Environmental conditions influence the onset and severity of illness and infection and may compromise survival. Energetically challenging conditions during winter may directly induce death through hypothermia, starvation, or shock. The ability to forecast and prepare for the arrival of challenging conditions associated with winter (e.g., low temperatures, decreased food) likely confers survival advantages. Siberian hamsters (*Phodopus sungorus*) stop reproduction and reduce body mass (~25%) during short, winter-like day lengths, resulting in energetic savings. Hamsters also increase circulating glucocorticoids and lymphocytes (e.g., T cells, NK cells), and exhibit enhanced antigen-specific delayed-type-hypersensitivity (DTH) responses in the skin during short days (SDs). We tested the hypothesis that Siberian hamsters use SD lengths to signal the onset of winter to mediate the energetic trade-offs among body mass, reproductive function, and immune function. Long-day (LD; 16 h light, 8 h dark) and SD (8 h light, 16 h dark) hamsters were either food restricted (25%) or provided ad libitum (ad lib) food for 4 wk; half of all hamsters in each food condition had voluntary access to a running wheel, and half remained sedentary. SD hamsters enhanced DTH responses compared with LD hamsters under sedentary ad lib conditions. Exercise enhanced DTH in LD hamsters regardless of food intake. Furthermore, food-restriction did not significantly influence DTH in LD hamsters. In contrast, food-restriction suppressed DTH in SD hamsters regardless of activity condition, and exercise modestly enhanced DTH only in SD hamsters with ad lib access to food. In sum, moderate energetic deficiency suppressed DTH in SD (but not LD) hamsters, and this suggests that hamsters may have evolved to enhance immune responses during winter in preparation for increased metabolic stressors. (*Endocrinology* 145: 556–564, 2004)

T HE IMMUNE SYSTEM requires significant energy to maintain its function; the onset and maintenance of inflammation and fever, and the production of humoral immune factors all require substantial energy (1–3). Animals have evolved mechanisms to maintain a balanced energy budget. Often, energy directed toward immune function must be balanced against competing activities such as reproduction, growth, and cellular maintenance (2, 4). Starvation or malnutrition often depresses immune function (3, 5–8). For many animals, a predictable energy shortage arrives each winter; low food availability often coincides with high thermoregulatory demands in low temperatures. Thus, energy availability for immune function waxes and wanes throughout the year.

Specific adaptations have evolved among animals to maximize energy conservation and prepare them for winter. Siberian hamsters (*Phodopus sungorus*) stop breeding during the winter by responding to photoperiodic cues that allow individuals to anticipate challenging conditions and prepare accordingly for them (9). Hamsters also undergo significant reductions of white adipose tissue and body mass (~25%) during the winter or when housed in short days (SDs) in the laboratory, despite ad libitum (ad lib) access to food and mild temperatures (10, 11). This strategy presumably evolved because maintenance of a smaller body size throughout winter requires less food and allows entrance into torpor, resulting in daily energetic savings (11).

Seasonal adjustments in immune function may also be critical for winter survival. Specific components of immune function are compromised in many species during the winter in the wild but are often enhanced in the laboratory during SD conditions when all other factors, such as food and temperature, are held constant (12–14). Hamsters increase circulating glucocorticoids, leukocytes, total lymphocytes, T cells, and NK cells and exhibit enhanced antigen-specific delayed-type-hypersensitivity (DTH) responses in the skin during SDs (15–17). Primary immune defense areas, such as the skin, lymph nodes, and gastrointestinal tract, represent the first line of bodily defense, and infection or injury is most likely to occur first in these peripheral areas (18). After antigenic challenge, the DTH immune reaction is characterized by inflammation at the site of challenge by an infiltration of monocytes and lymphocytes into the epidermis and dermis, and the physiological role of this system is to provide frontline defense against pathogens (19).

