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Primary Role of Interleukin-1α and Interleukin-1β in Lipopolysaccharide-Induced Hypoglycemia in Mice

Senri Oguri,[1,2] Katsutoshi Motegi,[2] Yoichiro Iwakura,[3] and Yasuo Endo[1]*

Departments of Pharmacology[1] and Maxillofacial and Plastic Surgery,[2] Graduate School of Dentistry, Tohoku University, 4-1 Seiryo-Machi, Aoba-Ku, Sendai 980-8575, and Center for Experimental Medicine, Institute of Medical Science, University of Tokyo, Minato-Ku, Tokyo 108-8639,[3] Japan

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Within a few hours of its injection into mice, lipopolysaccharide (LPS) induces hypoglycemia and the production of various cytokines. We previously found that interleukin-1α (IL-1α), IL-1β, and tumor necrosis factor alpha (TNF-α) induce hypoglycemia and that the minimum effective dose of IL-1α or IL-1β is about 1/1,000 that of TNF-α. In the present study, we examined the contribution made by IL-1 to the hypoglycemic action of LPS. Nine other cytokines tested were all inactive at inducing hypoglycemia. LPS produced hypoglycemia in mice deficient in either IL-1α or IL-1β but not in mice deficient in both cytokines (IL-1α and -1β knockout [IL-1α/β KO] mice). IL-1α, IL-1β, and TNF-α induced hypoglycemia in IL-1α/β KO mice, as they did in normal control mice. The LPS-induced elevation of serum cortisol was weaker in IL-1α/β KO mice than in control mice, and, in the latter, serum cortisol was markedly raised while blood glucose was declining. IL-1α decreased blood glucose both in NOD mice (which have impaired insulin production) and in KK-Ay mice (insulin resistant). These results suggest that (i) cortisol may not be involved in mediating the resistance of IL-1α/β KO mice to the hypoglycemic action of LPS, (ii) as a mediator, IL-1 is a prerequisite for the hypoglycemic action of LPS, (iii) IL-1α and IL-1β perform mutual compensation, and (iv) IL-1 plays a role as the primary stimulator of the many anabolic reactions required for the elaboration of immune responses against infection.

The endotoxin or lipopolysaccharide (LPS) of gram-negative bacteria strongly stimulates a variety of reactions involved in immune responses (3, 36, 45). It is also well known that LPS induces hypoglycemia in experimental animals as well as in humans (4, 19, 35). Incidentally, we have shown that various mitogenic substances other than LPS also induce hypoglycemia in mice (13).

The mechanisms reported to underlie LPS-induced hypoglycemia include an enhanced systemic consumption of glucose (34), depletion of glycogen from liver and muscle (33, 46), and impaired hepatic gluconeogenesis (18, 26, 33). The hyperthermic response often seen soon after LPS injection and the later hypothermic responses do not correspond well with the blood glucose changes induced by LPS (2, 28). Over the years, a variety of causal factors, such as insulin (55), the insulin-like action of LPS itself (50), glucocorticoids (22, 42), hepatic serotonin (14, 15), and other humoral factors (22), have been proposed as possible contributors to the LPS-induced hypoglycemia.

We were the first to identify the hypoglycemic humoral factor produced by macrophages as interleukin-1 (IL-1) (16), and indeed recombinant IL-1 was later shown to induce hypoglycemia (8, 15, 22, 48). Although tumor necrosis factor alpha (TNF-α) induces hypoglycemia in mice, the minimum effective dose of IL-1α or IL-1β is about 1/1,000 that of TNF-α (15). Both IL-1α and IL-1β are capable of reducing blood glucose in mice at a dose as low as 0.1 μg/kg of body weight (2.5 ng/mouse) when injected intraperitoneally (15). Interestingly, in normal mice IL-1 induces hypoglycemia at a dose much lower than the hypoglycemic dose of insulin, and the hypoglycemia induced by IL-1 remains moderate over a wide dose range, whereas a higher dose of insulin induces a profound hypoglycemia leading to convulsions or death within a few hours (15). In addition, IL-1 is effective at reducing blood glucose even in mice with alloxan-induced diabetes as well as in genetically insulin-resistant mice and rats (9, 10, 11). In spite of the hypoglycemic action of IL-1, it potently elevates the levels of the hyperglycemic factors glucocorticoid and glucagon in blood (8). del Rey and Besedovsky (10) reported data suggesting that the central nervous system may be involved in the hypoglycemic action of IL-1. These observations suggest that the mechanisms underlying the hypoglycemic action of IL-1 may be quite different from those underlying that of insulin and thus that the biological significance of hypoglycemia due to IL-1 may be quite different from that of hypoglycemia due to insulin.

