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The energetics of immunity: a neuroendocrine link between energy balance and immune function

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Introduction

Among the many significant contributions Frank A. Beach made to the field of behavioral endocrinology, particularly influential was his emphasis on the importance of *integration* in scientific pursuits; Beach believed that to fully understand physiology and behavior, one needed to understand not only the interrelationships among behavior and the nervous and endocrine systems, but also the complex dynamics that occur within the ecological context of the environment in which an animal lives. Furthermore, the mechanisms of behavior must also be understood in an evolutionary framework. Thus, it was Beach's strong belief that an ''integrative psychobiology would transcend all levels of analysis'' and would be ''rooted in the study of its physiological correlates on the one hand and its adaptive function on the other'' (Dewsbury, 1988). As students of behavioral neuroendocrinology, application of an integrative approach to the study of hormones, brain, and behavior remains one of our greatest challenges. This review will focus on how an integrative approach to the study of neuroendocrine–immune interactions can be useful in addressing important questions regarding the neural and hormonal mechanisms underlying the energetic regulation of immunity.

A role for immune function in behavioral neuroendocrinology

Vertebrate species rely on three physiological systems for cell–cell communication: the nervous, endocrine, and immune systems. Despite their unique labels and associated nomenclature, these three signaling systems do not operate in a vacuum. Rather, as the field of behavioral neuroendocrinology has consistently demonstrated, the nervous and endocrine systems interact with one another at several important physiological levels and the functions of either system depend on the status of the other system. For example, receptors for specific hormones are present throughout the central and peripheral nervous systems, and activation of these receptors is critical to proper nervous system development and functioning. In addition, several ''classical'' hormones have been isolated within specific neurons where they are released transynaptically and appear to serve local neuromodulatory functions (Baulieu et al., 2001). The nervous system, in turn, plays an important role in regulating the synthesis and secretion of a variety of hormones within specific endocrine tissues. For example, the release of adrenal hormones is, in part, dependent on the sympathetic nervous system innervation of this tissue (Vollmer, 1996).

In stark contrast to the integrative approach to the study of the endocrine and nervous systems, the study of immunity has traditionally occurred in relative isolation from other physiological systems. The immune system, a collection of specialized cells contained within primary (e.g., thymus, lymph nodes) and secondary (e.g., spleen) lymphoid organs whose integrated function is to differentiate ''self'' from ''non-self'' and eliminate foreign pathogens, has historically been viewed as a closed circuit. In other words, immunity was considered to be buffered, to a large extent, from the external world in that few if any environmental perturbations were thought to affect its normal day-to-day functioning. Furthermore, intrinsic physiological factors were not typically considered important effectors of immune responses.

In the last several decades alone, however, this view of immunity has been proven too simplistic; it is now known

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that a wide variety of extrinsic and intrinsic factors can affect and, in many cases, mediate immune responses (reviewed in Ader et al., 2001). Furthermore, a host of biologically active substances, collectively known as cytokines, has been identified and characterized within lymphoid tissues, although their specific biological functions are only just beginning to be understood. Cytokines, like hormones and neurotransmitters, are synthesized and released by specific immune and non-immune cells in both paracrine and endocrine fashion, and play an important role in the regulation of a variety of immunological as well as neuroendocrine processes (Eskandari and Sternberg, 2002; Masek et al., 2003). These and other important discoveries have led to a renaissance within the life sciences in which scientists in diverse fields including endocrinology, psychology, neuroscience, behavioral ecology, evolutionary biology, and environmental sciences are becoming increasingly interested in the role of the immune system in mediating a wide range of biological responses and thus, influencing susceptibility to disease. Furthermore, this increased research focus on the immune system has led to the formalization of several new and exciting scientific disciplines, including psychoneuroimmunology (Ader and Cohen, 1981), neuroimmunoendocrinology (Blalock, 1992), ecological immunology (Sheldon and Verhulst, 1996), and evolutionary immunology (Lochmiller and Deerenberg, 2000) whose goals are to explore the interactions among the endocrine, nervous and immune systems, and behavior at both ultimate and proximate levels of analysis. This emphasis on integration, as Beach predicted, has also led to many new and exciting findings within behavioral endocrinology. The remainder of this review will focus on the energetics of immunity as an example of how the study of the interactions among the endocrine, nervous and immune systems, and behavior can be achieved through an integrative, interdisciplinary fashion. Such an approach can lead to new and important insights and has the potential to make valuable contributions to the field of behavioral neuroendocrinology.

