frontiers in
IMMUNOLOGY

REVIEW ARTICLE
published: 07 April 2014
doi: 10.3389/fimmu.2014.00143

Neuro-endocrine networks controlling immune system in health and disease

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The nervous and immune systems have long been considered as compartments that perform separate and different functions. However, recent clinical, epidemiological, and experimental data have suggested that the pathogenesis of several immune-mediated disorders, such as multiple sclerosis (MS), might involve factors, hormones, and neural mediators that link the immune and nervous system. These molecules are members of the same superfamily, which allow the mutual and bi-directional neural–immune interaction. More recently, the discovery of leptin, one of the most abundant adipocyte-derived hormones that control food intake and metabolism, has suggested that nutritional/metabolic status, acting at central level, can control immune self-tolerance, since it promotes experimental autoimmune encephalomyelitis, an animal model of MS. Here, we summarize the most recent advances and the key players linking the central nervous system, immune tolerance, and the metabolic status. Understanding this coordinated interaction may pave the way for novel therapeutic approaches to increase host defense and suppress immune-mediated disorders.

Keywords: neuro-immune modulation, leptin, autoimmunity, MS, metabolism

INTRODUCTION

The central nervous system (CNS) has been considered for a long time, a privileged organ thanks to its inability to start an immune response against antigens. However, accumulating evidence has shown the presence of a mutual interaction between the immune system and CNS in physiological as well as in pathological conditions. Indeed, the CNS displays a well-organized innate immune reaction to infection and immune cells express on their surface several receptors for different neurotransmitters, which allow the brain to modulate the immune system functions and keep the homeostasis of the whole body in an appropriate manner, by responding to environmental changes (1–6). Moreover, immune cells can also synthesize and secrete several hormones with immunomodulatory properties (2, 7, 8) that can reduce or inhibit any exacerbated inflammatory response; for instance, the lymphocytes (9) and macrophages (10) produce the endogenous opioid peptides and catecholamines such as norepinephrine (NE) and epinephrine (E) (11). Furthermore, human lymphocytes secrete the growth hormone (GH) (12) and monocytes secrete the brain-derived neurotrophic factor (BDNF), whose expression is up-regulated by flogistic mediators such as TNF-α and IL-6 (13, 14). Recently, it has been shown that circulating LPS is able to induce the transcription of genes encoding for CD14 (its receptor) and toll-like receptor 2, as well as a wide variety of pro-inflammatory molecules in circum-ventricular organs (CVOs) (15).

A delayed response to LPS occurs in cells located at the edge of the CVOs and in microglia throughout the CNS. Pathogens can then induce the activation of the innate arm of the immune system in neuronal tissue, without having direct access to it.

IMMUNE-SURVEILLANCE IN THE CONTROL OF CNS

Although the CNS lacks lymphatics, it expresses major histocompatibility complex (MHC) molecules and the blood–brain barrier (BBB), and the blood–cerebrospinal fluid (CSF) are able to ensure protection of CNS by the diffusion of infectious agents (16). Conversely, alteration of immunity is often associated with cerebral infections. In physiological conditions, the immune system monitors the integrity of the brain and spinal cord (immune-surveillance), in order to highlight any inflammatory mediators resulting from infection and damage. In this context, a key role in the control of immune-surveillance is played by the resident microglia and immune cells (16). Indeed microglial cells are able to activate the adaptive immune system, when required, and these glia cells are in turn modulated by endogenous mechanisms, thus confirming the tune control of immune system in the CNS (17). Microglia secrete neurotrophins, such as nerve growth factor (NGF), able to sustain neuronal and macroglial survival and growth. In addition to microglia, peripheral immune cells can reach the inflammatory site in the CNS, through mechanisms similar to those observed in peripheral organs. T cells travel into the CNS through transient interactions with CNS endothelium,

which expresses cell adhesion molecules, moreover other immune cells (macrophages and dendritic cells) are located at the interface between the blood and brain, where they can promote antigen presentation and a powerful inflammatory response (18). Non-activated microglia express low levels of HLA-DR in the healthy human brain and MHC-II molecules (MHC-II, CD80, CD86, CD40, CD11a) in the rodent brain, thus suggesting their antigen presentation capability (19–24).

Recent evidence has revealed that T cells can be found in the CSF of healthy individuals, indicating that these cells can reach the CNS through the choroid plexus and meninges (25, 26). They have been characterized as $CD4^{+}CD45RA^{-}CD27^{+}CD69^{+}$ activated central memory T cells (27, 28), which expressed high levels of CCR7, CXCR3, and L-selectin (29, 30) and are located in brain areas, which lack of tight junctions in the BBB (31).

