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Interleukin 1 dose-dependently affects the biosynthesis of (pro)insulin in isolated rat islets of Langerhans

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Summary. Human crude and recombinant interleukin 1 (IL-1) was found to dose- and time-dependently affect the biosynthesis of (pro)insulin in isolated rat islets of Langerhans. Incubation of rat islets with either 0.5 U/ml or 5 U/ml of crude IL-1 for 1 h had no detectable effect on (pro)insulin biosynthesis. After 24 hours of exposure 0.5 U/ml of crude or 0.6 ng/ml of recombinant IL-1 (beta) increased the (pro)insulin biosynthesis by 42% and 58%, respectively, whereas a 10-fold greater concentration of IL-1 decreased the (pro)insulin biosynthesis by 74% and 89%, respectively. The increase in (pro)insulin biosynthesis was accompanied by an increase in total protein biosynthesis indicating a nonspecific stimulatory action of low IL-1 concentrations. In contrast, high IL-1 concentrations caused a more selective decrease of the (pro)insulin biosynthesis when compared to the total protein biosynthesis. In addition, low IL-1 concentrations were found to increase and high concentrations to decrease the relative levels of pre-proinsulin mRNA suggesting that IL-1 may act both at a pre- and post-translational level of insulin biosynthesis.

Key words: Interleukin 1, pancreatic islets, preproinsulin mRNA, proinsulin biosynthesis, Type 1 (insulin-dependent) diabetes mellitus.

Interleukin 1 (IL-1) is a pluripotent peptide hormone produced mainly by activated macrophages, but also by other lymphoid and nonlymphoid cells, such as B cells, keratinocytes, epithelial and astroglial cells. IL-1 plays a central role in lymphokine production and exerts a wide range of biological effects on various cell types, e.g. B lymphocytes, fibroblasts, synovial cells, hepatic cells, and hypothalamic cells [1-3].

We have previously shown that IL-1 dose- and time-dependently affects insulin release from isolated islets of Langerhans. Whereas low IL-1 doses increase insulin release and islet insulin content [4], higher concentrations during prolonged incubation exert a toxic effect on B cells [5, 6]. Since both insulin release and insulin content were concomitantly affected, we suggested that IL-1 may act on the biosynthesis of insulin in the B cells.

In the present study the effect of different IL-1 concentrations on the (pro)insulin biosynthesis in isolated rat islets of Langerhans was investigated.

We report here that low IL-1 concentrations increase and high IL-1 concentrations decrease the biosynthesis of (pro)insulin. In addition, preproinsulin mRNA-levels are increased at low IL-1 concentrations indicating a pretranslational action of the cytokine.

Materials and methods

IL-1 preparations

Preparation of crude human IL-1. Crude monocyte IL-1 was produced by stimulation of human macrophages (Mø) with 2 μg/ml lipopolysaccharide (LPS) or by phytohaemagglutinin (PHA) pulsing of peripheral blood mononuclear cells as previously described [4, 7]. The crude supernatants contained approximately 150 lymphocyte activating factor units (LAF)/ml [4] and showed identical dose-response effects on insulin release from isolated rat islets in culture. One LAF-unit is defined as doubling of the mitogen response of murine thymocytes. Since the crude supernatants were diluted approximately 200 times, the maximal concentrations of LPS was 10 ng/ml, or 25 ng/ml of PHA. Previous studies have shown that neither 0.1-10 μg/ml of LPS nor concentrations up to 250 ng/ml of PHA interfere with islet function [8].

The islet cytotoxic activity of either crude IL-1 preparations could be neutralized by an antibody to human monocyte IL-1 [6, unpublished data].

Preparation of recombinant IL-1 (rIL-1). The rIL-1 was expressed in *Escherichia coli* and consisted of the polypeptide sequence 112-269 (17.5 kD) of the predominant pI 7 or beta form as described previously [9]. The rIL-1 was purified to homogeneity and contained 20 mg of protein/l, and the specific activity of the preparation was approximately 250×10^6 LAF-U/g. Endotoxin contamination was less than 60 pg/mg IL-1.

