 8 wk before immune challenge to allow the reproductive system to adjust to the adult photoperiod treatment. We hypothesized that perinatal exposure to photoperiods would alter the immunological responses to day length

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in adulthood. Specifically, we predicted that *1*) perinatal SDs would enhance DTH responses in all groups, but to a greater extent in hamsters housed in SDs following weaning; and *2*) exposure to LD lengths perinatally would attenuate adult SD-induced elevated immune function.

MATERIALS AND METHODS

Animals

Hamsters (*P. sungorus*) in this study were bred in our colony at the Ohio State University from a wild-bred stock obtained from Dr. K. Wynne-Edwards, Queen's University, Kingston, Ontario, Canada. Animals were housed in polypropylene cages (28 × 17 × 12 cm) in colony rooms with constant temperature (21 ± 4°C) and humidity (50 ± 10%) and had ad libitum access to food (Harlan Teklad 8640 Rodent Diet, Indianapolis, IN) and filtered tap water. All studies were conducted with approval of the Ohio State Institutional Laboratory Animal Care and Use Committee and were conducted in compliance with all U.S. federal animal welfare requirements.

Breeding pairs were established in rooms illuminated with either long (16 h light/day; LD) or short (8 h light/day; SD) photoperiods. Pairs were inspected daily for the presence of pups, and the day of birth was designated *day 0*. Pups were weaned at *day 21* into either the opposite photoperiod (i.e., SD animals transferred to LD) or maintained in the perinatal photoperiod (i.e., SD animals remained in SD). Pups from each litter were distributed between the photoperiod groups in a pseudorandom fashion. No more than three pups of a single sex from any litters were used in any group. These photoperiodic manipulations produced four groups. Hamsters born in LD were either maintained in LD after weaning (LD-LD, $n = 8$ females, 11 males), or transferred to SD (LD-SD, $n = 6$ females, 11 males). Hamsters born in SD either remained in SD (SD-SD, $n = 13$ females, 14 males) or were moved into LD (SD-LD, $n = 10$ females, 9 males). The time of lights off was the same for both photoperiod treatments (1500 Eastern Standard Time). Experimental animals were individually housed at weaning and remained in their respective postweaning photoperiods for the remainder of the experiment. Seventeen litters were used to form the groups.

Experimental Procedures

Induction of DTH. DTH was induced by application of 2,4-dinitro-1-fluorobenzene (DNFB; Sigma) to the right pinna of each hamster after initial sensitization by application of DNFB to the dorsum. Sensitization was induced and DTH elicited as follows: following 8 wk of postweaning photoperiod treatment, all hamsters were anesthetized with isoflurane vapors, and an area ~2 × 3 cm was shaved on the dorsum. Twenty-five microliters of DNFB [0.5% (wt/vol) in 4:1 acetone-olive oil vehicle] was applied to the dorsal skin on 2 consecutive days. Seven days later, baseline thickness of both pinnae was measured in lightly anesthetized hamsters with a constant-loading dial micrometer (Long Island Indicator Service, Hauppauge, NY). Immediately after baseline pinnae thickness measurements were obtained, 20 μl of DNFB [0.2% (wt/vol) in 4:1 acetone-olive oil] were applied to the skin of the dorsal surface of the right pinna. Left pinnae were treated with vehicle. Pinnae thickness was measured every 24 h for the next 7 days. Pinnae thickness values obtained on each day following challenge were expressed as a percentage of baseline thickness. All DNFB treatments and pinna measurements were performed between 1300 and 1500, and all measurements were made on the same region of the pinna by the same person (Z. M. Weil). The DTH response in hamsters is extremely sensitive to stressors or increases in glucocorticoids; to minimize stress responses, hamsters were brought into the testing room one at a time.

