Interaction of β-Cell Activity and IL-1 Concentration and Exposure Time in Isolated Rat Islets of Langerhans

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This study was designed to test the hypothesis that target-cell activity influences the degree and time course of interleukin 1β (IL-1β)–mediated β-cell impairment in vitro. Functional and morphological studies were performed in cultured newborn rat islets of Langerhans exposed from 6 h to 6 days to 50–2000 ng/L recombinant human IL-1β. β-Cell activity was modulated by glucose and nonglucose agents (15 mM L-leucine and 10 μM of long-acting somatostatin analogue SMS 201-995). In 11 mM glucose, 2000 ng/L of IL-1β caused inhibition of insulin release after ~6 h of exposure to IL-1β; in 3.3 mM glucose culture, onset of inhibition was delayed by this IL-1β concentration until after 48 h of exposure. Similarly, stimulation and suppression of β-cell function with L-leucine and SMS 201-995, respectively, resulted in acceleration and delay of IL-1β–mediated inhibition. The dose-response curve of the IL-1β effect was shifted left- and rightward during high and low β-cell activity, respectively. In analogy, increasing IL-1β concentration, exposure time, and β-cell activity resulted in increasing islet disintegration. Thus, the resting β-cell is more resistant to IL-1β–mediated impairment than the working β-cell. *Diabetes* 38:1211–16, 1989

The cytokine interleukin 1β (IL-1β) causes selective morphological and functional changes to pancreatic β-cells in vitro strongly suggestive of cytotoxicity (1–3). Consequently, IL-1β has been implicated as a possible mediator of the autoimmunological β-cell destruction that occurs in insulin-dependent diabetes mellitus (IDDM; 4). Recently, it was shown that IL-1β has complex dual effects on β-cell function: at a low (0.5-U/ml) concentration and/or short (60- to 90-min) exposure, IL-1β stimulates proinsulin biosynthesis and insulin secretion; at a high (5-U/ml) concentration and long (>24-h) exposure, IL-1β causes inhibition of biosynthesis and insulin secretion (5–7). Because the inhibition of insulin secretion is closely paralleled by impaired proinsulin biosynthesis (5), glucose oxidation, oxygen uptake, and decreased islet insulin and DNA content (3), the dose- and time-dependent inhibition of insulin secretion may be used as a parameter of IL-1β–induced β-cell destruction (1,2). IL-1β's biphasic action on β-cell function is also related to the glucose concentration in the culture medium (8). Thus, the β-cell response to IL-1β is affected by the variables IL-1β concentration, duration of exposure to IL-1β, and ambient glucose concentration. High IL-1β and glucose concentrations cause earlier and more pronounced inhibition of insulin secretion; in contrast, low IL-1β and nonstimulatory glucose concentrations delay the shift from stimulation to inhibition, i.e., they move the stimulation/inhibition curve to the right. The glucose effect indicates that the IL-1β effect may depend on the degree of β-cell activity. The purpose of this study was to examine this hypothesis by use of different glucose concentrations, L-leucine as a nonglucose stimulator, and somatostatin as an inhibitor of β-cell activity.

RESEARCH DESIGN AND METHODS

L-Leucine was purchased from Fluka (Switzerland). SMS 201-995, a long-acting somatostatin analogue, was provided by Sandoz (Basel). Recombinant human IL-1β was kindly provided by A. Shaw (Biogen, Geneva). It had been expressed in *Escherichia coli* and was identical with the biologically active 153-residue protein derived from the COOH-terminal region of the 269-residue primary translational product of native pI7, IL-1β. The specific activity was ~4 × 10^7 lymphocytic activity factor U/mg (9,10).

Rat islets were isolated from collagenase-treated pancreases of outbred newborn (5- to 7-day-old) Wistar rats (Møllegård, Lille Skensved, Denmark) and precultured for 6–8 days as previously described (11). The precultured islets

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were washed twice in RPMI-1640 (Flow, Irvine, Scotland) supplemented with 20 mM HEPES buffer, 100,000 U/L penicillin, 100 mg/L streptomycin, 0.5% normal human serum, and 3.3, 5.5, or 11 mM glucose and distributed randomly in four-well plastic plates (Nunc, Roskilde, Denmark) with 30 islets/well in 1 ml of medium identical to the washing medium. Thus, islets cultured in 3.3 or 5.5 mM of glucose had been exposed to a lowered glucose concentration during the washing procedure for 30–60 min before culture. The islets were incubated free floating in a humidified atmosphere at 37°C without and with the addition of IL-1β (50, 200, or 2000 ng/L), SMS 201-995 (10 μM), and L-leucine (15 mM, only at 3.3 mM glucose).