Energetic trade-offs

As the age-old adage ‘‘feed a cold, starve a fever’’ suggests, there is an important biological link between energy balance and immune function and thus, disease susceptibility. Immunity, like all other physiological processes, requires adequate energy to sustain optimal functioning. Despite this obvious fact, the role of energy balance has only recently begun to be considered in the context of immune function and disease. Within the last few years, the concept of energetic ‘‘trade-offs’’ among competing physiological and behavioral systems has gained increasing popularity in a wide range of scientific disciplines. The underlying assumption of the trade-off concept is that animals require a relatively steady supply of energy to sustain biological functions. Energy, however, is not a limitless resource; finite energy reserves must serve all physiological processes and thus energy must be allocated to a wide variety of often competing physiological functions. Furthermore, the total energy budget is not static; substantial daily and seasonal fluctuations exist in both energy availability as well as energy expenditure. At times of reduced energy availability (e.g., winter), energy must be reallocated from less critical physiological functions (e.g., reproduction) to those most important for immediate survival (e.g., thermoregulation). The trade-off concept also provides a useful framework with which to consider neuroendocrine–immune interactions (Nelson and Demas, 1996; Sheldon and Verhulst, 1996).

One important question with respect to energetic trade-offs in neuroendocrine–immune interactions is whether or not immune function is energetically costly. It has been suggested that mounting an immune response requires resources that could otherwise be allocated to other biological functions (e.g., growth, reproduction). For example, a study conducted early last century suggested that for every 1 °C increase in body temperature due to the induction of fever there is a concomitant 7–13% increase in oxygen consumption (Barr et al., 1922). Surprisingly, virtually no data on the energetic costs of immunity have been published since this seminal study. Recently, our laboratory has examined the energetic costs of mounting specific antibody response in house mice (*Mus musculus*). House mice were injected with the non-replicating antigen keyhole limpet hemocyanin (KLH) to induce an antibody response in the absence of fever or sickness. Mice immunized with KLH display approximately 20–30% increases in oxygen consumption and metabolic heat production compared with pre-immunization baseline values (Demas et al., 1997a). It is important to note that this is a non-trivial increase in energy metabolism, given the relatively ‘‘benign’’ nature of the antigen. Antigens and pathogens that stimulate more robust immune responses (e.g., induction of fever or sickness) will likely prove even more energetically costly. Since this initial study, several studies have been published that have provided further evidence for the energetic costs of immunity using a variety of antigenic stimuli and across several vertebrate and invertebrate species (Bonneaud et al., 2003; Martin et al., 2002; Moret and Schmid-Hempel, 2000). Collectively, the results of these studies support the assumption that immune responses, like all other biological processes, require energy. Immunity, however, is a ‘‘double-edged sword’’. Increased energy dedicated to immune responses, although likely adaptive in the short term for increasing disease resistance, can ultimately come at the cost of decreased fitness, especially if immune activation is prolonged or excessive (Lochmiller and Deerenberg, 2000). The risk of infection and death is highest, however, when insufficient energy reserves are available to sustain optimal immunity (Nelson et al., 2002). Thus, some ‘‘optimal’’ level of immune function must be maintained to maximize fitness.

Adipose tissue and immunity

Despite the apparent link between energy availability and immunity, relatively little is known regarding the physiological mechanisms by which energy regulates immune function. On one hand, a chronic positive imbalance between energy intake and expenditure leads to obesity and can impair immune function and increase disease susceptibility in both clinical populations and genetically obese animal models (Marti et al., 2001). On the other hand, marked reductions in energy availability without concomitant reductions in energy output can also lead to substantial suppression of immunity (Chandra, 1996; Nova et al., 2002). For most mammalian species, and small rodents in particular, white adipose tissue (WAT) depots represent a substantial portion of the total energetic budget and thus WAT likely plays an important role in maintaining energetically expensive physiological processes, including immune function. Consistent with this idea, reductions in total body fat are correlated with impaired immunity in a wide range of species, including humans (Klasing, 1998; Norgan, 1997; Spurlock et al., 1997), and experimental reductions in body fat can impair antibody formation (Demas et al., 2003b). Furthermore, immunological disorders (e.g., AIDS) trigger marked changes in whole-body lipid metabolism, suggesting an important role of adipose tissue in immunity (Pond, 1996).