Reproductive and somatic responses to photoperiod. Following the conclusion of DTH measurements, animals were weighed, and pelages were scored on a scale from 1 to 5 (1 = dark, summer coat color; 5 = white, winter coat color) in whole integers for each group (10, 28). Hamsters were then deeply anesthetized with isoflurane vapors and killed by rapid decapitation, and trunk blood was collected. Reproductive tissues (testes and epididymal fat pads in males and uteri and ovaries in females) were removed, cleaned of connective tissue, and weighed to the nearest 0.1 mg. All animals housed in short photoperiods as adults having testes or uterine masses falling 2 standard deviations below the LD mean were considered reproductively responsive to short photoperiods. Any animals housed in a short photoperiod as adults whose testes or uterine mass fell within the range of the mean minus 2 standard deviations of the long photoperiod group were considered reproductive nonresponders and were excluded from further analyses. One male (LD-SD) and one female (SD-SD) were reproductively nonresponsive and were excluded.

An additional group of hamsters was used to verify that perinatal photoperiod treatment alone had an effect on reproductive morphology. To confirm this, a separate group of hamsters born in SD or LD was killed at weaning by cervical dislocation at 21 days of age, and their reproductive tissues were removed and weighed.

RIA procedures. Trunk blood samples were allowed to clot for 30 min; then they were centrifuged for 30 min at 2,500 rpm, and supernatants were stored in polypropylene microcentrifuge tubes at −70°C. Serum testosterone concentrations (from males) were determined in a single assay using a Diagnostic Systems Laboratories (Webster, TX) ^{125}I double-antibody kit. The intra-assay coefficient of variation was <5%. Serum cortisol concentrations were determined in a single assay using a Diagnostic Systems Laboratories ^{125}I double-antibody kit. The intra-assay coefficient of variation was <5%. Both kits have been validated previously for use in this species (29).

Data Analyses and Statistics

Reproductive tissue weights and testosterone concentrations were analyzed with a two-way (perinatal photoperiod × postweaning photoperiod) ANOVA separately for each sex. Spleen mass, final body mass, pelage score, and serum cortisol concentrations were analyzed with three-factor ANOVAs (sex × perinatal photoperiod × postweaning photoperiod). All tissue weights were corrected for final body mass before statistical comparisons. Testis length was analyzed with repeated-measures ANOVA for perinatal and adult photoperiod manipulation. DTH reactions were compared between sex and group with repeated-measures ANOVA using litter as a covariate. However, litter had no effect on any measure and was removed from subsequent analyses. Following a significant F score, repeated-measures data were analyzed with sequential Bonferroni multiple-comparison tests; differences were not considered statistically significant unless $P < 0.0083$. Within days and between groups, multiple comparisons that were planned a priori were conducted with Tukey's honestly significant difference tests. All comparisons other than the Bonferroni test results were considered significant if $P \leq 0.05$.

RESULTS

Reproductive Responses

After 10 wk of housing in their respective postweaning photoperiods, females were significantly lighter than males [$F(1,81) = 60.143$, $P < 0.0001$ data not shown]. Hamsters housed in SD as adults were lighter than those in LD, regardless of perinatal photoperiod [$F(1,81) = 106.235$, $P < 0.0001$; data not shown].

Perinatal exposure to SDs reduced both testis [$F(1,12) = 859.938$, $P < 0.0001$; Fig. 1*A*] and uterine mass [$F(1,14) = 32.637$, $P < 0.0001$; Fig. 1*B*] in animals killed at weaning. However, by the end of the experiment (10 wk postweaning), only adult photoperiod affected paired testis weight, such that animals housed in LD as adults had larger testes than those

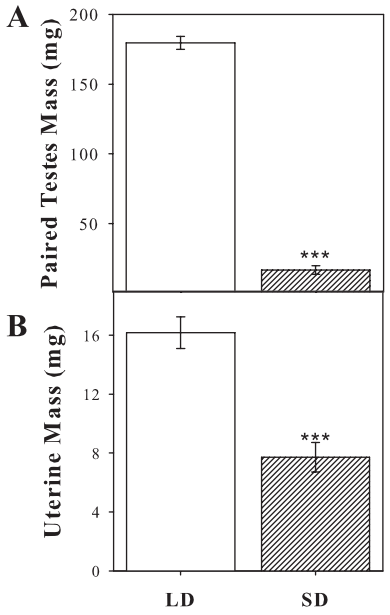

Fig. 1. Perinatal exposure to short days (SDs) reduced tissue masses at weaning. Means (±SE) are shown of paired testes mass (mg) of male (*A*) and uterine mass (mg) of female (*B*) *P. sungorus* at 21 days of age. ***Significantly different from hamsters housed in long days (LDs) perinatally: $P < 0.0001$.