Ten micromoles per milliliter SMS 201-995 was chosen as the optimal concentration because pilot experiments (data not shown) revealed that this concentration inhibited insulin secretion by >50% for the duration of the experiment (6 days). IL-1β and SMS 201-995 or L-leucine were added simultaneously. However, in selected experiments (n = 3), exposure for the final glucose concentration of 3.3 mM was extended to 24 h before the addition of IL-1β to make sure that the β-cells were at rest. Furthermore, three experiments were performed in which SMS was added 1 h before the addition of IL-1β.

After 6, 24, and 48 h and 6 days of culture, 100 μl of medium was sampled for insulin measurement. After 6 days of culture, the islets were washed once in 200 μl of distilled water and transferred to 400 μl of distilled water.

To avoid repeated exposure to IL-1β, the medium was not changed during the experiments. Because nutritional conditions might be changed during 6 days of culture, intra-experimental controls (paired design) were included in all experiments, allowing sufficient comparison between IL-1β- and non–IL-1β-exposed islets. The concentration of accumulated insulin was not likely to inhibit insulin secretion by feedback (12). The glucose concentration in the medium decreased <0.5 mM during the experiments (data not shown). In each experiment, conditions were set up in duplicate. Only experiments performed with different islet isolates were considered as separate observations. To properly determine stimulation and inhibition of insulin release, values are given as accumulated insulin secretion (absolute values or percentages of control) during exposure intervals divided by the number of interval hours (Tables 1 and 2). To evaluate the total net effect of IL-1β on insulin release, accumulated insulin values are also presented (Fig. 1). The insulin values measured at 24 and 48 h and 6 days of culture were corrected according to the loss of culture medium divided by 1.1, 1.25, and 1.42, respectively.

Immunoreactive insulin (IRI) was measured by radioimmunoassay (13) with a rat standard (Novo, Bagsvaerd, Denmark). Measurement of islet insulin content was performed on islets that had been cultured for 6 days (or for 24 h in selected experiments) with and without IL-1β. Insulin was measured after sonication of islets solubilized in distilled water.

The crude morphology of the islets in suspension was assessed with a dissection microscope. The following scoring system was used for evaluation of islet disintegration: 0, islets indiscernible from control islets; 1, islets ragged; and 2, islets dissolved.

TABLE 1
Effect of interleukin 1β (IL-1β) and glucose on immunoreactive insulin (IRI) release (pg · islet^{-1} · h^{-1})

IL-1β exposure time	IL-1β concn (ng/L)	Glucose (mM) 3.3	5.5	11
0–6 h	0	47 ± 7	140 ± 22	537 ± 23*
	50	56 ± 5†	292 ± 50†	675 ± 88*
	200	83 ± 8†	380 ± 77	813 ± 73*†
	2000	73 ± 7†	347 ± 32†	777 ± 92*
6–24 h	0	16 ± 6	86 ± 30	538 ± 124*
	50	41 ± 9†	145 ± 25†	518 ± 76*
	200	64 ± 9†	152 ± 44	189 ± 35†
	2000	56 ± 8†	70 ± 14	115 ± 25†
24–48 h	0	34 ± 12	119 ± 27	475 ± 65*
	50	33 ± 9	82 ± 22	188 ± 86‡
	200	45 ± 12	37 ± 6	98 ± 42†‡
	2000	50 ± 4	62 ± 10	53 ± 28†
48 h to 6 days	0	106 ± 37	186 ± 29	453 ± 21*
	50	62 ± 25	84 ± 13†	279 ± 34*†
	200	36 ± 14†	30 ± 9†	25 ± 5†
	2000	16 ± 3†	16 ± 5†	18 ± 7†

The effect of recombinant IL-1β and glucose on IRI release from isolated islets of Langerhans from newborn rats. Insulin values are means ± SE. n = 6 for all conditions.
*P < .01, ‡P < .05, for comparison between 3 glucose concentrations by Friedman's test.
†P < .05 vs. no IL-1β by Wilcoxon's matched-pairs test.