In times of increased energetic demands, WAT can be broken down to its constituent components, free fatty acids (FFAs) and glycerol, and subsequently converted to glucose to be utilized as energy. Several lines of research suggest an important role of FFAs in the regulation of immune function (reviewed in Pond, 1996). FFAs provide a major fuel source for lymphocytes and may be used preferentially over glucose (Ardawi and Newsholme, 1985). Furthermore, FFAs can either enhance or inhibit mitogen-induced proliferation of rodent and human lymphocytes in vitro (reviewed in Pond, 1996) and unsaturated FFAs are incorporated into proliferating lymphocytes (Calder et al., 1994). Alterations in FFAs can also affect responsiveness to infection and alter the severity of chronic infections (Erickson et al., 1992; Yaqoob et al., 1994).

In addition to its role as an energy depot, adipose tissue also serves as an important endocrine organ (Ahima and Flier, 2000). A wide variety of signaling molecules including hormones (e.g., leptin, adiponectin) and cytokines (e.g., interleukin-6, TNFα) are now known to be secreted by adipose tissue and these factors may play an important role in autocrine or paracine regulation of specific immune responses. For example, the cytokine tumor necrosis factor-α (TNFα), an important mediator of cytotoxic and inflammatory immune responses, is secreted by adipocytes and is believed to play a major role in changes in lipid metabolism. Furthermore, adipose tissue provides the necessary precursors for synthesis of lipid-based hormones (e.g., prostaglandins, leukotrienes, thromboxanes) which have been implicated in specific immunological responses (reviewed in Pompeia et al., 2000; Rocca and FitzGerald, 2002).

Body fat and immunity: lessons from seasonally breeding animals

Seasonally breeding rodents provide an excellent model with which to study the role of energy balance in the regulation of immunity because the majority of these species undergo substantial, naturally occurring fluctuations in total body fat throughout the year (reviewed in Bartness and Wade, 1985; Bartness et al., 2002). In addition, most rodent species studied to date display seasonal changes in immune function that are, in general, positively correlated with their energy stores. The exact seasonal response, however, varies according to the species; some rodents gain significant amounts of body fat during short winter-like days, whereas other species undergo short-day decreases in body fat. As a general rule, animals that gain weight in the short days of winter (e.g., Syrian hamsters (*Mesocricetus auratus*)) display increased immune function (Drazen et al., 2001); whereas animals that lose a significant portion of their total body fat in short days (e.g., Siberian hamsters (*Phodopus sungorus*), prairie voles (*Microtus ochrogaster*) display reduced immunity (Demas et al., 2002; Nelson et al., 1996). Although there appear to be some notable exceptions to this ‘‘rule’’ (e.g., deer mice decrease body fat, but increase immune function in short days), the general correlation is noteworthy, especially given that all of the abovementioned species display gonadal regression and subsequent decreases in circulating gonadal steroid hormones. Thus, seasonal fluctuations in gonadal steroid hormones cannot fully explain the differential changes in immune responses among these species. Interestingly, some species of tropical rodents that do not undergo seasonal fluctuations in reproductive and body fat responses (e.g., Aztec mice (*Peromyscus aztecus*)) also fail to undergo photoperiodic changes in immunity (Demas and Nelson, 2003). These data support the idea that seasonal changes in immune function correlate with seasonal fluctuations in total body fat. Recently, our lab has demonstrated that experimental reductions in total body fat in long-day animals (that approximate short-day levels of body fat) suppress humoral immune responses in two seasonally breeding rodents, prairie voles and Siberian hamsters (Demas et al., 2003b). Specifically, surgical removal of body fat (lipectomy; LIPx) was performed in which either epididymal white adipose tissue (EWAT) or inguinal (IWAT) pads were removed bilaterally and animals immunized with the antigen KLH. Initially, anti-KLH antibody responses are reduced in LIPx hamsters and voles compared with control animals. After a prolonged period of time (i.e., 12 weeks), compensatory increases in IWAT are seen in EWATx hamsters, restoring total body fat to control levels. Interestingly, humoral immunity also