In conclusion, the fact that endogenous factors (such as trauma or immuno-suppressive agents) may cause alteration in the migratory capacity of immune cells in the CNS, leading to an uncontrolled proliferation of infectious agents with consequent occurrence of neurological complications, would indicate a clear and unambiguous key role of immune system in the "immunosurveillance" of the CNS.

THE NEURAL AND IMMUNE SYSTEM COMMUNICATION

THE AUTONOMIC NERVOUS SYSTEM

The control of inflammation is realized by two major mechanisms: self-controlling immune mechanisms and brain-derived immunoregulatory output. The CNS regulates immune function, inflammation, and pathogens responses against host tissues, through the production of inhibitory cytokines, hormones, and other soluble molecules able to signal to the brain, which in turn exerts strong regulatory effects on the immune response (5, 32). Brain immunoregulatory action is mediated by the autonomic nervous system, through sympathetic and vagus nerve innervation. Recent evidence has reported that afferent neurons express receptors for several pro-inflammatory cytokines, such as tumor necrosis factor (TNF), IL-1, activating neural reflex circuits that regulates acute and chronic immune responses (5). A prototypical example of neural circuit is the inflammatory reflex mediated by the vagus nerve and the α7 subunit of the nicotinic acetylcholine receptor (α7 nAChR) expressed on immune cells (33).

Vagus nerve activation determines NE release from splenic neurons, which through the binding to β2 adrenergic receptor expressed on splenic T cells, favors choline acetyltransferase stimulation with consequent acetylcholine production (34) (**Figure 1**). T cell receptor (TCR)-mediated stimulation of splenic T cells significantly enhances their ability to produce acetylcholine, which binds to α7 nAChR expressed on macrophages resident in the red pulp and marginal zone of the spleen (35), thus suppressing NF-κB activity and consequently reducing cytokine synthesis (33, 35) (**Figure 1**). Activation of this pathway by electrical stimulation of the vagus nerve or administration of α7 selective agonists improves inflammation and survival in different clinical conditions (34). Moreover, confirming the essential role of T cells for vagus nerve action in the inhibition of cytokine release, it has been recently shown that the inflammatory reflex is impaired in nude mice, (34) and the adoptive transfer of T cells, which secrete enough amount of acetylcholine, since they express choline acetyltransferase, is able to revert this phenomenon, recovering the inflammatory reflex in these mice.

All these data have been confirmed also in humans; indeed patients with autoimmune disease and non-resolving inflammation display impaired vagus nerve signaling, which favors the progression of inflammation (32), whereas vagus nerve stimulation is able to attenuate leukocytes migration into the joints of synovitis affected patients (36). In line with this evidence, α7 nAChR deficient mice have increased synovial inflammation when compared to their littermate controls in a model of collagen-induced arthritis (37, 38). Treatment with α7 nAChR agonists or electrical vagus nerve stimulation significantly decreases arthritis in wild-type (WT) mice with collagen-induced arthritis. Finally, diet can also influence the inflammatory reflex; indeed dietary consumption of fish oil, significantly enhances the vagus nerve stimulation, favoring resolution of inflammation (39). On the other hand, in condition of obesity, where there is an inappropriate energy deposit and expenditure, leading to low grade inflammation and metabolic disease, an impaired vagus nerve activity has been found (40).

THE CATECHOLAMINERGIC PATHWAY

Catecholamines [i.e., epinephrine, NE, dopamine (DA)] can regulate several functions of the immune system activities, such as proliferation, cytolytic activity, cytokine and antibody release, and chemotaxis, by interacting with adrenoreceptors expressed on lymphoid organs and immune cells. In particular, it has been demonstrated that NE and beta-adrenergic agonists are able to inhibit cytotoxic activity and increase lymphocytes proliferation (41–43). At the same time, high amount of DA was found to significantly inhibit the *in vitro* proliferative response and cytotoxic activity of T cells (44) (**Figure 1**). Moreover, it has been recently reported an enhanced proliferation and an impaired secretion of interferon-γ (IFN-γ) in the spleen of mice treated with DA (45). Recent evidence shows an important role of the hypothalamic–pituitary–adrenal (HPA) axis also in the bi-directional comunication between the brain and the immune system. GH and prolactin (PRL) are known to modulate immune responses (45–48). Indeed, several authors have shown that human GH significantly antagonizes the dexamethasone-induced inhibition of human T cell proliferation (46, 47). Moreover, secretion of PRL sustains antibody production and cell-mediated immune functions and therefore its inhibition increases the susceptibility to infectious diseases (47, 49). Glucocorticoids also exert several immunomodulant effects, such as the enhancement of T cells proliferation and survival (50, 51), and in physiological doses, the shift in cytokine secretion from a Th1 toward a Th2 phenotype (52, 53).