We hypothesized that photoperiod may provide a useful cue by which stressors in the environment are anticipated. Thus, SD hamsters may augment immune function in response to day length cues, before the onset of conditions that would subsequently suppress immune responses. To test this, we investigated the influence of food restriction (FR)
and voluntary running wheel exercise on a DTH response in long-day (LD) and SD hamsters. Food restriction and exercise represent ecologically valid metabolic stressors for this species; hamsters have evolved adaptations to limit food requirements coincident with the increased foraging difficulties during the SDs of winter. Moderate exercise has beneficial effects on immune function in animals and humans (20–22), although this has only been demonstrated under summer-like, LD-length conditions. In contrast, exercise without adequate nutrition or food intake often has deleterious effects on the ability to mount an immune response and increases the incidence of infectious disease (23). We hypothesized that DTH responses are energetically expensive, and that imposed energetic restrictions will consequently reduce DTH responses. If true, then FR, alone or in combination with exercise, should suppress DTH in SD hamsters, comparable with sedentary (SED) LD hamsters supplied with ad lib food.

Materials and Methods

Animals

Adult (4–6 months of age) male 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-Edward, Queen’s University. Animals were single-housed, from weaning, 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) (unless otherwise noted) and filtered tap water. On wk 0, 46 hamsters were housed in LD conditions with a reverse 16-h light, 8-h dark cycle [lights on at 2400 h, Eastern Standard Time (EST)], and 65 hamsters were housed in SD conditions with a reverse 8-h light, 16-h dark cycle [lights on at 0600 h, EST].

Blood sampling and reproductive measures

On wk 8 (d = 3 of experimental conditions), all hamsters were lightly anesthetized with isoflurane vapor (Abbott Laboratories, Chicago, IL) and rapidly (<2 min) bled from the retro-orbital sinus (0.2 ml) into collection tubes. Serum was used for later determination of baseline cortisol concentrations via RIA. Animals were bled in the approximate middle (∼1 h) of the inactive phase of the light-dark cycle for each respective photoperiod (0900–1100 h EST); this time period was based on a previous study that determined basal cortisol concentrations (15). All animals received injections of 0.5 ml sterile isotonic saline to prevent dehydration. Immediately after blood sampling, hamsters were assessed for reproductive response to photoperiod via external testis measurements. The length and width of the left testis were measured (∼0.1 mm). The product of (testis width) × (testis length) provides a measure of estimated testis volume (ETV) that is highly correlated with testis weight (24). Fifty-two males from the SD conditions had ETV values at least 2 standard deviations (SDs) above the mean and were considered reproductive responders to SDs; of these, 46 were randomly chosen for inclusion in the study.

Experimental conditions

Three days after reproductive assessment, 34 hamsters from each photoperiod were divided into one of four groups: 1) SED and ad lib access to food (SED) (n = 8); 2) voluntary wheel running exercise and ad lib access to food (n = 9); 3) SED and moderate FR (SED FR) (25%) (n = 8); or 4) voluntary wheel running exercise and moderate FR (running FR) (25%) (n = 9). Hamsters with voluntary access to running wheels were housed in polypropylene cages (43 × 19 × 24 cm) equipped with a metal, freely moving running wheel (17 cm in diameter). To confirm running, a radio-telemetric transmitter (Mini-Mitter, Sunriver, OR) was affixed to the edge of each running wheel, such that rotation of the wheel by the animal rotated the transmitter in a circular fashion. Cages were placed on TR-3000 receiver boards and connected to DP-24 DataPorts (Mini-Mitter) and a personal computer. Wheel running activity was recorded in 10-min bins as the transmitters rotated along with the wheel; any change in the signal strength from a transmitter was interpreted by the DataPort as an indication that the transmitter moved. Hamsters in SED conditions were housed in identical polypropylene cages that did not contain a RUN wheel. Differences in food-restricted hamsters were determined based on previous studies of average food intake in LD and SD Siberian hamsters (25, 26).

Activity controls. Activity data in the experimental animals provided information only on hamsters with access to a RUN wheel. Therefore, the remaining 12 hamsters in each photoperiod group were used to confirm that hamsters with access to RUN wheels were significantly more active overall than hamsters without access to RUN wheels. All hamsters were implanted with radio-telemetric transmitters (Mini-Mitter) under sodium pentobarbital anesthesia and allowed to recover for 7 d before subsequent procedures. Cages were placed on TR-3000 receiver boards and connected to DP-24 DataPorts and a personal computer as described above. Six hamsters in each photoperiod group were then placed in cages (identical with previous groups) with access to RUN wheels, and six hamsters were placed in cages without RUN wheels. Activity was recorded (10-min bins) as any change in the signal strength from a transmitter and was interpreted by the DataPort as an indication that the transmitter moved.