housed in SD as adults, regardless of the perinatal photoperiod [$F(1,44) = 578.64$, $P < 0.0001$, Fig. 2]. Similarly, the size of the epididymal fat pads was affected by postweaning photoperiod [$F(1,44) = 85.85$, $P < 0.0001$, data not shown], but not perinatal photoperiod ($P > 0.05$). In females, uterine mass was also reduced by exposure to SD as adults, independent of perinatal photoperiod treatment [$F(1,37) = 30.42$, $P < 0.0001$, Fig. 2]. Ovarian mass was not affected by photoperiod treatment in any developmental periods ($P > 0.05$ for both perinatal and adult photoperiods). Pelage scores were significantly lower in all animals housed in SD as adults, irrespective of sex [$F(1,79) = 438.675$, $P < 0.0001$, data not shown], but no enduring effects of perinatal photoperiod were evident for pelage score. Only spleen mass was increased by perinatal exposure to SD [$F(1,79) = 5.325$, $P = 0.025$, Fig. 3], and this result was independent of both sex and adult photoperiod exposure.

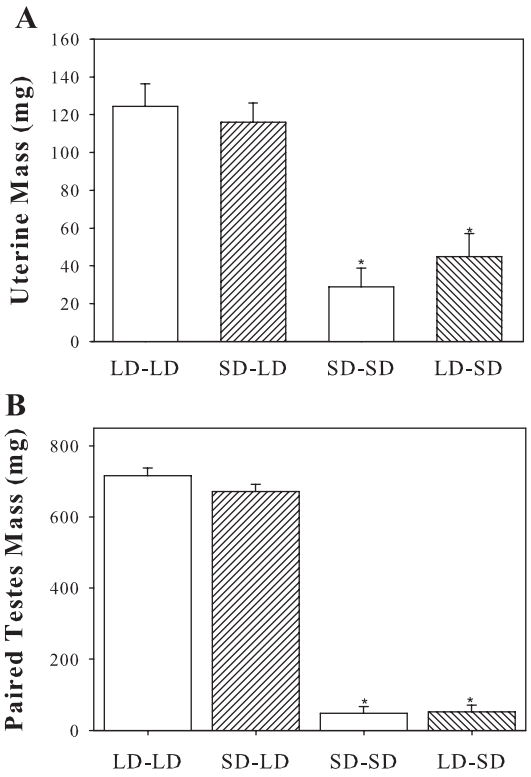

Fig. 2. Postweaning but not perinatal photoperiod affects means (±SE) uterine mass (mg) of female (*A*) and testes mass (mg) of male (*B*) *P. sungorus*. *Significantly different from hamsters housed in LD as adults (LD-LD and SD-LD): $P < 0.05$.

Hormones

Testosterone concentrations were reduced in animals housed in SD, regardless of perinatal photoperiod treatment [$F(1,40) = 39.165$, $P < 0.0001$; Fig. 4]. However, perinatal exposure to SD reduced circulating testosterone in animals housed in LD as adults, as indicated by a main effect of perinatal photoperiod [$F(1,40) = 6.128$, $P = 0.018$] and an interaction between perinatal and adult photoperiods [$F(1,40) = 6.213$, $P = 0.017$] on testosterone. Basal cortisol concentrations were higher in hamsters housed in SD as adults relative to those in LD during that period [$F(1,62) = 9.812$, $P = 0.003$; Fig. 5]. Perinatal photoperiod treatment and sex did not significantly alter cortisol concentrations ($P > 0.05$).

Immune Activity

Both perinatal [$F(1,79) = 8.976$, $P < 0.0001$; Fig. 6] and adult photoperiod [$F(1,79) = 7.588$, $P < 0.0001$] and the interaction between perinatal and adult photoperiods [$F(3,79) = 2.503$; $P < 0.05$] affected DTH responses. The effect of perinatal photoperiod was mediated by an enhanced swelling response in the SD-SD groups of both sexes relative to all other groups. Swelling responses from animals in all other groups did not differ statistically from each other.

