Hormones and Behavior 62 (2012) 272–279

Contents lists available at SciVerse ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

Review

Leptin, a neuroendocrine mediator of immune responses, inflammation, and sickness behaviors

Elizabeth D. Carlton [a,*], Gregory E. Demas [a], Susannah S. French [b]

[a] Department of Biology, Program in Neuroscience and Center for the Integrative Study of Animal Behavior, Indiana University, Bloomington, IN 47405, USA
[b] Department of Biology, Utah State University, Logan, UT 84322, USA

ARTICLE INFO

Available online 25 April 2012

Keywords:
Energy balance
Leptin
Inflammation
Seasonal
Cytokines
Lipopolysaccharide

ABSTRACT

This article is part of a Special Issue "Neuroendocrine-Immune Axis in Health and Disease."

Effective immune responses are coordinated by interactions among the nervous, endocrine, and immune systems. Mounting immune, inflammatory, and sickness responses requires substantial energetic investments, and as such, an organism may need to balance energy allocation to these processes with the energetic demands of other competing physiological systems. The metabolic hormone leptin appears to be mediating trade-offs between the immune system and other physiological systems through its actions on immune cells and the brain. Here we review the evidence in both mammalian and non-mammalian vertebrates that suggests leptin is involved in regulating immune responses, inflammation, and sickness behaviors. Leptin has also been implicated in the regulation of seasonal immune responses, including sickness; however, the precise physiological mechanisms remain unclear. Thus, we discuss recent data in support of leptin as a mediator of seasonal sickness responses and provide a theoretical model that outlines how seasonal cues, leptin, and proinflammatory cytokines may interact to coordinate seasonal immune and sickness responses.

Contents

Introduction

Over the past few decades, it has become increasingly clear that the immune system does not act in autonomy to clear infectious agents from an animal. Rather, it is the interplay among the immune, endocrine, and nervous systems that facilitates effective pathogen clearance. Communication among systems is therefore necessary to coordinate immune responses that are well suited to an organism's current physiological state, and in particular, the organism's nutritional condition. There is now little doubt that the development of the immune system and intensity of an immune response are constrained by access to and utilization of nutritional and energetic resources in an organism's environment (Faggioni et al., 2001; Kelly and Coutts, 2000; Lochmiller and Deerenberg, 2000; Long and Nanthakumar, 2004). As such, the focus of this review is to examine how one such molecule, the hormone leptin, may act pleiotropically to coordinate physiological systems to elicit immune responses and sickness behaviors that are appropriately balanced with an animal's available energy stores.

Energetic trade-offs

The majority of free-living animals have finite energy stores that they must allocate to different biological processes, such as reproduction, growth, thermoregulation, and immune function (reviewed in

* Corresponding author at: Department of Biology, 1001 E. 3rd Street, Indiana University, Bloomington, IN 47405, USA. Fax: +1 812 855 6705.
E-mail address: elcarlto@indiana.edu (E.D. Carlton).

0018-506X/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.yhbeh.2012.04.010

Sheldon and Verhulst, 1996). Immune responses are energetically costly to mount, and quantification of these costs has shown that inoculation with even a very mild antigen can increase oxygen consumption by approximately 20% (Demas et al., 1997). In some cases, the energetic costs of mounting an immune response may be sufficiently great that allocation to biological processes other than immune function is compromised. For example, animals stimulated with an immune challenge while engaging in reproduction and rearing of offspring often show reduced reproductive success (Bonneaud et al., 2003; Ilmonen et al., 2000; Uller et al., 2006). Similarly, animals that are mounting an immune response may show reduced growth and development (Fair et al., 1999; Romano et al., 2011).

The severity of these trade-offs is largely dependent on the quality of the animal's external environment, specifically the availability of energetic resources. Some of the strongest evidence that these trade-offs among physiological processes are a result of limited energetic resources come from studies where food availability is manipulated within the laboratory (French et al., 2009b). For instance, female tree lizards that are yolking eggs (the most energetically expensive component of reproduction in this species) and provided with restricted access to food under laboratory conditions take twice as long to heal a wound as compared with non-reproductive females provided a similarly restricted diet. When food is provided *ad libitum*, however, there is no difference in the wound healing time between the reproductive and non-reproductive groups (French et al., 2007). Clearly, balancing these trade-offs among competing physiological systems *via* appropriate allocation of energetic resources can be critical for maximizing an animal's current health, survival, and reproductive success.

Leptin, an endocrine mediator of energy balance

As reviewed briefly above, the presence of physiological trade-offs among competing systems, when resources are limiting, has been well established (reviewed in Demas, 2004; French et al., 2009b), but much less progress has been made in understanding the neural and endocrine mechanisms that mediate these trade-offs. One promising candidate is the metabolic hormone leptin. Leptin is a peptide hormone (composed of 167 amino acids) encoded by the *ob* gene that acts as a potent anorexigenic agent. Mice that do not produce leptin (*ob*/*ob*) or do not have the long-form leptin receptor (*db*/*db*) display an obese phenotype (Friedman and Halaas, 1998; Friedman and Leibel, 1992). Providing *ob*/*ob* mice with leptin results in reduced body weight, decreased food intake, and increased energy expenditure (Halaas et al., 1995; Pelleymounter et al., 1995). Additionally, when leptin is provided to wild type mice, body weight is reduced in a dose-dependent manner (Halaas et al., 1997).

In mammals, leptin is secreted primarily from white adipose tissue (WAT), but small amounts of leptin may also be secreted by the stomach, skeletal muscles, placenta, and brain (Ahima and Flier, 2000; Margetic et al., 2002). Furthermore, leptin has both central and peripheral effects on physiological systems. For instance, leptin regulates food intake and metabolism *via* the central nervous system. Leptin receptors are expressed in high quantities in the hypothalamus (Fei et al., 1997), and rats with hypothalamic lesions do not lose body weight or show decreases in food intake in response to leptin injections (Satoh et al., 1997). In addition, markedly lower doses of leptin can be injected intracerebroventricularly (i.c.v.) compared with peripherally to elicit effects of similar magnitude (Halaas et al., 1997), suggesting the behavioral effects of leptin are regulated centrally. Leptin receptors are also found in low quantities in the liver, kidney, lung, WAT, stomach, pancreatic β cells, skeletal muscle, and several types of immune cells (reviewed in Bjørbæk and Kahn, 2004; Frühbeck, 2002), and as such, leptin signaling affects processes such as lipolysis, insulin secretion, and blood pressure regulation.

Circulating concentrations of leptin are directly proportional to the mass of adipose tissue (Maffei et al., 1995), and leptin levels fall sharply in response to fasting (Ahima et al., 1996). Therefore, high levels of leptin indicate adequate energy stores, whereas low circulating levels of leptin are consistent with an energy deficit and may direct partitioning of energetic resources toward different systems and physiological processes. In particular, leptin may modulate reproduction (reviewed in Caprio et al., 2001; True et al., 2011), growth (Gat-Yablonski et al., 2004), development (Crespi and Denver, 2006) and immunity (discussed below). Since leptin acts to mediate the energetic regulation of multiple physiological systems, it is thought to be a primary mediator of energetic trade-offs among these systems.

Leptin and the immune response

The specific neuroendocrine mechanisms whereby adipose tissue availability is translated into a signal indicating the current energy balance for the immune system are not well known. A diversity of signaling molecules, including cytokines and hormones, that are secreted by the adipose tissue have the capability to mediate specific immune responses (Ahima and Flier, 2000). Work on mammals more definitively demonstrates that the adipose hormone leptin is involved in immunoregulation (Demas and Sakaria, 2005; Drazen et al., 2000, 2001; Fantuzzi, 2006; Lam and Lu, 2007; Zhang et al., 1994). Consistent with these findings, reductions in body fat are correlated with impaired immune function in a variety of species, including humans (Klasing, 1998; Lin and Shiau, 2003; Norgan, 1997; Spurlock et al., 1997), and experimental reductions in body fat can suppress humoral immunity, including the production of antibodies (Demas et al., 2003; Howard et al., 1999). In contrast, natural increases in body fat and experimental leptin replacement can restore prior impairments in immune function (Demas et al., 2003; Howard et al., 1999; Lord et al., 1998). Furthermore, immunological disorders (*e.g.*, AIDS) generate distinct adjustments in whole-body lipid metabolism, suggesting a significant role of adipose tissue in immunity (Pond, 1996).

