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NOTES

Roles of Interleukin-1 and Tumor Necrosis Factor in Lipopolysaccharide-Induced Hypoglycemia

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In this study, hypoglycemia induced by injection of lipopolysaccharide (LPS) or the recombinant cytokine interleukin-1α or tumor necrosis factor alpha (administered alone or in combination) was compared. LPS-induced hypoglycemia was reversed significantly by recombinant interleukin-1 receptor antagonist.

Among the varied responses elicited by administration of lipopolysaccharide (LPS) in vivo is a modulation of glucose metabolism, which in mice results in dose-dependent hypoglycemia (reviewed in references 18, 21, 22, and 30). LPS is also known to induce cytokines, among which are interleukin-1 (IL-1) and tumor necrosis factor (TNF), and both of these have been demonstrated to induce hypoglycemia when administered to mice in vivo (3, 4, 7, 8, 15, 21, 22, 25). Thus, it has been hypothesized that IL-1 and TNF act as probable intermediates in LPS-induced hypoglycemia. However, we recently demonstrated that administration of a rabbit polyclonal immunoglobulin prepared against recombinant murine TNF to mice failed to block LPS-induced hypoglycemia, under conditions in which a highly significant inhibition of serum colony-stimulating factor (CSF) activity was observed (27). In the present study, we attempted to determine the role of IL-1 in mediating LPS-induced hypoglycemia. Our results demonstrate that a recombinant IL-1 receptor antagonist (rIL-1ra) reversed significantly the hypoglycemia induced by LPS, even when administered 3 days prior to LPS challenge, suggesting that IL-1 is an intermediate in this process.

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Female mice, 5 to 6 weeks of age, were used for all experiments. The following strains were used during the course of this study: C3H/HeN (National Cancer Institute, Frederick, Md.), and C57BL/6J, C3H/OuJ, and C3H/HeJ (Jackson Laboratories, Bar Harbor, Maine). The experiments reported herein were conducted according to the principles set forth in *Guide for the Care and Use of Laboratory Animals* (16a). Mice were injected intraperitoneally with 0.5 ml of pyrogen-free saline (Abbott Laboratories, North Chicago, Ill.), 25 μg of *Escherichia coli* K235 LPS (prepared by the phenol-water extraction method of McIntire et al. [17]), or the indicated concentrations of recombinant murine IL-1α (rIL-1α; kindly provided by Peter Lomedico, Hoffmann-LaRoche, Inc., Nutley, N.J.) or recombinant human TNF-α (rTNF-α; kindly provided by Abla Creasey, Cetus Corporation, Emeryville, Calif.). rIL-1ra was the generous gift of Robert Thompson (Synergen, Inc., Boulder, Colo.). All dilutions of LPS, cytokines, or rIL-1ra were prepared in pyrogen-free saline. Levels of blood glucose in serum samples (pooled from two to six mice per treatment per experiment) were measured by using a glucose oxidase reagent kit (Sigma Chemical Co., St. Louis, Mo.), modified exactly as described elsewhere (13). A glucose standard curve was included in each assay. All data were analyzed by two-tailed Student's *t* tests.

The capacities of LPS (25 μg), rIL-1α (500 ng), and rTNF-α (7.5 μg) to induce hypoglycemia were first compared. For this initial series of experiments, the doses of LPS, rIL-1α, and rTNF-α chosen were based on previous experience in which these three reagents were compared for their ability to induce comparable CSF activity (26). The data in Fig. 1 confirm and extend previous work using these three inducers of hypoglycemia: injection of LPS leads to a statistically significant depression of blood glucose levels by 4 h after injection. In contrast, both rIL-1α and rTNF-α induced a significant degree of hypoglycemia by 2 h after administration, although the hypoglycemic response to rIL-1α was significantly greater than that induced by rTNF-α at 2 h ($P = 0.007$).