Experimental procedures

Hamsters were allowed to run voluntarily in wheels or remained SED for 4 wk (the duration of the study). Activity was continually recorded in RUN-wheel groups. Food intake was measured daily in all ad lib-fed groups; a premeasured quantity (g) of lab chow was delivered to each animal’s cage at the beginning of each week, and food was weighed each day thereafter to determine amount consumed. Hamsters in food-restricted groups were allowed to acclimate to cages for 3 d before the start of restriction. All SD hamsters were checked daily for the occurrence of torpor; no hamsters exhibited torpor at any time throughout the study. Blood samples (0.2 ml) were taken (<2 min) under light anesthesia via the retro-orbital sinus (0900–1100 h), on d 7 and 21 after the onset of experimental treatment conditions, to assess blood cortisol concentrations.

Induction of DTH. DTH was induced by application of the antigen, 2,4-dinitro-1-fluorobenzene (DNFB; Sigma, St. Louis, MO), to the pinnae of hamsters after initial immunization to the dorsum. On d 17 of exercise or SED conditions, all hamsters were lightly anesthetized, at 1000 h EST, with isoflurane vapor, and an area of approximately 2 × 3 cm was shaved on the dorsum. The shaved skin was swabbed with 70% alcohol, and 25 μl DNFB [0.5% (wt/vol) in 4:1, acetone-olive oil vehicle] was applied via pipet on d 17 and again on d 18. The thickness of both pinnae was measured on day 17, before sensitization, using a constant-loading digital micrometer (Mitutoyo, America Corp., Aurora, IL). Seven days post sensitization (d 24), baseline pinnae thickness was again measured. Next, 20 μl DNFB [0.2% (wt/vol) in 4:1, acetone-olive oil] was applied to the skin of the dorsal surface 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 thenext d 6, at 1000 h EST, and all measurements were made on the same relative region of the pinna.

RIA procedures. After all blood samplings, aliquots remained at room temperature for 30 min, the clot was removed, and samples were centrifuged at 4 C for 30 min at 2500 rpm. Supematant was collected and frozen at −70 °C until assayed for cortisol by RIA. Serum cortisol concentrations were determined in duplicate in a single assay using a 125I double-antibody kit (Diagnostic Products Corporation, Los Angeles, CA). Cortisol is the predominant glucocorticoid in this species, and this kit has previously been validated for use in Siberian hamsters (27). The high statistical limits of detectability of the cortisol assay were 530 and 5 ng/ml, respectively. The intraassay coefficient of variation was less than 10%.

Data analyses and statistics. Baseline body mass, ETV, and cortisol data were analyzed between photoperiod groups, using two-tailed t tests. Activity data for experimental animals were analyzed daily to confirm RUN in hamsters with access to a RUN wheel. An arbitrarily selected
criterion of more than 100 average daily activity counts was selected for inclusion in the study (average daily activity was between 200 and 400 counts). One LD, food-restricted hamster with RUN wheel access failed to run (<10 activity counts per day) and was removed from all data analyses. Activity data for control hamsters were averaged across 10-min bins and compared among groups separately for ad lib and food-restricted conditions using two-way (photoperiod x group) ANOVAs. Food intake data for ad lib-fed animals were analyzed for each week among groups using two-way ANOVAs. Body mass data were analyzed for each week among groups using two-way ANOVAs. Percent changes in body mass from baseline to the final day of the study were compared among groups using two-way ANOVAs. Body mass data were analyzed for each week among groups using two-way ANOVAs. Percent changes in body mass from baseline to the final day of the study were compared among groups using two-way ANOVAs. Cortisol data on d 7 and 21 were compared individually across groups, using two-way (photoperiod x group) ANOVA. Cortisol data were then compared among days (d – 3, 7, and 21) for each photoperiod group, using two-way repeated-measures ANOVAs. DTH reactions were analyzed as percent increases in pinna thickness over baseline for each animal and compared among groups for each day within conditions, using two-way ANOVAs. Two SD, food-restricted SED hamsters died during wk 2 of the experiment, and all data for those animals were excluded. After significant F scores, post hoc (Student-Newman-Keuls) tests were performed to further distinguish among groups, and all differences were considered statistically significant if P values were less than 0.05.