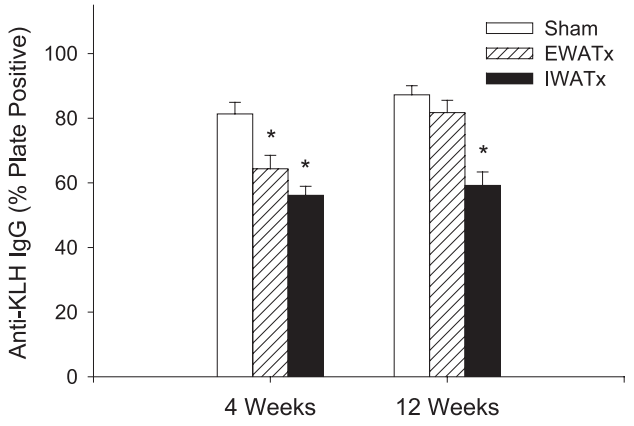

Fig. 1. Mean (± SEM) serum anti-KLH immunoglobulin G (IgG) levels in Siberian hamsters measured either 4 or 12 weeks after receiving bilateral EWAT lipectomies (EWATx), bilateral IWAT lipectomies (IWATx), or sham surgeries (SHAM). Significant differences between pairwise means are indicated by an asterisk (*) if $P < 0.05$. Modified from Demas et al. (2003a,b).

returns to normal control levels in these animals (Fig. 1). In IWATx hamsters, in contrast, no compensatory increase in EWAT occurs and immune function remains impaired in these animals (Fig. 1). Furthermore, no compensatory increases in WAT are seen in LIPx prairie voles and, as expected, humoral immunity remains impaired in these animals. These data suggest that humoral immune responses track seasonal fluctuations in body fat.

In addition to the effects of WAT on immunity, specific metabolic fuels have also been demonstrated to affect immune function in seasonally breeding rodents. For example, reductions in glucose availability via the metabolic inhibitor 2-deoxy-D-glucose (2-DG) inhibits splenic T lymphocyte in a dose-dependent fashion in rats (Lysle et al., 1988) and mice (Miller et al., 1994). Interestingly, 2-DG inhibits mitogen-induced splenocyte proliferation in long-day, but not short-day, deer mice (Demas et al., 1997b). Short day-housed animals appear buffered against 2-DG induced immune suppression (Demas et al., 1997b). Because 2-DG is a glucose analog that inhibits cellular utilization of glucose and induces a state of glucoprivation, these results suggest that reductions in energy availability suppress immunity. Collectively, these findings suggest an important connection between energy availability and the regulation of immunity.

Leptin: a neuroendocrine link between adipose tissue and immunity

The studies reviewed above suggest that body fat plays an important role in regulating immune function in many vertebrate species. However, the precise neuroendocrine mechanisms by which energy availability is translated into a physiological signal indicating current energy balance are not fully understood. In the past few years alone, however, a variety of endocrine factors have been identified as potential candidates for providing biochemical signals of current energy availability (reviewed in Woods and Seeley, 2000). One obvious endocrine candidate linking available energy stores with immune function is leptin. Leptin, a peptide hormone synthesized and secreted almost exclusively by adipose tissue, is directly proportional to adipose tissue mass. Initial studies on leptin suggested that the primary function of this hormone was that of a satiety factor, as exogenous leptin triggered marked reductions in food intake and body fat (Zhang et al., 1994). Interestingly, however, decreases in body fat were still evident, even when food intake was kept constant, suggesting that leptin also exerted a direct effect on energy metabolism, independent of food intake (Elmquist, 2001; Rayner, 2001; Scarpace et al., 2000).

A wide variety of diverse actions within the immune system are influenced by leptin. For example, specific immune responses are disrupted in mice with impaired leptin signaling due to genetic defects (e.g., *ob/ob* mice, *db/db* mice). *Ob/ob* mice that are unable to synthesize leptin experience atrophy of specific lymphoid tissues (e.g., spleen, thymus), accompanied by decreases in the number of circulating lymphocytes and increases in the number of circulating monocytes (Lord et al., 1998). Leptin deficiency also results in reduced sensitivity to T-cell-activating stimuli and the cytotoxic response of splenocytes. Similarly, *db/db* mice that are unresponsive to leptin due to a mutation of the leptin receptor, display similar immunological deficits. *Db/db* mice have reduced splenic and thymic masses and have a reduced capacity to reject skin grafts or to generate cytotoxic cells (Fernandes et al., 1978). More recently, a series of important studies using both in vitro and in vivo tests, have provided strong support for a role of leptin in mediating immune responses (Lord et al., 1998).