Leptin, similar to most hormones, may act directly by binding to receptors on lymphoid cells (*e.g.*, circulating lymphocytes) to affect immune responses. In recent years, leptin receptors have been identified on specific leukocytes (*e.g.*, monocytes, neutrophils, natural killer cells, dendritic cells, T lymphocytes, B lymphocytes) (Bruno et al., 2005; Martin-Romero et al., 2000; Mattioli et al., 2005; Papathanassoglou et al., 2006; Sanchez-Margalet et al., 2002; Zhao et al., 2003), and it is plausible that additional receptors on other lymphoid cells exist and have not yet been discovered. Furthermore, leptin has been shown to influence the development, maintenance, and activation of certain immune cells and tissues (*e.g.*, natural killer cells, thymic cells, dendritic cells, T lymphocytes) (Howard et al., 1999; Lam et al., 2006; Martin-Romero et al., 2000; Mattioli et al., 2005; Tian et al., 2002).

The presumed presence of leptin receptors on immune cells suggests that the effects of leptin on immune function are, in part, direct. For example, leptin appears to act directly on lymphocytes, as it enhances mitogen-stimulated T-cell proliferation *in vitro* (Lord et al., 1998; Martin-Romero et al., 2000). Additionally, leptin may act indirectly, through the nervous system, to influence immune function. Studies have shown that WAT is innervated by the sympathetic nervous system (SNS) and that administering sympathomimetic amines (*e.g.*, noradrenaline, adrenaline, isoprenaline) reduces leptin gene expression in white adipose tissue and reduce circulating leptin levels (reviewed in Fliers et al., 2003; Rayner and Trayhurn, 2001). A central injection of leptin suppresses *in vitro* proliferation of splenic lymphocytes, but the suppression can be alleviated if the splenic nerve is severed prior to injection (Okamoto et al., 2000). Furthermore, in Siberian hamsters (*Phodopus sungorus*), splenocyte proliferation is only enhanced by leptin treatment if leptin is provided *in vivo* but not *in vitro*, and chemical denervation of the spleen attenuates (but does not block completely) the leptin-induced splenocyte proliferation enhancement (Demas, 2010).

Leptin is categorized as a cytokine hormone, as its structure is similar to members of the type 1 cytokine superfamily, which includes interleukin (IL)-2 and IL-6 (reviewed in Otero et al., 2006). As such, leptin may act directly to affect hematopoiesis and inflammatory responses (Fantuzzi, 2005; Gainsford and Alexander, 1999), and recent evidence suggests that some of the actions of leptin on immune function are mediated by actions on specific pro- and anti-inflammatory cytokines (see Leptin and sickness behavior section below). Genetically engineered mice provide additional evidence for effects of leptin on immunity. Mice with genetically impaired leptin signaling (*e.g.*, *ob*/*ob* mice, *db*/*db* mice) show disruptions in specific immune responses (Lord et al., 1998). Specifically, *ob*/*ob* mice that are unable to produce leptin experience atrophy of lymphatic tissues (*e.g.*, spleen, thymus), and decreases in circulating lymphocyte numbers (Lord et al., 1998). Similarly, *db*/*db* mice that are unresponsive to leptin due to a mutation of the leptin receptor, display immunological deficits. *Db*/*db* mice have reduced splenic and thymic masses and have a reduced ability to reject skin grafts and to produce cytotoxic responses (Fernandes et al., 1978). Thus, it is clear that leptin has wide effects on immune function, influencing both the maintenance of immune tissues and activation of immune responses.

While much is known in rodents and humans concerning the role of leptin in the nutritional modulation of the immune system, recent advances have been made to understand the immunomodulatory actions of leptin in other physiological contexts. For example, leptin may mediate seasonal changes in immune function in vertebrates. In many mammalian species, studies demonstrate that leptin fluctuates according to both photoperiod and season (Gaspar-López et al., 2009; Rousseau et al., 2002). For example, Siberian hamsters exposed to short, winter-like days typically exhibit decreases in body fat and immunity; however, concurrent treatment with leptin prevents this seasonal immunosuppression (Drazen et al., 2001; Gaspar-López et al., 2009). Interestingly, leptin-induced immune enhancement only occurs in animals with reduced fat stores (*i.e.*, short-day animals) and not long-day breeding animals with relatively larger fat stores (Drazen et al., 2001). Similarly, experimental reductions in body fat (*i.e.*, lipectomy) also suppress immunity, and treatment with leptin blocks the immunosuppressive effects of lipectomy on humoral immune function (Demas and Sakaria, 2005). Exogenous leptin may also attenuate metabolic stress-induced decreases in humoral immunity in Siberian hamsters (Drazen et al., 2001). Specifically, animals treated with the metabolic inhibitor 2-DG display reduced humoral immunity and exogenous leptin reverses this 2-DG-induced immunosuppression.

Innate immune responses are also suppressed in pregnant female hamsters treated with leptin (French et al., 2009a). It is unclear whether the immune effects are mediated through direct effects of leptin treatment or indirectly *via* increased retention of embryos through parturition and offspring through weaning, which alter energy balance (French et al., 2009a). This established link between leptin, energy balance, and organismal immunocompetence makes leptin a likely mediator of physiological trade-offs between the immune and other systems, especially reproduction.

Leptin and immune function in non-mammalian vertebrates

There is increasing evidence that leptin is also present in non-mammalian vertebrates. Although a gene sequence homologous to mouse leptin has been reported in fishes (Johnson et al., 2000; Kurokawa et al., 2005) and avian species (Taouis et al., 1998), the probability that this gene represents an avian or fish leptin gene is still fiercely debated (Sharp et al., 2008; Simon et al., 2009; Volkoff et al., 2005). Studies have repeatedly demonstrated functional responses to treatment with leptin in non-mammalian species, as administration of mammalian leptin reduces food intake in chickens, great tits, and goldfish (de Pedro et al., 2006; Denbow et al., 2000; Löhmus et al., 2003). However, as there is low amino acid similarity in leptin across vertebrate groups (Denver et al., 2011), these results may not be clearly interpretable. More recently, the putative leptin gene has been identified in amphibians (Boswell et al., 2006; Crespi and Denver, 2006) and reptiles (Denver et al., 2011). Furthermore, several studies have shown that administration of taxon specific leptin (*i.e.*, administering fish, rather than mammalian, leptin to fish) results in a depression of food intake in frogs (Crespi and Denver, 2006) and fish (Li et al., 2010; Murashita et al., 2008). In addition to effects on food intake, administration of leptin to non-mammalian vertebrates has produced robust effects in other physiological processes (*e.g.*, temperature regulation, testicular regression, and development) (Crespi and Denver, 2006; Niewiarowski et al., 2000; Putti et al., 2009; Sciarrillo et al., 2005), suggesting that leptin or a leptin-like molecule may be mediating physiological trade-offs across a wide range of taxa.

Like the metabolic actions of leptin discussed prior sections, there is increasing evidence that leptin may affect immunity in non-mammalian vertebrates. Leptin and leptin receptor mRNA are expressed in important immune organs (*i.e.*, spleen) of the South African clawed frog (*Xenopus laevis*), and the leptin gene is constitutively expressed in both the spleen and thymus of common carp (*Cyprinus carpio*) (Crespi and Denver, 2006; Huising et al., 2006). Studies have demonstrated functional immune responses to treatment with leptin in non-mammalian species. For example, turkeys (*Meleagris gallopavo*) provided with the protein generated by the leptin-like avian gene (*i.e.*, isolated from chickens) show enhanced T-cell proliferation in response to the mitogen concavalin A (Löhmus et al., 2004), and zebra finches treated with recombinant murine leptin have enhanced wing-web swelling in response to the mitogen phytohemagglutinin (Alonso-Alvarez et al., 2007). Recent findings further demonstrate that leptin is partially responsible for energetic trade-offs in tree lizards (*Urosaurus ornatus*), whereby leptin treatment reinstates immunity to normal levels in immunosuppressed reproductive females (French et al., 2011). These results are as predicted if the effects of leptin are similar in birds, reptiles, amphibians, fishes, and mammals. While future studies will need to address the effects of leptin on the immune system in non-mammalian vertebrates by using taxon-matched leptin, the cumulative evidence concerning the physiological actions of leptin in non-mammalian vertebrates suggests that leptin, or at least some leptin-like protein, is present and functional across a wide range of vertebrate species. With the recent advances in the characterization of the leptin and leptin receptor sequences in these classes of non-mammalian vertebrates, we expect to see great progress in our understanding of how leptin affects immune function and physiological trade-offs in taxon-specific manners.

