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 db/db/db/db) 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 db/db/db/db 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 db/db/db/db 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 as IL-1 (12). In addition, the increase in corticosterone is related to hyperleptinaemia, but not to norepinephrine or TNF-α. Proc Nutl Acad Sci USA 83: 8374–8378, 1996.


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

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