THE PEPTIDERGIC PATHWAY: NEUROPEPTIDES

Recent evidence suggests a key role of the neuropeptidergic pathway in the control of immune system (54, 55). Activation of nociceptors leads to local axon reflexes through the release of neuropeptides [i.e., calcitonin gene-related peptide (CGRP), substance P (SP), adrenomedullin, neurokinins A and B, vasoactive intestinal peptide (VIP), neuropeptide Y (NPY), and gastrin releasing peptide (GRP), etc.], which locally recruit and activate both

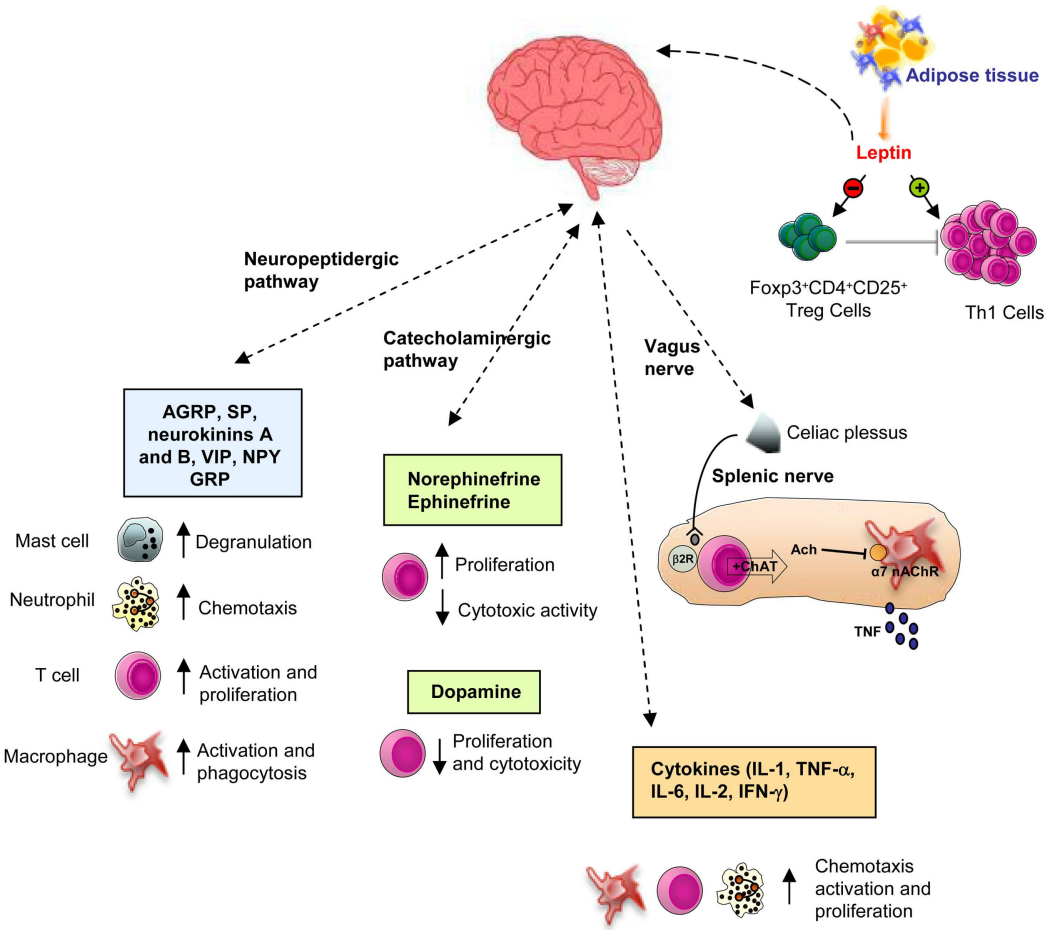

FIGURE 1 | Schematic representation of the CNS-immune system crosstalk. There are bi-directional circuits linking CNS and immune system. The CNS can communicate with the immune system to modulate its activity, through different ways: through the autonomic nervous system (via the sympathetic and vagus nerve innervation, see the text for deeper details), the catecholaminergic pathway, or the neuropeptides and hormones release. In this context, leptin modulates immune system, by increasing the activation of T cells and decreasing Treg cells functions, thus representing a key player in the susceptibility to immune-mediated disorders (β2R, β2 receptor; α7 nAChR, α7 subunit of the nicotinic acetylcholine receptor).

innate and adaptive immune cells. More specifically, it has been shown that these mediators sustain chemotaxis and activation of neutrophils, macrophages, lymphocytes, and mast cells, increase the presenting capability of antigen presenting cells (APCs) and stimulate signaling to vascular endothelial cells, enhancing the recruitment of inflammatory leukocytes (55, 56) (**Figure 1**).

