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Antidiabetic effects of interleukin 1

(glucose/insulin resistance/diabetes/immunohormone)

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ABSTRACT **Interleukin 1 (IL-1), a cytokine released mainly by activated macrophages–monocytes, affects glucose homeostasis and may mediate some of the metabolic derangements observed during certain inflammatory and infectious processes. In this report, it is shown that IL-1 acts as a hypoglycemic agent not only in normal animals but also in mice at early stages of alloxan-induced diabetes and in genetically diabetic, insulin-resistant C57BL/Ks *db/db* mice and C57BL/6J *ob/ob* mice. In these animal models, a single injection of a low dose of human recombinant IL-1 normalized glucose blood levels for several hours. This effect was not mediated by possible insulin secretagogue actions of the cytokine. Furthermore, IL-1 markedly reduced the levels of triglycerides in blood of streptozotocin-induced diabetic mice at later stages of the disease. Although the final mechanism of action is at present unknown, the results showed that IL-1 is a hormone with powerful antidiabetic properties. Defective production of this cytokine associated with diabetes could contribute to aggravate the course of the disease during infectious and inflammatory processes.**

Interleukin 1 (IL-1) is an endogenous hormone produced by activated monocytes and also by other cell types, and it exerts autocrine, paracrine, and endocrine effects. Multiple biological activities are attributed to IL-1 such as control of differentiation and activation of lymphocytes, stimulation of lymphokine and prostaglandin production, promotion of inflammation, induction of acute phase proteins, stimulation of bone resorption, alteration of the level of iron and zinc in blood, and induction of fever (1–3). More recently, it was found that IL-1 can stimulate the hypothalamus–pituitary–adrenal axis (4–8), an observation which suggests that this hormone is integrated in the complex neuroendocrine network that controls host homeostasis. This hypothesis is further supported by our studies showing that administration of low doses of IL-1 to normal mice results not only in a severalfold elevation of glucocorticoid output, but also in a profound and long-lasting decrease in glucose blood levels (9). It is noteworthy that IL-1-induced hypoglycemia develops despite the well-known stimulatory effect of increased levels of glucocorticoids and glucagon on glucose production by the liver. Furthermore, it can be dissociated from possible insulin secretagogue actions of IL-1 (9). It has been reported that addition of IL-1 to cultures of pancreatic islets results in cytotoxic effects several days later (10). Although this observation may be relevant in pathological situations in which there could be an increased local production of IL-1 in the pancreas, we have previously shown that the doses used in our experiments are not cytotoxic for the pancreas *in vivo* (9). The above-mentioned findings prompted us to investigate the possibility that IL-1 may be an endogenous antidiabetic agent. In this paper, we report that IL-1 has a potent hypoglycemic effect in mice at early stages of chemically induced diabetes and markedly reduces the levels of triglycerides in blood at more advanced stages of the disease. Furthermore, a single injection of this cytokine normalizes glucose blood levels of genetically diabetic, insulin-resistant C57BL/Ks *db/db* mice and C57BL/6J *ob/ob* mice for several hours.

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MATERIAL AND METHODS

Animals. C57BL/6J male mice (8–12 weeks old) were obtained from Kleintierfarm Madoerin (Fuellingsdorf, Switzerland) and C57BL/Ks *db/+* and *db/db* male mice were from Harlan Olac (Oxon, U.K.). C57BL/6J Ibm *ob/+* and *ob/ob* male and female mice were kindly provided by B. Hartmann (Institute for Biomedical Research, Hoffmann–La Roche, Fuellinsdorf, Switzerland). Animals were caged individually for 1 week before experimentation and were kept isolated throughout. They were fed ad libitum and housed in temperature- and light-controlled (12 hr/day) rooms.

IL-1. The purified human recombinant IL-1 (rIL-1, β form) used in the majority of the studies reported here was kindly provided by C. Dinarello (Tufts University, Boston). rIL-1 was expressed in *Escherichia coli* as described (11) and contained amino acids 112–269 (M_r 17,500) of the precursor sequence. For studies in *ob/ob* animals, purified human rIL-1 was kindly provided by A. Shaw (Glaxo Institute for Molecular Biology, Geneva). This rIL-1 was also expressed in *E. coli* and purified as described (12). rIL-1 was diluted to the desired concentration with endotoxin-free medium consisting of 0.15 M NaCl and 0.01% human serum albumin. Nonfasted mice received either rIL-1 or control medium injected i.p.

