

A role for leptin in rheumatic diseases?

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Leptin may influence RA in opposing ways: enhance the expression of Th1 cytokines or limit the inflammatory responses

Leptin is a peptide hormone that has an important role in the regulation of body weight by inhibiting food intake and stimulating energy expenditure. Moreover, leptin exhibits a variety of other effects, including the regulation of endocrine function, reproduction, and immunity.^{1,2} Consistently, leptin deficient (*ob/ob*) mice and leptin receptor deficient (*db/db*) mice are not only severely obese but also display hormonal imbalances, abnormalities in thermoregulation, infertility, and evidence of immune and haematopoietic defects. The role of leptin in the modulation of the immune response and inflammation has lately received particular attention.

LEPTIN AND IMMUNE RESPONSE

It has long been known that *ob/ob* and *db/db* mice have an altered immune response.^{3,4} More recent studies have shown that the long isoform of the leptin receptor (OB-Rb) is expressed in T and B cells and indicated that leptin exerts direct effects on lymphocytes.⁵⁻⁷ Leptin was reported to stimulate the proliferation of T cells in vitro, to promote T helper (Th)1 responses, and to protect T cells from corticosteroid induced apoptosis.^{5,7}

Consistently, *ob/ob* and *db/db* mice have a marked reduction in the size and cellularity of the thymus and exhibit defective T cell mediated immunity.^{3,4} Furthermore, starvation and malnutrition, two conditions characterised by low leptin levels, are also associated with alterations of the immune response and thymic atrophy, which can be reversed by leptin administration.^{5,7} Despite strong evidence for the direct effects of leptin on T cells in vitro, the connection between leptin deficiency and immune defects in vivo is likely to be more complex. *Ob/ob* and *db/db* mice indeed display multiple endocrine and metabolic modifications, including hypercorticonaeemia and diabetes, which may indirectly affect the immune system. Similarly, leptin deficiency after starvation in rodents is linked to increased glucocorticoid levels, and decreased levels of thyroid and growth hormone, each of which may mediate immune suppression.⁸ Both the

direct and indirect effects of leptin are thus likely to account for the immune defects observed in leptin deficient animals. In humans, congenital leptin deficiency is associated with a decreased number of circulating CD4+ T cells, and impaired T cell proliferation and cytokine release, all of which can be reversed by the administration of recombinant leptin.⁹

Its abovementioned immunomodulatory and Th1 promoting effects suggest that leptin may play a part in the regulation of autoimmune inflammatory conditions. Consistently, leptin deficient mice are protected from inflammation mediated by T and B cells in different disease models, including experimental autoimmune encephalomyelitis (EAE), type I diabetes, experimental colitis, and antigen induced arthritis (AIA).^{6,10-12} Administration of exogenous leptin restores the responsiveness of *ob/ob* mice to T cell-activating stimuli.¹⁰ In addition, in EAE, treatment with leptin after disease onset increases the severity of the symptoms.¹³ Similarly, in non-obese diabetic mice, leptin administration accelerates the autoimmune destruction of β cells and increases interferon γ production by peripheral T cells.¹¹

"Leptin may play a part in the regulation of autoimmune inflammatory conditions"

AIA is a model of immune mediated joint inflammation induced by administration of methylated bovine serum albumin (mBSA) into the knees of immunised mice. The severity of arthritis in leptin and leptin receptor deficient mice was reduced in this model.⁶ The milder form of AIA seen in *ob/ob* and *db/db* mice, as compared with their controls, was accompanied by decreased synovial levels of interleukin (IL)1 β and tumour necrosis factor (TNF) α , decreased proliferative response to antigen of lymph node cells in vitro, and a switch towards production of Th2 cytokines.⁶ Serum levels of all isotypes of anti-mBSA antibodies were significantly decreased in arthritic *ob/ob* mice as compared with controls. In AIA, leptin thus probably

contributes to joint inflammation by regulating both humoral and cell mediated immune responses.

LEPTIN AND INFLAMMATION

The innate immune system has a major role in the regulation of leptin production. In experimental animal models, leptin levels are acutely increased by inflammatory and infectious stimuli, such as lipopolysaccharide (LPS), turpentine, and proinflammatory cytokines.^{14,15} The increase in leptin production during infection and inflammation strongly suggests that leptin is part of the cytokine cascade, which orchestrates the innate immune response and host defence mechanisms. However, both pro- and anti-inflammatory effects have been described for leptin according to the experimental model investigated.