Results

Reproductive measures

After 8 wk of housing in LDs or SDs, before group assignment, all SD hamsters (n = 32) weighed significantly less and had significantly smaller ETVs, compared with LD hamsters (n = 33) (P < 0.05 for both; Fig. 1). Running wheel access and FR each significantly reduced ETVs in LD hamsters by d 28 of the study (P < 0.05 for each; data not shown); however, these reductions reflected reduced body mass and were no longer significant after correction for body mass (P > 0.05). Neither RUN wheel access nor FR significantly influenced ETVs in any group of SD hamsters by d 28, when analyzed either as raw data or when corrected for body mass (P > 0.05; data not shown). Therefore, photoperiod, but not exercise, had a direct influence on reproductive organs.

Activity

After 8 wk of housing in LDs or SDs, SD control hamsters (n = 12) weighed significantly less and had significantly smaller ETVs, compared with LD control hamsters (n = 12) (P < 0.05 for both; data not shown). All hamsters with access to a RUN wheel were significantly more active than hamsters without a RUN wheel, during both ad lib (F = 58.42; df = 1, 20; P < 0.05) and food-restricted conditions (F = 21.91; df = 1, 20; P < 0.05) (Fig. 2). Furthermore, SD hamsters as a group were significantly more active than LD hamsters as a group during both ad lib (F = 16.366; df = 1, 20; P < 0.05) and food-restricted conditions (F = 13.05; df = 1, 20; P < 0.05). In ad lib-fed hamsters, there was a significant interaction between photoperiod and group (F = 8.068; df = 1, 20; P < 0.05), because SD hamsters were more active than LD hamsters only in the RUN wheel condition (P < 0.05). Thus, SD hamsters were more active than LD hamsters only when given access to a RUN wheel.

Food intake and body mass

When fed ad lib, LD hamsters as a group ate significantly more food than SD hamsters during wk 1 of the study (F = 6.022; df = 1, 30; P < 0.05; Fig. 3). Post hoc analysis revealed that RUN LD hamsters ate significantly more food than all other groups during wk 1 (P < 0.05). RUN hamsters as a group ate significantly more food than SED hamsters (F = 14.093; df = 1, 30; P < 0.05). LD hamsters also ate significantly more food than SD hamsters during wk 2 and 4 of the study (F = 11.499; df = 1, 30; P < 0.05; and F = 5.796; df = 1, 30; P < 0.05, respectively). There was a significant effect of photoperiod on percent changes in body mass, because LD hamsters lost more weight overall than SD hamsters by the end of the study (F = 8.120; df = 1, 57; P < 0.05; Fig. 4). Furthermore, food-restricted groups lost more weight than ad lib-fed groups overall (F = 48.352; df = 3, 57; P < 0.05). There was a significant interaction between photoperiod and

![Fig. 1. Mean (±SEM) body mass (g) and ETV (mg) in LD (n = 33) vs. SD (n = 32) hamsters after 8 wk of photoperiod treatment. *P < 0.05.](image1)

![Fig. 2. Mean (±SEM) activity counts (averaged across 10-min bins) for the duration of the 4 wk study in LD vs. SD activity control hamsters during ad lib feeding or FR. a, Significantly different from no wheel condition; b, significantly different from LD same condition(s); P < 0.05.](image2)
group (F = 4.422; df = 3, 57; P < 0.05), because, within LD hamsters, all groups lost weight, compared with SED animals (P < 0.05, for all). Conversely, within SD hamsters, only food-restricted groups lost weight, compared with SED animals (P < 0.05, for both).