Leptin also appears to mediate seasonal changes in immune function. For example, Siberian hamsters housed in short days display decreases in total body fat as well as reduced humoral immunity and the degree of immune suppression is correlated with circulating leptin concentrations (Drazen et al., 2000a). In addition, if short-day hamsters are given exogenous leptin to mimic long-day levels of the hormone, the short-day impairment in immunity is attenuated (Drazen et al., 2001). Exogenous leptin has no effect on humoral immunity in long-day hamsters, however, suggesting the effect of leptin on humoral immunity is photoperiod-dependent (Drazen et al., 2001). Furthermore, more recent data suggest that exogenous leptin can attenuate metabolic stress-induced decreases in humoral immunity in Siberian hamsters (Drazen, 2001). Specifically, animals treated with the metabolic inhibitor 2-DG display reduced humoral immunity; exogenous leptin attenuates this 2-DG-induced immunosuppression. These results suggest that leptin acts as a neuroendocrine signal, communicating current energy availability, whether in the form of readily utilizable energy (i.e., glucose), or energy stores (i.e., WAT

depots) to the immune system. Recent data in our laboratory have provided support for this hypothesis. Specifically, surgical removal of IWAT suppressed serum IgG concentrations in response to the antigen KLH in Siberian hamsters, as previously reported. Treatment of LIPx animals with exogenous leptin via osmotic minipump, however, attenuates LIPx-induced decreases in humoral immunity (G.E. Demas, unpublished data). As in previous studies, exogenous leptin does not alter humoral immunity in control animals.

Collectively, these studies provide compelling support for the hypothesis that leptin provides a neuroendocrine signal from body fat to the immune system indicating current energy reserves. But how does leptin communicate with the immune system? As with most hormones, leptin can act directly by binding to receptors on lymphoid cells (e.g., circulating lymphocytes) to affect immune responses. Alternatively, leptin may also act indirectly, through the nervous or endocrine systems, to influence immunity. Unlike a wide variety of hormones (e.g., androgens, estrogens, glucocorticoids) in which specific receptors have been identified directly on peripheral immune cells (Compton et al., 1990; Grossman et al., 1979), high-affinity leptin receptors have yet to be identified on peripheral lymphoid tissues. Although it is plausible that such receptors exist and simply have not been identified to date, the putative lack of leptin receptors on immune tissues suggests that the effects of leptin on immune function may be indirect.

A role for the sympathetic nervous system?

Although many of the effects of leptin on the regulation total body fat are due to the effects of this hormone on food intake, an increasing number of studies suggest that the actions of leptin on energy balance are due, at least in part, to activation of the sympathetic nervous system (SNS) and subsequent increases in metabolism (Elmquist, 2001, Mizuno et al., 1998; Rayner, 2001; Scarpace et al., 2000). Furthermore, stimulation of the leptin system increases sympathetic activity in a variety of peripheral tissues (Rayner, 2001). Consistent with these findings, high-affinity leptin receptors have been identified in the CNS, especially in specific hypothalamic nuclei that are involved in SNS outflow to peripheral tissues (Harvey and Ashford, 2003). Collectively, these results suggest an important role of the SNS in regulating the metabolic effects of leptin.

Given the important role of the SNS in mediating the metabolic effects of leptin, a plausible hypothesis is that the SNS also mediates the effects of leptin on immune function. Very little data exist with which to answer this question. It is well known, however, that the SNS plays an important role in the regulation of immunity (Elenkov et al., 2000). Recently, direct SNS innervation of the spleen has been demonstrated in Siberian hamsters using the retrograde transneuronal tract tracer pseudorabies virus (PRV) (Drazen et al., 2000b). Specifically, PRV injected into the spleens of Siberian hamsters revealed infected neurons in areas traditionally implicated in SNS regulation (e.g., A5 and C1 cell groups, locus coeruleus). Labeled neurons were also identified in the paraventricular (PVN) and suprachiasmatic nuclei (SCN) of the hypothalamus (Drazen et al., 2000b), brain regions critical for the transduction of the photoperiodic signal (Goldman, 1999).