LPS stimulates the production of IL-1α, IL-1β, and TNF-α as well as a variety of other cytokines. Although the homology of IL-1α and IL-1β molecules is only 26%, they bind to common receptors on target cells with equal affinity (12). Vogel et al. (48) reported that a recombinant IL-1-receptor antagonist (IL-1ra) could reverse LPS-induced hypoglycemia. However, the effect of IL-1ra, even at a large dose, was only partial, suggesting that cytokines other than IL-1 may also be involved in the hypoglycemic action of LPS. In the present study, in

* Corresponding author. Mailing address: Department of Pharmacology, Graduate School of Dentistry, Tohoku University, 4-1 Seiryo-Machi, Aoba-Ku, Sendai 980, Japan. Fax: 81-22-717-8313. E-mail: endo@pharmac.dent.tohoku.ac.jp.

addition to investigating the effects of cytokines other than IL-1 and TNF, we examined the contributions made by IL-1α and IL-1β (by comparing the hypoglycemic effects of LPS in IL-1α-, IL-1β-, and IL-1α- and -1β-deficient mice) and we discuss the biological and clinical implications of the hypoglycemic actions of LPS and IL-1.

MATERIALS AND METHODS

IL-1-deficient and control mice. Homozygous BALB/cA mice deficient in IL-1α, IL-1β, or both (IL-1α knockout [KO], IL-1β KO, and IL-1α/β KO mice, respectively) were bred in our laboratory. These strains were originally produced by Horai and coworkers (23). These mice were all fertile, and the pups were born healthy. After birth, they developed normally in terms of their increase in body weight (23). Age-matched control BALB/cA mice (6 to 7 weeks old) were obtained from the facility for experimental animals in Tohoku University. Except where otherwise noted, males of both the control and IL-1 KO strains (more than F8 [eighth filial generation]) were used in the present study. Other strains of mice—NOD (female, 20 weeks of age), a model for insulin-dependent diabetes mellitus (32), and KK-Ay (female, 20 weeks of age), a model for non-insulin-dependent diabetes mellitus (see the characterization given by Than et al. (43)]—were kindly provided by Jo Satoh (Department of Internal Medicine, Tohuko University). All experiments complied with the *Guidelines for Care and Use of Laboratory Animals in Tohoku University*.

Reagents. An LPS from *Escherichia coli* O55:B5 prepared by Boivin's method was obtained from Difco Laboratories (Detroit, Mich.). Recombinant cytokines were kindly provided by the companies listed in our previous paper (40). LPS and cytokines were dissolved in sterile saline. Each of the test solutions was injected intravenously or intraperitoneally (0.1 ml per 10 g of body weight) in each experiment.

Determination of blood glucose. At 0900 on the morning of the day of the experiments, all mice were moved to cages with new wood chip bedding and kept without food but with free access to water. LPS or IL-1 was given from 1000 to 1200 at room temperature (23 ± 1°C). A segment of tail vein was pierced by a needle, and the blood extruded (about 5 μl) was directly applied to a strip so that glucose could be determined (by a method based on the glucose dehydrogenase method) with a glucometer (Accu-Chek Advantage; Roche Diagnostics K.K., Tokyo, Japan).