Another possible way of communication between immune cells and nociceptor neurons is also mediated by cytokine release. Indeed, sensory neurons display several cytokine receptors such as IL-1β receptor (IL-1βR) and TNF-α receptor (TNF-αR), which are able to recognize factors secreted by immune cells (i.e., IL-1β, TNF-α, NGF). They also express danger-associated molecular pattern (DAMP) receptors, toll-like receptors (TLRs), pathogen-associated molecular patterns (PAMPs), which recognize exogenous environmental signals (i.e., heat, acidity, chemicals, bacteria, viruses) or endogenous danger signals (i.e., ATP concentration, uric acid, hydroxynonenals) (56, 57), enhancing T cell functions (proliferation, cytokine secretion, and adhesion molecules expression) and thus representing a relevant player in CNS–immune system crosstalk in normal and pathophysiological conditions (58–61). In activated macrophages, VIP inhibits the expression of pro-inflammatory cytokines and chemokines (62–64), sustaining the differentiation of $CD4^+$ T cells in Th2 cells and promoting their proliferation and/or survival (64, 65). Among the other neuropeptides, several functions of the cellular immune system have been shown to be regulated by NPY, SP, and related-agouti protein (AgRP) (66). NPY is a neuropeptide that increases food intake and storage of energy as fat but it is also able to modulate lymphocytes proliferation, NK activity, and interleukin-2 (IL-2) and TNF-α release (67). SP stimulates lymphocyte migration, proliferation, and IgA secretion and promotes phagocytosis and chemotaxis in innate immune cells, during inflammation (68). On the other hand, AgRP is co-expressed with NPY and works by increasing appetite and decreasing metabolism and energy expenditure. Hypothalamic AgRP neurons are mandatory for feeding and survival (69, 70) and they mediate

effects of the histone deacetylase, Sirt1, on energy metabolism (71, 72). Recently, it has been shown that these neurons are involved in the regulation of adaptive immune responses. Indeed, knockdown of Sirt1 in Agrp neurons induce a pro-inflammatory state, characterized by a decrease in regulatory T cell functions with consequent increase of effector T cell activity, which determines an increased autoimmune disease susceptibility (73). This finding together with a recent paper by Luquet's group (74) confirms the notion that the sympathetic nervous system may play a central role in mediating the effect of impaired function of AgRP neurons on immune system activity.

CYTOKINES-RELATED PATHWAY

It is becoming well accepted that products of the immune system (cytokines) can signal the brain that infection has occurred. This cytokine-to-brain communication can result in marked alterations in brain function and behavior. In general, cytokines may traffic to the CNS at sites where the BBB is absent (75, 76), by carrier-mediated transport mechanisms, or by generating central mediators altering the permeability of the BBB to other substances (5, 77). Cytokines may also act directly on the CNS, by stimulating peripheral afferent neurons (5, 78). Indeed, peripherally generated cytokines can stimulate vagus nerve, which represents another very important pathway through which signals reach the brain (79). Several cytokines such as IL-1, IL-2, IL-6, IFN-γ, and TNF-α can regulate the activation of the HPA axis and are also influenced by glucocorticoid secretion (52, 80). IL-1 is one of the most studied cytokines linking immunological activation with the brain functions (81–83). Indeed, IL-1 has been shown to influence hypothalamic neurosecretory activity by stimulating CRH release by hypothalamic CRH neurons, and to enhance the turnover of NE in the hypothalamus (84, 85). IL-1 is also produced by several type of cells resident in the CNS, including astrocytes and microglia (86, 87) and IL-1 receptors have been identified in different brain areas, such as hippocampus and the dorsal raphe nucleus (88, 89). Furthermore, mRNA for IL-1α and TNF-α has been demonstrated in anterior pituitary cells (90, 91), which secrete IL-6 as well (91). IL-1 has been shown to be pivotal for the recruitment of leukocytes across the BBB. Indeed, recent studies have demonstrated that intracerebroventricular injection of IL-1β as well as IFN-γ and TNF-α induce neutrophils and leukocytes infiltration into the brain tissue (92), in a mouse model of experimental autoimmune encephalomyelitis (EAE) (93), by increasing the production of P-selectin on brain endothelial cells (94). In addition, also receptors for IL-2 were found in specific brain areas such as the hippocampal formation (95, 96) and it has been recently shown that that IL-2 deficiency results in altered septal and hippocampal structure, associated with changes in neurotrophins production (97).