Reagents. Alloxan (5,6-dioxyuracil) and streptozotocin were obtained from Sigma. Both diabetogenic drugs were injected i.p.—alloxan at 175 mg per kg of body weight in 0.9% NaCl and streptozotocin at 150 mg per kg of body weight dissolved in citric buffer. Control mice received 0.9% NaCl or citric buffer. Regular insulin (Velosulin; Nordisk Gentofte, Gentofte, Denmark) was also administered i.p.

Determinations of Glucose, Insulin, Triglyceride, Cholesterol, and Ketone Bodies. At the times indicated for each experiment, animals were bled through the orbital sinus under light ether anesthesia. Glucose concentrations in serum were determined by an enzymatic (hexokinase) method (Sigma kit 115A). Insulin serum levels were determined by radioimmunoassay (SB-INSI-5 kit; International CIS, Medipro, Switzerland). Triglycerides and cholesterol levels in serum were determined by enzymatic methods [Triglyceride (GPO-Trinder) and Total Cholesterol kits; Sigma]. Glucose and ketone bodies in urine were estimated with Keto-Diabur strips (Boehringer Mannheim).

Statistical Analysis. Data were analyzed by modified *t* statistics or two-tailed paired *t* test with Bonferroni correction for multiple comparisons as indicated in each table legend.

Abbreviations: IL-1, interleukin 1; rIL-1, recombinant IL-1.

RESULTS

Effect of IL-1 on Glucose, Insulin, and Triglyceride Blood Levels of Mice with Chemically Induced Diabetes. The first studies were performed during an early stage of alloxan-induced diabetes in C57BL/6J mice. Three days after alloxan injection, mice having glucose blood levels >450 mg/dl received control medium or 0.25 μg of rIL-1. As shown in Fig. 1, a tendency toward even more elevated levels of glucose in blood was observed in control-injected animals during the first 2 hr, probably because of the stress of repetitive bleeding. In contrast, IL-1-injected mice showed a sharp decrease in glucose levels, which was noticeable 30 min after IL-1 administration. The levels of glucose in blood attained the range of normal, nondiabetic animals within 4 hr and remained low for at least a further 4 hr. The level of insulin in blood of mice treated with alloxan 3 days before was reduced by ≈50% as compared to that of normal animals. No increase in the level of this hormone in serum was detected either in alloxan-treated mice or in normal control animals 1 hr after administration of rIL-1 (insulin, ng/ml: alloxan-treated control-injected mice, 0.68 ± 0.15; alloxan-treated rIL-1-injected mice, 0.75 ± 0.09; normal control-injected mice, 1.23 ± 0.07; normal rIL-1-injected mice, 1.28 ± 0.17).

Diabetes was also induced in mice by streptozotocin administration and, in this case, the effects of IL-1 were evaluated 1 week after injection of the diabetogenic drug. By this time, all animals had glucosuria and ketonuria. In ≈70% of the streptozotocin-treated animals, the average concentration of glucose in blood exceeded 800 mg/dl and the levels of insulin were below the detection limit of the radioimmunoassay used (0.40 ng/ml, 10 microunits/ml). After a single injection of 0.25 μg of rIL-1 into these mice, a very modest (12%), although statistically significant, reduction in glucose blood levels was observed 4 hr later. In an attempt to study whether it was possible to increase the effectiveness of IL-1, streptozotocin-treated animals having undetectable levels of insulin in blood received an injection of 0.5 μg of IL-1 every 4 hr. Four hours after the third injection, mice had their glucose levels reduced by ≈46% (glucose, mg/dl: time 0, 850 ± 24; after IL-1 treatment, 460 ± 48; $P < 0.001$), thus showing a considerable improvement as compared to those animals that received a single injection of IL-1. Although administration of the cytokine in the repetitive schedule used did not result in normalization of glucose levels, it caused a reduction of glucosuria and disappearance of ketonuria, thus suggesting that the general metabolic state of these diabetic mice was ameliorated.