These findings were further extended by analyzing the effects of the recombinant cytokines administered at various doses, alone or in combination, on blood glucose levels obtained 6 h after injection (Table 1). Both rIL-1α and rTNF-α induced dose-dependent decreases in blood glucose; however, when administered in combination, a more profound state of hypoglycemia was observed, resulting in a maximum decrease in blood glucose of ~50%. Certain dose combinations (i.e., IL-1 at 100 ng plus TNF at 5 μg, IL-1 at 500 ng plus TNF at 5 μg, and IL-1 at 100 ng plus TNF at 7.5 μg) were synergistic and resulted in hypoglycemia which is significantly greater than one would predict from the sum of the decreases observed following injection of either cytokine individually ($P < 0.001$). This pattern of induction of hypoglycemia by rIL-1α and/or rTNF-α was also observed in LPS-hyporesponsive C3H/HeJ mice under conditions in which 25 μg of LPS failed to induce a significant decrease in blood glucose levels (data not shown).

Given the fact that LPS has been demonstrated to induce both IL-1 and TNF in vivo (reviewed in references 19 and

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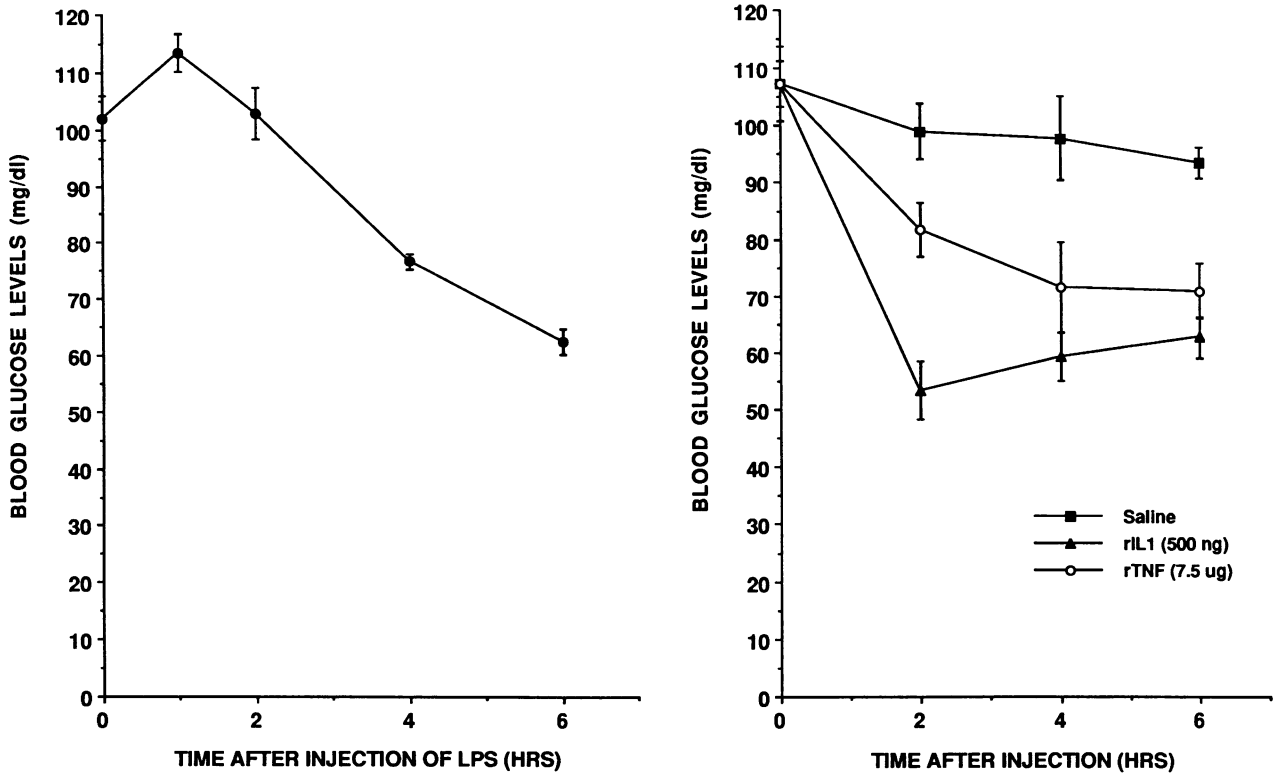

FIG. 1. Effect of administration of LPS, rIL-1α, and rTNF-α on blood glucose levels in mice. Groups of mice (C57BL/6J, C3H/HeN, and C3H/OuJ; two to five mice per treatment per experiment) were injected with 25 μg of LPS (left panel) or saline, rIL-1α (500 ng), or rTNF-α (7.5 μg) (right panel). Serum samples were collected and pooled at the indicated times after injection, and blood glucose was measured as described in the text. The results represent the arithmetic means ± standard errors of the means of 4 to 12 separate experiments for each data point. For LPS, levels of blood glucose were significantly different ($P < 0.05$) from saline controls at 4 and 6 h after injection. Levels of blood glucose were significantly different from saline controls at 2, 4, and 6 h after injection of either rIL-1α or rTNF-α.