**DTH**

**Photoperiod effects.** SD hamsters had significantly higher DTH responses than LD hamsters on each day of measurement when fed ad lib (Fig. 5) (F = 68.1, F = 43.32, F = 26.89, F = 23.13, F = 19.11, and F = 30.24, d 1–6, respectively; df = 1, 30; P < 0.05 for all). In food-restricted hamsters, there no longer was a main effect of photoperiod on DTH (P > 0.05). However, there was a significant interaction between photoperiod and group on DTH on d 3–6 post challenge in food-restricted groups (F = 5.05, F = 6.05, F = 6.06, and F = 9.74, d 3–6, respectively; df = 1, 27; P < 0.05 for all). Post hoc analyses revealed that RUN wheel access suppressed the DTH response in SD (but not LD) FR hamsters on d 3 (P < 0.05). On d 4–6, LD RUN FR hamsters had significantly higher DTH responses than SD RUN FR hamsters (P < 0.05 for all).

**Exercise effects.** In LD hamsters, exercise significantly enhanced DTH responses, compared with SED groups, on d 3, 4, and 6 post DNFB challenge (Fig. 6) (F = 5.83; df = 1, 29; P < 0.05; and F = 5.86; df = 1, 29; P < 0.05; and F = 8.06; df = 1, 29; P < 0.05, respectively). DTH was not significantly influenced by FR, on any day, in LD hamsters (P > 0.05). In SD hamsters, FR significantly suppressed DTH responses, compared with ad lib-fed groups, on every day of measurement (F = 62.68, F = 47.408, F = 17.99, F = 11.436, F = 17.75, and F = 24.359 on d 1–6, respectively; df = 1, 28 and P < 0.05 for all). There was a significant interaction in SD hamsters between group and FR on d 2 post challenge (F = 5.53; df = 1, 28; P < 0.05), because RUN wheel access enhanced DTH on this day in ad lib-fed hamsters only (P < 0.05).

In sum, Fig. 7 illustrates that FR suppressed DTH in SD (but not LD) hamsters, and this served to normalize SD responses to the level of LD hamsters.

**Cortisol**

Baseline serum cortisol concentrations were significantly higher in SD than LD hamsters on d −3 of the experiment (P < 0.05, Fig. 8). To control for the possibility that concentrations may differ by experimental group (i.e., RUN vs. SED, ad lib vs. FR) before group assignment, baseline concentrations were also analyzed by future group separately within each photoperiod; there were no significant differences in cortisol on this day within either LD or SD animals (P > 0.05). On d 7, there was a significant interaction between photoperiod and group on cortisol concentrations (F = 4.875, df = 3.57, P < 0.05). Post hoc analyses revealed that cortisol concentrations were significantly higher in SD SED than LD SED (P < 0.05) and significantly higher in LD RUN FR hamsters than all other groups (P < 0.05, for all). On d 21, there was also a significant interaction between photoperiod and group (F = 2.801, df = 3.57, P < 0.05). Cortisol concentrations were significantly higher in LD RUN FR than both LD SED and SD RUN FR animals (P < 0.05 for both). Repeated measures revealed there was a significant interaction between group and day on cortisol in LD hamsters (F = 3.36, df = 6.58, P < 0.05); cortisol was significantly higher in RUN FR hamsters on d 7 than d −3 (P < 0.05) and was higher in RUN, SED FR, and SED FR groups on d 21 than d −3 (P < 0.05 for all). In SD hamsters, no sample days differed significantly from d −3 in any group (P > 0.05). In sum, only LD hamsters mounted significant cortisol responses to the RUN and FR conditions throughout the study.

**Discussion**

We hypothesized that hamsters use SD lengths to signal the onset of winter to enhance specific components of immune function when metabolic stressors are typically high. In agreement with previous studies, SD hamsters exhibited enhanced DTH responses, compared with LD hamsters, under SED ad lib food conditions (15, 17). All hamsters that were allowed access to a RUN wheel were significantly more active than hamsters without a wheel. SD RUN hamsters were more active than LD RUN hamsters under both ad lib and food-restricted conditions, an observation that was most likely attributable to the extended active phase in SD hamsters. Activity did not differ between LD and SD hamsters without RUN wheels. RUN exercise enhanced DTH in LD hamsters, regardless of food intake. Furthermore, food restriction did not significantly influence DTH in LD hamsters. In contrast, food restriction suppressed DTH in SD hamsters regardless of activity condition, and exercise modestly enhanced DTH in SD hamsters only when fed ad lib. These data provide support for the hypothesis that DTH responses are energetically expensive, and that metabolic restriction reduces immune function in SD (but not LD) hamsters, perhaps because they have fewer metabolic reserves.
DTH reactions have generally been considered a measure of T cell function (28) but also involve immunological memory for a specific antigen and play a significant role in the development of resistance to infections (29, 30). The intensities of DTH reactions are strongly correlated with increased resistance to viral infections in hamsters (31) and cats (32), as well as resistance to tumor formation in mice (33, 34). One independent marker of HIV progression into AIDS in humans is a loss of a DTH response (35). Thus, the quantification of DTH reactions provides an important representation of the ability of the individual's immune system to resist a specific immunologic challenge (36).

