Multiple neuroendocrine pathways mediate seasonal immunity

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REGULATING THE ACTIVITY of the immune system involves a balancing act that must allow organisms to recognize and resist pathogens, while at the same time, keeping in check the potentially harmful effects of an overactive immune system. Activation of the immune system can be energetically costly (3, 4), and the energy allocated to immune activity at any given time likely represents a trade-off between physiological functions relating to growth and reproduction vs. survival. In support of this hypothesis, activating the immune system of Siberian hamsters by simulated infection in the laboratory results in inhibition of reproductive maturation (14). At temperate latitudes, winter poses a seasonally recurring energetic bottleneck, when temperatures are relatively low and food availability is decreased, necessitating a trade-off between reproduction and immune function. For more than a decade, Nelson and colleagues (7, 8, 9) have characterized the seasonal regulation of immune function in rodents. In common with the seasonal quiescence and reactivation of the reproductive system, seasonal alterations in the function of the immune system are cued by changes in day length (7, 8). Both reproductive and immunological seasonality in this species are dependent on photoperiod-driven changes in melatonin production (17). In Siberian hamsters, exposure to short photoperiods in the laboratory induces regression of the gonads and withdrawal of gonadal steroid production. In parallel with reproductive quiescence, short days also alter the immune system. Increases in the number of circulating leukocytes (e.g., T-cells, NK cells; 1, 18) and decreases in LPS-induced proinflammatory cytokine production are two of the more robust short-day changes evident in the immune system. Decreased cytokine responses to LPS in short days result in an attenuation of energetically expensive acute-phase sickness behaviors; winter alterations in immune responses to simulated infections conserve energy and increase the likelihood of survival (13).

The mechanisms by which short day lengths (and melatonin) alter immune function have not been fully characterized. In seasonally breeding animals, alterations in immune function may be a direct result of the seasonal pattern of gonadal hormone secretion. Photoperiodic changes in some measures of immune function (antibody production, skin inflammation) occur independent of reproductive hormone production (5, 12), whereas others track gonadal condition (15). A study by Prendergast et al. (10) in this issue of American Journal of Physiology-Regulatory, Integrative and Comparative Physiology directly tested whether changes in gonadal hormone production are required for photoperiod to affect immune function and behavioral responses to infection. The work documents photoperiod-induced alterations in immune function that persist in castrated male Siberian hamsters. Following castration, hamsters retained the short photoperiod-dependent attenuation of sickness behaviors, as well as the typical increase in lymphocyte numbers. Notably, the work includes multiple measures of the immune system and statistical analyses designed to partition the relative contribution of both gonadal-hormone dependent and -independent factors with regard to seasonal changes in immune function. For every measure of immune function examined, a gonadal hormone-dependent and -independent effect of photoperiod was identified. The degree of gonadal hormone dependence varied on a trait-by-trait basis; however, some measures of immunity were dominated by gonadal responses to photoperiod (circulating lymphocytes), whereas other measures were affected by photoperiod to a comparable degree in gonad-intact and castrated animals (thermoregulatory responses to simulated infection).

The work sheds light on earlier reports that exposure to intermediate-duration day lengths dissociate immune responses from reproductive responses (11). When housed in intermediate day lengths, hamsters exhibited gonadal growth or regression, depending on whether they were previously exposed to shorter or longer photoperiods, respectively. Despite marked differences in reproductive status, hamsters in intermediate day lengths exhibited comparable measures of immunity (antibody production, inflammatory responses, leukocyte counts; 11). In light of the present study, this work suggests that gonadal steroid-independent effects of photoperiod may manifest under conditions that simulate ecologically relevant responses to photoperiod. Melatonin may be a prime candidate as a gonadal hormone-independent mediator of photoperiodic changes in immune function. Hypothalamic microimplants of melatonin sufficient to induce short-day-like gonadal regression engaged short-day-like changes in some (LPS-induced anorexia) but not all (leukocyte counts) measures of immune function (6). Steroid-independent effects of melatonin appear to be mediated, at least in part, by an action of melatonin in the central nervous system. This does not exclude a role for melatonin, or gonadal steroids, directly on immune cells and tissues in the periphery, however. Indeed, both melatonin and testosterone have been shown to have an effect on Siberian hamster lymphocyte function in vitro (2, 16).

In conclusion, the results of this study indicate that seasonal rhythms in immune function are driven by both gonadal hormone-dependent and -independent mechanisms. Taken together, the results are consistent with multiple neuroendocrine pathways controlling photoperiod-driven immune responses in a trait-specific manner.

REFERENCES

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