In vitro, leptin stimulates both pro- and anti-inflammatory cytokine production in monocytes and macrophages.¹⁶⁻¹⁹ Macrophages isolated from *ob/ob* mice show increased basal expression of IL6 and seem to be constitutively activated, implying that leptin may inhibit macrophage activation in vivo.²⁰ However *ob/ob* mice also display impaired innate host response to bacterial pneumonia, indicating that here leptin plays an important part in the activation of host defence against infection.²¹ Finally, leptin deficient mice display an increased sensitivity to TNF α and LPS induced lethality, indicating that a functional leptin system confers protective anti-inflammatory effects against these systemic proinflammatory stimuli.^{18,22}

The intravenous injection of *Staphylococcus aureus* results in a severe form of septic arthritis in mice, which is associated with decreased circulating levels of leptin. In this model, treatment with leptin significantly decreased the severity of arthritis without interfering with the staphylococcal load in the joints.²³ Preceding the effect on joint manifestations, serum levels of IL6 decreased in mice treated with leptin. In this model of septic arthritis, leptin thus reduced both the severity of joint manifestations and the inflammatory response. Similarly, we recently explored the role of leptin in zymosan induced arthritis (ZIA), a model of monoarticular arthritis which is not dependent on the adaptive immune response (Bernotiene E *et al*, unpublished data). In contrast with AIA, ZIA was not impaired in *ob/ob* and *db/db* mice. On the contrary, the resolution of joint swelling in ZIA was delayed in the absence of leptin or leptin signalling. The acute phase response, assessed by measuring circulating levels of IL6 and serum amyloid A, remained higher for a longer period of time in *ob/ob* mice than in control littermates. Furthermore, histological features of arthritis tended to be

more severe at late time points in ob/ob mice. The delayed resolution of ZIA in ob/ob and db/db mice suggests that, in this model, leptin displays anti-inflammatory properties. As previously observed with systemic proinflammatory stimuli,^{18,22} leptin may thus also be involved in the control of local inflammatory events in the joint.

A ROLE FOR LEPTIN IN HUMAN RHEUMATIC DISEASES?

In patients with rheumatoid arthritis (RA) it was reported that fasting leads to an improvement of different clinical and biological measures of disease activity, which was associated with a marked decrease in serum leptin and a shift towards Th2 cytokine production.²⁴ These features, resembling those seen during AIA in ob/ob mice, suggest that leptin may also influence the inflammatory mechanisms of arthritis in humans through the induction of Th1 responses. However, the same investigators showed that after a seven day ketogenic diet in patients with RA, there were no significant changes in any clinical or biological measurements of disease activity, despite a significant decrease in serum leptin concentrations.²⁵

"A ketogenic diet reduces leptin concentrations but does not improve measures of disease activity"

In this issue of the *Annals*, Bokarewa *et al* report increased plasma levels of leptin in 76 patients with RA as compared with healthy controls.²⁶ The authors also observed that circulating plasma concentrations of leptin were significantly higher than leptin levels in matched synovial fluid samples and that the difference between plasma and synovial fluid was particularly pronounced in non-erosive arthritis. The authors concluded that intra-articular leptin may exert a protective effect against the destructive course of RA. Consistent with this hypothesis, these investigators previously observed that treatment with leptin decreases the severity of joint damage in an experimental model of septic arthritis.²³ Unfortunately, several problems limit the interpretation of their results in patients with RA: (a) their study was cross sectional and thus, does not provide any information on the role of leptin on the course of the disease, particularly on the progression of joint damage; (b) besides the measurement of C reactive protein (CRP) levels, the authors did not give any indication about disease activity; (c) most importantly, the authors did not provide any information about the body mass index (BMI) of the subjects studied. This

makes interpretation of the results difficult, because plasma leptin levels are strongly influenced by BMI and fat mass.

How do the results of Bokarewa *et al* compare with those of other studies? Two different groups showed that serum levels of leptin were not increased in patients with RA as compared with controls. In addition, they did not find any correlation between leptin levels and either clinical or biological signs of disease activity, whereas a positive correlation was seen between leptin and BMI or the percentage of body fat.^{27,28} Another group reported lower plasma leptin levels in patients with RA than in controls. In patients with RA from this cohort, leptin did not correlate with BMI, CRP, total fat mass, or disease activity score.²⁹ Leptin levels were also examined in other inflammatory rheumatic diseases. Forty one women with systemic lupus erythematosus (SLE) were compared with 23 healthy controls. After adjustment for BMI, patients with SLE had significantly higher serum levels of leptin than healthy subjects. However, there was no correlation between leptin levels and the Mexican SLE disease activity index (Mex-SLEDAI).³⁰ Finally, in 35 patients with Behçet's syndrome, leptin levels were significantly higher than in healthy controls and correlated positively with disease activity.³¹

Taken together, the data of different clinical studies indicate that leptin levels cannot be used to assess the disease activity in RA and SLE. However, the results of Bokarewa *et al* suggest that leptin may influence the outcome of RA. Despite the presence of methodological problems in their study, this point is of interest because experimental models suggest that leptin may influence the disease process in two opposing ways, either by enhancing the expression of Th1 cytokines or by limiting the inflammatory responses. Thus, longitudinal studies including patients with early RA are still needed to clarify the potential influence of leptin on disease outcome, and particularly the progression of joint damage. Likewise, it would certainly be worth performing similar studies in other immune mediated inflammatory rheumatic diseases.

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