Leptin and sickness behavior

A critical component of immunity, and one of the first responses of the body to infection, is the acute phase response (APR), and subsequent accompanying behavioral and physiological manifestations of sickness. During the APR, proinflammatory cytokines, released from activated neutrophils and macrophages, aid in the recruitment of other immune cells to the local site of infection. These cytokines also act on the brain to generate a sickness response, which is characterized by additional release of proinflammatory cytokines, fever, anorexia, and reductions in social, exploratory, and sexual behaviors (Hart, 1988; Tizard, 2008). While behavioral patterns associated with the sickness response may appear to be a result of infection-induced weakness, these responses are actually a well adapted response to aid the host organism in clearance of the infectious agent (Hart, 1988). For instance, fever acts to inhibit the growth of some viral and bacterial pathogens, and the elevated temperature may increase the efficiency of immunological responses by enhancing bacterial killing by neutrophils and lymphocyte proliferation

(Kluger, 1986). Additionally, blocking the fever response increases the likelihood of death in response to infection in lizards, fish, and rabbits, suggesting that the fever response is critical for animals to survive illness (Covert and Reynolds, 1977; Kluger et al., 1975; Vaughn et al., 1980). Anorexia may also be adaptive because it promotes a more efficient immune response (*i.e.*, force feeding some organisms to achieve normal dietary intake during sickness results in increased mortality), and it may lead to greater stringency in diet selection, which allows an animal to alter its internal environment, rendering it less favorable for pathogen growth. Additionally, anorexia may be a strategy for conserving energy that would be used during foraging bouts (Kyriazakis et al., 1998; Tizard, 2008). Mounting a sickness response is clearly beneficial to an organism's survival, but being sick is also a significant energetic investment. Maintaining a fever results in an increased metabolic rate (Buchanan et al., 2003; Maier et al., 1994), while anorexic behavior limits an animal's energetic stores and contributes to body mass loss during illness. Thus, given the role of leptin in metabolism, food intake, and immunomodulation, it seems likely that leptin may play a role in coordination of aspects of the sickness response.

Much of the work on sickness behavior has been performed by experimentally inducing sickness with lipopolysaccharide (LPS), an inert antigen from the cell wall of gram-negative bacteria. LPS is recognized by Toll-like receptor (TLR) 4, and activation of TLR4 stimulates the production of the proinflammatory cytokines, interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, which are released by activated neutrophils and macrophages and then act on the brain *via* the vagus nerve or humoral pathways (Konsman et al., 2002; Quan and Banks, 2007). The connection between leptin and the proinflammatory cytokines that are integral to the sickness response is bidirectional. Leptin enhances the production of the proinflammatory cytokines TNF-α and IL-6 from macrophages when cultured with LPS, and leptin deficient (*ob*/*ob*) mice produce lower levels of TNF-α and IL-6 after injection with LPS when compared with wild type littermates (Loffreda et al., 1998). Additionally, leptin administered either i.c.v. or peripherally (i.p.) results in increased levels of IL-1β in the hypothalamus (Luheshi et al., 1999), and intravenous (i.v.) administration of leptin can induce IL-1β mRNA expression even when the vagus nerve is cut, suggesting that the induction of IL-1β by leptin can occur directly within the brain (Hosoi et al., 2002). Moreover, administration of LPS or proinflammatory cytokines (IL-1β, TNF-α) results in increased production of leptin, in the forms of increases in mRNA expression and circulating serum levels (IL-6 injection results in a non-significant trend to increase circulating leptin levels), while LPS administration does not increase leptin levels in IL-1β deficient mice (Faggioni et al., 1998; Finck et al., 1998; Grunfeld et al., 1996; Sarraf et al., 1997). Further evidence that proinflammatory cytokines trigger leptin release comes from endotoxin insensitive mice (*i.e.*, mice in which a mutation has rendered their macrophages unresponsive to LPS). These mice do not show increases in circulating leptin when injected with LPS, but do show increases in leptin levels when treated with TNF-α, suggesting that it is proinflammatory cytokines that are acting directly on adipocytes, rather than some upstream effects of LPS, that are triggering release of leptin in these animals (Finck et al., 1998).

While it is evident that leptin levels are both modulated by and can modulate proinflammatory cytokines, debate remains as to how leptin may influence the actual sickness response. Two separate studies have shown that rats that are administered leptin anti-serum, to neutralize circulating leptin levels, show a lack of or attenuated fever following LPS injections (Harden et al., 2006; Sachot et al., 2004). Some evidence suggests that leptin may act in concert with IL-1β to induce fever. Administration of leptin anti-serum to mice that have been treated with LPS not only attenuates fever but also simultaneously reduces IL-1β mRNA expression in the hypothalamus (Sachot et al., 2004). Additionally, treatment of rats with leptin alone results in increases in body temperature, and these leptin-induced increases in temperature can be abolished when these rats are provided with an IL-1 receptor antagonist (Luheshi et al., 1999).

Although these results imply that leptin is involved in the regulation of fever, other studies suggest the opposite, that leptin has little involvement in fever induction. For example, Zucker obese rats (*fa*/*fa*), which have a non-functional leptin receptor, show no difference in their fever response to LPS treatment when compared with lean rats, suggesting that leptin signaling is not necessary for fever production (Ivanov and Romanovsky, 2002). Rats that are fasted (resulting in a decline in circulating leptin concentrations) and injected with a high (1000 μg/kg) or low (100 μg/kg) dose of LPS show an attenuated fever response as compared to rats that are fed *ad libitum*; however, leptin replacement only rescues the fever response in rats that receive high doses of LPS, and fever remains attenuated in rats receiving lower doses (Inoue and Luheshi, 2010). While earlier work showed that leptin treatment alone can induce fever and that fever may be induced through interactions with IL-1β (Luheshi et al., 1999; Sachot et al., 2004), several recent studies have provided results that contradict these conclusions. For instance, Wistar rats that are food deprived show a mild hypothermic response, and infusion with leptin can alleviate this hypothermia; however, leptin infusion only rescues temperature to pre-food deprivation levels when provided at high doses (250 μg/kg, 1000 μg/kg) and not a lower dose (100 μg/kg). Additionally, leptin infusion does not generate fever (*i.e.*, temperature above pre-food deprivation levels) with any of the doses (Steiner et al., 2009). Finally, whereas treatment with leptin anti-serum impairs LPS-induced fever in rats, treatment of rats with IL-1β anti-serum does not impair LPS-induced fever (*c.f.* Luheshi et al., 1999 and Sachot et al., 2004), but treatment with IL-6 anti-serum abolishes the LPS-induced fever similarly to leptin anti-serum (Harden et al., 2006). Thus, leptin appears to influence changes in body temperature; however, the magnitude of its effect and the mechanism by which it coordinates these changes remain unclear.

Leptin is a likely candidate mediating the anorexic response to sickness as this hormone mediates food intake in non-sick individuals and is increased in response to infection. The evidence linking leptin to the control of sickness-induced anorexia, however, is mixed. For example, treating rats with leptin antiserum eliminates the anorexic effects of LPS-induced inflammation (Harden et al., 2006; Sachot et al., 2004), suggesting that leptin is critical for anorexic behavior in response to sickness. In addition, mice provided a calorie-restricted diet, which lowers circulating leptin levels, show no anorexia when treated with LPS (MacDonald et al., 2011). Alternatively, other evidence suggests that leptin may not have a role in sickness-induced anorexia. For instance, LPS administration produces the anorexic effect in *ob*/*ob* mice, *db*/*db* mice, and *fa*/*fa* rats, even though these animals lack functional leptin signaling (Faggioni et al., 1997; Lugarini et al., 2005). Furthermore, the relationship (or lack of relationship) between leptin and sickness-induced anorexia becomes even more complicated because the patterns of LPS-induced anorexia differ between the leptin deficient (*ob*/*ob*) and leptin receptor deficient (*db*/*db*) mice, as *ob*/*ob* mice display more severe anorexia than controls while *db*/*db* mice show attenuated anorexia as compared to controls (Faggioni et al., 1997). The exact role of leptin in sickness-induced anorexia has not been uncovered, but it appears that leptin plays a role in this anorexic response. Leptin, however, may be only one player among many orexigenic and anorexigenic peptides that coordinate sickness-induced anorexia (Table 1).

There is mixed evidence that leptin may mediate sickness-induced changes in activity levels. *Db*/*db* mice show a greater reduction in social exploration in response to LPS or IL-1β injection as compared to non-mutant animals (O'Connor et al., 2005). Conversely, treating rats with leptin anti-serum does not alleviate the suppressive effects of LPS on voluntary wheel running (Harden et al., 2006). Due to the

Table 1
Orexigenic and anorexigenic hormones that may contribute to the sickness-induced anorexic response.

