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Sympathoadrenal System Differentially Affects Photoperiodic Changes in Humoral Immunity of Siberian Hamsters (*Phodopus sungorus*)

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Abstract

Siberian hamsters (*Phodopus sungorus*) rely on photoperiod as a primary cue to coordinate seasonally appropriate changes in physiology and behaviour. Among these seasonal changes is reduced immune function in short 'winter-like' days, compared to long 'summer-like' days. Previous evidence suggests that immune function is regulated, in part, by the sympathoadrenal system. The precise role of the sympathoadrenal system in regulating photoperiodic changes in immune function, however, remains unspecified. The goal of the present study was to examine the differential contributions of direct sympathetic innervation of immune target tissue, as well as adrenal medullary catecholamines, to photoperiodic changes in immune function in male Siberian hamsters. In Experiment 1, hamsters underwent either bilateral surgical removal of the adrenal medulla (ADMEDx), or sham surgeries, and were maintained in long (LD 16 : 8) or short days (LD 8 : 16). In Experiment 2, hamsters received either surgical denervation of the spleen, or sham surgeries, and were then housed in long or short days. Serum anti-KLH IgG concentrations and splenic norepinephrine (NE) content were determined in both experiments. Short-day hamsters had reduced humoral immunity compared to long-day hamsters. ADMEDx reduced immune function, but only in long-day hamsters. In contrast, splenic denervation reduced humoral immunity, but only in short-day hamsters. Splenic NE content was increased in short days and by ADMEDx. NE content was markedly reduced in denervated hamsters compared to sham-operated hamsters. Collectively, these results suggest that the sympathoadrenal system is associated with photoperiodic changes in immune function.

In addition to marked seasonal changes in reproductive, metabolic, and other physiological processes, many mammalian and nonmammalian species undergo seasonal changes in immune function and disease (1–3). Field studies of seasonal changes in immunity typically report reduced immune function and increased disease susceptibility during winter compared to spring and summer (4–7). In addition, laboratory studies have documented photoperiodic changes in immune function for several rodent species, including deer mice (*Peromyscus maniculatus*) (8) and prairie voles (*Microtus ochrogaster*) (9), as well as Syrian (*Mesocricetus auratus*) (10) and Siberian (*Phodopus sungorus*) (11, 12) hamsters. In contrast to field studies, some species (e.g. deer mice, Syrian hamsters), display *enhanced* immune function in days with a short 'winter-like' length compared to long 'summer-like' days. In other species (e.g. Siberian hamsters, prairie voles), however, some aspects of immune function are suppressed in short days, in accordance with the majority of field studies. It is currently not known why rodent species differ in their immune responses to

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short days in the laboratory, but these differences are probably due to differences in the environments in which these animals evolved. For example, seasonal changes in immune function are due, in part, to environmental factors (e.g. ambient temperature, food availability) that fluctuate on a seasonal basis (2).

Siberian hamsters (*Phodopus sungorus*) display reductions in several humoral and cell-mediated immune parameters in short compared to long days (11, 12). Despite the growing evidence for photoperiodic changes in immune function, the precise neuroendocrine mechanisms mediating these changes have not been fully characterized. Recent evidence however, suggests that the sympathoadrenal system may play an important role in photoperiodic changes in immune function. The primary function of the sympathoadrenal system is to maintain homeostasis; disruption of homeostatic balance leads to activation of the hypothalamic-pituitary-adrenal (HPA) axis, as well as the sympathetic nervous system (SNS). Activation of the HPA axis in response to stress, and the subsequent release of glucocorticoids (e.g. corticosterone, cortisol) by the adrenal cortex triggers a wide range of physiological responses including suppression of virtually all aspects of immune function (reviewed in 13). Glucocorticoids, however, are only one of several classes of hormones that affect immunity. For example, because of the rather extensive literature demonstrating suppression of immunity by glucocorticoids, as well as the robust effects of these hormones on immune function, sympathoadrenal contributions to immune regulation have been largely overlooked.

Recent evidence suggests that a wide range of environmental and intrinsic factors, including changes in photoperiod, activate the sympathoadrenal system, leading to the release of catecholamines and subsequent suppression of immune function (14). Catacholamines, primarily epinephrine (EPI) released from the adrenal medulla in an endocrine fashion, and norepinephrine (NE) released from nerves directly innervating lymphoid tissue, have profound effects on both humoral and cell-mediated immunity (15–17). Furthermore, the actions of these substances on immunity appear to be direct; adrenergic receptors have been localized on lymphoid tissue (14) and both NE and EPI can alter immune function *in vitro* (16, 18, 19).

