Salmonella abortus equi Endotoxin Does Not Affect Leptin Plasma Levels in Healthy Humans

To the Editor—We read with interest the recent paper of Bornstein et al. [1], who report that 4 ng/kg body weight Escherichia coli endotoxin injected intravenously into healthy volunteers fails to increase circulating leptin levels, despite a clear-cut activation of the hypothalmo-pituitary-adrenal system and an increase in rectal temperature. This finding is surprising, because endotoxin has been shown to stimulate leptin production in animals [2] and because the administration of pivotal mediators of endotoxin’s effects on host defense, such as tumor necrosis factor-α (TNF-α) [3] and glucocorticoids [4], has been shown to increase leptin levels in humans. We report here on the effects of another endotoxin preparation on rectal temperature, and on the plasma levels of interleukin-6 (IL-6), TNF-α, and cortisol in healthy volunteers.

The study comprised 10 male subjects (age: 26 ± 4 years). Five subjects received 0.4 ng/kg body weight and 5 received 0.8 ng/kg body weight Salmonella abortus equi endotoxin (for details about the endotoxin preparation see [5]) intravenously in a single-blind placebo-controlled design. On two experimental occasions separated by 2 weeks, they fasted, starting at 7 p.m. Endotoxin or 0.9% saline solution was injected at 11 p.m., when temperature and cortisol responses are much more pronounced than in the morning [6]. After the injection, the subjects were kept awake throughout the experiment. They participated in a larger study of the interactions between host responses to endotoxin and sleep-wake behavior (the respective results will be presented elsewhere).

Rectal temperature was monitored continuously, and blood samples were taken through an intravenous catheter. Plasma was frozen to −20°C. IL-6 and TNF-α levels were determined by ELISAs (Medgenix Diagnostics, Brussels); RIAs were used to measure cortisol (ICN Biomedicals, Carson, CA) and leptin (DRG Instruments, Marburg, Germany) levels. The effects of endotoxin (expressed as the difference between values obtained on the endotoxin and placebo occasions) are depicted in Figure 1.

Figure 1. Host responses to intravenous injection in 5 healthy subjects of 0.4 ng/kg body weight (□) or 0.8 ng/kg body weight (■). S. abortus equi endotoxin. For all variables, mean differences between endotoxin and placebo conditions at every time point are depicted. Bars = SE of mean. For description of results and for statistics, see text.
after the endotoxin and saline injections) were statistically tested by analysis of variance, with dose as the between-subjects factor and time (hourly values from 11 p.m. to 4 a.m.) as the within-subject factor.

The results are shown in figure 1. Endotoxin did not affect the plasma levels of leptin (F(5,40) = 1.10; P = .377). However, endotoxin induced prominent increases in the plasma levels of TNF-α (F(5,40) = 58.37; P < .01), IL-6 (F(5,40) = 24.17; P < .01) and cortisol (F(5,40) = 7.74; P < .01) and in rectal temperature (F(5,40) = 10.96; P < .01). Effects of endotoxin on TNF-α (F(1,8) = 15.89; P < .01), IL-6 (F(1,8) = 9.06; P < .05), and cortisol levels (F(1,8) = 12.76; P < .01) were dose-dependent, whereas the increase in temperature (F(1,8) = 0.03; P = .870) was not.

In this study, 2 different doses of S. abortus equi endotoxin injected intravenously into healthy volunteers failed to increase plasma leptin levels, despite the clear-cut induction of increases in the plasma levels of TNF-α, IL-6, and cortisol and in rectal temperature. The higher dose that we have used here has biologic effects that are quantitatively similar to 4 ng/kg body weight E. coli preparation [7]. Therefore, it is likely that cytokine levels that have not been measured by Bornstein et al. [1] in their subjects were similar to the levels we report here. Thus, using a different endotoxin preparation and a different leptin assay, we confirmed the results obtained by Bornstein et al. [1]. We agree with the conclusion of those authors that leptin is not involved in human host responses to experimental endotoxin administration.

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References


All participants gave written informed consent and the experimental protocol was approved by an independent ethics committee.

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Reply

To the Editor—In their letter above, Pollmacher et al. [1] present interesting data showing that experimental endotoxemia with Salmonella abortus equi does not influence circulating leptin levels in healthy volunteers [1]. This study confirms our recent report demonstrating that 4 ng/kg Escherichia coli endotoxin failed to increase circulating leptin levels [2]. Further, their study confirms that no change occurs in nocturnal leptin levels during endotoxemia. Therefore, different types and doses of gram-negative endotoxemia resulted in a prominent inflammatory response that did not influence circulating leptin [1, 2].

Recent results clearly establish a role for leptin in modulating immune function by increasing Th1, and suppressing Th2, cytokine production [3]. Therefore, low leptin levels in starvation may contribute to the higher frequency of infections that develop in this setting. Low leptin levels have been associated with a poor prognosis in critically ill patients with acute sepsis [4]. A failure of leptin to increase in humans after endotoxin administration may thus explain the greater sensitivity to endotoxin in humans compared with rodents, which do show increased leptin levels after endotoxin administration. Leptin is a stress-related peptide [5] linked to cytokines, and we are only beginning to understand its role in immune defense and infection. Future studies will also have to consider the local paracrine and autocrine effects of leptin produced in tissues other than the adipocyte.

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