LEPTIN: AT THE CROSSROAD BETWEEN CNS AND IMMUNE SYSTEM FUNCTION

Leptin, the product of the obese (*ob*) gene, has been recently recognized as one of the most studied molecule linking CNS, nutrition, metabolism, and immune homeostasis (98). Leptin is mainly produced by the adipose tissue in proportion to the body fat mass and also by tissues such as the stomach, skeletal muscle, and placenta (98). At central level, this hormone regulates food intake, bone mass homeostasis, autonomic nervous system outflow, and the secretion of HPA hormones (98). Originally, leptin has been identified as the hormone responsible for the regulation of the balance between food intake and energy expenditure, being able to signal to the brain any changes in stored energy. However recent evidence has indicated that leptin is much more than a "fat-o-stat" sensor (99–101); indeed, leptin-deficient (*ob/ob*) and leptin-receptor-deficient (*db/db*) mice are not only strongly obese, but they also display several alterations, due to the effects of leptin on reproduction (102), hematopoiesis (103), angiogenesis (104), metabolism of bone (105), lipids and glucose (98) and, more importantly, innate and adaptive immunity (106, 107).

LEPTIN AND IMMUNE SYSTEM REGULATION

Leptin has a well-established role in the modulation and regulation of innate immunity. Leptin increases phagocytic activity (108) and cytokine secretion (i.e., TNF-α, IL-6, and IL-12) (109, 110) in monocytes and macrophages, up-regulating the expression of activation markers, such as CD25 [α-chain of IL-2 receptor (IL-2R)], CD71 (transferring receptor), CD69, and CD38. Moreover, leptin can stimulate neutrophils chemotaxis and the oxidative burst (111, 112) and sustain proliferation, development, differentiation, activation, and lytic activity of NK cells, through the increase in perforin and IL-2 secretion (113). On the other hand, leptin exerts its effects also on adaptive immunity. Indeed, leptin modulates proliferation and cytokine production by both human naive (CD45RA) and memory (CD45RO) $CD4^+$ T. On naïve T cells leptin promotes the proliferation and IL-2 secretion, whereas, on memory T cells, it promotes the switch toward T helper (Th)1-cell phenotype by increasing the secretion of pro-inflammatory cytokines such as IFN-γ and TNF-α (99). Leptin also supports immune cells migration to inflammatory sites, through the induction of IFN-γ production and the expression of adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1, CD54) and very late antigen-2 (VLA-2, CD49b) on $CD4^+$ T cells.

Recent evidence indicates that leptin inhibits thymic T cells apoptosis, thus supporting their generation, maturation, and survival (114). Indeed, DTH responses and thymic atrophy have been shown to be decreased after acute caloric deprivation and serum leptin reduction; these conditions were restored by leptin treatment (114). Moreover, leptin can negatively modulate the expansion of human natural $Foxp3^+CD4^+CD25^{high}$ regulatory T cells (nTregs) (115) (**Figure 1**), a cellular subset, which suppress autoreactive response mediated by $CD4^+25^-$ T (Teffs) cells. Treg cells produce leptin and express high levels of leptin receptor (ObR) (114). *In vitro* neutralization with anti-leptin monoclonal antibody (mAb) plus anti-CD3/CD28 stimulation causes Treg cells proliferation (115). This mechanism is mainly due to the down-regulation of the cyclin-dependent kinase inhibitor $p27^{kip1}$ and the phosphorylation of the extracellular-related kinases 1/2 (ERK1/2), pivotal molecular pathways in the Treg cells activation and anergy (115). Moreover, an increased Treg cells proliferation has been observed in leptin- and ObR-deficient mice. Recently, it has been shown that leptin can potentiate the mTOR pathway activation, thus inhibiting rapamycin-induced proliferation of Tregs. In physiological circumstances, Tregs secreted leptin, which

in turn activated mTOR pathway, a condition which sustains their state of hyporesponsiveness and anergy. Accordingly, Tregs from *db/db* mice had a reduced mTOR activity and enhanced proliferation compared with that of WT Tregs (116). Experiments by the same group have shown that leptin activates mTOR pathway also in Teffs, thus causing a defined cellular, biochemical, and transcriptional modification that determines the outcome of their responses, both *in vitro* and *in vivo*. Indeed, the blockade of leptin/leptin receptor signaling, induced by genetic means or by starvation, leads to impaired mTOR activity, which in turn inhibits the proliferation of Teffs (100). Taking together, these data suggest that the leptin-mTOR axis sets the threshold for the responsiveness of Treg and Teff cells, confirming that this pathway might integrate cellular energy status with metabolic-related signaling in Treg/Teff that use this information to control immune tolerance.