More recently, our laboratory has demonstrated that the SNS plays an important *functional* role in regulating photoperiodic changes in immune function in Siberian hamsters. Specifically, short day-housed hamsters receiving surgical denervation of the spleen displayed reduced humoral immunity compared with sham-operated hamsters; splenic denervation, however, had no effect on immunity of long-day hamsters (Demas et al., 2002). Furthermore, norepinephrine (NE), the predominant neurotransmitter of the SNS, differentially affects in vitro lymphocyte proliferation in long and short day-housed Siberian hamsters (Demas et al., 2003a). Specifically, NE added in culture reduces mitogen-induced (Concanavalin A) splenocyte proliferation in hamsters housed in short but not long days. Furthermore, the suppression of proliferation elicited by NE in vitro can be attenuated by the co-administration of the β-adrenergic receptor (AR) antagonist propranolol, but not the α-AR antagonist phenoxybenzamine (Demas et al., 2003a). Collectively, these results suggest that the SNS is associated with photoperiodic changes in immune function in Siberian hamsters, most likely acting on β-AR present on lymphocytes.

Given the important role of SNS modulation of immune function, as suggested above, it is likely that leptin may act via the SNS to modulate seasonal changes in immune function (Okamoto et al., 2000). One recent study provides some support for this hypothesis. In contrast to studies demonstrating leptin-induced enhancement of immunity, central leptin administration appears to *reduce* splenic cell-mediated immune function in mice (Okamoto et al., 2000). Specifically, intracerebroventricular administration of leptin to mice reduces splenocyte proliferation in response to the T-cell mitogen concanavalin A (Con A). This effect, however, is abolished by surgical denervation of the spleen (Okamoto et al., 2000). Why exogenous leptin decreased in vitro lymphocyte proliferation in this study, despite the growing evidence for an immunoenhancing role of leptin in vivo, is not presently known. Because > 95% of the efferent innervation of the spleen is sympathetic in origin (Elenkov et al., 2000), these results are consistent with the idea that leptin acts via the SNS to mediate immune responses. To further test this hypothesis, we evaluated the role of sympathetic denervation of lymphoid tissue in exogenous leptin-induced increases in immunity in Siberian hamsters. Specifically, hamsters were housed in long or short days and half of the animals in each photoperiod were administered exogenous leptin via osmotic minipumps. Half of the animals in each hormonal condition received surgical

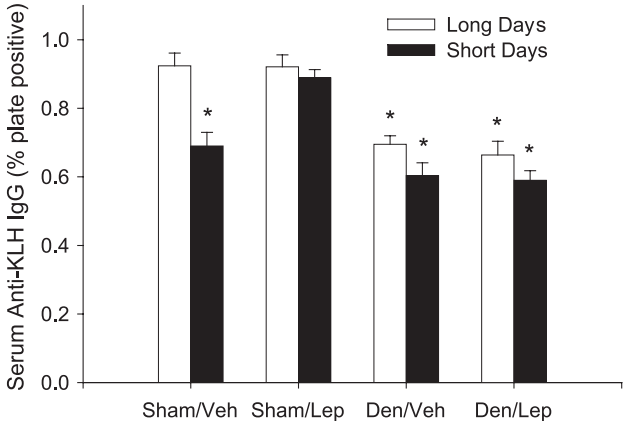

Fig. 2. Mean (±SEM) serum anti-KLH immunoglobulin G (IgG) of splenic-denervated (Den) or sham-operated (Sham) hamsters housed in long or short days and treated with exogenous leptin (Lep) or vehicle control (Veh). Significant differences between pairwise means ($P < 0.05$) are indicated by an asterisk (*). Modified from Demas, 2002.

denervation of the spleen whereas the remaining animals were left intact. As previously reported, anti-KLH antibodies are reduced in short days and the short-day reduction in humoral can be reversed by exogenous leptin administration. Surgical denervation of the spleen, however, attenuated the immune-enhancing properties of exogenous leptin; short day-denervated hamsters receiving leptin displayed suppressed immunity comparable to short-day control animals not receiving the hormone (Demas, 2002) (Fig. 2). These results suggest that immunoregulating actions of leptin, consistent with the metabolic effects of this hormone, are due, at least in part, to the indirect actions on the SNS. A schematic of a proposed mechanism of action of leptin on immunity is illustrated in Fig. 3.