Hormone	Effect on food intake	Response to LPS or pro-inflammatory cytokine injection	Relationship to sickness-induced anorexia	Key references
Ghrelin	Orexigenic	Circulating levels decrease	Providing ghrelin alleviates LPS- and cytokine-induced anorexia, suggesting that decreases in circulating ghrelin facilitate anorexia	Baatar et al. (2011), Basa et al. (2003), Gonzalez et al. (2006)
Neuropeptide Y (NPY)	Orexigenic	No change or small decreases in hypothalamic mRNA expression	Simultaneous i.c.v. infusion of NPY with IL-1 eliminates sickness-induced anorexia, but lack of increase in mRNA expression suggests NPY plays little natural role in sickness-induced anorexia	Gautron et al. (2005), Gayle et al. (1997), Lennie et al. (2001), Sergeyev et al. (2001), Sonti et al. (1996)
Alpha-melanocyte-stimulating hormone (α-MSH)	Anorexigenic	Circulating levels increase	Blocking melanocortin receptor-4 after LPS injection eliminates anorexia, while i.c.v. infusion of α-MSH enhances LPS-induced anorexia, suggesting that increased α-MSH levels facilitate anorexia	Huang et al. (1999), Marks et al. (2003), Martin and Lipton (1990)
Cholecystokinin (CCK)	Anorexigenic	Mixed results--some work shows circulating levels increase, some shows circulating levels decrease	Results are inconclusive--blocking CCK receptors during LPS-induced sickness does not alleviate anorexic response, but CCK_2 receptor knock-out mice show attenuated anorexic responses to LPS as compared to wild type mice	Bret-Dibat and Dantzer (2000), Daun and McCarthy (1993), Weiland et al. (2005), Weiland et al. (2007)
Corticotropin-releasing hormone (CRH)	Anorexigenic	Circulating levels increase	Results are inconclusive--neutralizing CRH with CRH antiserum before IL-1 injection attenuates anorexic response but CRH knockout mice display similar anorexic responses to LPS and IL-1β as wild type mice	Berkenbosch et al. (1987), Sapolsky et al. (1987), Swiergiel and Dunn (1999), Uehara et al. (1989)

equivocal and sparse empirical data reported to date, it is not clear how or if leptin plays a role in the changes in activity levels that accompany sickness, but it does seem probable that leptin may be involved in this sickness-induced behavior as it has been demonstrated to modulate activity levels in non-sick individuals (Pelleymounter et al., 1995).

The results of the studies examining the role of leptin in mediating aspects of the sickness response are rather inconclusive. Mutant leptin models (*e.g.*, *ob*/*ob*, *db*/*db*, *fa*/*fa*) are examples of extreme leptin phenotypes, as they are models for either leptin deficiency (*ob*/*ob*) or leptin resistance (*db*/*db*, *fa*/*fa*). As such, it is impossible to disentangle the effects of leptin on the sickness response from the concurrent effects of obesity, diabetes, and other metabolic disorders that these animals display. Rather studies in which food availability is manipulated likely provide a more natural examination of how leptin influences sickness responses, investigating more closely the role of leptin as a starvation signal (Ahima et al., 1996).

If we consider the results of studies in which food availability is manipulated or in which leptin levels are experimentally altered within normal physiological ranges, it seems plausible that leptin may not be acting directly to influence fever or anorexic response to sickness. Instead, leptin is likely acting indirectly to affect these sickness responses by providing a signal to modulate pro- and anti-inflammatory cytokine release and cytokine sensitivity. For instance, male Wistar rats that are fasted for 48 h show a 30% reduction in hypothalamic IL-1β mRNA (Wisse et al., 2004), and rats displaying diet-induced obesity show greater levels of circulating proinflammatory cytokines and hypothalamic proinflammatory cytokine mRNA compared to lean controls after LPS injection (Pohl et al., 2009), suggesting that changes in energy stores may alter cytokine production. Additional support for this hypothesis comes from the experiments employing leptin anti-serum to neutralize circulating leptin levels, as it not only depresses the LPS-induced fever response but also results in decreased LPS-induced hypothalamic IL-1β mRNA expression (Sachot et al., 2004). Although treating rats with IL-1β antiserum does not depress the LPS-induced sickness response (Harden et al., 2006), as would be expected from the results of Sachot et al. (2004), this does not necessarily contradict the hypothesis that leptin is acting to influence cytokine release and sensitivity that ultimately influences the magnitude of an organism's sickness response. Alternatively, these results suggest that multiple proinflammatory and anti-inflammatory cytokines interact to generate fever and anorexia (reviewed in Buchanan and Johnson, 2007; Conti et al., 2004). Additional experiments addressing if and how natural circulating leptin levels *versus* LPS-induced leptin levels differentially affect sickness responses will help us elucidate if leptin is acting to provide a continuous signal of current energy stores in order to "prime" the immune system to respond appropriately given the organism's finite energy availability.

Leptin as an integrator of seasonal sickness responses

There is little doubt that sickness demands a substantial energetic investment by an organism. However, as animals vary in their fat (energy) stores, there may be limits to the degree to which the animal can afford to maintain a metabolically demanding fever or restrict food intake. One potential role of leptin in the sickness behavior phenotype is that it may provide a signal of current energy availability that allows the organism to modulate the intensity of its sickness response. Seasonally breeding animals provide a system in which this hypothesis may be tested, as many of these animals display great fluctuations in body fat stores across the annual cycle. For example, male Siberian hamsters, which exhibit sharp decreases in body fat stores and circulating leptin levels when housed in winter-like, short-day photoperiods, display highly attenuated sickness responses to LPS as compared with hamsters housed in summer-like, long-day photoperiods (Bilbo et al., 2002). Specifically, when these short-day housed hamsters are treated with LPS, they show a shorter fever duration, less pronounced decrease in body mass and food intake, and reduced production of the proinflammatory cytokines, IL-1β and IL-6, as compared to long-day housed animals treated with the same dose of LPS. A similar pattern is observed in captive male white-crowned sparrows (*Zonotrichia leucophrys gambelii*). Males housed in long-day photoperiods have more fat than males housed in short-day photoperiods, and subsequently, the long-day males show a greater percent decrease in body mass in response to LPS treatment as compared to short-day males (Owen-Ashley et al., 2006). Furthermore, there is a negative correlation between initial body mass and the percent change in body mass in response to LPS

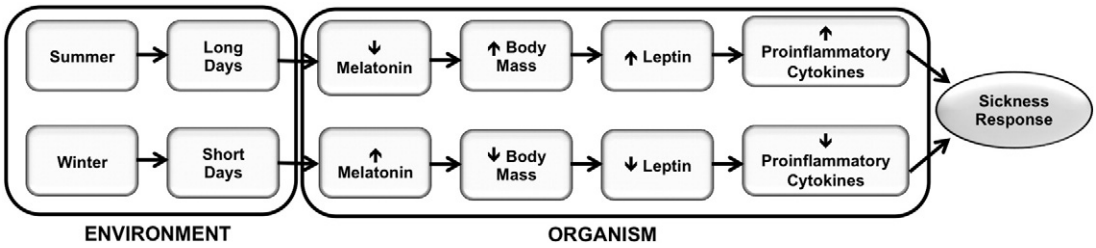

Fig. 1. Theoretical model for how leptin may influence seasonal variation in sickness responses in Siberian hamsters. In this model, environmental cues (*e.g.*, photoperiod) trigger a change in the organism's physiology and/or behavior. Specifically, decreases in photoperiod are encoded *via* increases in the duration of melatonin release which, in turn, induces decreases in body mass and fat stores. Decreases in body fat are accompanied by corresponding decreases or increases in circulating leptin concentrations, which in turn facilitate changes in proinflammatory cytokines in response to infection.

injection across all birds (short- and long-day, males and females), showing that initially fatter birds exhibit greater weight loss in response to LPS-induced sickness.

While these studies provide data that are suggestive of energetic modulation of sickness behaviors, there are other immunomodulatory hormones that vary seasonally and could affect sickness responses (*i.e.*, sex steroids, melatonin, glucocorticoids) (reviewed in Adelman and Martin, 2009; Ashley and Wingfield, 2012). It may be difficult to uncouple the effects of these hormones from the effects of energetic stores on modulation of the sickness response, as many animals tend to have higher body fat stores during the long day breeding season. However, free-living male song sparrows (*Melospiza melodia morphna*) have lower fat stores during the spring breeding season and display an attenuated sickness response (*i.e.*, no decrease in territorial aggression, smaller change in percent body mass loss) in the spring as compared to the winter, suggesting that it may be energy stores rather than breeding status or a seasonal melatonin cue that is driving seasonal variation in sickness response intensity (Owen-Ashley and Wingfield, 2006).