Determination of serum cortisol. Cortisol is the main glucocorticoid in humans, while corticosterone is believed to be the major glucocorticoid in rats and mice, because 17α-hydroxylase activity in the adrenal glands of these animals is poor (25, 29, 41). However, this does not mean that cortisol is not produced in these animals. Although in adult mice and rats the above enzyme is not detectable in the adrenal cortex, it is expressed in the gonads (29, 41) and it is detectable in the adrenal glands in mouse embryos (25). Indeed, in mice some types of stress have been shown to increase cortisol in the plasma (39, 44) as well as in the adrenal glands (51). It should also be noted that the glucocorticoid activities of cortisol are known to be several times more potent than those of corticosterone and that the antibodies used for the assay of corticosterone may have some, albeit weak, cross-reactivities for other glucocorticoids or steroids, although this is not explicitly stated in many reports. In the present study the level of glucocorticoids was determined by using an antibody with a high affinity for cortisol, so the levels are expressed as cortisol levels for convenience. To avoid any stress associated with blood collection (times of collection are indicated in the figures and figure legends), each mouse was instantly decapitated and blood was collected directly in a tube; the tube was kept on ice. The serum was recovered by centrifugation at 2,000 × *g* at 4°C within 1 h after the blood collection and then stored at −80°C until used. The cortisol in the serum was assayed by using enzyme-linked immunosorbent assay kits (Neogen Corp., Lexington, Ky.), and the assay procedures were performed as described by the manufacturer. The cross-reactivities for cortisol, corticosterone, cortisone, and deoxycorticosterone shown by the kit are 100.0, 3.4, 2.1, and 2.0%, respectively. The amount of cortisol is expressed as nanograms per milliliter of serum.

Data analysis. Experimental values are given as means ± standard deviations (SD). The statistical significance of differences was analyzed by using an unpaired *t* test after analysis of variance; *P* values less than 0.05 were considered to indicate significance.

RESULTS

Effects of LPS on blood glucose and serum cortisol. In our previous study using ddI and ddY mice, the fall in blood glucose was at its maximum 3 to 6 h after the intravenous injection of a sublethal dose of LPS (13) and the magnitude of the decline at 4.5 h was dependent on the dose of LPS. In BALB/cA mice, too, LPS decreased blood glucose in a dose-dependent manner at this time (Fig. 1). However, there was no such LPS-induced decline in IL-1α/β KO mice, and there was no significant difference in blood glucose between the control and IL-1α/β KO mice in the absence of LPS (see also time zero in Fig. 2). The resistance shown by IL-1-deficient mice to the hypoglycemic action of LPS was significant at 3 to 6 h after the injection of 100 μg of LPS/kg (Fig. 2).

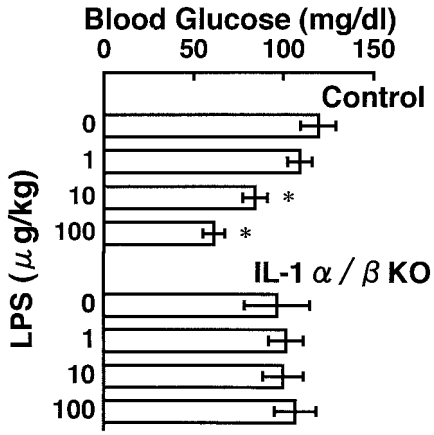

FIG. 1. LPS dose dependently reduces blood glucose in BALB/cA mice but not in IL-1α/β KO mice. Mice were each given one of the doses of LPS (intravenously), and blood was taken 4 h later. Each value is the mean ± SD from four mice. *, $P < 0.001$ versus the value for the zero dose (saline injection).

In our previous study, we showed that the above dose (100 μg/kg) of the type of LPS used in the present experiment elevated both IL-1α and IL-1β in the serum in BALB/cA mice, the effects peaking 2 h after the intravenous injection of the LPS. In addition, we confirmed that neither IL-1α nor IL-1β is detectable in the serum of IL-1α/β KO mice after injection of this LPS (53).