LEPTIN AND AUTOIMMUNITY

Recent evidence indicates that leptin promotes pro-inflammatory cytokine secretion, thus enhancing immune responses in autoimmune disorders. In several autoimmune diseases, such as rheumatoid arthritis (RA), high serum leptin levels have been found, while, on the contrary, fasting, which associates with a marked decrease in serum leptin amount and a shift toward Th2-type cytokine secretion, improves clinical disease activity in RA patients (117). In line with these findings, another suggestion on the involvement of leptin signaling in the modulation of antigen-induced arthritis comes from studies showing that leptin-or leptin receptor (LepR)-deficiency protects mice from the development of autoimmune arthritis, after immunization with methylated bovine serum albumin (BSA) into knee joints, as these genetic conditions associate with decreased antigen-specific T cell proliferative responses (118). Recently, it has been reported that Th17 cell frequency is reduced in *ob/ob* mice and that the administration of leptin to *ob/ob* mice restore Th17 cell numbers to values comparable to those found in WT animals. Leptin promotes Th17 responses in normal human $CD4^+$ T cells and in (NZB × NZW) F1 lupus-prone mice, by inducing RORγ transcription, whereas, on the contrary, its neutralization in those autoimmune-prone mice inhibits Th17 responses (119).

Leptin deficiency has been also associated with protection toward other inflammatory disease such as the experimentally induced glomerulonephritis, which is an immune-complex-mediated disorder (120). More specifically, studies from Lord's group have shown that the renal protection observed in *ob/ob* mice has to be ascribed to a reduced glomerular-crescent formation and to an impaired macrophage recruitment in the site of inflammation (120). The reduced T cell proliferative profile and the altered humoral responses to sheep IgG, further support the authors's hypothesis of consistent defects in innate and adaptive immune responses that can be considered crucial factors at the base of the protection to glomerulonephritis development in leptin-deficient mice.

Leptin has also been linked to spontaneous autoimmune disease such as Type 1 Diabetes (T1D) in the non-obese diabetic (NOD) mice. Indeed, this cytokine-like hormone accelerates the disease onset and progression by stimulating destruction of pancreatic β-cells by autoreactive T cells, which are further sustained to produce IFN-γ by leptin treatment (121).

Another indication for the important role of leptin in autoimmunity is the sexual dimorphism of serum leptin levels; indeed women display serum leptin levels two to three times higher than those observed in age- and BMI-matched men, and moreover, they are more prone to develop autoimmune diseases such as multiple sclerosis (MS), RA, or systemic lupus erythematosus, thus suggesting that leptin could favor the predisposition of females to this kind of disorders (122, 123).

Recent clinical studies on autoimmune disease patients demonstrate that high serum leptin levels may play a causal role in the disease progression, as previously mentioned, but at the same time might be utilized as a diagnostic marker for novel clinical application (122).

ROLE OF LEPTIN IN THE PATHOGENESIS OF MULTIPLE SCLEROSIS

Multiple sclerosis is an autoimmune disorder of the CNS, in which T cells specifically recognize myelin antigens and induce tissue damage, leading to lesion evolvement in the CNS with subsequent demyelination and axonal injury (124). Clinically, this disorder may present as relapsing-remitting type of MS (RRMS) (85%) or it may convert over time to a secondary chronic progressive type of MS (SP-MS). About 15% of cases present with a primary progressive disease course (PP-MS) and only few patients display a progressive relapsing MS disease course (PR-MS) with fast progression of the disease (125). In Europe and North America, the incidence is about 6/100,000/year and the prevalence 1/1000. For the pathogenesis of MS, both genetic (HLA II genes) and environmental factors (i.e., vitamin D levels, smoking) contribute to disease susceptibility (126, 127). The autoimmune process involves both the gray and white matter, thus explaining the cognition alterations often found in MS patients. The destruction patterns in the MS plaque can include $CD4^+$ T cells, which play a key role in the immune cascade activation, leading to tissue damage, cytotoxic attack mediated by $CD8^+$ T cells and macrophages, as well as a humoral-mediated destruction of the myelin structure through the local production of antibodies with consequent complement activation (128).