28) and since both of these cytokines (either alone or in combination) induce hypoglycemia faster than LPS (Fig. 1), it has been hypothesized that both of these cytokines mediate the hypoglycemia induced by LPS. However, unless a specific LPS-mediated effect is blocked with a cytokine-specific antagonist, it cannot be presumed that the cytokine in question is indeed an intermediate in the response being studied. For example, we recently observed that administration of a monospecific anti-murine rTNF-α antibody to mice failed to block LPS-induced hypoglycemia, even at concentrations that were 10 times higher than that required to ablate LPS-induced serum TNF (27), reduce LPS-induced CSF activity significantly (27), and neutralize in vivo all of the TNF activity produced in the spleens and sera of tumor-bearing mice injected with 25 μg of LPS (20). Thus, it was concluded that TNF-α may not serve as an intermediate in the induction of hypoglycemia by LPS, even though its exogenous administration results in a significant decrease in blood glucose levels (3, 4, 25).

Recently, a human rIL-1ra was cloned and purified (10). This protein binds to high-affinity murine IL-1 receptors (6, 12) and has been shown to inhibit IL-1-induced prostaglandin E_2 and collagenase secretion from synovial cells in vitro (2). We have used this reagent to inhibit significantly LPS-induced CSF activity, as well as the induction of early endotoxin tolerance by LPS, in vivo (14). Table 2 illustrates the effects of simultaneous or prior administration of rIL-1ra on LPS-induced hypoglycemia. Separate groups of mice were injected on day 0 with either saline (treatment groups A to D) or the rIL-1ra (treatment group E). Three days later, individual groups were challenged with saline (treatment group A), LPS only (treatment group B), rIL-1ra only (treatment group C), or both LPS and rIL-1ra (treatment group D). This experimental design was chosen so that we could concurrently assess both the simultaneous and long-term efficacy of the rIL-1ra in this system (treatment group D versus group E). The dose of rIL-1ra (300 μg) used in this study was based on two in vivo observations: (i) this concentration of rIL-1ra was found to result in a highly significant reduction of LPS-induced CSF activity and early endotoxin tolerance in vivo (14), and (ii) in preliminary experiments, 300 μg of rIL-1ra was found to reverse the hypoglycemia induced by 300 ng of rIL-1α from 45 to 91% of the saline control. As shown in Table 2, 25 μg of LPS induced the expected level of hypoglycemia (~54% of the saline control; compare treatment groups A and B). Injection of rIL-1ra (300 μg) only (treatment group C) had no effect on blood glucose levels. However, when the rIL-1ra and LPS were administered simultaneously (treatment group D), blood glucose levels were significantly higher than when mice were treated with LPS only. Thus, rIL-1ra partially, but significantly, reverses the hypoglycemia induced by LPS. LPS-induced hypoglycemia was reversed to the same extent even if the rIL-1ra was administered 3 days prior to LPS (treatment group E), and the extent of the reversal with rIL-1ra is comparable to that observed in mice rendered

TABLE 1. Effects of combined treatment with rIL-1α and rTNF-α on levels of blood glucose[a]