A substantial amount of physiological and neuroanatomical evidence has accumulated in support of the direct innervation of lymphoid tissue by the SNS (reviewed in 17). The presence of noradrenergic fibers has been identified in several lymphoid organs (e.g. thymus, spleen, bone marrow) of virtually all species examined using traditional histofluorescence and tract tracing (20–22). Furthermore, SNS innervation appears to play a *functional* role in mediating immune function; surgical or chemical denervation of lymphoid tissue alters both humoral and cell-mediated immunity (14, 17).

Another possible mechanism of action of the sympathoadrenal system to affect immune function is through activation of the adrenal medulla and the subsequent release of catecholamines, primarily EPI, into the bloodstream. Both *in vitro* and *in vivo* EPI administration can exert marked effects on several indices of immune function (16). Despite the robust effects of EPI on immunity, no studies published to date have tested the specific, *functional* role of the adrenal medulla (the primary source of EPI) in mediating immune responses. Furthermore, despite robust photoperiodic changes in the sympathoadrenal system, virtually nothing is known regarding the role of catecholamines in mediating seasonal changes in immune function.

Recently, direct SNS innervation of the spleen has been demonstrated in Siberian hamsters using the retrograde transneuronal tract tracer pseudorabies virus (PRV) (23). Specifically, PRV injected into spleens of Siberian hamsters revealed infected neurones in areas traditionally implicated in SNS regulation (e.g. the A5 and C1 noradrenergic cells groups and the locus coeruleus of the brainstem). Infected neurones were also seen in the paraventricular (PVN) and suprachiasmatic nuclei (SCN) of the hypothalamus (23), brain regions involved in transduction of the photoperiodic signal. These results indicate that the SNS directly innervates lymphoid tissue in Siberian hamsters and that this innervation may play a functional role in regulating photoperiodic changes in immune function in this species. For example, previous research has demonstrated photoperiodic changes in SNS activity in a variety of peripheral tissues in both Syrian and Siberian hamsters (24, 25). The precise role of the sympathoadrenal system in photoperiodic changes in immune function, however, remains unknown. The goal of the present experiment was to test the relative contributions of adrenal medullary catecholamines and the direct sympathetic innervation of the spleen in mediating photoperiodic changes in humoral immunity of Siberian hamsters.

Materials and methods

Animals and housing conditions

Adult (>60 days of age) male Siberian hamsters (*Phodopus sungorus*) were obtained from our laboratory breeding colony at Georgia State University, Georgia, USA. This colony was originally derived from stock hamsters supplied by Dr Bruce Goldman (University of Connecticut, Connecticut, USA) in 1988 and interbred with wild-trapped hamsters in 1990 from Dr Katherine Wynne-Edwards (Queens University, Kingston, Ontario, Canada). Hamsters were weaned at 21 days of age and housed with same sex siblings. Two weeks prior to initiation of the experiments, hamsters were housed individually in polypropylene cages ($27.8 \times 7.5 \times 13.0$ cm) in colony rooms with a 24 h LD 16 : 8 cycle (lights on 0300 h EST). Temperature was kept constant at 20 °C and relative humidity was maintained at $50 \pm 5\%$. Food (Purina Rat Chow) and tap water were available *ad libitum* throughout the experiment.

Experiment 1: Role of the adrenal medulla

The goal of experiment 1 was to assess the role of adrenal medullary catecholamines on photoperiodic changes in humoral immunity in Siberian hamsters. Hamsters ($n=50$) were selected randomly and assigned to either long (LD 16:8) ($n=20$) or short days (LD 8:16) ($n=30$). Half of the hamsters in each photoperiodic condition received bilateral adrenal demedullations (ADMEDx), while the remaining hamsters received sham demedullations. ADMEDx was performed according to a modification of the method described in (26), while the hamsters were anaesthetized with sodium pentobarbital (50 mg/kg). Briefly, bilateral incisions were made on the dorsum over the kidneys and the adrenal glands were visualized using a dissecting microscope. A small incision was made on the adrenal cortex and the adrenal medulla was extirpated using minimal pressure. Every effort was made to leave the adrenal cortex intact. The remaining adrenal tissue was removed and analysed for EPI content by HPLC at the end of the experiment. Hamsters with adrenal EPI concentrations >0.05 ng/mg were excluded as they were considered to represent incomplete ADMEDx (see below for HPLC methodology).