The most studied model of MS in animals is EAE, in which autoimmune attack toward CNS is induced in susceptible strains of mice, through immunization with self-antigens derived from basic myelin protein. Autoreactive T cells traffic to the brain and to the spinal cord and damage the myelin structure of CNS, resulting in a chronic or relapsing-remitting paralysis (depending on the antigen used for immunization and the strain of mice). In the inflammatory lesions, and increased secretion of Th1 cytokines has been detected, whereas Th2 cytokines typically associate with recovery and protection from EAE (129).

Recent findings have shown that the immunomodulatory effects of leptin are involved in the induction and progression of EAE, a mouse model of MS (129, 130). The *ob/ob* mice do not develop EAE, a condition associated with increased IL-4 production and a decrease in IFN-γ secretion by T cells upon antigen-specific stimulation. On the contrary exogenous leptin treatment renders *ob/ob* mice susceptible to EAE development, by increasing pro-inflammatory cytokine production (129).

Leptin neutralization in EAE-affected WT mice inhibits T cell functions, significantly delays disease progression with the final effect of improvement of the clinical symptoms (131).

In addition, high leptin levels have been reported also in active inflammatory lesions of the CNS of MS patients (132) and in the sera of MS patients treated with IFN-β before the relapses (133). In humans, it has been also shown that leptin production was significantly increased in both serum and CSF of naïve-to-therapy RRMS patients and its levels inversely correlated with frequency of Treg cells (134).

Recently the adipose tissue, through leptin production, has been shown to play a pivotal role in the survival of autoantigen-specific $CD4^+$ T cells *in vivo*, through the activation of mTOR pathway and the induction of Bcl-2 (direct mechanism) and through the reduction of a series of cytokines, whose production is important for autoreactive cell survival (IL-6, IL-15, IL-21, and GM-CSF) (indirect mechanism) (135). Recently, it has been demonstrated that Tregs proliferation is impaired in RRMS patients because of altered IL-2 secretion and IL-2R-signal transducer and activator of transcription 5 (STAT5) signaling. These results suggest the presence of an altered metabolic control accounting for the progressive loss of Treg cells in autoimmune disease (136). The expression of LepR has been found to be significantly higher in $CD8^+$ T cells and monocytes from MS patients in relapse phase than those observed in patients in remission (or in healthy controls). Moreover, relapsing patients display high levels of phospho-signal transducer and activator of transcription-3 (P-STAT-3) and low expression of suppressor of cytokine signaling-3 (SOCS-3) and exogenous leptin treatment sustains STAT3 phosphorylation only in the monocytes from relapsing patients, suggesting that LepR might play a role in the modulation of clinical relapses during MS (137). A recent report has shown that obesity and high leptin levels at age of 18 associate with a greater than twofold increased risk of MS development (138). Comparable epidemiological evidence has suggested that subjects whose BMI exceeded 27 kg/m^2, had a twofold increased risk to develop MS in a cohort of Swedish population (139). In addition, Hedström et al. have also shown that a possible interactions between BMI and MS could be associated to HLA genotype (DRB1*15 and absence of A*02) (140). The authors hypothesized that one possible explaination for this association is the lower levels of 25-hydroxy vitamin D discovered in obese patients compared to non-obese subjects, since 25-hydroxyvitamin D levels have been shown to be protective from MS development (126). The finding of an interaction between obesity and HLA genotype with regard to MS supports the hypothesis that the Th1-promoting effects of obesity increase the risk of developing MS, in particular among subjects with a genetic susceptibility to the disease. In this context, prevention of obesity in adolescents may therefore play a role in reducing the risk to develop MS, above all in subjects with a genetic susceptibility.

Importantly, a dycothomous role of leptin on the CNS has recently emerged. While leptin can participate in the immune-mediated attack to myelin, new evidence suggests that leptin may have differential effects on myelination and neural cell survival, acting as a neurotrophic factor (141, 142). Indeed, the brain weight of *ob/ob* and *db/db* mice is significantly reduced and these mice express synaptic and glial proteins with immature characteristics. They also display elevated expression of growth-associated protein in the neocortex and hippocampus, and decreased expression of syntaxin-1, synaptosomal-associated protein-25, and synaptobrevin (141, 142). Leptin deficiency also associates with a decreased expression of myelin basic protein (MBP) and/or proteolipid protein (PLP) in the neocortex, hippocampus. By contrast, recombinant leptin administration is able to revert this phenotype, by increasing brain weight, restoring a proper proteic asset, and sustaining the overall locomotor activity of these animals, thus suggesting that leptin requirement is essential for the physiological development of the nervous system.