Islet isolation and culture

Rat islets were isolated from collagenase-treated pancreata of outbred newborn (5-7 days old) Wistar rats (Møllegard, Lille Skensved, Denmark) and pre-cultured for 6-8 days as described in detail elsewhere [10]. The precultured islets were pooled, washed once in medium RPMI 1640 (Flow Laboratories, Irvine, Scotland) and distributed randomly in plastic Petri dishes (Falcon, Oxnard, Calif, USA) at a concentration of 30 islets/ml in medium supplemented with 20 mmol/l HEPES buffer, 11 mmol/l glucose, 100000 IU/l penicillin, 100 mg/l streptomycin and 0.5% normal human serum (NHS). The islets were incubated free-floating for 1 h, 24 h or 6 days in humidified atmosphere at 37 °C with or without the addition of either crude or recombinant IL-1. Each condition was set up in quadruplicate. After 1 h, 24 h or 6 days of culture, 100 µl of culture medium was sampled for determination of insulin by RIA [11] using rat insulin as standard (NOVO Research Institute, Bagsværd, Denmark). The interassay coefficient of variation for the radioimmunoassay was less than 6%.

Determination of (pro)insulin biosynthesis

In order to determine the biosynthesis of (pro)insulin [12, 13], the islets were harvested, washed in Hanks' balanced salt solution (HBSS, Flow) containing 1% human serum albumin and 20 mmol/l glucose and incubated for 3 h in 100 µl HBSS with 1% human serum albumin, 20 mmol/l glucose and 500 µCi/ml of L-(4.5-^{3}H)leucine (130 Ci/mmol) (Amersham, UK). The islets were then washed in HBSS with 10 mmol/l unlabelled leucine and sonicated in 200 µl of 0.2 mol/l glycine (pH 8.8), 2.5 mg/ml bovine serum albumin (BSA), and 0.5% Nonidet P-40. Radioactively labelled (pro)insulin was determined by immunoprecipitation of 20 µl islet homogenate corresponding to 0.5 islet with 50 µl of guinea pig anti-insulin serum at a dilution of 1:100 for 24 h and separation of the antibody-antigen complexes by the addition of 100 µl of protein A-Sepharose (50 mg/ml, Pharmacia, Uppsala, Sweden) for 30 min [14]. The precipitate was resuspended in 250 µl 1 mol/l acetic acid containing 2.5 mg/ml bovine serum albumin, and counted in a liquid scintillation counter after addition of 10 ml Aquasol 2 (New England Nuclear, Boston, Mass, USA). Non specific binding of radioactive material was determined by precipitation with non-immune serum. This amounted to 1.6% of the total radioactivity. Total protein biosynthesis was assessed after precipitation of 20 µl of the islet homogenate containing 2.5 mg/ml BSA as carrier protein with 10% trichloracetic acid (TCA) for 40 min.

Reversed-phase high performance liquid chromatography (RP-HPLC) of the islet homogenates

The polypeptide content in the islet homogenates of 2 experiments was analysed by reversed-phase high performance liquid chromatography (RP-HPLC) using a modification (see legend to Fig. 2) of a previously described method for RP-HPLC separation of porcine insulin and insulin derivatives [15]. Identification of individual peaks was based upon retention time of authentic standards of rat insulin 1 and 2 and bovine glucagon, amino acid sequencing of C-peptides 1 and 2, or insulin radioimmunoassay of insulin and the presumed proinsulin peaks. Since a rat proinsulin standard is not available, the proinsulin peak was identified by its immunoreactivity and on the basis of its disappearance concomitantly with equimolar increases of the insulin and C-peptide peaks during a 30-60 min chase period after pulse labelling with ^{3}H-leucine and ^{35}S-methionine [16]. A similar method was described recently [17].