Hamsters were maintained in their respective photoperiods for 10 weeks. At this time, all hamsters received a single subcutaneous injection of 100 μg of antigen keyhole limpet haemocyanin (KLH), suspended in 0.1 mL sterile saline (Day 0) and were then returned to the colony room. KLH is an innocuous respiratory protein derived from the giant keyhole limpet (*Megathura crenulata*). KLH was used to generate a robust antigenic response without making the hamsters ill (e.g. inflammation or fever). All hamsters were naive to KLH and therefore mounted a primary antibody response to this antigen. Blood was drawn from the retro-orbital sinus at two different sampling periods (days 5 and 10 postimmunization). These sampling periods were chosen in order to capture peak IgG production during the course of the immune response to KLH (27). On each sampling day, hamsters were brought into the surgery room individually, lightly anaesthetized with methoxyflurane vapours (Metofane, Mundelein, IL, USA), and blood samples (500 μL) were drawn between 1.00 hours and 12.00 hours EST. Samples were allowed to clot for 1 h, the clots were removed, and the samples centrifuged (at 4 °C) for 30 min at 5000 ***g***. Serum aliquots were aspirated and stored in sealable polypropylene microcentrifuge tubes at −80 °C until assayed for IgG. On the last day of sampling (Day 10), hamsters were killed by cervical dislocation. Paired testes and spleens were removed and cleaned of connective tissue at ecropsy. Laboratory assistants who were naive to the experimental hypotheses and treatment assignments weighed all tissues to the nearest 0.1 mg.

Experiment 2: Role of direct SNS innervation of the spleen

The goal of experiment 2 was to assess the role of sympathetic nerves directly innervating the spleen on photoperiodic changes in humoral immunity in Siberian hamsters. Hamsters ($n=50$) were selected randomly and assigned to either long ($n=20$) or short days ($n=30$). Half of the hamsters in each photoperiodic condition received surgical denervation of the spleen according to the method described in (23) modified from (28), whereas the remaining hamsters received sham denervations. Briefly, a small incision was made on the left dorsal surface of the hamster. The underlying musculature was cut, the spleen was visualized and carefully inverted. The splenic nerve bundle innervating the spleen was identified under a dissecting microscope and carefully teased away from the nearby vasculature. Every effort was made to leave the blood vessels intact. The nerve was cut in two locations with a pair of microscissors; the spleen was irrigated with sterile 0.9% saline, and returned to the body cavity. The muscle layer was then sutured and the skin was closed and nitrofurozone antibacterial powder was applied to the incision. Hamsters were allowed to recover from surgery for 2 weeks and then transferred to their respective photoperiods. Hamsters were then maintained in their respective photoperiods for 10 weeks. At this time, all hamsters received a single *s.c.* injection of 100 μg of KLH as described in Experiment 1.

HPLC determination of catecholamine content

Splenic NE content was determined by reverse-phase high pressure liquid chromatography with electrochemical detection (HPLC-EC) according to the method described in (29), after (30). Briefly, tissue was thawed, weighed and carefully minced. A 250 mg sample was added to 1 mL of 0.3 M perchloric acid in microcentrifuge tubes and 10 μl of dihydroxybenzoacetic acid (DHBA) was added to each sample and served as an internal standard. Tissue was minced further and then sonicated for 5 min on ice (5× for each sample). Catecholamines were extracted from the remaining infranatant using alumina (200 mg/sample). The extracted samples were assayed using an ESA (Chelmsford, MA) HPLC system with electrochemical detection (guard cell: +35 mV; cell 1: +10 mV; cell 2: −30 mV). The mobile phase was Cat-A-Phase II purchased from a commercial supplier (ESA, Inc., Chelmsford, MA, USA). Standard solutions were prepared from commercially supplied standard kit (ESA, Inc.) and were run at the beginning, in the middle and at the end of the sets of unknown. Assay results were analysed offline and expressed as ng/g tissue.