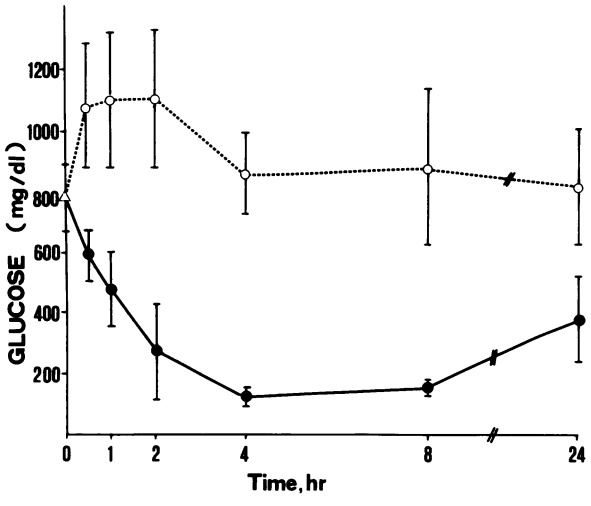

FIG. 1. Effect of IL-1 administration on glucose blood levels of alloxan-injected diabetic mice. Alloxan was injected i.p. to C57BL/6J male mice (2 months old; 25–30 g). Three days later, animals were bled through the orbital sinus and immediately thereafter were injected i.p. with either 0.25 ml of control medium (○) or 0.25 μg of rIL-1 (●) in 0.25 ml of control medium. Blood samples were obtained 30 min, and 1, 2, 4, 8, and 24 hr later, and glucose concentrations in serum were determined. Each point in the curves represents the mean ± SEM of glucose determinations from three (control injected) or four (IL-1 injected) animals. △, mean ± SEM of glucose determinations at time 0. Four hours after injection of control medium or 0.25 μg of rIL-1 into normal animals, glucose concentrations in serum were 170 ± 6 mg/dl or 93 ± 13 mg/dl, respectively.

As indicated above, 1 week after streptozotocin administration, a small percentage of mice had low but still detectable levels of insulin in the blood. A single injection of rIL-1 to these animals resulted in a more marked reduction in glucose blood levels than the same treatment to mice with undetectable levels of insulin (glucose, mg/dl: time 0, 518 ± 17; 4 hr after IL-1 injection, 334 ± 29; $P < 0.001$). It should be noted, however, that the basal level of glucose of these diabetic mice was lower than that of diabetic mice having no detectable insulin in blood.

While studying effects of IL-1 in mice with streptozotocin-induced diabetes, it was macroscopically noticed that the lipemic aspect of the serum disappeared after injection of the cytokine. We therefore studied the effect of a single injection of rIL-1 on the levels of triglycerides and cholesterol in serum of streptozotocin-injected diabetic mice 1 week after administration of the diabetogenic agent. As reported above, IL-1 injection did not normalize glucose concentration. No significant changes were detected in cholesterol levels of IL-1-treated mice when compared to those of the simultaneous control-injected diabetic animals (data not shown). However, the levels of triglycerides were markedly diminished, reaching the basal levels of normal animals within 8 hr after IL-1 injection (Table 1).

Effect of IL-1 on Glucose Levels of Genetically Diabetic Insulin-Resistant *db/db* and *ob/ob* Mice. The results described above showed that IL-1 was much more effective in reducing glucose levels when the cytokine was administered at early stages of chemically induced diabetes. Metabolic derangements coupled to aggravation of the disease might have played a relevant role in reducing the effectiveness of IL-1 at more advanced stages of diabetes. Regardless of the cause, the diminution of the capacity of IL-1 to decrease glucose levels was correlated to the disappearance of detectable

Table 1. Effect of IL-1 on glucose and triglyceride serum levels of streptozotocin-injected diabetic mice