Determination of preproinsulin mRNA

In separate experiments, rat islets precultured for 7 days as described above were incubated in the presence or absence of either 0.6 ng/ml, 1.2 ng/ml or 6 ng/ml rIL-1 for 4 or 24 h. The time points were chosen on the basis of the results obtained in the biosynthesis experiments. The islets were then washed, and the preproinsulin mRNA determined by means of a cytoplasmic dot hybridization method [18]. In brief, islets were resuspended in 50 µl HBSS, and NP-40 was added to 1% in the presence of 40 units of the RNase inhibitor RNasin (Promega Biotec, Madison, Wis, USA). Following incubation for 1 h at 4 °C, the nuclei were pelleted and the supernatant was made 0.9 mol/l NaCl, 0.09 mol/l trisodium citrate, and 7% formaldehyde. After incubation at 60° for 15 min, the supernatant was spotted onto nitrocellulose (Schleicher & Schuell, BA-85) using a minifold apparatus (Schleicher & Schuell). The filter was baked under vacuum for 1 h at 80 °C and then used for hybridization. Alternatively, the cytoplasmic supernatant was incubated for 2 h with proteinase K (0.25 mg/ml, Merck, Darmstadt, FRG) in 50 mmol/l Tris-HCl (pH 7.4), 60 mmol/l EDTA, 50 mmol/l NaCl, and 0.5% SDS at 50 °C. Following extraction with phenol and chloroform, and ethanol precipitation, the RNA was coupled to a diaminobenzoxyethyl filter (Schleicher & Schuell) according to the manufacturer's recommendations.

A cloned fragment containing the full-length rat insulin cDNA was labelled to a specific activity of approximately 1×10^8 dpm/ng with ^{32}P-dCTP by nick translation. Hybridization was overnight at 42 °C in 50% formamide, 2X Denhardt's solution, 0.9 mol/l NaCl, 0.09 mol/l sodium citrate, 50 mmol/l sodium phosphate (pH 6.5), and 0.1 mg/ml sheared salmon sperm DNA. After hybridization, filters were washed 4 times in 15 mmol/l NaCl, 1.5 mmol/l sodium citrate, and 0.1% SDS at 52 °C. Hybridization was visualized by autoradiography using Kodak XAR film.

Statistical analysis

Results are shown as means (or means of percentages of controls) ± SEM. Only experiments with different islet batches were considered as separate observations. A two-tailed unpaired Wilcoxon's test was used and 5% was chosen as the level of significance.

Results

Effects of IL-1 on insulin release and insulin content of isolated rat islets

After 1 h of incubation with 0.5 or 5 U/ml of crude IL-1 the insulin release did not differ from control values (Table 1). After 24 h of exposure 0.5 U/ml caused a 63% increase ($p < 0.05$), whereas 5 U/ml resulted in a 45% decrease ($p = 0.05$) in insulin release. After an in-

Table 1. Effect of interleukin 1 on insulin release (ng insulin/10 islets) from isolated rat islets of Langerhans

Preparation	Incubation period		
	1 h	24 h	6 days
Crude IL-1			
Controls	5 ± 0.6 (4)	100 ± 7 (5)	862 ± 159 (5)
0.5 U/ml	6 ± 1.2 (4)	163 ± 16[a] (5)	954 ± 141 (5)
Controls	5 ± 0.7 (4)	113 ± 23 (5)	693[b] (2)
5 U/ml	6 ± 0.3 (4)	62 ± 3[a] (5)	226[b] (2)
rIL-1			
Controls		130 ± 13 (6)	
0.6 ng/ml	NT	198 ± 14[a] (6)	NT
6 ng/ml		94 ± 22 (4)	

Data are means and SEM of *(n)* experiments, except for [b], which is the mean of two experiments. NT not tested. [a] $p \leq 0.05$

Table 2. Effect of crude human IL-1 on total protein (TP) and (pro)insulin (PI) biosynthesis from isolated rat islets of Langerhans

Crude IL-1	Incubation period					
	1 h		24 h		6 days	
	TP[a]	PI[a]	TP	PI	TP	PI
0.5 U/ml	109 ± 9 (4)	93 ± 2 (4)	174 ± 20 (5)[c]	145 ± 8 (5)[c]	132 ± 16 (5)[c]	135 ± 16 (5)
5 U/ml	92 ± 18 (4)	95 ± 13 (4)	52 ± 12 (5)[c]	27 ± 9 (5)[c]	38[b] (2)	22[b] (2)

[a] Total protein (TP) and (pro)insulin (PI) biosynthesis (cpm/islet) are expressed in percent of respective control islets (=100%). Data are means and SEM of *(n)* experiments, except for [b], which is the mean of two experiments. [c] $p = 0.01$, when compared with respective control islets