Whereas the relationship between sickness response intensity and body fat stores has been shown in these species, it is not yet known whether the changes in circulating leptin concentrations that accompany decreases in body fat are providing the signal that leads to the seasonal modulation of these sickness behaviors. We have developed a theoretical model by which leptin may mediate sickness responses in the seasonally breeding Siberian hamster (Fig. 1). In this model, an environmental cue (in this case, photoperiod) triggers a change in the organism's physiology and/or behavior. In Siberian hamsters, photoperiod is translated within the organism *via* changes in the duration of melatonin release. This change in the duration of release results in other changes in the organism's physiology, which includes decreases (short-day photoperiods) or increases (long-day photoperiods) in body mass and fat stores. Decreases or increases in body fat stores are accompanied by corresponding decreases or increases in circulating leptin concentrations, which in turn facilitate lesser or greater release (and potentially naturally circulating levels) of proinflammatory cytokines in response to infection. Ongoing studies in our lab are aimed at testing these ideas.

Conclusions

In this review, we have highlighted the progress that has been made in understanding how leptin may mediate an animal's response to illness. Since the discovery of leptin in the 1990s, researchers have made incredible progress understanding its functions in regulating energy balance and communicating with the immune system. Many studies have shown that manipulating leptin levels *via* treatment with exogenous leptin or removal or replacement of body fat stores can modulate both innate and humoral immune responses. Although there is evidence to support a role of leptin in the sickness response (*i.e.*, increased mRNA expression and release in response to LPS and proinflammatory cytokine injection and attenuation of LPS-induced fever and anorexia with treatment with leptin anti-serum), there are also results from studies in mutant mouse and rat models that suggest that leptin may not have a significant effect in modulating sickness behaviors. These conflicting results are not unexpected, as leptin does not act in autonomy but rather acts in concert with other orexigenic (*e.g.*, ghrelin, NPY) and anorexigenic (*e.g.*, CCK, α-MSH, CRH) peptides and neuropeptides, many of which have been shown to interact with the immune system (reviewed in Baatar et al., 2011; Bedoui et al., 2003; Luger et al., 2003; Matarese and La Cava, 2004; Szekely et al., 2004). Past research has established that leptin levels may influence the magnitude of immune responses and sickness behaviors in response to noninfectious, inert antigens, but the next step is to address how population variation in body fat stores and leptin levels among organisms and also, how temporal variation in fat stores within an organism may influence susceptibility, resistance, and spread of replicating pathogens in the wild.

References

Adelman, J.S., Martin, L.B., 2009. Vertebrate sickness behaviors: adaptive and integrated neuroendocrine immune responses. Integr. Comp. Biol. 49, 202–214.
Ahima, R.S., Flier, J.S., 2000. Adipose tissue as an endocrine organ. Trends Endocrinol. Metab. 11, 327–332.
Ahima, R.S., Prabakaran, D., Mantzoros, C., Qu, D.Q., Lowell, B., Maratos-Flier, E., Flier, J.S., 1996. Role of leptin in the neuroendocrine response to fasting. Nature 382, 250–252.
Alonso-Alvarez, C., Bertrand, S., Sorci, G., 2007. Energetic reserves, leptin and testosterone: a refinement of the immunocompetence handicap hypothesis. Biol. Lett. 3, 271–274.
Ashley, N.T., Wingfield, J.C., 2012. Sickness behavior in vertebrates: allostasis, life-history modulation, and hormonal regulation. In: Demas, G.E., Nelson, R.J. (Eds.), Ecoimmunology. Oxford University Press, New York, pp. 45–91.
Baatar, D., Patel, K., Taub, D.D., 2011. The effects of ghrelin on inflammation and the immune system. Mol. Cell. Endocrinol. 340, 44–58.
Basa, N.R., Wang, L., Arteaga, J.R., Heber, D., Livingston, E.H., Tache, Y., 2003. Bacterial lipopolysaccharide shifts fasted plasma ghrelin to postprandial levels in rats. Neurosci. Lett. 343, 25–28.
Bedoui, S., Kawamura, N., Straub, R.H., Pabst, R., Yamamura, T., von Horsten, S., 2003. Relevance of neuropeptide Y for the neuroimmune crosstalk. J. Neuroimmunol. 134, 1–11.
Berkenbosch, F., Vanoers, J., Delrey, A., Tilders, F., Besedovsky, H., 1987. Corticotropin-releasing factor producing neurons in the rat activated by interleukin-1. Science 238, 524–526.
Bilbo, S.D., Drazen, D.L., Quan, N., He, L., Nelson, R.J., 2002. Short day lengths attenuate the symptoms of infection in Siberian hamsters. Proc. R. Soc. Lond. B Biol. Sci. 269, 447–454.
Bjørbæk, C., Kahn, B.B., 2004. Leptin signaling in the central nervous system and the periphery. Recent Prog. Horm. Res. 59, 305–331.
Bonneaud, C., Mazuc, J., Gonzalez, G., Haussy, C., Chastel, O., Faivre, B., Sorci, G., 2003. Assessing the cost of mounting an immune response. Am. Nat. 161, 367–379.
Boswell, T., Dunn, I.C., Wilson, P.W., Joseph, N., Burt, D.W., Sharp, P.J., 2006. Identification of a non-mammalian leptin-like gene: characterization and expression in the tiger salamander (*Ambystoma tigrinum*). Gen. Comp. Endocrinol. 146, 157–166.
Bret-Dibat, J.L., Dantzer, R., 2000. Cholecystokinin receptors do not mediate the suppression of food-motivated behavior by lipopolysaccharide and interleukin-1 beta in mice. Physiol. Behav. 69, 325–331.
Bruno, A., Conus, S., Schmid, I., Simon, H.U., 2005. Apoptotic pathways are inhibited by leptin receptor activation in neutrophils. J. Immunol. 174, 8090–8096.
Buchanan, J.B., Johnson, R.W., 2007. Regulation of food intake by inflammatory cytokines in the brain. Neuroendocrinology 86, 183–190.
Buchanan, J.B., Peloso, E., Satinoff, E., 2003. Thermoregulatory and metabolic changes during fever in young and old rats. Am. J. Physiol. Regul. Integr. Comp. Physiol. 285, R1165–R1169.