Immunoglobulin G ELISA

Humoral immunity was assessed separately for Day 5 and Day 10 serum samples by measuring serum anti-KLH IgG concentrations using an enzyme-linked immunosorbent assay (ELISA). Microtitre plates were coated with antigen, incubated overnight at 4 °C with 0.5 mg/mL KLH in sodium bicarbonate buffer (pH = 9.6), washed with phosphate buffered saline (PBS; pH = 7.4) containing 0.05% Tween 20 (PBS-T; pH = 7.4), then blocked with 5% nonfat dry milk in PBS-T overnight at 4 °C to reduce nonspecific binding, and washed again with PBS-T. Thawed serum samples were diluted 1 : 20 with PBS-T, and 300 μL of each serum dilution was added in duplicate to the wells of the antigen-coated plates. Positive control samples (pooled sera from hamsters previously determined to have high levels of anti-KLH antibody, similarly diluted with PBS-T) and negative control samples (pooled sera from KLH-naive hamsters, similarly diluted with PBS-T) were also added in duplicate to each plate; plates were sealed, incubated at 37 °C for 3 h, then washed with PBS-T. Secondary antibody (alkaline phosphatase-conjugated-antimouse IgG diluted 1 : 100 with PBS-T; Cappel, Durham, NC, USA) was added to the wells, and the plates were sealed and incubated for 1 h at 37 °C. Plates were washed again with PBS-T and 150 μL of the enzyme substrate p-nitrophenyl phosphate (Sigma Chemical, St Louis, MI, USA: 1 mg/mL in diethanolamine substrate buffer) was added to each well. Plates were protected from light during the enzyme-substrate reaction, which was terminated after 20 min by adding 50 μL of 1.5 M NaOH to each well. The optical density (OD) of each well was determined using a plate reader (Bio-Rad Benchmark; Richmond, CA, USA) equipped with a 405-nm wavelength filter, and the mean OD for each set of duplicate wells was calculated. To minimize intra-assay variability for statistical analyses, the mean OD for each sample was expressed as a percent of its plate-positive control OD. The mean absorbance values for the positive control were 1.44 nm and 1.22 nm for experiment 2. Intra-assay variability was < 8% for both experiments.

Statistical Analyses

Differences between experimental conditions in Experiments 1 and 2 were assessed via separate 2 (photoperiod) × 2 (surgery) between-groups analyses of variance (ANOVAS). *Post hoc* comparisons between pair-wise means were conducted using Tukey-HSD tests when the overall ANOVAS were significant. In all cases, differences between group means were considered statistically significant if $P < 0.05$.

Results

Experiment 1

Short-day housed hamsters had significantly smaller body and paired testes masses, but larger splenic masses, compared to long-day hamsters ($P < 0.05$ in all cases) (Table 1). ADMEDx, however, had no effect on body, paired testes or splenic masses in either photoperiod ($P > 0.05$ in both cases) (Table 1). Short-day housed hamsters had significantly increased splenic NE content compared to long-day hamsters ($P < 0.05$) (Fig. 1). ADMEDx also significantly increased splenic NE content, compared to sham surgeries ($P < 0.05$).

TABLE 1. Mean (±SEM) body, paired testes, and splenic masses of long-day (LD) or short-day (SD) housed hamsters receiving bilateral adrenal demedullations (ADMEDx), splenic denervations (Denervated), or sham surgeries (Sham). Statistically significant differences between pair-wise means are indicated by an asterisk (*) at < 0.05.

	Body mass (g)	Testes mass (mg)	Splenic mass (mg)
Experiment 1			
LD/ADMEDx	47.18 ± 1.07	789.0 ± 37.1	208.0 ± 10.5
LD/Sham	49.98 ± 1.18	887.0 ± 55.5	185.0 ± 12.9
SD/ADMEDx	39.53 ± 1.58*	215.0 ± 59.7*	259.0 ± 4.5*
SD/Sham	42.62 ± 1.68*	135.0 ± 33.7*	259.0 ± 6.3*
Experiment 2			
LD/Denervated	40.24 ± 4.95	883.0 ± 72.6	206.0 ± 7.8
LD/Sham	40.12 ± 4.29	917.0 ± 42.1	194.0 ± 9.4
SD/Denervated	36.49 ± 2.91*	314.0 ± 96.0*	237.0 ± 9.8*
SD/Sham	35.12 ± 1.36*	148.0 ± 71.8*	242.0 ± 10.7*

Serum anti-KLH IgG concentrations were significantly reduced in short- compared to long-day hamsters ($P<0.05$) (Fig. 2). ADMEDx also significantly reduced IgG compared to sham surgeries, but only in long-day hamsters ($P<0.05$). The absorbance values were 1.27 ± 0.10 nm for long-day sham hamsters and 0.89 ± 0.11 nm for long-day ADMEDx hamsters, respectively. Serum IgG concentrations were unaffected by ADMEDx in short-day housed hamsters ($P>0.05$) (Fig. 2). The absorbance values were 1.07 ± 0.08 nm for short-day sham hamsters and 0.79 ± 0.08 nm for short-day ADMEDx hamsters, respectively.