DISCUSSION

Perinatal photoperiod treatment altered immunological responses to day length in adulthood, but these immunological effects were dissociated from photoperiod-induced changes in the reproductive system. Hamsters of both sexes held in SDs throughout the experiment (SD-SD) displayed stronger cell-mediated immune responses relative to all other groups. Adult photoperiod evoked more modest changes in DTH responses.

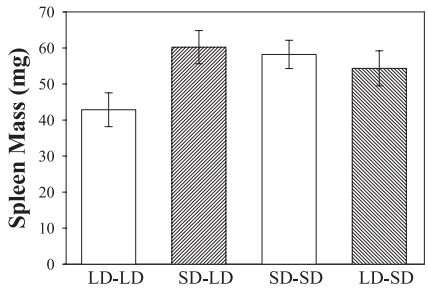

Fig. 3. Perinatal but not postweaning photoperiod affects spleen mass (mg; means ± SE) of male and female *P. sungorus*. SD-SD and SD-LD groups significantly different from LD-LD and LD-SD: $P < 0.05$.

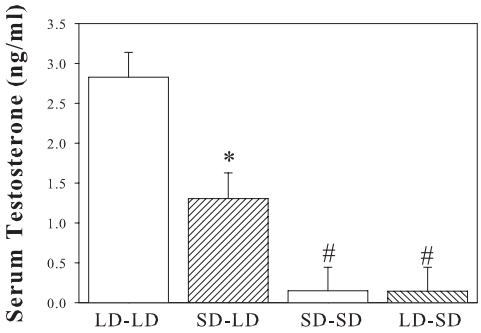

Fig. 4. Perinatal and postweaning photoperiods interact to affect serum testosterone concentrations. Means (±SE) are shown of serum testosterone of male *P. sungorus* (ng/ml). *Significantly different from LD-LD, #significantly different from LD-LD and SD-LD groups: $P < 0.05$.

Reproductive tissue masses, on the other hand, were affected exclusively by adult photoperiod. No persistent effects of perinatal photoperiod were detected on reproductive tissues, even though testosterone was markedly decreased and reproductive development was inhibited (as indicated by smaller testis length at weaning) in male hamsters housed in SDs perinatally.

This experiment was designed to determine whether or not the immune system was attending to perinatal photoperiod cues, even after extended housing in a different photoperiod after weaning. Enhanced DTH responses alone are not necessarily indicative of some global increase in "immunocompetence." Assays of other aspects of the immune system would be necessary to determine whether this effect is generalizable. However, it is clear from the data here that the specific immunological processes involved in producing the DTH response are permanently altered by perinatal day lengths. However, the DTH response is not without meaning, as it incorporates immunological memory, cell proliferation, antigen presentation, leukocyte trafficking, and inflammatory processes into an integrative measure. DTH responses are associated with resistance to bacteria, fungi, and viruses (9).

Photoperiodic conditions early in life and in adulthood can be conceptualized as having organizational and activational effects on the immune system, respectively (23). In the present study, SDs early in life were necessary for the expression of SD-induced enhancement of immune function. However, perinatal SD lengths were not sufficient to elevate DTH responses in LD hamsters. These results are reminiscent of the effects of testosterone on male mating behavior in rats. That is, testosterone early in life is necessary to organize the neural substrate on which testosterone in adulthood can activate the neural circuits associated with mating (13).

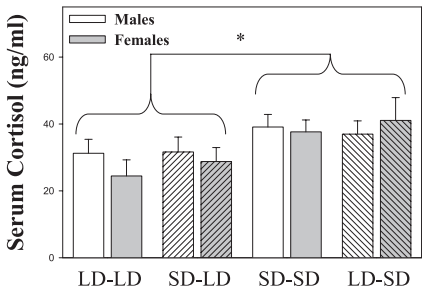

Fig. 5. Hamsters housed in SDs after weaning had significantly higher serum cortisol (means ± SE) concentrations than the hamsters housed in LDs after weaning. This effect was not modulated by perinatal photoperiod. Shaded bars indicate females, and hatched bars indicate hamsters transferred from their perinatal photoperiod into the opposite day length at weaning. *Hamsters in SD perinatally have significantly higher cortisol concentrations than animals in LD perinatally: $P < 0.05$.