Calculations and statistics. Nonparametric statistics were used. For paired differences, Wilcoxon's matched-pairs test was used. Interactions among concentrations of IL-1β and glucose and exposure time were analyzed with Friedman's test. All values are given as means ± SE. P < .05 was chosen as the level of significance.

RESULTS

Effect of increasing glucose concentrations, L-leucine, SMS 201-995, and IL-1β on insulin secretion. Increasing glucose concentration in the incubation medium and the addition of L-leucine (at 3.3 mM glucose) resulted in increased insulin secretion during all 6 days of culture, whereas SMS 201-995 (at 5.5 mM glucose) decreased insulin secretion. IL-1β exerted stimulation followed by inhibition under all culture conditions. The stimulatory effect of IL-1β did not interfere with the stimulation caused by high glucose and 15 mM L-leucine; i.e., during stimulatory IL-1β conditions, high glucose concentrations and L-leucine still resulted in consistently higher insulin values than low glucose and the absence of L-leucine. Likewise, despite the stimulatory effect of IL-1β, SMS 201-995 still inhibited insulin secretion during islet exposure to IL-1β (0–6 h). In contrast, during IL-1β–mediated inhibitory conditions, the stimulatory effect of glucose and L-leucine and the inhibitory effect of SMS 201-995 were reduced. At 2000 ng/L IL-1β (24–48 h) and at 200 and 2000 ng/L IL-1β (48 h to 6 days), insulin secretion at 3.3, 5.5, and 11 mM did not differ statistically from one another; at 2000 ng/L IL-1β (6 h to 6 days), L-leucine did not stimulate insulin secretion significantly. No significant inhibitory effect of SMS 201-995 was seen under the influence of 2000 ng/L IL-1β during the 6-h to 6-day interval.

TABLE 2
Effect of interleukin 1β (IL-1β), L-leucine, and SMS 201-995 on immunoreactive insulin (IRI) release (pg · islet^{-1} · h^{-1})

IL-1β exposure time	IL-1β concn (ng/L)	Glucose (3.3 mM)		Glucose (5.5 mM)	
		+L-Leucine	−L-Leucine	+SMS 201-995	−SMS 201-995
0–6 h	0	168 ± 28*	55 ± 8	32 ± 3*	180 ± 35
	50	372 ± 68*†	75 ± 10†	153 ± 45*†	525 ± 147†
	200	373 ± 63*†	87 ± 8†	165 ± 23*†	512 ± 115†
	2000	315 ± 50*†	73 ± 8†	235 ± 32*†	445 ± 95†
6–24 h	0	148 ± 21*	8 ± 2	14 ± 2*	110 ± 17
	50	320 ± 55*†	32 ± 3†	71 ± 13*†	194 ± 25
	200	137 ± 30*	49 ± 6†	84 ± 23*†	172 ± 31
	2000	67 ± 28†	53 ± 11†	106 ± 24†	95 ± 33
24–48 h	0	80 ± 19*	24 ± 8	36 ± 15*	102 ± 23
	50	95 ± 31*	20 ± 5	47 ± 15	113 ± 45
	200	83 ± 30*	39 ± 7	83 ± 18†	57 ± 17†
	2000	35 ± 12*	45 ± 13	87 ± 28	92 ± 13
48 h to 6 days	0	271 ± 19*	62 ± 23	91 ± 32*	220 ± 48
	50	191 ± 11*†	30 ± 9	29 ± 7*	70 ± 16†
	200	80 ± 16*†	20 ± 3†	16 ± 2*†	37 ± 6†
	2000	28 ± 7†	13 ± 2†	12 ± 2†	15 ± 4†

The effect of 15 mM L-leucine and 10 μM somatostatin analogue SMS 201-995 on IL-1β–mediated IRI release from isolated islets of Langerhans from newborn rats. Insulin values are means ± SE. n = 6 for all conditions.
*P < .05, ±L-leucine or ±SMS 201-995 by Wilcoxon's matched-pairs test.
†P < .05 vs. no IL-1β by Wilcoxon's matched-pairs test.