Experiment 2

As in experiment 1, short-day housed hamsters had significantly smaller body and paired testes masses, but significantly larger splenic masses, compared to long-day housed hamsters ($P<0.05$ in all cases) (Table 1). Surgical denervation had no effect on body, paired testes, or splenic masses in either photoperiod ($P>0.05$ in all cases) (Table 1). Short-day hamsters also had significantly increased splenic NE content compared to long-day hamsters ($P<0.05$) (Fig. 3). Surgical denervation of the spleen dramatically

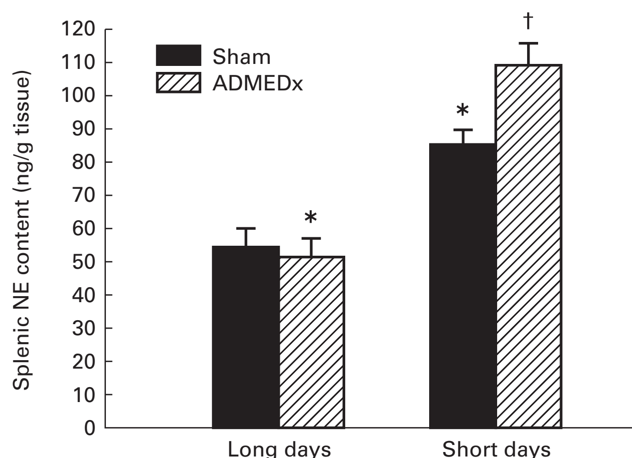

Fig. 1. Mean (±SEM) splenic norepinephrine (NE) content of hamsters housed in long or short days and receiving either adrenal demedullations (ADMEDx) or sham (Sham) surgeries. Columns with no symbol, or sharing the same symbol, are statistically equivalent. Columns with different symbols are significantly different at $P<0.05$.

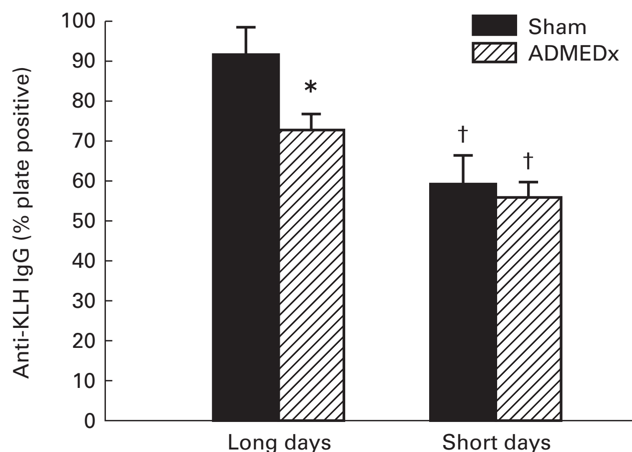

Fig. 2. Mean (±SEM) serum IgG concentrations (% plate-positive) of hamsters housed in long or short days and receiving either adrenal demedullations (ADMEDx) or sham (Sham) surgeries. Columns with no symbol, or sharing the same symbol, are statistically equivalent. Columns with different symbols are significantly different at $P<0.05$.