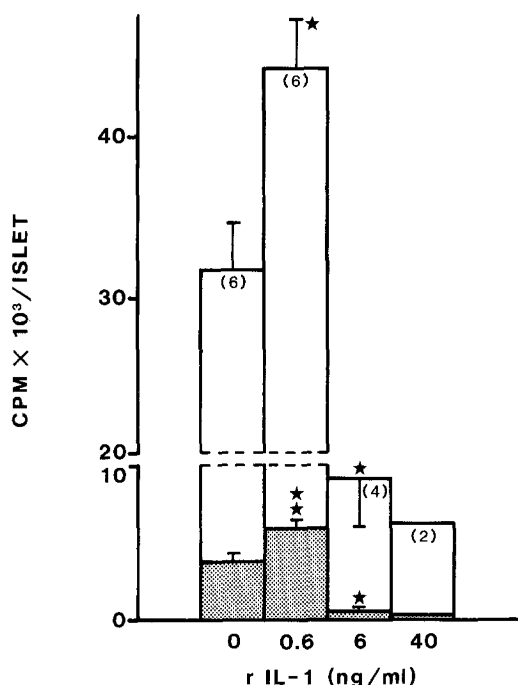

Fig. 1. Effect of rIL-1 (beta) on total protein biosynthesis (open bars) and on (pro)insulin biosynthesis (hatched bars) of isolated rat islets of Langerhans after 24 h of exposure. The bars represent means ± SEM of (n) experiments. $^{**}p = 0.01$, $^{*}p = 0.05$ when compared with respective control islets

cubation period of 6 days, 0.5 U/ml showed no significant increase in the insulin release, while 5 U/ml decreased the insulin release by 67%.

Similarily, the insulin release from isolated rat islets was increased by 50% in the presence of 0.6 ng/ml rIL-1 for 24 h ($p = 0.02$) while no significant decrease was observed with 6 ng/ml (NS). The insulin content of the islets exposed to 0.6 ng/ml was increased by 53% ($p < 0.025$) while no change was observed in islets exposed to 6 ng/ml for 24 h.

Effects of IL-1 on (pro)insulin and total protein biosynthesis in rat islets

As shown in Table 2 there was no significant difference in the total protein (TP) biosynthesis (as assessed after TCA precipitation) and the (pro)insulin biosynthesis between control islets and islets incubated with 0.5 U/ml or 5 U/ml for 1 h. After 24 h of exposure, both (pro)insulin and TP biosynthesis were increased by

Table 3. (Pro)insulin biosynthesis in percent of total protein biosynthesis in rat islets of Langerhans incubated with interleukin 1

Preparation	Incubation period		
	1 h	24 h	6 days
Crude IL-1			
Controls	13.7 ± 0.7 (4)	15.6 ± 0.7 (5)	14.5 ± 0.5 (5)
0.5 U/ml	11.8 ± 1.0 (4)	13.5 ± 1.5 (5)	15.0 ± 0.9 (5)
Controls	21.0 ± 2.9 (4)	15.6 ± 2.4 (5)	15.0[b] (2)
5 U/ml	22.2 ± 2.6 (4)	7.5 ± 1.1 (5)[a]	8.9[b] (2)
rIL-1			
Controls		11.5 ± 1.1 (6)	
0.6 ng/ml	NT	12.8 ± 1.1 (6)	NT
6 ng/ml		4.0 ± 0.5 (4)[a]	

Data are means and SEM of *(n)* experiments, except for [b], which is the mean of two experiments. NT not tested. [a] $p = 0.05$ when compared with respective control islets

45% and 74%, respectively, with 0.5 U/ml ($p = 0.01$), and decreased by 73% and 48%, respectively, with 5 U/ml ($p = 0.01$).

TP but not (pro)insulin biosynthesis remained increased after 6 days of exposure to 0.5 U/ml by 32% ($p = 0.01$), and both were decreased by 62% and 78%, respectively, when exposed to 5 U/ml in two experiments.

Similarily, rIL-1 at a concentration of 0.6 ng/ml significantly increased the biosynthesis of (pro)insulin by 58% ($p = 0.01$) and TP by 40% ($p < 0.05$) after an exposure time of 24 h (Figure 1). In contrast, 6 ng/ml of rIL-1 suppressed the biosynthesis of (pro)insulin by 89% ($p = 0.05$) and of TP by 68% ($p = 0.05$), and 40 ng/ml decreased the (pro)insulin and TP biosynthesis by 96% and 85%, respectively, in two experiments.

