Role of leptin and leptin receptor in inflammation

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ON OCTOBER 30th, 2002, the World Health Organization was launched subtitled Reducing risks, promoting healthy life. Many of the health risks discussed in this report concern food consumption—either too little, in the case of the poor, or too much, in the case of the better off. Two of the most striking findings in this report are to be found almost side by side. One is that in poor countries today there are 170 million underweight children, over three million of whom will die this year as a result. The other is that there are more than one billion adults worldwide who are overweight and at least 300 million who are clinically obese. Among these, about half a million people in North America and Western Europe combined will have died this year from obesity-related diseases. These data illustrate the pivotal importance of understanding the pathophysiology of starvation and obesity for solving major health problems in this century and thereafter.

In this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, Madiehe and colleagues (13) present interesting data in this respect that improve our understanding of the relationship between starvation, obesity, and host response to infection. This relationship has been linked to leptin, a key hormone in the control of body weight (7). Leptin is an adipocyte-derived hormone that influences the central regulation of food intake and energy expenditure via cerebral leptin receptors. Obesity is associated with elevated systemic leptin concentrations, whereas fasting induces a fall. The latter is a signal for the brain to initiate adaptive responses to starvation-like suppression of reproductive and thyroid function and stimulation of the hypothalamic-pituitary-adrenal axis. Counteracting the starvation-induced fall of systemic leptin levels by injecting exogenous leptin substantially blunts these changes. Interestingly, reduced leptin levels are also crucial for the impairment of the immune function observed during starvation, which is characterized by lymphoid atrophy and T-lymphocyte dysfunction. This can also be restored by administration of exogenous leptin (12).

Two genetic animal models, the ob/ob and db/db mouse, have been extensively investigated in obesity research, the former being defective in leptin synthesis, the latter in receptor function. Several isoforms (a-f) of the leptin receptor (Ob-R) exist as a result of alternative mRNA splicing (3). Leptin-resistant db/db mice lack the long isoform of the Ob-R (Ob-Rb) that has a cytoplasmic domain required for activation of signal transducers and activators of transcription. The other short isoforms exhibit abbreviated intracellular amino acid sequences and have little intracellular signaling capacity (3). Their physiological role is less clear.

The group of Madiehe and colleagues (13) from the Department of Foods and Nutrition of the University of Georgia investigated db/db mice and challenged them with intraperitoneal endotoxin [lipopolysaccharide (LPS)] injection, investigating hormonal and inflammatory response as well as mortality (13). Two strains of C57BL/6J db/db mice were investigated, one strain, the classical db/db mouse, expressing four of five isoforms of the leptin receptor (the short isoforms Ob-Ra, Ob-Rc, Ob-Rd, Ob-Re), the other strain (termed db3J/db3J) expressing only one short isoform, the Ob-Re. The latter receptor is a circulating Ob-R in contrast to the others that are membrane bound. Therefore studies with both db/db and db3J/db3J mice strains are unique, as membrane-bound short isoform receptor effects can be differentiated. Both strains were additionally challenged with food restriction, as starvation increases susceptibility to endotoxic shock (6). The study showed that endotoxin injection induced a 50% mortality in fasted db/db but not in fasted db3J/db3J mice, which implies that the membranous isoforms of the leptin receptor are essential for the deleterious effects of LPS. This is supported by former studies showing that animals with normal function of the leptin receptor (wild-type and ob/ob mice) are more susceptible to endotoxin than leptin receptor-deficient mice (db/db) (5). The pathomechanism of the link between leptin receptor, immune system, and mortality is still uncertain. Therefore Madiehe et al. (13) deter-
mice. The response was, however, markedly lower in administration of leptin in wild-type and after LPS injection can be diminished by simultaneous cyte function and interferes with other cytokines such mice may be explained by higher systemic leptin concentrations of corticosterone and TNF-α in fasted db/db mice. This led to the hypothesis that increases in corticosterone, TNF-α, and mortality are mediated directly or indirectly by the membranous short isoforms of the leptin receptor.

In addition, inflammatory stimuli have previously been shown to induce elevated systemic leptin concentrations, proposing that leptin induction is part of the ubiquitous acute phase reaction. This has been explained by the cytokine properties of leptin and its receptor, as the secondary structure of leptin resembles that of cytokines and the leptin receptor is homologous to the signal-transducing subunit of the IL-6 receptor family (2, 5). LPS also induced an increase in leptin in the present study in both strains of db/db mice. The response was, however, markedly lower in db/db than in db/db mice (13). Therefore, the leptin response seems to be independent of the membranous part of the leptin receptor. Whether the circulating leptin receptor interferes with this reaction remains to be shown.

The higher resistance to LPS in fasted db/db mice may be explained by higher systemic leptin concentrations in this strain. Leptin restores T-lymphyocyte function and interferes with other cytokines such as IL-1 (12). In addition, the increase in corticosterone after LPS injection can be diminished by simultaneous administration of leptin in wild-type and db/db mice (6, 13), attenuating TNF-α production and reducing TNF-α toxicity (16). However, impaired macrophage phagocytic function also observed in db/db mice is not restored by recombinant leptin (11).

The evaluation of the short forms of the leptin receptors and their physiological and pathophysiological role have just been started. The short isoforms Ob-Ra and Ob-Rc seem to be important for blood-brain barrier function (9), whereas the role of the others, particularly the circulating Ob-Re isoform, is still hypothetical. The present study is one of the first steps in beginning to understand the role of the short isoforms of the leptin receptor for the immunological host response to endotoxin challenge.

We await further studies on the relationship between leptin, leptin receptor, and immunological reaction, as these findings might have important clinical implications (8). Likewise it has been shown that patients with severe sepsis or septic shock have significantly higher IL-6 and leptin concentrations that both proved to be predictors of survival (1). In addition, refeeding in malnourished infants restores T helper cell type 1 activity (19), and administration of leptin in patients with lipodystrophy improves insulin resistance (18). Subcutaneous administration of long-acting human leptin for 8 wk did not, however, change body weight or inflammatory status in healthy, obese subjects (10). The role of leptin and its receptor can certainly be extended beyond the immunological response during infection, as leptin has also been shown to be involved in chronic disease such as insulin resistance, cardiovascular disease, heart failure, neurological disorders, osteoporosis, and cancer (4, 14, 15, 17, 20). Understanding the role of leptin for the immunological host response and disease progression during voluntary and nonvoluntary weight reduction will be a crucial task for future research. We, therefore, await more data on the pathophysiological link between starvation and obesity on the one side and immunology and acute as well as chronic disease on the other that will enable us to improve intervention and treatment strategies for the underweight and overweight population alike. Nonetheless, above all, supplying sufficient food for the poor and reducing body fat in the obese will remain the primary aims in the prevention of disease and premature death.

REFERENCES


13. Madielie AM, Mitchell TD, and Harris RBS. Hyperleptinemia and reduced TNF-α secretion causes resistance of db/db