Caprio, M., Fabbrini, E., Isidori, A.M., Aversa, A., Fabbri, A., 2001. Leptin in reproduction. Trends Endocrinol. Metab. 12, 65–72.
Conti, B., Tabarean, I., Andrei, C., Bartfai, T., 2004. Cytokines and fever. Front. Biosci. 9, 1433–1449.
Covert, J.B., Reynolds, W.W., 1977. Survival value of fever in fish. Nature 267, 43–45.
Crespi, E.J., Denver, R.J., 2006. Leptin (ob gene) of the South African clawed frog *Xenopus laevis*. Proc. Natl. Acad. Sci. U. S. A. 103, 10092–10097.
Daun, J.M., McCarthy, D.O., 1993. The role of cholecystokinin in interleukin-1-induced anorexia. Physiol. Behav. 54, 237–241.
de Pedro, N., Martinez-Alvarez, R., Delgado, M.J., 2006. Acute and chronic leptin reduces food intake and body weight in goldfish (*Carassius auratus*). J. Endocrinol. 188, 513–520.
Demas, G.E., 2004. The energetics of immunity: a neuroendocrine link between energy balance and immune function. Horm. Behav. 45, 173–180.
Demas, G.E., 2010. *In vivo* but not *in vitro* leptin enhances lymphocyte proliferation in Siberian hamsters (*Phodopus sungorus*). Gen. Comp. Endocrinol. 166, 314–319.
Demas, G.E., Sakaria, S., 2005. Leptin regulates energetic tradeoffs between body fat and humoural immunity. Proc. R. Soc. Lond. B Biol. Sci. 272, 1845–1850.
Demas, G.E., Chefer, V., Talan, M.I., Nelson, R.J., 1997. Metabolic costs of mounting an antigen-stimulated immune response in adult and aged C57BL/6J mice. Am. J. Physiol. Regul. Integr. Comp. Physiol. 273, R1631–R1637.
Demas, G.E., Drazen, D.L., Nelson, R.J., 2003. Reductions in total body fat decrease humoral immunity. Proc. R. Soc. Lond. B Biol. Sci. 270, 905–911.
Denbow, D.M., Meade, S., Robertson, A., McMurtry, J.P., Richards, M., Ashwell, C., 2000. Leptin-induced decrease in food intake in chickens. Physiol. Behav. 69, 359–362.
Denver, R.J., Bonett, R.M., Boorse, G.C., 2011. Evolution of leptin structure and function. Neuroendocrinology 94, 21–38.
Drazen, D.L., Kriegsfeld, L.J., Schneider, J.E., Nelson, R.J., 2000. Leptin, but not immune function, is linked to reproductive responsiveness to photoperiod. Am. J. Physiol. Regul. Integr. Comp. Physiol. 278, R1401–R1407.
Drazen, D.L., Demas, G.E., Nelson, R.J., 2001. Leptin effects on immune function and energy balance are photoperiod dependent in Siberian hamsters (*Phodopus sungorus*). Endocrinology 142, 2768–2775.
Faggioni, R., Fuller, J., Moser, A., Feingold, K.R., Grunfeld, C., 1997. LPS-induced anorexia in leptin-deficient (ob/ob) and leptin receptor-deficient (db/db) mice. Am. J. Physiol. 273, R181–R186.
Faggioni, R., Fantuzzi, G., Fuller, J., Dinarello, C.A., Feingold, K.R., Grunfeld, C., 1998. IL-1 beta mediates leptin induction during inflammation. Am. J. Physiol. 274, R204–R208.
Faggioni, R., Feingold, K.R., Grunfeld, C., 2001. Leptin regulation of the immune response and the immunodeficiency of malnutrition. FASEB J. 15, 2565–2571.
Fair, J.M., Hansen, E.S., Ricklefs, R.E., 1999. Growth, developmental stability and immune response in juvenile Japanese quails (*Coturnix coturnix japonica*). Proc. R. Soc. Lond. B Biol. Sci. 266, 1735–1742.
Fantuzzi, G., 2005. Adipose tissue, adipokines, and inflammation. J. Allergy Clin. Immunol. 115, 911–919.
Fantuzzi, G., 2006. Leptin: nourishment for the immune system. Eur. J. Immunol. 36, 3101–3104.
Fei, H., Okano, H.J., Li, C., Lee, G.H., Zhao, C., Darnell, R., Friedman, J.M., 1997. Anatomic localization of alternatively spliced leptin receptors (Ob-R) in mouse brain and other tissues. Proc. Natl. Acad. Sci. U. S. A. 94, 7001–7005.
Fernandes, G., Handwerger, B.S., Yunis, E.J., Brown, D.M., 1978. Immune response in the mutant diabetic C57BL/Ks-dt + mouse. Discrepancies between *in vitro* and *in vivo* immunological assays. J. Clin. Invest. 61, 243–250.
Finck, B.N., Kelley, K.W., Dantzer, R., Johnson, R.W., 1998. *In vivo* and *in vitro* evidence for the involvement of tumor necrosis factor-alpha in the induction of leptin by lipopolysaccharide. Endocrinology 139, 2278–2283.
Fliers, E., Kreier, F., Voshol, P.J., Havekes, L.M., Sauerwein, H.P., Kalsbeek, A., Buijs, R.M., Romijn, J.A., 2003. White adipose tissue: getting nervous. J. Neuroendocrinol. 15, 1005–1010.
French, S.S., DeNardo, D.F., Moore, M.C., 2007. Trade-offs between the reproductive and immune systems: facultative responses to resources or obligate responses to reproduction? Am. Nat. 170, 79–89.
French, S.S., Greives, T.J., Zysling, D.A., Chester, E.M., Demas, G.E., 2009a. Leptin increases maternal investment. Proc. R. Soc. Lond. B Biol. Sci. 276, 4003–4011.
French, S.S., Moore, M.C., Demas, G.E., 2009b. Ecological immunology: the organism in context. Integr. Comp. Biol. 49, 246–253.
French, S.S., Dearing, M.D., Demas, G.E., 2011. Leptin as a physiological mediator of energetic trade-offs in ecoimmunology: implications for disease. Integr. Comp. Biol. 51, 505–513.
Friedman, J.M., Halaas, J.L., 1998. Leptin and the regulation of body weight in mammals. Nature 395, 763–770.
Friedman, J.M., Leibel, R.L., 1992. Tackling a weighty problem. Cell 69, 217–220.
Frühbeck, G., 2002. Peripheral actions of leptin and its involvement in disease. Nutr. Rev. 60, S47–S55 (discussion S68-84, 85–47).
Gainsford, T., Alexander, W.S., 1999. A role for leptin in hemopoieses? Mol. Biotechnol. 11, 149–158.
Gaspar-López, E., Casabiell, J., Estevez, J.A., Landete-Castillejos, T., De La Cruz, L.F., Gallego, L., Garcia, A.J., 2009. Seasonal changes in plasma leptin concentration related to antler cycle in Iberian red deer stags. J. Comp. Physiol. B 179, 617–622.
Gat-Yablonski, G., Ben-Ari, T., Shtaif, B., Potievsky, O., Moran, O., Eshet, R., Maor, G., Segev, Y., Phillip, M., 2004. Leptin reverses the inhibitory effect of caloric restriction on longitudinal growth. Endocrinology 145, 343–350.
Gautron, L., Mingam, R., Moranis, A., Combe, C., Laye, S., 2005. Influence of feeding status on neuronal activity in the hypothalamus during lipopolysaccharide-induced anorexia in rats. Neuroscience 134, 933–946.