Effect of exposure time on IL-1β action. During the 0- to 6-h interval, all concentrations of IL-1β increased insulin secretion. Maximal stimulation (potentiation; IRI = +271% of control) was obtained at 200 ng/L IL-1β and 5.5 mM glucose; minimal potentiation (+119%) occurred at 50 ng/L IL-1β and 3.3 mM glucose. Judged by incremental insulin release, the highest stimulation was obtained with 200 ng/L of IL-1β at 11 mM glucose. During 6–24 and 24–48 h of exposure, both stimulation and inhibition of insulin secretion occurred (depending on ambient glucose concentration). During 48 h to 6 days of exposure, only inhibition was seen. Maximal inhibition (4% of control, i.e., 96%) was observed at 2000 ng/L IL-1β and 11 mM glucose.

Effect of glucose concentration on IL-1β action. Stimulation and inhibition of insulin secretion by IL-1β was observed at all glucose concentrations. During the first 6 h of

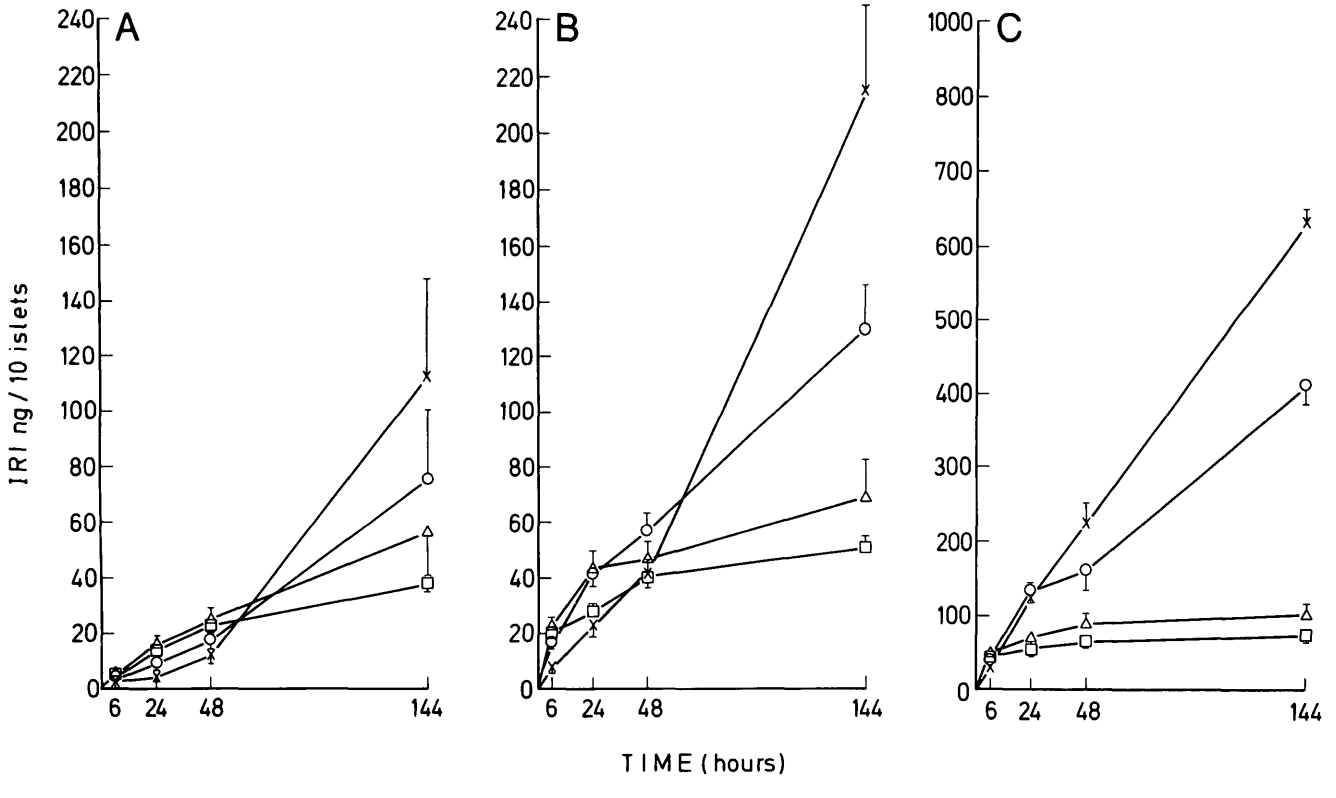

FIG. 1. Effect of 0 (x), 50 (○), 200 (△), and 2000 (□) ng/L interleukin 1β on accumulated immunoreactive insulin (IRI) release from isolated islets cultured in 3.3 (*A*), 5.5 (*B*), or 11 (*C*) mM glucose. Values are means ± SE; n = 6.