Since glucocorticoid has a hyperglycemic effect (as indicated in the introduction), one possibility that occurred to us is that LPS induces a higher elevation of serum cortisol in IL-1-defi-

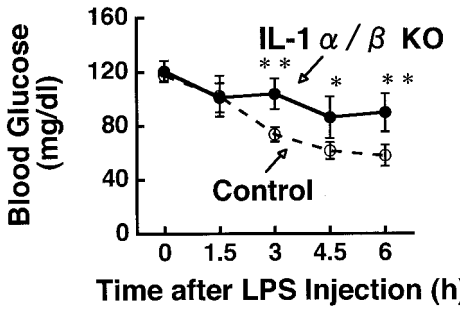

FIG. 2. IL-1α/β KO mice show resistance to the hypoglycemic action of LPS at 3 to 6 h after LPS injection. Mice (IL-1α/β KO or control BALB/cA) were given an intravenous injection of LPS (100 μg/kg), and then blood was taken at the times indicated. Each value is the mean ± SD from four mice. * and **, $P < 0.05$ and $P < 0.01$, respectively, versus value for control BALB/cA mice at the corresponding time.

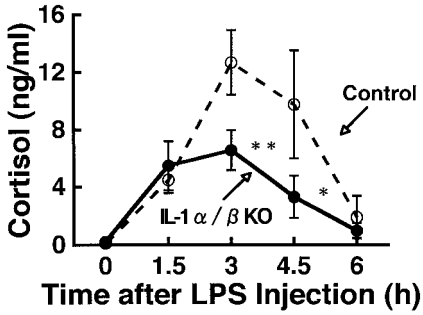

FIG. 3. LPS-induced elevation of serum cortisol is weaker in IL-1α/β KO mice than in control BALB/cA mice. Mice were given an intravenous injection of LPS (100 μg/kg), and then blood was taken at the times indicated. Each value is the mean ± SD from four mice. * and **, $P < 0.05$ and $P < 0.01$, respectively, versus value for control BALB/cA mice at the corresponding time.

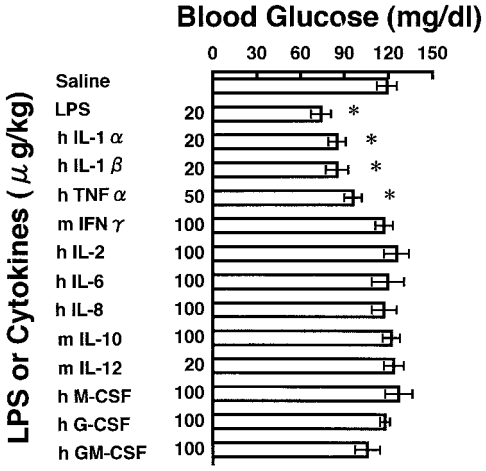

FIG. 4. Effects of intraperitoneal injection of LPS and various cytokines on blood glucose in control BALB/cA mice. Mice were each given an intraperitoneal injection of saline, LPS, or one of the cytokines listed (at the doses indicated), and then blood was taken 4 h later. Each value is the mean ± SD from four mice (except for the saline group, which consisted of 16 mice). *, $P < 0.01$ versus value for saline-injected mice. h, human; m, mouse; IFN-γ, gamma interferon; M-CSF, macrophage CSF; G-CSF, granulocyte CSF; GM-CSF, granulocyte-macrophage CSF.

cient mice than in control BALB/cA mice. However, our finding was that the serum cortisol level in control BALB/cA mice was markedly raised while blood glucose was declining (compare Fig. 2 and 3) and that the LPS-induced elevation of serum cortisol in IL-1-deficient mice was significantly weaker than that in control BALB/cA mice (Fig. 3). Saline induced a slight elevation of serum cortisol at 3 h after its intravenous injection, and its level in IL-1α/β KO mice (0.9 ± 0.3 ng/ml) was also significantly ($P < 0.01$) lower than that in control mice (3.0 ± 1.6 ng/ml).

Effects of other cytokines on blood glucose in control BALB/cA mice. Within several hours of LPS injection, a variety of cytokines are known to be produced. However, at least at the doses used and at 4 h after injection, the nine cytokines tested other than IL-1 and TNF (namely, gamma interferon, IL-2, IL-6, IL-8, IL-10, IL-12, macrophage colony-stimulating factor [CSF], granulocyte CSF, and granulocyte-macrophage CSF) were all inactive at inducing hypoglycemia (Fig. 4). Although TNF-α had a hypoglycemic action at 50 μg/kg, it was somewhat weaker than those of IL-1α and IL-1β at 20 μg/kg (Fig. 4). In these experiments, each cytokine or LPS was injected intraperitoneally to allow comparison with our previous study of the hypoglycemic effects of IL-1 and TNF (15).