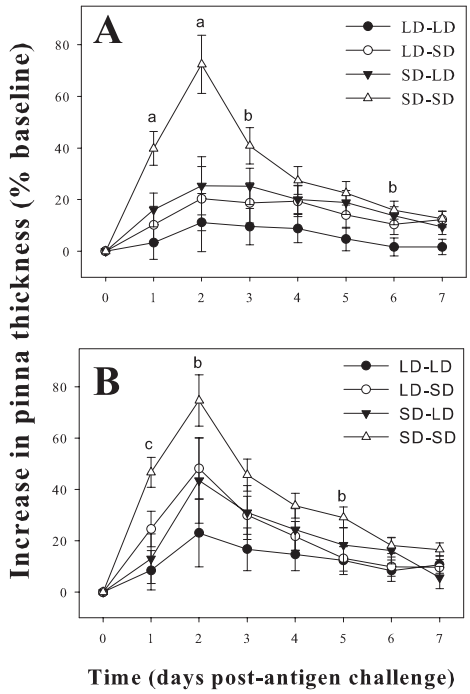

Fig. 6. Exposure to SDs both perinatally and postweaning enhances delayed-type hypersensitivity responses (means ± SE expressed as a percentage increase in pinna thickness) for male (*A*) and female (*B*) *P. sungorus*. [a]SD-SD significantly greater than all other groups, [b]SD-SD group significantly greater than LD-LD group, [c]SD-SD significantly different from LD-LD and LD-SD: $P < 0.05$.

The critical photoperiod information encoded by hamsters in this study was likely communicated during prenatal development. Transfer of photoperiod information occurs prenatally via the maternal melatonin rhythm. Pinealectomy abolishes prenatal photoperiodic effects on reproductive development (16), and cross-fostering experiments have revealed that pups respond to the photoperiod of birth, rather than the photoperiod experienced by the foster dam (14). Siberian hamster pups are responsive to maternal melatonin infusions in utero during the period between ~6 and 2 days before birth (34). Following birth, pups are unable to produce melatonin in response to photoperiod information until ~15 days of age (36). Gonadal responses to postnatal photoperiods first occur at ~20 days (35). Taken together, these results suggest that maternal melatonin rhythm in utero is responsible for programming the immunological differences detected in adulthood. Early exposure to long-duration melatonin signal may be the proximate mediator of the effect of early day lengths on adult immune function. In support of this interpretation, melatonin treatment of turkeys (*Meleagris gallopavo*) in ovo enhanced both cell-mediated and humoral immune function in juveniles (20). Furthermore, pinealectomy of neonatal rats reduced adult expression of antibody-dependent cellular cytotoxicity (33) and slowed cutaneous wound healing; these effects were reversed by melatonin administration (1).

At an ultimate level of explanation, energetic trade-offs between reproductive development and immune function are likely to underlie the photoperiod-induced differences in immune function in this study. Day length is an important proximate cue that hamsters use to prioritize these physiological processes. SD lengths early in life can delay the onset of puberty until the subsequent breeding season. Hamsters born in SDs become refractory to day length and undergo reproductive development after ~25 wk. This interval is well within the treatment duration used in this study. Taken together, this would suggest that animals held in SDs perinatally delayed reproductive development. Subsequently, this interpretation means that SD-LD animals were stimulated to develop, whereas SD-SD animals remained inhibited by SD lengths throughout the experiment. Animals in LD lengths, on the other hand, underwent rapid reproductive development, as indicated by testes size at weaning. This gonadal growth was then arrested in the LD-SD group by transfer to SDs. These data suggest that the SD-SD hamsters had not experienced any stimulatory effects of day length on their reproductive systems. This delay in sexual maturation may serve as a possible proximate cause of the enhanced immune function in the SD-SD group. Growth and maintenance of tissue is expensive and often incompatible with maximum investment in immune function (18). Furthermore, induction of fever at 20 days of age attenuated pubertal development in Siberian hamsters in LD (26).