As shown in Table 3, the ratio between (pro)insulin and TP biosynthesis remained unchanged in islets incubated with low doses of crude (0.5 U/ml) or rIL-1 (0.6 ng/ml). 5 U/ml of crude IL-1 did not alter the (pro)insulin:TP ratio after 1 h of exposure. However, after an exposure time of 24 h, both 5 U/ml of crude and 6 ng/ml of rIL-1 caused a significant decrease in the (pro)insulin:TP ratio. Similar results were obtained after an 1-h labelling period, indicating that release of newly synthesized insulin does not influence the PI/TP ratio. Control experiments performed in the presence of 0.4 mmol/l unlabelled leucine gave the same percentual incorporation of radioactivity in (pro)insu-

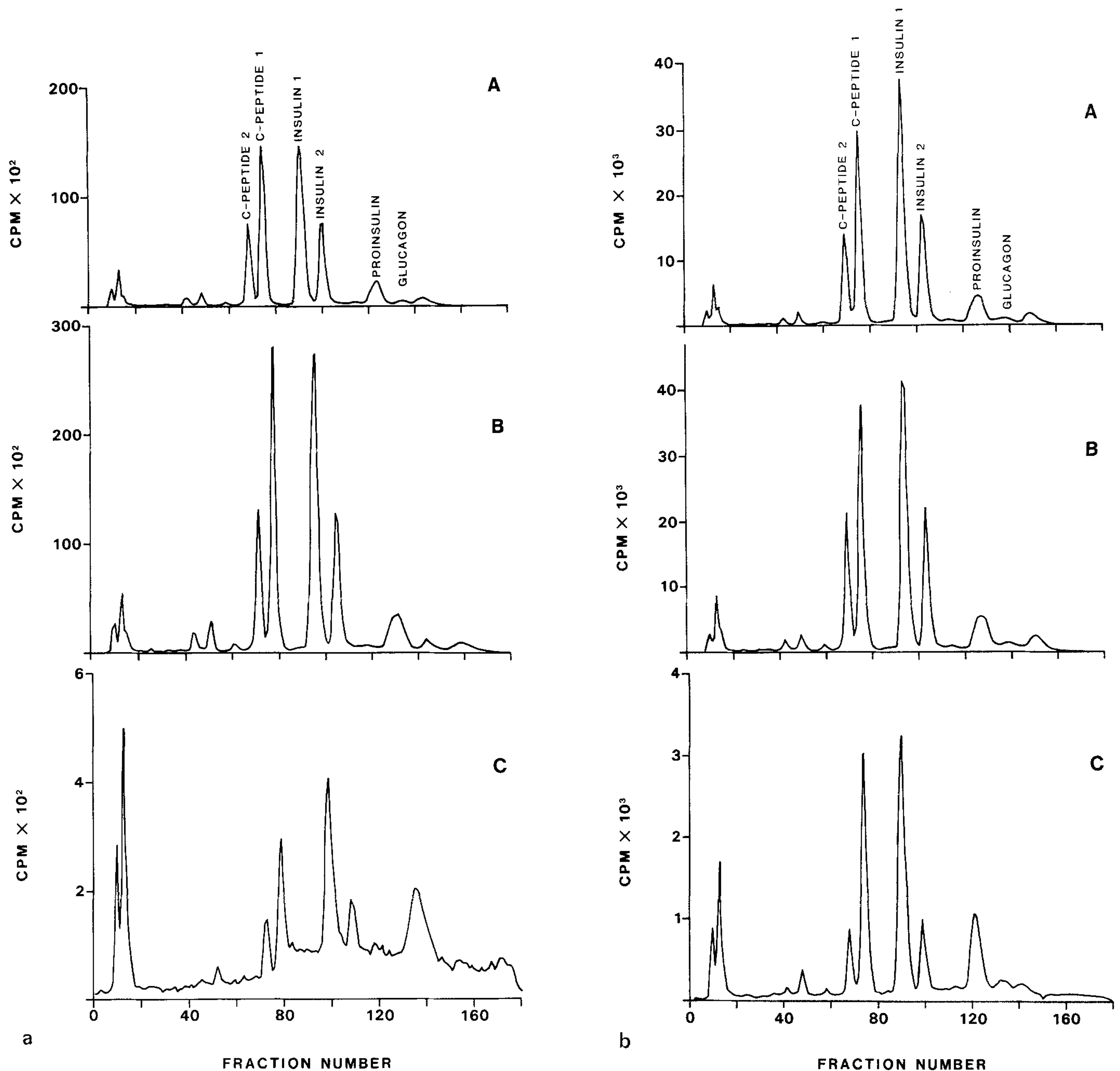

Fig. 2a and b. RP-HPLC fractionation of isolated rat islets incubated with ^{3}H-leucine after a 24-h culture period in the absence (A) or in the presence of either 0.6 ng/ml (B) or 6 ng/ml (C, extended scale) rIL-1 (beta). RP-HPLC fractionation was performed using a LiChrosorb RP-18 (5 μm), 250 × 4 mm column eluted at 1 ml/min with TEAP/acetonitrile (pH 4.0). Fractions of 0.3 ml were collected and counted for ^{3}H after addition of 2.5 ml Aquasol (NEN). Panels a and b are results of two separate experiments

lin, indicating that the observed results did not depend on changes in the pool size of the aminoacid (data not shown).

RP-HPLC analysis of the islet components

The results of the separation of the ^{3}H-labelled islet homogenates by means of RP-HPLC are shown in Figure 2 (panel a and b). Islets incubated with 0.6 ng/ml rIL-1 for 24 h showed an increase of labelled insulin 1 and 2 (more pronounced in panel a than b), C-peptide 1 and 2, proinsulin and glucagon as compared with control islets. Six ng/ml of rIL-1 caused a marked decrease in all the fractions (most pronounced in panel b). The glucagon peak was only detectable in the experiment shown in panel b (note the extended scale).

Effects of rIL-1 on the preproinsulin mRNA-content of isolated rat islets of Langerhans

As shown in Figure 3a, the preproinsulin cytoplasmic mRNA-content of islets was unchanged after 4 h of exposure to 0.6 ng/ml rIL-1, but increased approximately 2-fold after 24 h as compared with respective control