Treatment	Blood glucose level (% of saline controls) [n]	P value
Saline	100.0 ± 2.9 [8]	
IL-1		
10 ng	87.8 ± 6.0 [5]	0.066 (NS[b])
100 ng	80.2 ± 4.9 [7]	0.003
500 ng	70.0 ± 6.5 [7]	0.001
TNF		
5 μg	88.5 ± 6.8 [7]	0.128 (NS)
7.5 μg	80.0 ± 5.9 [7]	0.007
IL-1 (10 ng) + TNF (5 μg)	75.4 ± 5.8 [4]	0.002
IL-1 (100 ng) + TNF (5 μg)	52.3 ± 6.2 [6]	<0.001
IL-1 (500 ng) + TNF (5 μg)	48.1 ± 3.7 [4]	<0.001
IL-1 (10 ng) + TNF (7.5 μg)	68.8 ± 4.3 [4]	<0.001
IL-1 (100 ng) + TNF (7.5 μg)	54.4 ± 5.4 [5]	<0.001
IL-1 (500 ng) + TNF (7.5 μg)	48.9 ± 4.1 [6]	<0.001
LPS (25 μg)	58.6 ± 5.5 [4]	<0.001

[a] Groups of mice were injected with saline, LPS, or the indicated concentrations of rIL-1α and/or rTNF-α. Mice were bled 6 h later, and the level of blood glucose was measured in pooled samples as described in Materials and Methods. Results represent the arithmetic means ± standard errors of the means of *n* separate experiments per treatment group. The level of significance (*P*), determined by comparison by Student's *t* test with the saline treatment group, is provided.

[b] NS, not significant.

"endotoxin tolerant" by injection of LPS 3 days prior to challenge with LPS (treatment group F). Significant reversal of LPS-induced hypoglycemia in mice which have been rendered endotoxin tolerant has been reported previously (13). Simultaneous treatment of mice with a higher concentration (600 μg) of rIL-1ra and 25 μg of LPS was no more efficacious in the reversal of hypoglycemia than that observed with 300 μg of rIL-1ra, and the inhibition observed with 150 μg of rIL-1ra was found not to be statistically significant (data not shown).

Since TNF-α has been shown to induce IL-1 at high concentrations (9), the capacity of the rIL-1ra to antagonize TNF-induced hypoglycemia was also examined. Table 3 shows that simultaneous administration of rIL-1ra (300 μg) and LPS (25 μg) results in partial reversal of hypoglycemia (as was seen in the data in Table 2). In contrast, rIL-1ra had no effect on the induction of hypoglycemia by rTNF-α (7.5 μg), whereas the hypoglycemia induced by rIL-1α (500 ng) was reversed completely by simultaneous administration of the inhibitor. These findings suggest that if TNF-α-induced IL-1 is responsible for hypoglycemia, it is either acting intracellularly or through an IL-1 receptor type (e.g., type II) which does not bind the rIL-1ra.

TABLE 2. Effect of rIL-1ra on LPS-induced hypoglycemia

Group	Treatment (day 0/day 3)[a]	Mean blood glucose level ± SEM (mg/dl) [n][b]	P value[c]
A	Saline/saline	105.0 ± 3.1 [12]	
B	Saline/LPS (25 μg)	56.7 ± 3.4 [14]	<0.001, A vs B
C	Saline/rIL-1ra (300 μg)	100.9 ± 5.9 [6]	
D	Saline/LPS + rIL-1ra	79.1 ± 4.6 [3]	0.011, B vs D
E	rIL-1ra (300 μg)/LPS	79.9 ± 3.3 [4]	0.003, B vs E
F	LPS/LPS	80.4 ± 7.1 [10]	0.003, B vs F

[a] Mice (C57BL/6J) were injected on day 0 with saline, rIL-1ra (300 μg), and/or LPS (25 μg) and then challenged 3 days later (day 3) with saline, LPS (25 μg), rIL-1ra (300 μg), or LPS plus rIL-1ra, as indicated. Mice were bled 6 h after the day-3 injection, and blood glucose levels were measured as described in Materials and Methods.

[b] Results represent arithmetic means ± standard errors of the means of blood glucose levels measured on pooled serum samples (four or five mice per treatment group per experiment) from the indicated number (*n*) of individual experiments.

[c] Differences were assessed by unpaired Student's *t* test, and *P* values for specific comparisons are reported.