	Glucose, mg/dl		Triglyceride, mg/dl	
Time, hr	Control	IL-1	Control	IL-1
0	667 ± 109	681 ± 98	447 ± 16	636 ± 63
1	810 ± 73	600 ± 40	516 ± 66	465 ± 71*
2	946 ± 91†	689 ± 29	445 ± 71	241 ± 59‡
4	834 ± 93*	631 ± 43	362 ± 69	207 ± 37†
8	860 ± 114†	517 ± 65*	356 ± 188	121 ± 19‡

One week after streptozotocin administration, C57BL/6J male mice were bled (time 0) and immediately injected with either control medium ($n = 3$) or rIL-1 (0.25 μg per mouse) ($n = 5$). Animals were bled again at the times indicated and glucose and triglyceride serum levels were determined as described. Statistical analysis was performed by the two-tailed paired t test comparing pre- (time 0) and postinjection values. It should be noted that the basal value of triglycerides (time 0) of the IL-1-injected group was significantly higher than that of the control-injected group (animals were divided into two groups at random before control or IL-1 administration). The concentrations of glucose and triglycerides in serum of normal C57BL/6J male mice of the same age were 169 ± 6 mg/dl and 124 ± 12 mg/dl, respectively ($n = 8$).

*$P < 0.02$.
†$P < 0.01$.
‡$P < 0.001$.

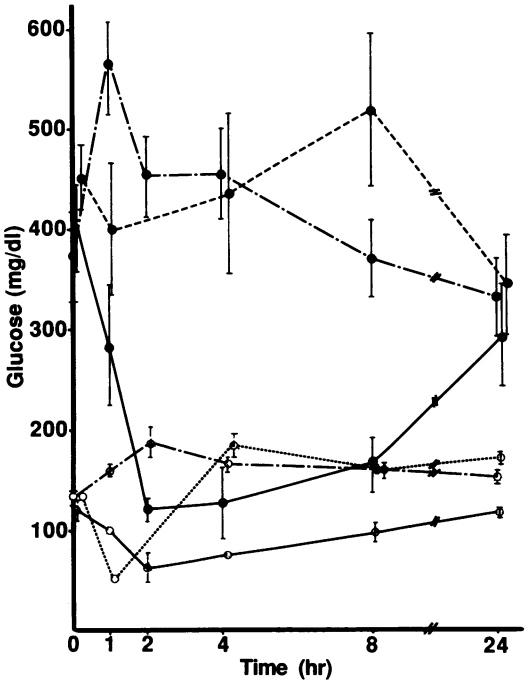

FIG. 2. Changes in glucose blood levels of genetically diabetic mice after administration of rIL-1. Eleven-week-old genetically diabetic C57BL/Ks *db/db* male mice (●; body weight, 42.0 ± 0.9 g) and heterozygous euglycemic C57BL/Ks *db/+* littermates (○; body weight, 22.3 ± 0.4 g) were bled (time 0) and immediately injected with control medium (-·-·-), insulin (------; 0.5 unit per mouse for *db/db* and 0.25 unit per mouse for *db/+*), or rIL-1 (——; 0.5 μg per mouse for *db/db* and 0.25 μg per mouse for *db/+*). Animals were bled again 1, 2, 4, 8, and 24 hr later and glucose serum levels were determined as described. Each point in the curves represents the mean ± SEM of glucose determinations from the number of animals (*n*) shown in Table 2. Similar effects of IL-1 were obtained in 15-, 19-, and 24-week-old C57BL/Ks *db/db* mice.

insulin in blood. This observation suggested that insulin may play a role in IL-1-induced hypoglycemia and led us to study the effect of IL-1 in animal models of diabetes in which hyperglycemia is not a consequence of decreased insulin levels in blood. We have used genetically diabetic C57BL/Ks *db/db* mice when these animals are both hyperglycemic and markedly hyperinsulinemic and, furthermore, resistant to administration of insulin (13–16). The results of experiments in which rIL-1 was injected into diabetic *db/db* mice and into the heterozygous euglycemic littermates *db/+* are shown in Fig. 2 and Table 2. rIL-1 reduced the levels of glucose in blood of euglycemic *db/+* by ≈50%.