Gayle, D., Ilyin, S.E., Plata-Salaman, C.R., 1997. Central nervous system IL-1 beta system and neuropeptide Y mRNAs during IL-1 beta-induced anorexia in rats. Brain Res. Bull. 44, 311–317.
Gonzalez, P.V., Cragnolini, A.B., Schioth, H.B., Scimonelli, T.N., 2006. Interleukin-1 beta-induced anorexia is reversed by ghrelin. Peptides 27, 3220–3225.
Grunfeld, C., Zhao, C., Fuller, J., Pollack, A., Moser, A., Friedman, J., Feingold, K.R., 1996. Endotoxin and cytokines induce expression of leptin, the ob gene product, in hamsters. J. Clin. Invest. 97, 2152–2157.
Halaas, J.L., Gajiwala, K.S., Maffei, M., Cohen, S.L., Chait, B.T., Rabinowitz, D., Lallone, R.L., Burley, S.K., Friedman, J.M., 1995. Weight reducing effects of the plasma protein encoded by the obese gene. Science 269, 543–546.
Halaas, J.L., Boozer, C., BlairWest, J., Fidahusein, N., Denton, D.A., Friedman, J.M., 1997. Physiological response to long-term peripheral and central leptin infusion in lean and obese mice. Proc. Natl. Acad. Sci. U. S. A. 94, 8878–8883.
Harden, L.M., du Plessis, I., Poole, S., Laburn, H.P., 2006. Interleukin-6 and leptin mediate lipopolysaccharide-induced fever and sickness behavior. Physiol. Behav. 89, 146–155.
Hart, B.L., 1988. Biological basis of the behavior of sick animals. Neurosci. Biobehav. Rev. 12, 123–137.
Hosoi, T., Okuma, Y., Ono, A., Nomura, Y., 2002. Subdiaphragmatic vagotomy fails to inhibit intravenous leptin-induced IL-1beta expression in the hypothalamus. Am. J. Physiol. Regul. Integr. Comp. Physiol. 282, R627–R631.
Howard, J.K., Lord, G.M., Matarese, G., Vendetti, S., Ghatei, M.A., Ritter, M.A., Lechler, R.I., Bloom, S.R., 1999. Leptin protects mice from starvation-induced lymphoid atrophy and increases thymic cellularity in ob/ob mice. J. Clin. Invest. 104, 1051–1059.
Huang, Q.H., Hruby, V.J., Tatro, J.B., 1999. Role of central melanocortins in endotoxin-induced anorexia. Am. J. Physiol. 276, R864–R871.
Huising, M.O., Geven, E.J., Kruiswijk, C.P., Nabuurs, S.B., Stolte, E.H., Spanings, F.A., Verburg-van Kemenade, B.M., Flik, G., 2006. Increased leptin expression in common Carp (*Cyprinus carpio*) after food intake but not after fasting or feeding to satiation. Endocrinology 147, 5786–5797.
Ilmonen, P., Taarna, T., Hasselquist, D., 2000. Experimentally activated immune defence in female pied flycatchers results in reduced breeding success. Proc. R. Soc. Lond. B Biol. Sci. 267, 665–670.
Inoue, W., Luheshi, G.N., 2010. Acute starvation alters lipopolysaccharide-induced fever in leptin-dependent and -independent mechanisms in rats. Am. J. Physiol. Regul. Integr. Comp. Physiol. 299, R1709–R1719.
Ivanov, A.I., Romanovsky, A.A., 2002. Fever responses of Zucker rats with and without fatty mutation of the leptin receptor. Am. J. Physiol. Regul. Integr. Comp. Physiol. 282, R311–R316.
Johnson, R.M., Johnson, T.M., Londraville, R.L., 2000. Evidence for leptin expression in fishes. J. Exp. Zool. 286, 718–724.
Kelly, D., Coutts, A.G., 2000. Early nutrition and the development of immune function in the neonate. Proc. Nutr. Soc. 59, 177–185.
Klasing, K.C., 1998. Nutritional modulation of resistance to infectious diseases. Poult. Sci. 77, 1119–1125.
Kluger, M.J., 1986. Is fever beneficial? Yale J. Biol. Med. 59, 89–95.
Kluger, M.J., Ringler, D.H., Anver, M.R., 1975. Fever and survival. Science 188, 166–168.
Konsman, J.P., Parnet, P., Dantzer, R., 2002. Cytokine-induced sickness behaviour: mechanisms and implications. Trends Neurosci. 25, 154–159.
Kurokawa, T., Uji, S., Suzuki, T., 2005. Identification of cDNA coding for a homologue to mammalian leptin from pufferfish, *Takifugu rubripes*. Peptides 26, 745–750.
Kyriazakis, I., Tolkamp, B.J., Hutchings, M.R., 1998. Towards a functional explanation for the occurrence of anorexia during parasitic infections. Anim. Behav. 56, 265–274.
Lam, Q.L., Lu, L., 2007. Role of leptin in immunity. Cell. Mol. Immunol. 4, 1–13.
Lam, Q.L., Liu, S., Cao, X., Lu, L., 2006. Involvement of leptin signaling in the survival and maturation of bone marrow-derived dendritic cells. Eur. J. Immunol. 36, 3118–3130.
Lennie, T.A., Wortman, M.D., Seeley, R.J., 2001. Activity of body energy regulatory pathways in inflammation-induced anorexia. Physiol. Behav. 73, 517–523.
Li, G.G., Liang, X.F., Xie, Q., Li, G., Yu, Y., Lai, K., 2010. Gene structure, recombinant expression and functional characterization of grass carp leptin. Gen. Comp. Endocrinol. 166, 117–127.
Lin, Y.H., Shiau, S.Y., 2003. Dietary lipid requirement of grouper, *Epinephelus malabaricus*, and effects on immune responses. Aquaculture 225, 243–250.
Lochmiller, R.L., Deerenberg, C., 2000. Trade-offs in evolutionary immunology: just what is the cost of immunity? Oikos 88, 87–98.
Loffreda, S., Yang, S.Q., Lin, H.Z., Karp, C.L., Brengman, M.L., Wang, D.J., Klein, A.S., Bulkley, G.B., Bao, C., Noble, P.W., Lane, M.D., Diehl, A.M., 1998. Leptin regulates proinflammatory immune responses. FASEB J. 12, 57–65.
Löhmus, M., Sundstrom, L.F., El Halawani, M., Silverin, B., 2003. Leptin depresses food intake in great tits (*Parus major*). Gen. Comp. Endocrinol. 131, 57–61.
Löhmus, M., Olin, M., Sundstrom, L.F., Troedsson, M.H.T., Molitor, T.W., El Halawani, M., 2004. Leptin increases T-cell immune response in birds. Gen. Comp. Endocrinol. 139, 245–250.
Long, K.Z., Nanthakumar, N., 2004. Energetic and nutritional regulation of the adaptive immune response and trade-offs in ecological immunology. Am. J. Hum. Biol. 16, 499–507.
Lord, G.M., Matarese, G., Howard, J.K., Baker, R.J., Bloom, S.R., Lechler, R.I., 1998. Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. Nature 394, 897–901.
Lugarini, F., Hrupka, B.J., Schwartz, G.J., Plata-Salaman, C.R., Langhans, W., 2005. Acute and chronic administration of immunomodulators induces anorexia in Zucker rats. Physiol. Behav. 84, 165–173.
Luger, T.A., Scholzen, T.E., Brzoska, T., Bohm, M., 2003. New insights into the functions of alpha-MSH and related peptides in the immune system. Melanocortin System, 994, pp. 133–140.