Effects of IL-1 and TNF on blood glucose in IL-1α/β KO and diabetic mice. Intraperitoneal injection of IL-1α at 10 μg/kg reduced blood glucose in IL-1α/β KO mice in essentially the same manner as in control BALB/cA mice (in terms of both time course and magnitude) (Fig. 5). IL-1β (10 μg/kg) and TNF-α (50 μg/kg) also reduced blood glucose in IL-1α/β KO mice (data not shown). Intraperitoneal injection of IL-1α also reduced blood glucose in insulin-resistant KK-Ay mice (type 2 diabetes model mice), the level being decreased almost to the level seen in normal mice even at 5 μg of IL-1α/kg (Fig. 6). IL-1α also markedly reduced blood glucose in NOD mice (type 1 diabetes model mice) (Fig. 6).

Effects of LPS on blood glucose in IL-1α KO and IL-1β KO mice and in female control BALB/cA and IL-1α/β KO mice. It has been shown that, in macrophages in vitro, IL-1α and IL-1β exhibit a type of mutual interaction, with LPS-induced expression of the IL-1α gene in macrophages taken from IL-1β KO mice being significantly reduced and vice versa (23). However, in our experiment on single-KO mice, LPS reduced blood glucose in both IL-1α KO and IL-1β KO mice to an extent similar to that seen in control BALB/cA mice (Fig. 7). This experiment also demonstrated that, while female single-KO mice (IL-1α KO and IL-1β KO) show a normal hypoglycemic response to LPS, female IL-1α/β KO mice, like their male counterparts, are resistant to the hypoglycemic action of LPS.

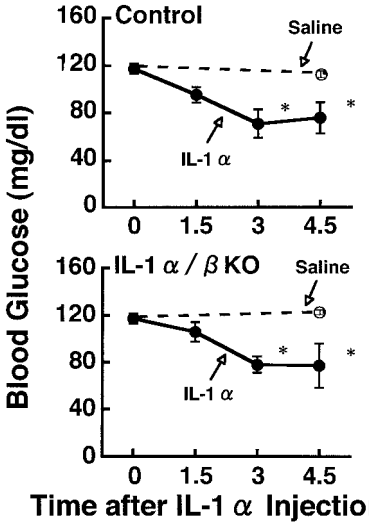

FIG. 5. IL-1α/β KO mice are susceptible to the hypoglycemic action of IL-1α. Mice were given an intraperitoneal injection of IL-1α (10 μg/kg), and then blood was taken at the times indicated. Each value is the mean ± SD from four mice. *, $P < 0.01$ versus value for the saline group at 4.5 h.

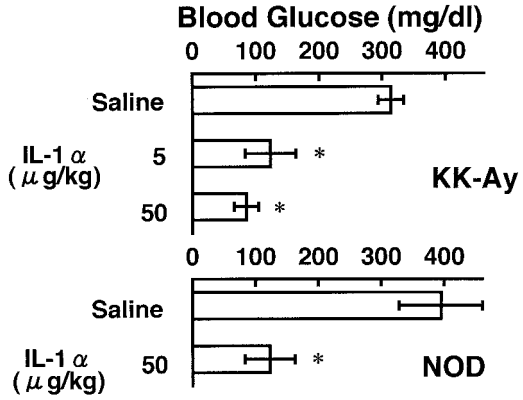

FIG. 6. IL-1α decreases blood glucose even in diabetic mice. KK-Ay and NOD mice were each given an intraperitoneal injection of saline or IL-1α at the doses indicated, and then blood was taken 4 h later. Each value is the mean ± SD from four mice. *, $P < 0.001$ versus the value for the saline group.