Administration of regular insulin also resulted in a 60% reduction in glucose levels in *db/+* mice. As expected (13–16), insulin (0.5 unit, 20.8 μg per mouse) was unable to decrease the levels of glucose in *db/db* mice. In contrast, a single i.p. injection of 0.5 μg of rIL-1 completely normalized glucose blood levels in *db/db* mice for at least 6 hr. Although IL-1 induces an acute reduction in glucose blood levels in both euglycemic heterozygous *db/+* and in hyperglycemic *db/db* mice, the effect was proportionally more pronounced in diabetic animals and the values reached were below the basal levels of glucose of euglycemic *db/+* mice. Table 2 also shows the results of measurements of insulin levels. As previously reported (13–16), *db/db* mice had ≈20-fold more insulin in blood than normal animals. The administration of IL-1 or control medium resulted in a reduction of insulin levels in *db/+* as well as in *db/db* mice, thus showing that IL-1 has no insulin secretagogue effect in these animals.

To extend our studies to another model of spontaneously diabetic animals, we have used genetically obese *ob/ob* mice. These animals are characterized by marked obesity, hyperinsulinemia, hyperglycemia, and insulin resistance (14, 16–18). Furthermore, the number of insulin receptors on liver and fat cells and thymic lymphocytes (19, 20) is decreased in these animals. Injection of rIL-1 to *ob/ob* mice also resulted in a marked reduction of their glucose blood levels (Table 3).

DISCUSSION

The effect of IL-1 in the models of diabetic animals explored reinforces the proposal that IL-1 plays a crucial role in glucose homeostasis. Although the results reported here do not clarify the intimate mechanism of action of IL-1, several conclusions can be drawn. Since IL-1-induced hypoglycemia in normal and diabetic mice is observed shortly after injection, it cannot be attributed to reduced food intake. Neither can it be due to glucose loss in the urine, since no changes in the content of the sugar are detected in the urine of normal mice, and, as reported above, glucosuria diminishes or even disappears in diabetic animals treated with IL-1. We have previously shown that in normal animals the IL-1-induced decrease in glucose levels develops against increased levels of hormones such as glucocorticoids and glucagon and that counterregulatory mechanisms such as those mediated by

Table 2. Effect of IL-1 on glucose and insulin blood levels of diabetic (*db/db*) and euglycemic (*db/+*) mice

	db/+			*db/db*		
Time, hr	Control (*n*)	IL-1 (*n*)	Insulin (*n*)	Control (*n*)	IL-1 (*n*)	Insulin (*n*)
			Glucose, mg per dl of serum			
0	132 ± 8 (11)	121 ± 10 (11)	135 ± 3 (6)	372 ± 44 (10)	403 ± 48 (11)	454 ± 33 (7)
1	161 ± 9 (11)	100 ± 4 (11)	53 ± 3* (6)	567 ± 52† (10)	285 ± 60 (11)	400 ± 64 (7)
2	187 ± 16† (5)	62 ± 15* (5)	ND	452 ± 39 (5)	119 ± 14* (5)	ND
4	165 ± 8† (11)	74 ± 4* (11)	185 ± 13* (6)	455 ± 44 (10)	127 ± 35* (11)	436 ± 81 (7)
8	161 ± 6† (10)	98 ± 11 (11)	163 ± 10 (6)	373 ± 39 (10)	167 ± 28* (11)	520 ± 77 (7)
24	152 ± 9 (10)	120 ± 7 (8)	173 ± 7* (6)	332 ± 41 (10)	292 ± 52 (11)	344 ± 50 (7)
			Insulin, ng per ml of serum			
0	2.2 ± 0.9 (7)	2.8 ± 0.8 (7)	2.5 ± 0.5 (6)	39.1 ± 9.2 (6)	48.4 ± 13.1 (7)	30.7 ± 7.4 (7)
1	0.9 ± 0.1 (7)	1.2 ± 0.2 (7)	>16 (6)	16.9 ± 3.9 (6)	29.0 ± 5.8 (7)	>80 (7)
4	1.1 ± 0.1 (7)	1.5 ± 0.4 (7)	1.3 ± 0.2 (6)	18.3 ± 2.9 (6)	18.5 ± 5.1 (7)	20.2 ± 2.3 (7)
8	1.3 ± 0.2 (7)	1.3 ± 0.2 (7)	1.0 ± 0.1 (6)	12.5 ± 1.2† (6)	17.3 ± 4.2 (7)	20.1 ± 4.0 (7)
24	1.8 ± 0.8 (5)	0.9 ± 0.1 (4)	1.4 ± 0.3 (6)	28.3 ± 5.1 (6)	21.8 ± 8.3 (7)	30.1 ± 3.5 (7)