The future of "psychoneuroimmunoendocrinology"

Although significant progress has been made in our understanding of the energetic regulation of immunity, many important questions still remain. For example, we are just beginning to identify the wide array of endocrine and nervous system factors involved in the metabolic regulation of immune function. In addition, much less is known about the mechanisms by which the immune system, in turn, communicates with metabolic systems to inform the body of current immunological requirements relative to energy status. Lastly, little is known regarding how metabolically induced changes in specific immune responses (e.g., antibody or cytokine concentrations, immune cell numbers) correlate with disease resistance to specific pathogens to which an animal is likely to be exposed in its natural environment. The search for the answers to these and other important research questions, however, should provide exciting findings in the years to come. In a larger framework, the primary goal of this review is to provide one salient example whereby an integrative approach is beginning to

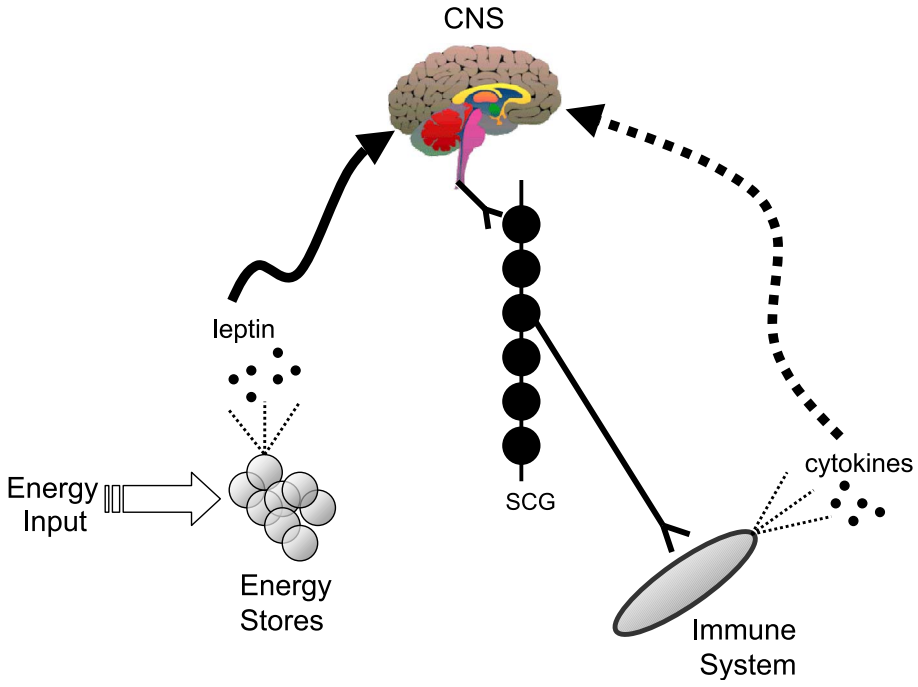

Fig. 3. Schematic representation of one potential mechanism for the regulation of immune function by leptin. In this model, increased food (energy) intake increases total body fat, which leads to elevated levels of circulating leptin. Leptin, in turn, acts on receptors within the CNS (e.g., hypothalamus), modulating sympathetic nervous system (SNS) outflow to peripheral targets, including lymphoid tissue (e.g., spleen). Changes in SNS outflow to lymphoid tissue can regulate immune responses via the release of catecholamines (e.g., epinephrine, norepinephrine). Lastly, feedback from the immune system to the brain can occur either by sensory afferent nerves (not pictured) or by the release of specific cytokines from immune cells.

yield important insights regarding the neuroendocrine mechanisms of immune function. For example, early studies on seasonal alterations in immune function (e.g., Demas and Nelson, 1996) suggested that immune function is enhanced by short days or following short day-like durations of melatonin secretion. A more comparative approach, however, revealed that, whereas some species experience enhanced immune function in short days, others experience *decreased* immune function. The application of an integrative approach reconciled this apparent discrepancy; whereas reproductive status (and resulting hormonal changes) was not predictive of seasonal changes in immune function, seasonal changes in energy availability accurately predicts the direction of change. Thus, as Frank Beach proposed several decades ago, an integrative, cross-disciplinary approach is important for attaining a comprehensive understanding of the interactions among hormones, brain, and behavior; this approach should continue to serve as a useful guide for investigating the interactions between the neural, endocrine, and immune systems.

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