It is well documented that insufficient metabolic energy generally decreases immune responses (3, 5–8). During disease states or acute phase responses, abnormal protein metabolism and turnover rates, the breakdown of fatty acids, and the production of humoral and inflammatory mediators all increase energy expenditure (37). Mice that mount an antibody response to a novel protein challenge consume more oxygen than noninjected control animals (2). Mice that are subjected to glucoprivation (2-deoxyglucose) oxidative stress, which prevents cellular utilization of glucose, exhibit reduced splenocyte proliferation to a mitogen (38). Bumblebees (Bombus terrestris) down-regulate immune responses during starvation, and allocate energy instead to cardiac and cerebral metabolism, processes vital for immediate survival. Bees that are forced to mount an immune response during starvation suffer increased mortality (3). Information on the effects of FR or starvation on DTH responses is relatively lacking and somewhat inconclusive. Ahmed et al. (39) report no effect of moderate FR within a balanced diet on DTH responses in mice, whereas Pocino et al. (40) report a decrease in DTH after moderate-severe restriction. These inconsistencies may be attributable to differences in specific macronutrient intake, rather than total caloric intake. Significant nutritional costs, namely protein, are associated with immune up-regulation, and protein malnutrition is associated with abnormal DTH responses in cotton rats (41).

Previous research in various photoperiodic species has provided support for the so-called winter immunoenhancement hypothesis, which states that mechanisms have evolved in animals to combat the energetic bottleneck of winter and promote survival (42, 43). These mechanisms include increases in immune responses that work to counteract suppression caused by stressful conditions such as lack of food and low temperatures. For instance, deer mice (Peromyscus maniculatus) increase antibody production during SDs in the lab; low temperatures suppress antibody titers comparable to the level of LD housed animals in mild temperatures (44). Syrian hamsters (Mesocricetus auratus) increase antibody production during SDs as well (45), but DTH responses do not differ by photoperiod (46). Food restriction alone, or in combination with exercise, depresses the acute phase response to bacterial lipopolysaccharide in Syrian hamsters (47). However, the influence of FR, low temperatures, exercise, or similar environmental stressors on im-
mune responses in Syrian hamsters in different photoperiods has not, to our knowledge, been reported. In contrast to Siberian hamsters that decrease body mass and increase activity, Syrian hamsters gain significant body mass, decrease activity, and may hibernate during SDs (48–50). The lack of enhancement of DTH responses observed in SDs in this species may therefore reflect an alternative strategy attributable to increased energy stores.

Until now, the impact of environmental stressors superimposed on photoperiod-induced changes in immune function had not been tested in Siberian hamsters. Food restriction did not significantly suppress DTH in LD hamsters as it did in SD hamsters, presumably because LD hamsters began the immunological assessment phase of the study at a higher baseline of body mass and, thus, energy availability. It remains possible that DTH responses in LD hamsters under *ad lib* conditions may represent a decrease in immune function, compared with a higher so-called normal baseline observed in SD hamsters. A decrease in DTH in LD males may be a consequence of the immunosuppressive influences of testosterone, the energetic burden of reproductive investment, or both. Nevertheless, FR failed to suppress the response even further in LD hamsters. We originally predicted that SD hamsters would be less influenced by FR, in terms of immune outcomes, compared with LD hamsters, because this species has evolved to survive winter with less food coincident with increased foraging requirements. However, Siberian hamsters exhibit daily torpor during winter conditions in the wild, an adaptation resulting in dramatically reduced energy expenditure (51, 52). No SD hamsters exhibited torpor at any time in the current study, a physiological adjustment that has required more severe FR (~40%), and/or FR in combination with low temperatures (~4°C) in our laboratory (Drazen and Nelson, unpublished observations). Entrance into daily torpor may therefore counteract the immunosuppressive influences of FR on DTH in SD hamsters, a possibility that remains to be fully investigated.