TABLE 3. Effect of rIL-1ra on LPS-, rTNF-α-, and rIL-1α-induced hypoglycemia

Treatment[a]	Mean blood glucose level ± SD (mg/dl)[b]
Saline	93.9 ± 2.2
LPS (25 μg)	61.5 ± 0.7
LPS (25 μg) + rIL-1ra (300 μg)	72.4 ± 1.2 (*P* = 0.041)
rTNF-α (7.5 μg)	72.6 ± 3.1
rTNF-α (7.5 μg) + rIL-1ra (300 μg)	71.7 ± 0.4 (*P* = 0.765)
rIL-1α (500 ng)	78.7 ± 5.4
rIL-1α (500 ng) + rIL-1ra (300 μg)	96.0 ± 7.0 (*P* = 0.042)

[a] Mice (C57BL/6J; four mice per treatment group) were injected with saline, LPS (25 μg), rTNF-α (7.5 μg), or rIL-1α (500 ng), with or without rIL-1ra (300 μg), as indicated. The mice were bled 6 h later, serum samples were collected, and blood glucose levels were measured as described in Materials and Methods.

[b] Results represent arithmetic means ± standard deviations of blood glucose levels measured in two separate assays of pooled sera from a single representative experiment. Differences were assessed by a paired Student's *t* test, and *P* values for comparison of a specific treatment in the absence and presence of rIL-1ra are provided in parentheses.

Administration of LPS to experimental animals causes a profound carbohydrate "dyshomeostasis" (21, 22, 31) which is dose, time, and species dependent. Typically, one observes in sera or plasma of LPS-injected animals a pattern of initial hyperglycemia, which is followed by a profound hypoglycemia (reviewed in reference 21). The effect of LPS on specific pathways involved in carbohydrate metabolism has also been examined by many, and it appears that the basis for the observed hypoglycemia is multifaceted: inhibition of gluconeogenesis, increased glycogenolysis, increased peripheral glucose oxidation, induction of hyperinsulinemia, and increased glucose tolerance have all been suggested (11, 18, 21, 22, 30). The seminal work of Berry and his colleagues (reviewed in reference 18) provided important insights into the regulation of glucose levels following endotoxin administration. These investigators demonstrated that in response to LPS, a macrophage-derived soluble factor is produced which inhibits gluconeogenesis. This soluble factor was called glucocorticoid antagonizing factor. It is detectable in the serum within 2 h of LPS administration and acts on hepatocytes by blocking corticosteroid-induced phosphoenolpyruvate carboxykinase (PEPCK), a rate-limiting enzyme in the conversion of oxaloacetate to phosphoenolpyruvate during gluconeogenesis. This provided the first evidence that the hypoglycemia induced by LPS could be mediated indirectly by a macrophage-derived soluble factor. However, this may not be the only pathway by which LPS induces hypoglycemia. Recently, Silverstein et al. (23) demonstrated that hydrazine sulfate, a specific inhibitor of gluconeogene-

sis, counteracted the LPS-induced decrease in PEPCK activity; however, the mice were still hypoglycemic. This points to the possibility that inhibition of PEPCK activity as a mechanism for disrupting gluconeogenesis may be but one of several pathways in the induction of LPS-induced hypoglycemia. For example, in an earlier study, Snyder et al. (24) reported that LPS induced an increase in the glycolytic enzyme pyruvate kinase, which could also have a net effect of counteracting gluconeogenesis.