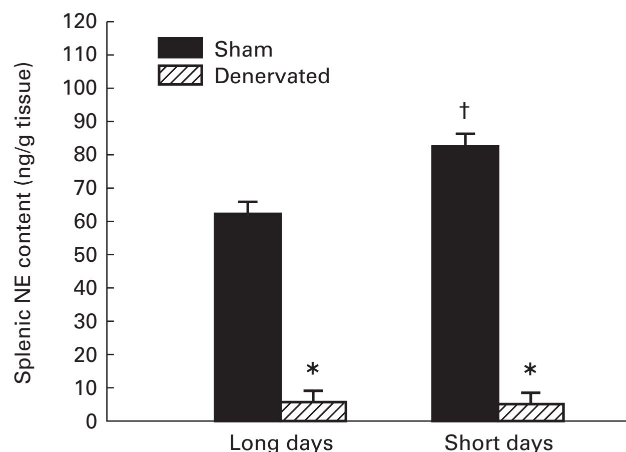

Fig. 3. Mean (±SEM) splenic norepinephrine (NE) content of hamsters housed in long or short days and receiving either surgical denervations of the spleen (Denervated) or sham surgeries (Sham). Columns with no symbol, or sharing the same symbol, are statistically equivalent. Columns with different symbols are significantly different at $P<0.05$.

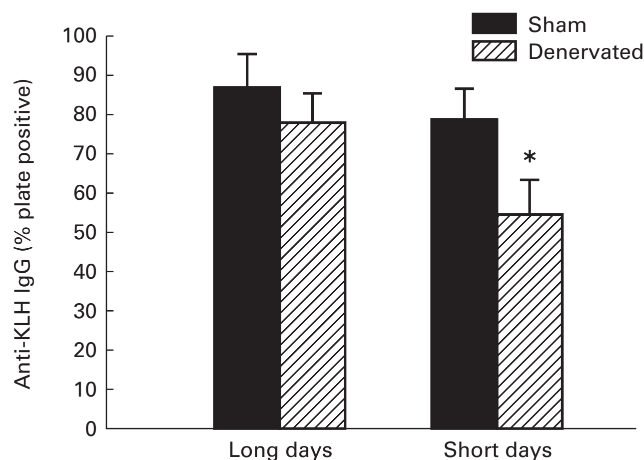

Fig. 4. Mean (±SEM) serum IgG concentrations (% plate-positive) of hamsters housed in long or short days and receiving either surgical denervations of the spleen (Denervated) or sham surgeries (Sham). Columns with no symbol, or sharing the same symbol, are statistically equivalent. Columns with different symbols are significantly different at $P<0.05$.

reduced splenic NE content compared to hamsters receiving sham denervations ($P < 0.05$) (Fig. 3).

Unlike experiment 1, there were no significant differences in serum IgG concentrations between long- and short-day-housed hamsters ($P > 0.05$) (Fig. 4), although there was a nonsignificant trend towards reduced IgG in short- compared to long-day-housed hamsters. Hamsters receiving surgical denervations of the spleen had reduced serum IgG compared to sham-denervated hamsters, but only when housed in short days ($P < 0.05$). The absorbance values were 0.90 ± 0.09 for short-day sham hamsters and 0.65 ± 10 for short-day denervated hamsters, respectively. Denervated hamsters maintained in long days had comparable serum IgG concentrations to long-day, sham-denervated hamsters (Fig. 4). The absorbance values were 1.06 ± 0.09 nm for long-day sham hamsters and 0.96 ± 0.08 nm for long-day denervated hamsters, respectively.

Discussion

The present data support previous studies demonstrating short-day decreases in immune function (11, 12) and provide the first demonstration that the sympathoadrenal system is involved in photoperiodic changes in humoral immunity in Siberian hamsters. Additionally, these results suggest that direct innervation of the spleen and adrenal medullary catecholamines *differentially* affect photoperiodic changes in immune function. Specifically, adrenal demedullation reduced immune function in long-, but not short-day-housed hamsters; alternately, surgical denervation of the spleen reduced immune function in short but not long days. Collectively, the present results suggest that the sympathoadrenal system interacts with photoperiodic changes in immune function with adrenal medullary catecholamines playing a greater role in humoral immunity of long-day hamsters, and direct SNS innervation of the spleen more involved in mediating humoral immunity of short-day hamsters.

Recent preliminary data from our laboratory support the idea of photoperiod-dependent effects of the sympathoadrenal system on immunity in Siberian hamsters. Specifically, whole-blood lymphocyte proliferation, a test of cell-mediated immunity, was suppressed by the addition of NE *in vitro* in short-, but not long-day hamsters (31).