IL-1β exposure, the highest stimulation (potentiation) was obtained at 5.5 mM glucose at all IL-1β concentrations. During 6–24 and 24–48 h of exposure, the IL-1β effect was highly dependent on the glucose concentration. At 6–24 h of exposure, all concentrations of IL-1β at 3.3 mM glucose caused stimulation by ≥256%, in contrast to the effect at 11 mM, where 200 and 2000 ng/L of IL-1β produced consistent inhibition by 65–79%; i.e., IRI was 21–35% of the control level ($n = 6$, $P < .01$, and $n = 6$, $P < .05$, respectively). At 6–24 h, 200 ng/L of IL-1β caused stimulation of insulin secretion by 400% in 3.3 mM glucose, stimulation by 177% in 5.5 mM glucose, and inhibition by 65% (35% of control) in 11 mM glucose ($n = 6$, $P < .01$). The shift from stimulation to inhibition occurred in the 6- to 24-h interval in 11 mM glucose, whereas the shift was delayed until the 48-h to 6-day interval in 3.3 mM glucose. The stimulation/inhibition shift at 5.5 mM occurred between.

In experiments with extended (24-h) exposure of islets to 3.3 mM glucose before exposure to IL-1β, IL-1β caused stimulation of insulin release during the first 6 h (2000 ng/L IL-1β vs. control IRI, 256 ± 29 vs. 55 ± 7 pg · islet^{-1} · h^{-1}, $n = 3$) and subsequent inhibition (6–24 h of IL-1β exposure vs. control IRI, 59 ± 26 vs. 78 ± 8 pg · islet^{-1} · h^{-1}; 48 h to 6 days of IL-1β exposure vs. control IRI, 20 ± 0.9 vs. 186 ± 47 pg · islet^{-1} · h^{-1}).

Effect of increasing IL-1β concentration on IL-1β action. A slight biphasic effect on insulin secretion of increasing IL-1β concentrations was seen in 5.5 mM glucose during 6–24 h of IL-1β exposure, i.e., 50 ng/L IL-1β being stimulatory and 2000 ng/L inhibitory. However, under most conditions, all IL-1β concentrations were stimulatory or inhibitory. High IL-1β concentrations were the most inhibitory compared with low IL-1β concentrations. For example, in 11 mM glucose during the 48-h to 6-day interval, 50 ng/L IL-1β resulted in only a 38% inhibition (IRI was 62% of control) compared with 96% inhibition by 2000 ng/L IL-1β (IRI was 4% of control; $n = 6$, $P < .01$). Regarding accumulated IRI values (Fig. 1), increasing IL-1β concentrations resulted in less insulin release from islets cultured in 11 mM of glucose after >24 h of culture. At all IL-1β concentrations, the insulin concentration in the medium increased throughout the experimental period. Qualitatively, the same results were obtained at 3.3 and 5.5 mM glucose. Furthermore, islets exposed to 11 mM glucose and 50 ng/L of IL-1β released ~40 ng of insulin/islet during the experimental period, exceeding the islet insulin content by more than three times.

Effect of L-leucine on IL-1β action at 3.3 mM glucose. The presence of 15 mM L-leucine (without IL-1β) significantly increased insulin secretion during all exposure periods. Compared to 3.3 mM glucose alone, the addition of 15 mM L-leucine shifted the IL-1β time- and dose-response curves to the left, producing less stimulation and earlier inhibition. L-Leucine suppressed the stimulatory IL-1β effect (6–24 h, 50 and 200 ng/L IL-1β) and caused more pronounced inhibition (200 ng/L IL-1β at 48 h to 6 days). At 2000 ng/L IL-1β, the shift from stimulation to inhibition occurred after only 6 h of exposure in the presence of L-leucine but after 48 h without L-leucine.