Exercise enhanced DTH in SD hamsters only if they were fed *ad lib*, again suggesting that this immune response is
dependent on metabolic energy availability. Exercise has well-documented effects on various aspects of immune function. Recurring moderate exercise is associated with increased resistance to infectious agents, cardiovascular disease, and diabetes (53). Exercise is associated with changes in inflammatory factors, including the activation of the complement cascade and the release of acute phase proteins. However, chronic exercise or overtraining often leads to immunosuppression via decreases in T, B, and NK cell function, including impaired proliferation and cytotoxic activity (54, 55). These alterations may be induced via increases in cortisol release after high-intensity or prolonged activity, which may then induce neutrophilia, lymphopenia, and decreases in cytokine production (reviewed in Ref. 23). As such, exercise is generally considered to be a stressor to the organism (23, 56). Importantly, insufficient food intake or malnutrition often contributes to the interpretation of exercise as a stressor by the animal, which then results in immunosuppression as discussed previously (57).

In contrast, voluntary moderate exercise with adequate food intake often counteracts the immunosuppressive effects of psychological stressors (20, 58–60). Thus, there seems to be a multifactorial set of interactions among exercise, food intake, and stress responses on immune responses in animals. LD hamsters exhibited the expected increases in cortisol in response to exercise combined with food-restriction...
by d 7 and in response to both exercise and food restriction alone by d 21 of the study. These data suggest that LD hamsters did perceive the decreases in food, particularly in combination with exercise, as a stressor. No group of SD hamsters exhibited elevated concentrations of cortisol by d 7 or 21 of the study. However, high concentrations of glucocorticoids after stress are often associated with increases, rather than decreases, in DTH responses (15, 61). Accordingly, chronic stress suppression of DTH is attributed to a lack of glucocorticoid release in response to the stressor over time (62). Thus, the lack of elevated cortisol in SD hamsters by wk 2 of the study may have resulted in the suppression of DTH in food-restricted groups. It remains to be determined whether SD food-restricted hamsters that exhibited blunted cortisol and DTH responses in the current study simply adapted to the experimental conditions by d 7 without energetic compromise, or whether inadequate metabolic reserves in these hamsters resulted in a lack of a glucocorticoid response and, thus, DTH response via negative feedback mechanisms. A third possibility is that increased RUN in SD hamsters may have served as a signal that prevented increases in cortisol in these animals. Given, however, that RUN exercise generally increases the release of glucocorticoids (56, 63), this explanation seems unlikely.

Taken together, the current data both confirm and extend the results of previous studies. SD hamsters exhibit higher increases in cortisol and higher DTH responses, compared with LD hamsters, after an acute (2 h) restraint stressor (15). Given the adaptive value of mounting a DTH response to an antigen challenge, we suggest that SD hamsters may initially mount a greater immune response to a stressor in the short-term but that prolonged periods of stress exhaust the limited metabolic reserves of these animals over time, resulting in decreased responses. Alternatively, increased DTH responses in SD hamsters under ad lib food and moderate conditions in the lab may represent an overreaction, a hypothesis not consistent with the current one. If increased DTH in SD hamsters represents an immune overreaction, then we suggest that this may occur in preparation for conditions during winter, which will limit energy availability and thus suppress immune responses (which will then return it to normal). In sum, the mechanisms underlying baseline (ad lib food) differences in DTH between photoperiod groups remain to be determined. However, regardless of the mechanism, it seems that SD hamsters may augment immune function, compared with LD hamsters, to prepare for the increased metabolic stressors of winter.

Acknowledgments

We thank Stephanie L. Bowers for technical assistance, Tricia Uhor for expert animal care, and three anonymous reviewers for helpful suggestions on the manuscript.

Received August 11, 2003. Accepted October 24, 2003.

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This work was supported by National Science Foundation Grant IBN00-08454 and NIH Grants MH 57535 and MH 66144.

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