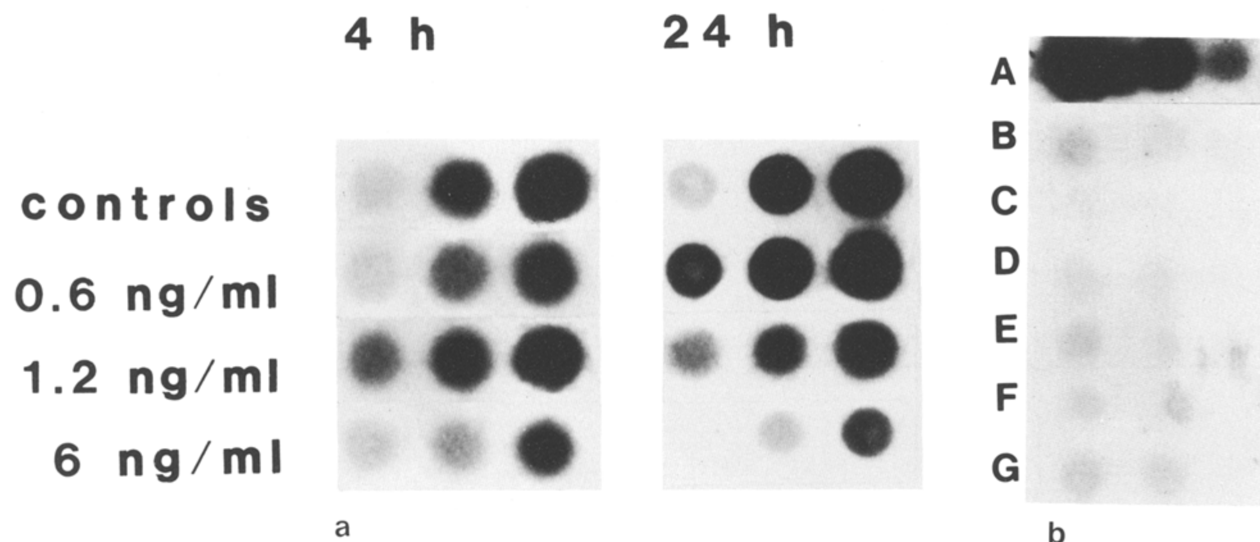

Fig. 3. **a** Relative levels of pre-proinsulin mRNA of isolated rat islets of Langerhans cultured in the absence (control) or in the presence of either 0.6 ng/ml, or 1.2 ng/ml, or 6 ng/ml of rIL-1 (beta) for 4 and 24 h are shown. From left to right, total cytoplasmic RNA from 30, 60, and 120 islets was denatured and spotted onto filters, and hybridized with rat insulin cDNA as described under Methods. **b** Control hybridizations to (B) testis total RNA, (C) testis poly A+ RNA, (D) liver total RNA, (E) kidney total RNA, (F) kidney poly A+ RNA, and (G) spleen total RNA are shown. 10, 5, and 2.5 μg RNA was used, respectively, which was in vast excess of the amount of RNA from 120, 60, and 30 islets on the same film (A)

islets. 1.2 ng/ml rIL-1 increased the mRNA-content by 4 h, but decreased it after 24 h of exposure. Six ng/ml rIL-1 caused a slight decrease in mRNA by 4 h and an approximately 2-fold decrease after 24 h of incubation. Similar results were observed using two different methods of coupling the RNA preparations to filters (see Methods). In Figure 3b are shown control hybridizations with RNA preparations from various tissues (see legend to Figure 3b).

Discussion

IL-1 is the major inducer of acute phase responses associated with infection or inflammation and thereby exerts stimulatory and proliferative effects on various unrelated cell types. Besides the activation of T- and B-cells, it stimulates chondrocytes to release collagenase and neutral proteases [19, 20], induces the biosynthesis of procoagulant activity in endothelial cells [21], increases acute phase protein synthesis in hepatocytes [22], and collagen type IV production in epidermal cells [23]. A cytotoxic action of the cytokine has been reported for certain tumour cell lines [24, 25], and for pancreatic B cells [5, 6].

In previous reports we could show that low IL-1 concentrations increase and high IL-1 concentrations decrease, insulin release as well as insulin content in isolated rat islets of Langerhans [4, 5]. The present data demonstrate that human IL-1 dose- and time-dependently affects the biosynthesis of (pro)insulin in rat islets. Low concentrations of IL-1 increase, and high concentrations decrease the biosynthesis of (pro)insulin. In addition, the relative level of preproinsulin mRNA is increased in islets exposed to low IL-1 concentrations and decreased after exposure to high IL-1 concentrations.