Effect of SMS 201-995 on IL-1β action. At 5.5 mM glucose, SMS 201-995 inhibited insulin secretion significantly during all exposure periods. SMS 201-995 shifted the IL-1β time- and dose-response curves to the right, resulting in higher stimulation and delayed inhibition. At 200 ng/L IL-1β, the inhibitory effect was delayed by 24 h. The inhibitory effect of 2000 ng/L of IL-1β at 48 h to 6 days was significantly decreased (inhibition by 93 vs. 87%, $n = 6$, $P < .05$). The effect of SMS 201-995 on the IL-1β effect was only statistically significant with 5.5 mM glucose in the mediums (data for 3.3 and 11 mM glucose not shown). Exposure of islets to SMS 201-995 for 1 h before the addition of IL-1β did not influence the stimulatory or inhibitory effects of IL-1β (data not shown).

Effect of IL-1β on islet insulin content. During the standard culture condition (11 mM glucose at 6 days of culture with no β-cell–modulating agents, islets exposed to 2000 ng/L of IL-1β contained significantly less insulin than control islets (3.23 ± 0.30 vs. 12.98 ± 1.13 ng/islet, $n = 6$, $P < .05$). However, no significant effect of IL-1β on islet insulin content was observed at a lower (200-ng/L) IL-1β concentration (11.58 ± 1.29 vs. 12.98 ± 1.13 ng/islet) or shorter (24-h) culture period (10.80 ± 1.12 vs. 11.23 ± 1.56 ng/islet).

Morphology. At all glucose concentrations, increasing IL-1β exposure time and concentration resulted in increased islet disintegration. Furthermore, increasing the concentration of glucose caused earlier and more pronounced islet disintegration (Table 3).

DISCUSSION

This study substantiates our earlier findings that the effect of IL-1β on β-cells is biphasic, stimulation being followed by inhibition (8). The prevailing effect of IL-1β on glucose-stimulated insulin secretion was inhibitory. The sequential effect on IRI release was dependent on the activity level of the β-cells, the IL-1β exposure time, and, to a lesser degree, the IL-1β concentration. The influence of exposure time and IL-1β concentration was also expressed by the IL-1β effect on islet insulin content and morphology. However, during

TABLE 3
Islet morphology after interleukin 1β (IL-1β) exposure

IL-1β exposure time	IL-1β concn (ng/L)	Morphology scores at glucose concn (mM)		
		3.3	5.5	11
6 h	0	0	0	0
	50	0	0	0
	200	0	0	1
	2000	0	0	2
24 h	0	0	0	0
	50	0	0	1
	200	1	1	4
	2000	4	5	4
48 h	0	0	0	0
	50	0	0	1
	200	1	5	9
	2000	5	7	9
6 days	0	0	0	0
	50	1	0	1
	200	5	9	12
	2000	11	12	12

Results of morphological scoring in the dissection microscope of islets after 6, 24, and 48 h and 6 days of culture with and without IL-1β. Values represent the sum of scores of all experiments of each condition (12 max). $n = 6$.

stimulatory conditions (e.g., 2000 ng/L IL-1β, 3.3 mM glucose, 6–24 h) a slight disintegration of some islets was observed, suggesting a heterogeneous reaction of the β-cells to the IL-1β effect, resulting in net stimulation despite morphological signs of toxicity. In analogy, a recent observation indicates that β-cells respond heterogeneously to glucose-induced proinsulin biosynthesis (14).

By analyzing net IRI release over time rather than cumulative IRI values (8), earlier inhibition is observed because cumulative values during IL-1β–mediated inhibition express the sum of values for released insulin during stimulation and inhibition. For example, in 5.5 mM glucose, all concentrations of IL-1β tended to inhibit insulin secretion after ~24 h, whereas with cumulative IRI values, the shift was estimated to occur after >48 h. A more precise determination of the time point of shift from stimulation to inhibition would require more frequent sampling, which was not possible in our design. Nevertheless, this sampling frequency made a sufficient discrimination between the IL-1β effects under the different culture conditions possible.