An increasing amount of evidence demonstrates an important role for the sympathoadrenal system in the regulation of immunity (14–16). For example, an inhibitory role of the SNS in the regulation of immune function has been suggested in several species following denervation of a variety of lymphoid tissue (14). Specifically, global chemical denervation of adult animals via systemic injections of 6-hydroxy-dopamine (6-OHDA), enhances antibody responses to T-independent antigens, but has no effect on T-independent antibody production (32). In contrast, it has also been reported that 6-OHDA-induced denervation *reduces* antibody responses to T-dependent antigens in adult rats (33, 34), whereas surgical denervation of the splenic nerve *enhances* antibody production in neonatal animals (28, 35). More recently it has been demonstrated that chemical denervation results in a modest increase in anti-KLH antibody production in young rats, but a more marked increase in antibodies in older animals (36). These results suggest that the effects of the sympathoadrenal system on immune function depend on several factors, including the age of the animals, the type of denervation, as well as the type of immune response measured. It is important to note that the chemical denervation technique used in some of the cited studies (i.e. systemic injections of 6-OHDA) results in a global SNS denervation throughout the entire animal; subsequent changes in immunity may be the indirect result of disruptions in other physiological systems. Thus, extrapolation of the results of these previous studies is limited. Surgical denervation of the spleen utilized in the present study, however, allows the *tissue-specific* effects of SNS innervation on immune function to be evaluated. Surgical denervation, in contrast, has the disadvantage of destroying not only SNS nerves, but also parasympathetic (PNS) and sensory nerves because they are virtually indistinguishable from SNS nerves at the light microscopic level. Thus, although the results of the present study suggest a role of SNS nerves in the regulation of photoperiodic changes in immune function, future studies are needed to evaluate the relative contributions of SNS and sensory innervation. It is possible that some of the effects reported in the present study are due to changes in PNS activity, although this is unlikely. Unlike other lymphoid tissue, the majority (>98%) of the nerves innervating the spleen are sympathetic in origin; the spleen appears to receive very little innervation from the PNS (17).

The lack of a substantial effect by either adrenal demedullation on immune function in short-day hamsters or sympathetic denervation of the spleen on immune function in long-day hamsters suggests that *both* adrenal medullary catecholamines *and* sympathetic innervation of the spleen are involved in photoperiodic changes in immune function in Siberian hamsters. One possible explanation for the differential effects by these experimental manipulations on immune function is that the loss of one branch of the sympathoadrenal system could result in compensation by the remaining, intact branch. Evidence for this exists in other physiological systems. For example, there is a significant increase in the NE content of neurally intact white adipose tissue in ADMEDx hamsters compared with their sham-operated counterparts (37). The results of the present study also support this, in that splenic NE is significantly increased in ADMEDx hamsters compared to sham-operated hamsters.

Although the underlying cause of the increase in NE cannot be determined in the present study, it seems likely to be due to increased SNS activity, based on the typical increase in NE content that normally is coupled with an increase in NE turnover. Moreover, NE turnover is increased in the pancreas after ADMEDx, and EPI turnover is increased in the adrenal gland after systemic chemical denervation produced by 6-OHDA (38). Thus, compensation by the remaining intact system may alter the effects of either splenic denervation or ADMEDx alone. Future studies in which animals receive *combined* ADMEDx *and* splenic denervations will address this. It is important to note that the interpretation of the splenic denervation data are complicated by the fact that the effects of photoperiod on humoral immunity did not

reach statistical significance in Experiment 2. It is possible that some of the differential effects of splenic denervation on humoral immunity of long- and short-day hamsters may be due to the lack of a significant main effect of photoperiod in this experiment. Thus, although the results of Experiment 2 are consistent with those of Experiment 1, suggesting differential effects of the sympathoadrenal system on photoperiodic changes in humoral immunity, these results should be interpreted cautiously *in lieu* of the lack of an effect of photoperiod on immunity in Experiment 2.

Regardless of the precise mechanisms, the results of the present study demonstrate that the sympathoadrenal system plays an important role in photoperiodic changes in immune function in Siberian hamsters and that adrenal medullary catecholamines and SNS innervation of lymphoid tissue differentially affect immune function in long and short days. Collectively, these results support the notion that the two arms of the SNS (i.e. direct innervation of lymphoid tissue and adrenal medullary catecholamines) appear to work in a coordinated manner to regulate photoperiodic changes in humoral immune function in Siberian hamsters, and possibly other species. Additionally, these data provide novel and important insights into the neuroendocrine mechansims underlying environmentally induced fluctuations in humoral immunity.

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