High IL-1 concentrations and prolonged exposure time to the agent, i.e. 5 U/ml of crude or 6 ng/ml of rIL-1 for 24 h, cause a significant reduction of the (pro)insulin biosynthesis when calculated as a percentage of the total protein biosynthesis. On the other hand, low IL-1 concentrations, i.e. 0.5 U/ml of crude or 0.6 ng/ml of rIL-1, or an incubation of 1 h with 5 U/ml do not alter the ratio of (pro)insulin to TP. These results indicate that low concentrations of IL-1 exert a non-specific stimulatory action on the isolated islet organ. In contrast, higher concentrations or a longer exposure time to the agent cause a marked perturbation of the differentiated function of the B cell, i.e. insulin production, whereas the non-insulin related proteins are less affected.

Furthermore, HPLC analysis of the islet proteins revealed changes in all the fractions including glucagon and proinsulin. However, if a proinsulin to insulin ratio is calculated on a molar basis (taking into account the different number of leucine residues of proinsulin and insulin), this ratio is found to be increased three-fold (33 and 20 in Figure 2a, b respectively) in islets incubated with high concentrations of IL-1 as compared with control islets (8.5 and 8.4) and islets incubated with a low IL-1 concentration (9.8 and 9.6). It seems unlikely that this is due to increased secretion of newly synthesized insulin during the labelling period, since the insulin release was decreased at the high IL-1 concentration. Preliminary pulse-chase experiments have confirmed the reduced rate of conversion at the high IL-1 concentration [16].

A dose- and time-dependent bimodal effect of IL-1 on protein biosynthesis of normal cells has recently been observed in rat osteoblasts. While IL-1 concentrations of 0.1–5 U/ml were found to stimulate calvarial collagen and non-collagen protein synthesis, higher doses or longer exposure time to IL-1 had an inhibitory effect on the synthesis of collagen [26].