ROLE OF CENTRAL LEPTIN SIGNALING IN THE CONTROL OF IMMUNE SYSTEM

Despite the studies previously mentioned focused mainly on the role of leptin in the modulation of peripheral immune cells functions (106, 110, 112), only recently it has become increasingly evident that the leptin signaling at the central level (CNS) is itself able to directly modulate immune system.

Recent papers have suggested that leptin deficiency reduced renal macrophage infiltration in a model of unilateral ureteral obstruction (UOO) (143). Interestingly, central leptin administration in *ob/ob* mice was able to revert this condition. The authors also showed that co-treatment with a melanocortin-3 receptor (MC3R)/melanocortin-4 receptor (MC4R) antagonist, blunted leptin effects, thus suggesting that leptin increases renal macrophage infiltration through the activation of the central melanocortin system (143).

In addition, intracerebroventricular leptin injection was sufficient to prevent the alteration of B-cell development in the bone marrow of fasted mice (characterized by altered balance between immature and mature B-cells), thus providing again the *in vivo* evidence for the role of central leptin signaling in B-cell development (144). Other studies have shown that leptin-deficient mice showed an increased susceptibility to sepsis and mortality, due to an impaired recruitment and function of neutrophils. On the contrary, the treatment with leptin exclusively at the intracerebral level, improved the survival, and the risk of infection of these mice, again suggesting the importance of the central leptin signaling in the modulation of immune functions (145).

CONCLUDING REMARKS

It is becoming increasingly evident that there is a dense and intricate relationship between the immune and nervous system (146). This type of interaction is explicated through the production of molecules (cytokines, hormones, and peptides) from the CNS and through the activation of afferent and efferent neurological pathways in lymphoid organs, with both immuno-suppressive and immuno-stimulating effects. On the other hand, also the cytokines themselves are able to communicate with the CNS and ensure the passage of specific signals and information from the periphery to the brain. In this context, leptin represents a key factor linking immune system, metabolism, and CNS functions.

The comprehensive and extensive understanding of the mechanisms underlying the interaction between the CNS and immune systems, may allow the modulation of certain brain functions as

a possible clinic therapeutic approaches for immune-mediated diseases.

Recent reports have shown that caloric restriction (CR) (associates with a fall in plasma leptin levels) can significantly increase the overall survival in several experimental animal models of autoimmune diseases (147). More specifically, CR has anti-inflammatory, antioxidant, and neuroprotective effects that could be instrumental for an improvement of clinical outcomes in MS, since this regimen is able to impair pathological proliferation of autoreactive cells and pro-inflammatory cytokine production in EAE (147).

Although several evidence has suggested that diet may alter the course and progression of autoimmune diseases (i.e., the case of MS), only few randomized studies of dietary alterations in MS have been conducted so far, and none of them seem to include CR regimen.

The future goal of the research will be to assess how and whether CR might actually be a useful therapeutical approach for MS. A careful monitoring of patients could in fact ensure beneficial effects in terms of reduction of inflammation and at the same time could determine the improvement of other clinical parameters such as insulin sensitivity, low-density lipoprotein, cholesterol, blood pressure, which would be crucial for the disease amelioration.

ACKNOWLEDGMENTS

Giuseppe Matarese is supported by grants from Fondazione Italiana Sclerosi Multipla (FISM) 2012/R/11, the European Union IDEAS Programme European Research Council Starting Grant "menTORingTregs" 310496, the Ministero della Salute Grant GR-2010-2315414 and Grant CNR "Medicina Personalizzata." Veronica De Rosa is supported by the Fondo per gli Investimenti della Ricerca di Base (FIRB) grant RBFR12I3UB_004. This work is dedicated to the memory of Eugenia Papa and Serafino Zappacosta.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 31 January 2014; paper pending published: 18 March 2014; accepted: 19 March 2014; published online: 07 April 2014.

*Citation: Procaccini C, Pucino V, De Rosa V, Marone G and Matarese G (2014) Neuro-endocrine networks controlling immune system in health and disease. Front. Immunol. **5**:143. doi: 10.3389/fimmu.2014.00143*

This article was submitted to Inflammation, a section of the journal Frontiers in Immunology.