DISCUSSION

In the present study, we examined the hypoglycemic action of sublethal doses of LPS in the acute phase, i.e., within a few hours of its injection. The results may be summarized as follows: (i) at least at the doses used and at 4 h after injection, the nine cytokines tested other than IL-1 and TNF were inactive at inducing hypoglycemia; (ii) LPS induced hypoglycemia in IL-1α KO mice and IL-1β KO mice but not in IL-1α/β KO mice; (iii) IL-1α, IL-1β, and TNF-α all induced hypoglycemia in IL-1α/β KO mice, as they also did in normal control mice; (iv) following an LPS injection into normal control mice, serum cortisol was markedly raised while blood glucose was falling and the LPS-induced elevation of serum cortisol in IL-1α/β KO mice was weaker than that in control mice; (v) IL-1α decreased blood glucose in NOD and KK-Ay mice. We discuss these findings in the following paragraphs.

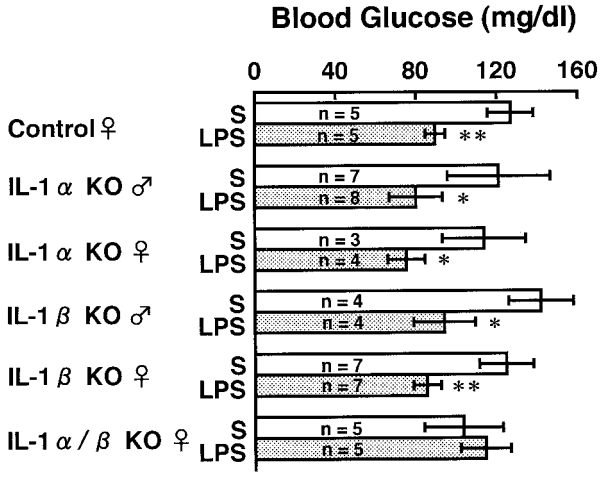

FIG. 7. Effects of LPS on blood glucose in male and female IL-1α KO and IL-1β KO mice and in female control BALB/cA and IL-1α/β KO mice. Mice were each given an intraperitoneal injection of saline (S) or LPS (100 μg/kg), and then blood was taken 4 h later. Each value is the mean ± SD (*n*, number of mice used). * and **, $P < 0.05$ and $P < 0.01$, respectively, versus the value for the corresponding saline group.

Role of IL-1α and IL-1β in LPS-induced hypoglycemia. Vogel et al. (48) observed that, although IL-1ra reversed LPS-induced hypoglycemia, the reversal was only partial even at a large dose. Thus, they suggested that IL-1 is not the only intermediate, and they proposed a contribution of TNF or IL-6. However, the same group had already shown that a TNF antibody did not reverse the hypoglycemia (47), and we found that IL-6 failed to produce hypoglycemia even at a dose of 100 μg/kg at 4 h after its injection (Fig. 4). These results and the resistance of IL-1α/β KO mice to LPS suggest that IL-1 plays a prerequisite role as a mediator in the induction of hypoglycemia following LPS injection. Our results may also support the finding by Vogel et al. (48) that TNF-α and IL-1α act synergistically to elicit a hypoglycemic response, because TNF-α is able to induce IL-1β (20), which in turn may act in concert with IL-1α to mediate the hypoglycemic response to LPS.

Fantuzzi et al. (17) reported that IL-1β KO mice had a nearly normal response to LPS in terms of glucocorticoid production, hypoglycemia, serum amyloid-A production, anorexia (or body weight loss), and lethality when LPS was given alone or in combination with galactosamine. IL-1β KO mice are even hyperresponsive to IL-1α and LPS with regard to their febrile reactions (1). In the present study, LPS induced hypoglycemia in both IL-1α KO and IL-1β KO mice. These results suggest that, when the ability to produce one of the two types of IL-1 is absent or reduced to some extent, the gross responses to LPS are not essentially different from normal responses; in other words, IL-1α and IL-1β perform mutual compensation.

Contribution of insulin. It has been reported that IL-1-induced hypoglycemia is paralleled by an increase in serum insulin in C3H/HeJ mice (it was also paralleled by an increase in glucagon and corticosterone) (8). However in C57BL/6J mice, rats, and adrenalectomized animals, IL-1 decreased serum insulin (5). Like alloxan-induced diabetic mice and insulin-resistant *db/db* mice (10), both NOD (impaired insulin production) and KK-Ay (insulin-resistant) mice also responded to IL-1 with a reduction in blood glucose. These results support the idea that insulin is probably not essential for the hypoglycemic action of IL-1, although it may play some role.