In islet cells, dual dose-dependent effects on insulin release and insulin content have been reported for hydrocortisone as well. At near physiological concentrations, i.e. 10^{-7} mol/l, hydrocortisone stimulated both insulin release and insulin content in rat [27] as well as preproinsulin mRNA, proinsulin biosynthesis and insulin release in mouse islets [28, 29]. Higher hydrocortisone concentrations (10^{-5} mol/l), however, failed to stimulate insulin release and insulin content in either rat or mouse islets.

The changes in preproinsulin mRNA demonstrate that IL-1 acts at a pretranslational level of insulin biosynthesis. Since we only measured steady-state mRNA levels, we cannot say whether IL-1 triggers the transcription of the insulin gene(s) or inhibits the degradation of mRNA. It can be ruled out that IL-1 increases mRNA by inducing DNA replication and cell division, since we have previously observed that although IL-1 at low concentrations increased the islet insulin content, the DNA content of the islets remained unchanged [4]. This was also found in rat osteoblasts, where IL-1 was shown to stimulate collagen and non-collagen protein synthesis in the presence of hydroxyurea, which blocks DNA-replication [26].

A stimulatory effect on the transcription of the insulin gene(s) has been reported for glucose in normal rat islets and for cholera toxin in the insulin-producing cell line RIN-5F [30, 31]. In these studies it was demonstrated that in addition to a stimulation of the insulin gene(s) transcription, cyclic AMP mediated inhibition of mRNA degradation played an important part in increasing specific mRNA levels. Since a stimulation of insulin release at low IL-1 concentrations has been found in the presence of high but not low glucose concentrations [4, 32, 33], it is possible that IL-1 may act by potentiating glucose effects both at pre- and post-translational levels.

However, IL-1 in itself can act at the pretranslational level of protein biosynthesis, as recently shown by Ramadori et al. [22]. In mouse hepatocytes IL-1 increased serum amyloid A and factor B, yet decreased albumin synthesis at the transcriptional level.

At high IL-1 concentrations, the decrease in preproinsulin mRNA may, together with the inhibited biosynthesis of (pro)insulin and the decreased insulin secretion, merely reflect a toxic effect of IL-1 on B-cell function.

In vivo counterparts of the observed dose-dependent biologic response of islet cells to IL-1 may hypothetically exist. Low circulating IL-1 concentrations may have an endocrine effect and increase insulin secretion as has been observed during the acute phase response induced by infection or in experimental animal models, where hyperinsulinaemia occurs with a time lag of 4 h after injection of endotoxin or 1 h after injection of crude IL-1 preparations into rats [34, 35]. Furthermore, IL-1 may play a role in priming the physiological secretion of insulin, since prevention of the "normal" low grade portal endotoxemia by diminishing intestinal derived endotoxin in rats results in decreased basal and stimulated insulin levels [36].

When IL-1 is produced in high concentrations in situ, i.e. as a part of the insulitis process, it may be toxic to B cells and cause insulin-dependent diabetes mellitus. The possible mechanisms involved in this process have been reviewed [33]. A crucial point is the specificity of the IL-1 action. The stimulatory effect does not appear to be B-cell specific, but there are certain indications for a particular susceptibility of the B cell to the toxic effect of IL-1. Although the total protein biosynthesis is inhibited after 24-h exposure to high IL-1, (pro)insulin biosynthesis is more affected. Because of the marked time dependence of the IL-1 effect, resulting in early stimulation by any dose of IL-1 and later inhibition depending of the dose [32, 33], a more differentiated time-course must be considered. Recently a morphological time-course study showed that B cells were subjected to pathological changes already after 30 min exposure to IL-1, while no changes in A-cell morphology was observed during 24-h exposure [37]. Thus, a short half-life of IL-1 in vivo together with a high local concentration may create conditions for a selective destruction of the B cells.

In summary we have demonstrated that low IL-1 concentrations increase preproinsulin mRNA, (pro)insulin biosynthesis and insulin secretion indicating pre- and post-translational effects of the cytokine. Higher IL-1 concentrations or prolonged exposure to the agent, however, decrease preproinsulin mRNA, (pro)-insulin biosynthesis and insulin secretion and possibly conversion of proinsulin to insulin, reflecting a sick cell.

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