The Energy Request of Inflammation

The paper by Marion den Boer et al. (1), in this issue, addresses an important but complex topic: the role of antiinflammatory cytokines (IL-10) in energy metabolism. Surprisingly, their results appeared to be negative with respect to peripheral insulin-mediated glucose uptake. However, the authors did report effects on fat metabolism in general, particularly in the liver. Their findings represent an important contribution to understanding the network that links inflammatory processes, energy metabolism, and the behavioral state.

**Reflex Inhibition of Inflammation**

Upon microbial invasion or injury, the organism responds with a local protective process of inflammation. This process is fine-tuned at both the local cell-to-cell level and a systemic level that is monitored by the brain. TNF, a proinflammatory cytokine, is produced by activated immunologically competent cells in response to pathogens and injurious stimuli. It is a necessary and sufficient mediator of local and systemic inflammation (2). Inflammatory products, such as TNF, produced in damaged tissue activate afferent vagal signals that are related to the nucleus of solitary tract. Subsequent activation of vagus efferent activity inhibits cytokine synthesis via the cholinergic antiinflammatory pathway (Fig. 1) (3). Circulating TNF also accesses the sensory nuclei of the solitary tract and alters motor activity in the vagus nerve. Thus, the nervous system receives both neural and humoral information about the ongoing inflammatory process and responds with fever, anorexia, activation of the sympathetic nervous system and the hypothalamus-pituitary-adrenal (HPA) axis, and sickness behavior. The activated HPA system exerts humoral antiinflammatory actions via cortisol, whereas the sympathetic nervous system stimulates the release of IL-10, a potent antiinflammatory cytokine, from monocytes (4, 5). Thus, both neural and humoral pathways exert feedback inhibition on the inflammatory process. The importance of the antiinflammatory pathways becomes apparent for example in animals deficient in IL10, which develop a chronic inflammatory bowel disease or collagen-induced arthritis.

**Energy Fluxes during Inflammation**

The inflammatory response to pathogenic threats consumes large amounts of energy. A systemic immune response in particular puts a heavy load on energy metabolism. In the febrile state, a massive loss of thermal energy puts an additional burden on metabolism. In life-threatening infection, defense against pathogens becomes a goal of very high priority. The organism employs two strategies to cope with this relative shortage of energy: 1) allocating the valuable energy to the process where it is needed, in this case toward the active immune cells; and 2) shutting off all other energy consuming processes that are not essentially needed (certain brain functions, locomotor activity, growth processes).

**Energy request of active immune cells**

Upon the release of TNF from activated immunologically competent cells, glucose uptake by these cells is enhanced (Fig. 2) (6). Glucose uptake into immune cells is carried out by the glucose transporter 1 (GLUT-1), which is independent of insulin. TNF has been shown to enhance GLUT-1 expression and to increase GLUT-1-mediated glucose uptake. On the other hand, TNF decreases the uptake of glucose into the muscle and adipose cells governed by the insulin-dependent glucose transporter 4 (GLUT-4). TNF has been shown to decrease GLUT-4-mediated glucose uptake in skeletal muscle (7). In this way, the active immune cell via secretion of TNF can fuel itself with more glucose by inhibiting the uptake of glucose into muscle cells. This process can be regarded as a local energy request process. It operates by actively controlling the ratio of GLUT-1- and GLUT-4-mediated glucose uptake. Energy request is carried out just in time, i.e. when the immune cell is active and has increased energy requirements.

**Saving energy in other organs**

When circulating proinflammatory cytokines (like TNF, IL-1, and IL-6) enter the brain, they exert profound effects on behavior (Fig. 2) (8). The behavioral manifestations of illness include fatigue and sleepiness as well as the minimization of social and locomotor behavior. In this way, the organism can withdraw considerable amounts of energy used otherwise by the brain and the skeletal muscle. The saved energy can instead be used for heat generation in the febrile state and for the inflammatory response. Although in severe disease the brain is set to a low functional state, a mismatch between the low brain need and its energy supply may occur in such a metabolic crisis. In case of energy shortage in the brain, the central nervous system requests energy for itself by activating the sympathetic nervous and the HPA system, and in so doing it restricts the inflammatory response (Fig. 1).

**Conclusions**

Marion den Boer et al. (1) studied IL-10-deficient mice in an overfed state. Their original hypothesis was that a deficiency in the antiinflammatory system (IL-10) would result in...
in an enhanced glucose uptake by the insulin-sensitive tissues. Why did they not detect such an effect?

To assess information about the peripheral glucose metabolism, the authors employed the hyperinsulinemic, euglycemic clamp technique. They found equal glucose infusion rates in IL-10-deficient and wild-type mice. Glucose infusion rate essentially reflects the sum of GLUT-1- and GLUT-4-mediated glucose uptake. The glucose clamp technique provides only information about the sum of these uptakes. Additional measurements are required to assess the ratio of GLUT-1- and GLUT-4-mediated glucose uptake, a ratio that is actively controlled by an energy request processes of the immune system (see above). Even though the sum of GLUT-1- and GLUT-4-mediated glucose uptake was unchanged in IL-10-deficient mice, a change in the ratio of both uptakes may still have occurred. I agree with the authors that there may have been changes in insulin-mediated uptake that were not uncovered by the glucose clamp method. This view is supported by the fact that the authors could demonstrate protective effects of IL-10 on hepatic fat content showing that IL-10 is indeed metabolically active.

Provided that the inflammatory process exerts an active energy request, it is conceivable that den Boer’s findings were negative with respect to the peripheral glucose metabolism. The knockout mice lacked one braking function of the antiinflammatory pathway. Because the authors examined mice during a basal condition, i.e. not challenged by an acute infection, there was no additional energy need for the immune system, and consequently no energy request, and ultimately no need for an antiinflammatory braking function.
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