Contribution of glucocorticoids. The only relevant pathway known to produce glucose is gluconeogenesis, a process largely carried out by the liver. Lactate (the metabolite of glucose itself), amino acids (produced by protein degradation), and glycerol (formed from fat or lipid) are used in this pathway, which is stimulated by glucocorticoids and suppressed by insulin. Although LPS and IL-1 stimulate the production of glucocorticoids, the glucocorticoid-induced stimulation of gluconeogenesis is suppressed by LPS and by IL-1 itself, although the mechanism has not been clarified (21, 22, 42). In the present study, the serum cortisol level in IL-1α/β KO mice following LPS injection was significantly lower than that in control mice, suggesting that the resistance of IL-1α/β KO mice to the hypoglycemic action of LPS is independent of any effect of cortisol. The lower cortisol production in IL-1α/β KO mice may be related to the findings that IL-1 stimulates adrenocorticotropin release (6) and/or may decrease glucocorticoid receptors (22). In any event, it should be remembered that a

limited amount of gluconeogenesis remains in hypoglycemic animals given a sublethal dose of LPS or IL-1 (22, 33), and this may help protect such animals from death. The lethality of LPS in adrenalectomized animals is actually greatly augmented (presumably a reflection of their lack of glucocorticoids).

Implications of the resistance of IL-1-deficient mice to the hypoglycemic action of LPS. IL-1α/β KO mice are susceptible to mycobacterial infection (52), and IL-1 type I receptor (IL-1RI)-deficient mice are susceptible to infection by *Listeria monocytogenes* (27). The functions of eosinophils in IL-1RI-deficient mice are also reduced (7). It is known that there is an increased need for amino acids and glucose during infections. Thus, our finding that LPS induced no significant reduction in blood glucose in IL-1α/β KO mice indicates that the number of individual immune reactions induced by LPS in these mice is not so great as to cause a large amount of glucose to be consumed. In other words, the anabolic reactions needed for self-defense may not be sufficiently induced in IL-1α/β KO mice.

LPS-induced IL-1-independent reactions. LPS potently stimulates the production of IL-1, and IL-1 has a large number of biological activities (12, 31, 36, 49). Thus, the activities of LPS are believed to be mostly mediated by IL-1 or by a cytokine network involving IL-1. However, mice deficient in both IL-1α and IL-1β (or both of their receptors) have been shown to be susceptible, to a nearly normal extent, to LPS, as judged by the various responses tested (such as production of fever, some cytokines, glucocorticoids, and some acute-phase proteins; lethality; and the induction of enzymes such as the histamine-forming enzyme) (23, 27, 30, 53). These results suggest that, for these LPS-induced reactions, IL-1 is not a prerequisite or, alternatively, a compensatory mechanism may be mobilized.

Clinical relevance of hypoglycemic action of IL-1. Allogeneic bone marrow transplantation and administration of OK-432, *Mycobacterium bovis* BCG, or complete Freund's adjuvant are excellent antidiabetes strategies in both type 1 and type 2 diabetes models (24, 37, 38, 43, 54, 56). It should be noted that these methods are all based on the introduction of foreign biomaterials, i.e., materials which will elicit host immune responses. Therefore, it is likely that IL-1 is important for the operation of these strategies. Indeed, it has been shown that IL-1 improves glucose tolerance in KK-Ay mice, a type 2 diabetes model (37, 56).

Conclusions. Our results suggest that (i) cortisol may not be involved in mediating the resistance of IL-1α/β KO mice to the hypoglycemic action of LPS, (ii) as a mediator, IL-1 is a prerequisite for the hypoglycemic action of LPS, (iii) IL-1α and IL-1β perform mutual compensation, and (iv) IL-1 plays a role as the primary stimulator of the multiple anabolic reactions required for the elaboration of immune responses against infection.

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