Nonetheless, the finding that LPS-induced hypoglycemia could be reproduced in vivo by injection of an LPS-induced, macrophage-derived soluble factor led to the testing of specific LPS-induced cytokines as more purified cytokines, and subsequently, recombinant cytokines became available. Since it is well documented that both IL-1 and TNF are induced very early in response to LPS, some of the initial studies were carried out using partially purified preparations of natural IL-1. For example, in a study by Hill et al. (15), an IL-1-rich preparation was shown to induce hypoglycemia and to decrease PEPCK activity; however, the methods used to purify this material could not have ensured the elimination of other cytokines, such as TNF or IL-6. In a subsequent study, Del Rey and Besedovsky (7) showed that injection of rIL-1 into mice and rats led to hypoglycemia. In mice, this decrease in blood glucose was accompanied by enhanced levels of insulin, glucagon, and corticosterone, whereas in rats, only the last two were enhanced. In rats which were adrenalectomized, rIL-1 induced severe hypoglycemia, as well as hypoinsulinemia, and therefore it was concluded that the effect of IL-1 was independent of its capacity to induce insulin. Subsequently, these investigators showed that rIL-1 induced hypoglycemia in normal animals and exerted normalizing effects in mice rendered diabetic by alloxan treatment and in two insulin-resistant, diabetic mouse strains. In these studies, they found a decrease in insulin levels in mice injected with rIL-1 and again concluded that rIL-1 did not cause hypoglycemia by inducing insulin (8). In contrast, Sacco-Gibson and Filkens (21) and Yelich et al. (31) showed that rIL-1 induced in glucose-challenged rats both increased glucose clearance and hyperinsulinemia and that both responses were a clear potentiation of the response to glucose alone. In a subsequent review (22), Sacco-Gibson and Filkens postulated that additional cofactors induced by LPS, such as TNF, might synergize with IL-1 to potentiate hyperinsulinemia. Recently, Bird et al. (5) showed that rIL-1 increased the rate of glycolysis (as measured by increased lactate production) and also caused an increase in hexose transport by increasing the net rate of glucose transporter synthesis in vitro. LPS-induced increases in plasma lactate levels in vivo have also been documented (30, 31).

Since TNF has many of the same biological properties as IL-1 (reviewed in references 16 and 19) and has been shown to induce IL-1 at high doses (10), it is not surprising that rTNF-α was also found to modulate blood glucose levels in both rats and mice (4, 25). Tracey et al. (25) demonstrated that continuous infusion of rTNF-α into rats for 20 min led to a dose-dependent induction of hyperglycemia, followed by a profound hypoglycemia ~4 h postinfusion. Bauss et al. (4) subsequently showed that a single injection of rTNF-α into mice led to a decrease in plasma glucose levels in both LPS-responsive and LPS-hyporesponsive mouse strains. In addition, they observed an increase in plasma lactate levels when very high doses of rTNF-α were administered; however, this was not observed in LPS-hyporesponsive C3H/HeJ mice. Bagby et al. (3) found that infusion of culture supernatants which contained LPS-induced monokines into rats which had been made endotoxin tolerant had a much more profound effect on alterations in plasma insulin, glucagon, and catecholamines than administration of rTNF alone, suggesting the possibility of soluble-factor synergy.

The data presented in this report confirm and extend many of these previous findings. It is clear that (i) either rIL-1α or rTNF-α is capable of inducing significant hypoglycemia by 2 h after injection (equivalent to levels induced by LPS at 4 h after injection) and (ii) rIL-1α appears to be more potent, acting somewhat more quickly than rTNF-α (Fig. 1 and Table 1). When injected in combination, rIL-1α and rTNF-α synergize to induce hypoglycemia (Table 1). This finding extends an increasingly growing list of biological effects in which IL-1 and TNF have been found to synergize: death, weight loss, early endotoxin tolerance, hematopoeitic changes, radioprotection, and others (29; reviewed in reference 19). The finding that rIL-1ra significantly reversed LPS-induced hypoglycemia (Table 2) directly demonstrates that IL-1, induced by LPS, is an intermediate in the induction of hypoglycemia by LPS. This reversal is incomplete, is induced to the same extent when rIL-1ra is administered simultaneously with or 72 h prior to LPS, and is not augmented by administration of higher doses of rIL-1ra, suggesting strongly that IL-1 is not the only intermediate in this complex process. This notion is further strengthened by the data in Table 3 showing that the rIL-1ra failed to reverse rTNF-α-induced hypoglycemia. Thus, it seems unlikely that hypoglycemia induced by rTNF-α is mediated by elaborated IL-1. However, previous findings that anti-rTNF-α antibody failed to reverse LPS-induced hypoglycemia or corticosterone levels, under conditions in which induction of CSF was significantly inhibited (26), suggest that TNF may not be the additional intermediate in this LPS-induced cascade and that perhaps other cofactors, such as IL-6 (1), participate in the induction of hypoglycemia. However, an alternative explanation may be that anti-rTNF-α antibodies are unable to extravasate into the liver in sufficient quanities to neutralize TNF effects on hepatocytes. The prolonged half-life in the circulation of anti-TNF antibody (several days) supports this possibility. Future experiments using TNF receptor antagonists will be required to address these possibilities.

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