The data plotted in Fig. 2 for glucose blood levels following control, insulin, or IL-1 injection to C57BL/Ks *db/db* and C57BL/Ks *db/+* mice are shown together with simultaneous determinations of insulin blood levels. Results are presented as the means ± SEM of determinations from the number of animals indicated. ND, not done. Data were analyzed by modified *t* statistics with Bonferroni correction for multiple comparisons.
*$P < 0.01$
†$P < 0.05$.

Table 3. Effect of IL-1 on glucose blood levels of genetically obese hyperglycemic *ob/ob* mice

Time, hr	Males		Females	
	Control (n = 8)	IL-1 (n = 5)	Control (n = 9)	IL-1 (n = 7)
0	471 ± 54	473 ± 68	567 ± 82	521 ± 38
4	380 ± 48	170 ± 10*	609 ± 61	230 ± 63†

Genetically obese diabetic C57BL/6J Ibm *ob/ob* mice (9-week-old males: body weight, 37.5 ± 0.7 g; 9- to 10-week-old females: body weight, 38.5 ± 0.8 g) were bled (0 hr) immediately after injection with either control medium or rIL-1 (0.5 μg per mouse) and bled again 4 hr later. Results are expressed as means ± SEM of glucose determinations (mg per dl of serum) from the number of animals indicated. Statistical analysis was performed by Student's t test. The basal value of insulin in serum of 9-week-old *ob/ob* mice was 64.10 ± 4.01 ng/ml for males (n = 14) and 30.21 ± 4.50 ng/ml for females (n = 17). The basal concentrations of glucose and insulin in serum of 9-week-old heterozygous euglycemic female C57BL/6J Ibm *ob/+* littermates were 141 ± 7 mg/dl and 1.52 ± 0.28 ng/ml (n = 10), respectively.

*$P < 0.001$ compared to time 0.

†$P < 0.005$ compared to time 0.

epinephrine and glucocorticoids can only moderate IL-1-induced hypoglycemia (9). In addition, the hypoglycemic effect of IL-1 is dissociable from a possible insulin secretagogue action of the cytokine. The studies reported so far on the effects of IL-1 on basal or glucose-induced insulin release using either *in vitro* techniques or perfused pancreas are controversial (21–23). However, under more physiological conditions, we have observed that IL-1 decreases glucose levels in association with decreased insulinemia in normal rats and in adrenalectomized mice and rats. Furthermore, as shown here, no increases in insulin levels were observed in diabetic animals at any of the points in time studied after IL-1 administration. Also, an eventual increase in insulin levels is expected to be of no significance in, e.g., *db/db* mice since, as shown in Table 2, administration of a large dose of insulin, which resulted in high levels of this hormone in blood, had no effect on their glucose blood levels.

As mentioned above, the diminution of the capacity of IL-1 to reduce glucose blood levels of animals with chemically induced diabetes that have undetectable levels of insulin in blood, as compared to animals with reduced but still detectable levels of insulin, suggested that insulin may play a role in IL-1-induced hypoglycemia. The observation that IL-1 can normalize triglyceride levels despite its modest effect on glucose levels during advanced stages of chemically induced diabetes deserves further experimentation.