The β-cells cultured in low glucose concentrations may not have been truly at rest before the addition of IL-1β because IRI release decreased after the first 6 h of culture. However, the IRI value differences were statistically significant between the different culture conditions, indicating different β-cell activity levels. Preexposure of the islets to a nonstimulatory glucose concentration for 24 h before the addition of IL-1β did not qualitatively influence the IL-1β effect. Islets cultured in 3.3 and 5.5 mM of glucose in the glucose experiments (Table 1) compared with islets cultured in the same glucose concentrations in the L-leucine/SMS 201-995 experiments (Table 2) showed some differences as to IRI release, presumably because of variability among islet preparations. Therefore, in this study, only experiments performed in a paired design allowed valid conclusions.

Analogous to the functional effects of IL-1β, the IL-1β–mediated disintegration of islets was influenced by the IL-1β concentration and exposure time as well as the glucose concentration in the medium (Table 3). The fact that there was no net decline in accumulated IRI values suggests that no degradation of insulin occurred during the experiment (Fig. 1).

This study demonstrates that in vitro β-cells at rest are less susceptible to the inhibitory effect of IL-1β than stimulated β-cells. In parallel, islets cultured in a stimulatory glucose concentration are more sensitive to IL-1β–mediated islet disintegration than islets cultured in a nonstimulatory glucose concentration. Other investigators have shown that the metabolic status of the β-cell may influence the effect of diabetogenic agents in animals. Rats with electrolytic lesions of the ventromedial hypothalamus resulting in augmented insulin secretion showed increased sensitivity to streptozocin (STZ; 15). Recently, it was demonstrated that increasing the glucose concentration increased the islet susceptibility to STZ damage directly (16). Conversely, insulin-treated rats with suppressed endogenous insulin secretion had improved spontaneous remission of neonatal STZ-induced diabetes (17), and insulin treatment of BB rats reduced the incidence of diabetes (18).

In humans, suppression of endogenous insulin secretion by intensive insulin therapy for 2 wk after diagnosis of IDDM resulted in improved β-cell function and better metabolic control 1 yr postdiagnosis compared with conventionally treated patients (19). In the Diabetes Control and Complications Trial, it appears that intensive insulin therapy may preserve β-cell function (C-peptide) compared with standard treatment (20).

There are data to support the hypothesis that the effects of glucose, L-leucine, and SMS 201-995 on the IL-1β effects on the β-cell may have a common molecular mechanism. It has been shown that IL-1β and the Ca^{2+} ionophore A 23187 have a similar effect on fibroblasts in causing expression of the interferon-β2 gene (21). Additionally, IL-1β induced stimulatory effects on IL-1β receptor–bearing T-lymphocyte cell lines (e.g., induction of IL-2 transcription, synthesis, and secretion) are greatly enhanced by agents that raise the cytosolic Ca^{2+} concentration and activate protein kinase C (22). The glucose-mediated and the L-leucine-mediated stimulatory effects on β-cells are dependent on Ca^{2+} fluxes (23,24), whereas SMS 201-995 may impede mobilization of extracellular Ca^{2+} (25). Thus, IL-1β may exert its bimodal effects on β-cells, at least in part, by increasing Ca^{2+} influx, and the modulation of IL-1β's effect by glucose, L-leucine, and SMS 201-995 may be mediated through the effect of these substances on Ca^{2+} fluxes. We earlier hypothesized that the cytotoxic effect of IL-1β on β-cells is caused by induction of free radicals (4). This is compatible with IL-1β–induced enhancement of Ca^{2+} influx because cytoplasmic free Ca has been shown to regulate the generation of H_2O_2 in porcine thyroid cells (26), and Ca^{2+} was found to accelerate exocytosis, H_2O_2 generation, and protein iodination in isolated porcine thyroid follicles (27).

In summary, in isolated islets of Langerhans from newborn rats, the activity of the β-cells has been shown to influence the IL-1β–mediated impairment of β-cell function and islet morphology. Stimulation of the β-cells with moderate hyperglycemia or L-leucine accelerates and intensifies IL-1β effects; suppressing β-cell function by SMS 201-995 and hypoglycemia impedes and delays the effects. This in vitro finding is in agreement with earlier observations in experimental animals and in human IDDM and may have pathophysiological and therapeutic implications.

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