One of the major downstream targets of photoperiod (via the effects of melatonin) is the HPG axis. SDs reduce circulating gonadotrophins and arrest both spermatogenesis and steroidogenesis in the testes (22, 32). Although testosterone was elevated in hamsters maintained in LD lengths and is often considered immunosuppressive (17), sex steroid hormones are unlikely to account for group differences in immune function in this study, at least in an activational sense. Previous studies indicate that testosterone did not inhibit DTH responses in SD hamsters (24); indeed, sex steroid administration enhanced antibody production and lymphocyte proliferation in gonadectomized hamsters (5). However, the possibility that photoperiod-induced alterations in androgen exposure may have contributed to the differences in adult immune function cannot be ruled out.

Another possible effector system that is modulated by melatonin is the hypothalamic-pituitary-adrenal (HPA) axis. HPA reactivity alters immune responses (19), and adult Siberian hamsters have elevated basal and stress-induced cortisol concentrations in SDs relative to LDs. Stress immediately before challenge enhances DTH responses in mice (8), and SD lengths augment the enhancement of the DTH responses in hamsters (2). In the present study, basal cortisol concentrations were higher in hamsters housed in SDs as adults, regardless of perinatal photoperiod treatment or sex. Therefore, adult cortisol concentrations cannot directly explain differences in DTH responses between LD-SD and SD-SD groups. However, differences in HPA activity cannot be completely ruled out; cortisol concentrations may have differed during other developmental periods. Also, it is possible that circadian regulation or HPA reactivity to stressors was altered by perinatal photoperiod treatment (30). The regulation of the HPA axis and its effects on immune function in this paradigm deserve future attention.

This study is the first to our knowledge to demonstrate SD enhancements of immune function in female Siberian hamsters. Previous studies reported that DTH responses in restrained female hamsters were higher in SD compared with LD, but no differences between unstressed groups were detected (4). However, SD-SD hamsters significantly enhanced DTH responses in the present study relative to all other groups, providing further evidence that the age of photoperiod treatment is critical to determining immunological outcomes.

Hamsters housed in SDs perinatally and then transferred to LDs at weaning had significantly higher circulating testosterone concentrations compared with hamsters in LDs, both perinatally and postweaning. This occurred without detectable differences in testes mass. This suggests that perinatal exposure to SDs alters the set point for androgen concentrations. This effect is likely mediated via alterations in either hypothalamic gonadotropin-releasing hormone signaling, steroid negative feedback, or the Leydig cells themselves. Future studies will address both the proximate mediators of this phenomenon, as well as the behavioral and physiological sequelae of alterations in androgen exposure. In addition, the possible effects of perinatal exposure to SDs on female estrous cycles and fertility will also be addressed.

Immune responses in the other three photoperiodic groups (not including SD-SD) did not differ statistically from one another. Hamsters in SDs, either perinatally or as adults, exhibited numerically larger responses compared with hamsters in LDs throughout their lives (LD-LD). However, several previous studies have shown enhanced DTH responses in SDs relative to LDs when the animals were born in LDs and only transferred after reaching adulthood (e.g., Refs. 2–4). Hamsters in SDs as adults in this study exhibited DTH responses comparable to those of the SD-SD hamsters in other studies. Although it is possible that variations in experimental procedures are responsible for this discrepancy, it is more likely that the age of animals at which time the photoperiod transfer was made [~55 days previously (2, 24), 21 days in this experiment] affected subsequent immunological responsiveness to day length. These data suggest that exposure to LD through puberty enhances SD-induced augmentation of immune function.

This study demonstrated enhanced immune function in animals kept in SD throughout their lives relative to all other groups. This effect was not complementary of reproductive changes induced by photoperiod, as the perinatal effects on the reproductive system had, for the most part, been resolved by the end of the experiment. Photoperiod early in life regulates both reproductive and immunological responses to day length in adulthood. SD exposure both perinatally and in adulthood was necessary but not sufficient to induce increases in DTH responses. Taken together, these data suggest that early-life photoperiod can have important organizational effects on subsequent immunological responses to day length.

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