The effect of IL-1 in *db/db* mice is, to the best of our knowledge, the only example of an endogenous product capable of normalizing glucose blood levels in these animals. Elevated insulin levels together with the lack of responsiveness to exogenous insulin and reduction in the number of insulin receptors in different tissues (24) confirm that *db/db* mice are "insulin resistant." Therefore, the possibility should be considered that IL-1 may reestablish sensitivity to endogenous insulin, since this constitutes the main defect of these animals. If this possibility would hold true, one conceivable mechanism of action would be facilitation of expression of functional insulin receptors. The ineffectiveness of high levels of insulin to regulate the activity of gluconeogenic enzymes is also an important defect of *db/db* mice (13). Again, reestablishment of insulin sensitivity of these enzymes by IL-1 could mediate the hypoglycemic effects of this monokine. Alternatively, the effect of IL-1 could be based on reduction of endogenous glucose production—for example, by direct inhibition of gluconeogenic enzymes. It has been recently reported that IL-1 can partially inhibit *in vitro* the glucocorticoid induction of phospho*enol*pyruvate carboxykinase, the rate-limiting enzyme in gluconeogenesis (25). This finding might be relevant in the context of our studies since IL-1 causes a marked increase in glucocorticoid blood levels in normal animals (4–6). However, a mechanism based only on the capacity of IL-1 to inhibit phospho*enol*pyruvate carboxykinase induction by glucocorticoids would not explain the *in vivo* effect of IL-1 since hypoglycemia is even more pronounced in adrenalectomized animals with undetectable levels of glucocorticoids in blood (9).

Another possible mechanism by which IL-1 may affect glucose blood levels is by increasing glucose transport and utilization in peripheral tissues, particularly since it has been reported that crude supernatants from activated macrophages stimulate glucose oxidation in fat pads (26). However, using adipocytes freshly obtained from fat pads of normal and *ob/ob* mice, we have recently observed no direct effect of IL-1 on glucose oxidation to CO_2 or incorporation into lipids, regardless of whether IL-1 was added alone or in combination with suboptimal doses of insulin. The possibility remains that these parameters are affected *in vivo* by a secondary mediator induced by IL-1. Another mechanism based on a possible antilipolytic effect of IL-1 may indirectly affect glucose transport and explain the capacity of IL-1 to reduce glucose and triglyceride levels. Such an antilipolytic action would, at the same time, eliminate the competitive effect of free fatty acids on glucose utilization and reduce their delivery to the liver for reesterification to triglycerides. However, we have recently observed that while IL-1 also reduces glucose and triglyceride levels in hyperlipemic Zucker *fa/fa* rats, the levels of free fatty acids in blood are increased for several hours as compared to those of control-injected *fa/fa* rats (unpublished data).

At present, it is difficult to assess the degree of IL-1 contribution to the multiple endocrine control of glucose levels under basal physiological and pathological conditions. However, it is likely that IL-1, a cytokine of critical significance for the immune response, also participates in a host response directed to satisfy enhanced metabolic demands during infections and inflammations (27). This host response may be disturbed in certain types of diabetes. In fact, there is evidence that the production of some lymphomonokines, among them IL-1, is severely diminished and that macrophages, a major cell source of IL-1, are defective in different types of experimental and naturally occurring diabetes (28–34). A remarkable example derives from *db/db* mice, one of the animal models used in our studies. The capacity of macrophages from these animals to phagocytose is abnormal and their number at inflammatory sites is reduced by 95% when compared with *db/+* mice. Furthermore, the production of certain lymphomonokines and all the cell-mediated immune responses so far tested in *db/db* mice are markedly decreased (35–38). A deficient IL-1-mediated host response, which normally would be directed at adjusting glucose metabolism during infective and inflammatory processes, may affect the clinical course of diabetes. In fact, it is well known that mild infections or inflammations, with which normal individuals cope quite well, can aggravate diabetes and increase the risk of ketoacidosis.

Apart from their possible clinical relevance and in view of the important role of IL-1 during the immune response, the results reported here constitute further proof of the existence of a high degree of connectivity between immune and neuroendocrine mechanisms under normal and pathological conditions.

We dedicate this paper to the late Prof. Dr. A. Renold, who continuously encouraged us during the execution of this work. We thank Dr. C. A. Dinarello and Dr. A. Shaw for kindly providing the IL-1 used in these studies, Dr. B. Hartmann for the *ob/ob* mice, Prof. E. Sorkin for careful review of the manuscript, and Mr. T. Wilhelm

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