Luheshi, G.N., Gardner, J.D., Rushforth, D.A., Loudon, A.S., Rothwell, N.J., 1999. Leptin actions on food intake and body temperature are mediated by IL-1. Proc. Natl. Acad. Sci. U. S. A. 96, 7047–7052.
MacDonald, L., Radler, M., Paolini, A.G., Kent, S., 2011. Calorie restriction attenuates LPS-induced sickness behavior and shifts hypothalamic signaling pathways to an anti-inflammatory bias. Am. J. Physiol. Regul. Integr. Comp. Physiol. 301, R172–R184.
Maffei, M., Halaas, J., Ravussin, E., Pratley, R.E., Lee, G.H., Zhang, Y., Fei, H., Kim, S., Lallone, R., Ranganathan, S., Kern, P.A., Friedman, J.M., 1995. Leptin levels in human and rodent — measurement of plasma leptin and ob RNA in obese and weight-reduced subjects. Nat. Med. 1, 1155–1161.
Maier, S.F., Watkins, L.R., Fleshner, M., 1994. Psychoneuroimmunology — the interface between behavior, brain, and immunity. Am. Psychol. 49, 1004–1017.
Margetic, S., Gazzola, C., Pegg, G.G., Hill, R.A., 2002. Leptin: a review of its peripheral actions and interactions. Int. J. Obes. 26, 1407–1433.
Marks, D.L., Butler, A.A., Turner, R., Brookhart, G., Cone, R.D., 2003. Differential role of melanocortin receptor subtypes in cachexia. Endocrinology 144, 1513–1523.
Martin, L.W., Lipton, J.M., 1990. Acute phase response to endotoxin: rise in plasma alpha-MSH and effects of alpha-MSH injection. Am. J. Physiol. 259, R768–R772.
Martin-Romero, C., Santos-Alvarez, J., Goberna, R., Sanchez-Margalet, V., 2000. Human leptin enhances activation and proliferation of human circulating T lymphocytes. Cell. Immunol. 199, 15–24.
Matarese, G., La Cava, A., 2004. The intricate interface between immune system and metabolism. Trends Immunol. 25, 193–200.
Mattioli, B., Straface, E., Quaranta, M.G., Giordani, L., Viora, M., 2005. Leptin promotes differentiation and survival of human dendritic cells and licenses them for Th1 priming. J. Immunol. 174, 6820–6828.
Murashita, K., Uji, S., Yamamoto, T., Ronnestad, I., Kurokawa, T., 2008. Production of recombinant leptin and its effects on food intake in rainbow trout (*Oncorhynchus mykiss*). Comp. Biochem. Physiol. B Biochem. Mol. Biol. 150, 377–384.
Niewiarowski, P.H., Balk, M.L., Londraville, R.L., 2000. Phenotypic effects of leptin in an ectotherm: a new tool to study the evolution of life histories and endothermy? J. Exp. Biol. 203, 295–300.
Norgan, N.G., 1997. The beneficial effects of body fat and adipose tissue in humans. Int J Obes. 21, 738–746.
O'Connor, J.C., Satpathy, A., Hartman, M.E., Horvath, E.M., Kelley, K.W., Dantzer, R., Johnson, R.W., Freund, G.G., 2005. IL-1beta-mediated innate immunity is amplified in the db/db mouse model of type 2 diabetes. J. Immunol. 174, 4991–4997.
Okamoto, S., Irie, Y., Ishikawa, I., Kimura, K., Masayuki, S., 2000. Central leptin suppresses splenic lymphocyte functions through activation of the corticotropin-releasing hormone-sympathetic nervous system. Brain Res. 855, 192–197.
Otero, M., Lago, R., Gomez, R., Lago, F., Gomez-Reino, J.J., Gualillo, O., 2006. Leptin: a metabolic hormone that functions like a proinflammatory adipokine. Drug News Perspect. 19, 21–26.
Owen-Ashley, N.T., Wingfield, J.C., 2006. Seasonal modulation of sickness behavior in free-living northwestern song sparrows (*Melospiza melodia morphna*). J. Exp. Biol. 209, 3062–3070.
Owen-Ashley, N.T., Turner, M., Hahn, T.P., Wingfield, J.C., 2006. Hormonal, behavioral, and thermoregulatory responses to bacterial lipopolysaccharide in captive and free-living white-crowned sparrows (*Zonotrichia leucophrys gambelii*). Horm. Behav. 49, 15–29.
Papathanassoglou, E., El-Haschimi, K., Li, X.C., Matarese, G., Strom, T., Mantzoros, C., 2006. Leptin receptor expression and signaling in lymphocytes: kinetics during lymphocyte activation, role in lymphocyte survival, and response to high fat diet in mice. J. Immunol. 176, 7745–7752.
Pelleymounter, M.A., Cullen, M.J., Baker, M.B., Hecht, R., Winters, D., Boone, T., Collins, F., 1995. Effects of the obese gene product on body weight regulation in ob/ob mice. Science 269, 540–543.
Pohl, J., Woodside, B., Luheshi, G.N., 2009. Changes in hypothalamically mediated acute-phase inflammatory responses to lipopolysaccharide in diet-induced obese rats. Endocrinology 150, 4901–4910.
Pond, C.M., 1996. Interactions between adipose tissue and the immune system. Proc. Nutr. Soc. 55, 111–126.
Putti, R., Varricchio, E., Gay, F., Elena, C., Paolucci, M., 2009. Leptin effects on testis and epididymis in the lizard *Podarcis sicula*, during summer regression. Gen. Comp. Endocrinol. 160, 168–175.
Quan, N., Banks, W.A., 2007. Brain-immune communication pathways. Brain Behav. Immun. 21, 727–735.
Rayner, D.V., Trayhurn, P., 2001. Regulation of leptin production: sympathetic nervous system interactions. J. Mol. Med. (Berl.) 79, 8–20.
Romano, A., Rubolini, D., Caprioli, M., Boncoraglio, G., Ambrosini, R., Saino, N., 2011. Sex-related effects of an immune challenge on growth and begging behavior of barn swallow nestlings. PLoS One 6.
Rousseau, K., Atcha, Z., Cagampang, F.R., Le Rouzic, P., Stirland, J.A., Ivanov, T.R., Ebling, F.J., Klingenspor, M., Loudon, A.S., 2002. Photoperiodic regulation of leptin resistance in the seasonally breeding Siberian hamster (*Phodopus sungorus*). Endocrinology 143, 3083–3095.
Sachot, C., Poole, S., Luheshi, G.N., 2004. Circulating leptin mediates lipopolysaccharide-induced anorexia and fever in rats. J. Physiol. 561, 263–272.
Sanchez-Margalet, V., Martin-Romero, C., Gonzalez-Yanes, C., Goberna, R., Rodriguez-Bano, J., Muniain, M.A., 2002. Leptin receptor (Ob-R) expression is induced in peripheral blood mononuclear cells by *in vitro* activation and *in vivo* in HIV-infected patients. Clin. Exp. Immunol. 129, 119–124.
Sapolsky, R., Rivier, C., Yamamoto, G., Plotsky, P., Vale, W., 1987. Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor. Science 238, 522–524.
Sarraf, P., Frederich, R.C., Turner, E.M., Ma, G., Jaskowiak, N.T., Rivet III, D.J., Flier, J.S., Lowell, B.B., Fraker, D.L., Alexander, H.R., 1997. Multiple cytokines and acute inflammation raise mouse leptin levels: potential role in inflammatory anorexia. J. Exp. Med. 185, 171–175.
Satoh, N., Ogawa, Y., Katsuura, G., Tsuji, T., Masuzaki, H., Hiraoka, J., Okazaki, T., Tamaki, M., Hayase, M., Yoshimasa, Y., Nishi, S., Hosoda, K., Nakao, K., 1997. Pathophysiological significance of the obese gene product, leptin, in ventromedial hypothalamus (VMH)-lesioned rats: evidence for loss of its satiety effect in VMH-lesioned rats. Endocrinology 138, 947–954.
Sciarrillo, R., Virgilio, F., De Falco, M., Laforgia, V., Varano, L., Paolucci, M., 2005. Localization and role of leptin in the thyroid gland of the lizard *Podarcis sicula* (Reptilia, Lacertidae). J. Exp. Zool. A 303A, 628–634.
Sergeyev, V., Broberger, C., Hokfelt, T., 2001. Effect of LPS administration on the expression of POMC, NPY, galanin, CART and MCH mRNAs in the rat hypothalamus. Brain Res. Mol. Brain Res. 90, 93–100.
Sharp, P.J., Dunn, I.C., Waddington, D., Boswell, T., 2008. Chicken leptin. Gen. Comp. Endocrinol. 158, 2–4.
Sheldon, B.C., Verhulst, S., 1996. Ecological immunology: costly parasite defences and trade-offs in evolutionary ecology. Trends Ecol. Evol. 11, 317–321.
Simon, J., Rideau, N., Taouis, M., 2009. Reply to viewpoints by PJ Sharp, IC Dunn, D Waddington and T Boswell [Chicken leptin: general and comparative endocrinology, 158, 2–4 (2008)]. Gen. Comp. Endocrinol. 161, 159.
Sonti, G., Ilyin, S.E., Plata-Salaman, C.R., 1996. Neuropeptide Y blocks and reverses interleukin-1 beta-induced anorexia in rats. Peptides 17, 517–520.
Spurlock, M.E., Frank, G.R., Willis, G.M., Kuske, J.L., Cornelius, S.G., 1997. Effect of dietary energy source and immunological challenge on growth performance and immunological variables in growing pigs. J. Anim. Sci. 75, 720–726.
Steiner, A.A., Krall, C.M., Liu, E., 2009. A reappraisal on the ability of leptin to induce fever. Physiol. Behav. 97, 430–436.
Swiergiel, A.H., Dunn, A.J., 1999. CRF-deficient mice respond like wild-type mice to hypophagic stimuli. Pharmacol. Biochem. Behav. 64, 59–64.
Szekely, M., Petervari, E., Szelenyi, Z., 2004. Orexigenic vs. anorexigenic peptides and feeding status in the modulation of fever and hypothermia. Front. Biosci. 9, 2746–2763.
Taouis, M., Chen, J.W., Daviaud, C., Dupont, J., Derouet, M., Simon, J., 1998. Cloning the chicken leptin gene. Gene 208, 239–242.
Tian, Z., Sun, R., Wei, H., Gao, B., 2002. Impaired natural killer (NK) cell activity in leptin receptor deficient mice: leptin as a critical regulator in NK cell development and activation. Biochem. Biophys. Res. Commun. 298, 297–302.
Tizard, I., 2008. Sickness behavior, its mechanisms and significance. Anim. Health Res. Rev. 9, 87–99.
True, C., Grove, K.L., Smith, M.S., 2011. Beyond leptin: emerging candidates for the integration of metabolic and reproductive function during negative energy balance. Front. Endocrinol. 2, 1–12.
Uehara, A., Sekiya, C., Takasugi, Y., Namiki, M., Arimura, A., 1989. Anorexia induced by interleukin 1: involvement of corticotropin-releasing factor. Am. J. Physiol. 257, R613–R617.
Uller, T., Isaksson, C., Olsson, M., 2006. Immune challenge reduces reproductive output and growth in a lizard. Funct. Ecol. 20, 873–879.
Vaughn, L.K., Veale, W.L., Cooper, K.E., 1980. Antipyresis — its effect on mortality-rate of bacterially infected-rabbits. Brain Res. Bull. 5, 69–73.
Volkoff, H., Canosa, L.F., Unniappan, S., Cerda-Reverter, J.M., Bernier, N.J., Kelly, S.P., Peter, R.E., 2005. Neuropeptides and the control of food intake in fish. Gen. Comp. Endocrinol. 142, 3–19.
Weiland, T.J., Kent, S., Voudouris, N.J., Shulkes, A., 2005. The effect of lipopolysaccharide on cholecystokinin in murine plasma and tissue. Peptides 26, 447–455.
Weiland, T.J., Voudouris, N.J., Kent, S., 2007. CCK(2) receptor nullification attenuates lipopolysaccharide-induced sickness behavior. Am. J. Physiol. Regul. Integr. Comp. Physiol. 292, R112–R123.
Wisse, B.E., Ogimoto, K., Morton, G.J., Wilkinson, C.W., Frayo, R.S., Cummings, D.E., Schwartz, M.W., 2004. Physiological regulation of hypothalamic IL-1beta gene expression by leptin and glucocorticoids: implications for energy homeostasis. Am. J. Physiol. Endocrinol. Metab. 287, E1107–E1113.
Zhang, Y., Proenca, R., Maffei, M., Barone, M., Leopold, L., Friedman, J.M., 1994. Positional cloning of the mouse obese gene and its human homologue. Nature 372, 425–432.
Zhao, Y., Sun, R., You, L., Gao, C., Tian, Z., 2003. Expression of leptin receptors and response to leptin stimulation of human natural killer cell lines. Biochem. Biophys. Res. Commun. 300, 247–252.