Descriptive and Mechanistic Considerations of Interleukin 1 and Insulin Secretion

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Insulin-dependent diabetes mellitus (IDDM) may be mediated in part by an autoimmune mechanism, as suggested by associated cytologic and serologic phenomena, e.g., insulitis, β-cell necrosis, and the presence of both islet cell and insulin antibodies. Immunological approaches to the prediction and intervention in the progression of β-cell destruction in this disease are under evaluation. A recent hypothesis is that cytokines, including interleukin 1 (IL-1), play causative roles in such autoimmune processes. Several studies have convincingly demonstrated that IL-1 is a potent modulator of β-cell function and can potentiate or inhibit glucose-induced insulin secretion, depending on the concentration and length of exposure to IL-1. IL-1 alone or in concert with other cytokines is cytotoxic to β-cells. The cellular mechanisms responsible for the potent effects of IL-1 on the β-cell are unknown and just beginning to emerge. Although speculative at this time, this perspective delineates cellular mechanisms that are likely to represent possible primary sites for the IL-1 action on β-cells. A mechanistic understanding of the effects of IL-1 on the β-cell may clarify its role in modulating insulin release in vivo or yield insight into the pathogenesis of IDDM. *Diabetes* 37:1311–15, 1988

A growing body of evidence suggests that insulin-dependent diabetes mellitus (IDDM) is caused by autoimmune destruction of β-cells of the pancreatic islet. Findings supporting this hypothesis include *1*) the lymphocytic infiltration of the pancreatic islets, or insulitis observed in biopsy specimens taken from patients in the early stages of IDDM; *2*) the identification of islet cell–reactive autoantibodies in patients with IDDM; *3*) the association of IDDM with other diseases thought to involve an autoimmune component; *4*) indirect evidence of active cell-mediated immunity toward pancreatic islet cells and islet cell antigens in IDDM patients; and *5*) the association of IDDM with certain HLA haplotypes associated with other autoimmune diseases (1). Despite this impressive body of evidence linking the pathogenesis of IDDM to an underlying autoimmune component, little is known about the molecular mechanisms of immunomodulation of islet function in either diabetic patients or normal subjects. A recent hypothesis is that the soluble immune mediator interleukin 1 (IL-1) may play both a pathogenic and physiological role in modulating insulin secretion from the pancreatic islet (2).

IL-1 is a 17,500-M_r polypeptide released by activated macrophages and other cells (e.g., keratinocytes, corneal epithelial cells, astrocytes, and renal mesangial cells) (3). Numerous agents induce IL-1 production from mononuclear phagocytes in vitro, including microorganisms, microbial products, inflammatory agents, and plant lectins (3,4). IL-1 is an important mediator of inflammation and immunity and exerts biologic effects on many target cells. IL-1 induces proliferation of T-lymphocytes at inflammatory loci (5) and circulates to distant sites. For example, IL-1 induces fever by an action at the hypothalamus and stimulates synthesis of acute-phase proteins by hepatocytes (6,7). Two molecular forms of IL-1 (α and β) have been isolated and cloned. These two polypeptides display only 26% homology in amino acid sequence (8–10). The cell surface receptors for IL-1α and IL-1β are identical, however, and the two molecules appear to have identical effects on target tissues (11).

DESCRIPTIVE EFFECTS OF IL-1 ON β-CELL FUNCTION

Nerup et al. (2) and Mandrup-Poulsen et al. (12,13) observed that when either human or rat islets were exposed to a conditioned medium derived from activated mononuclear cells, there was significant inhibition of insulin secretion and a reduction of β-cell insulin content after 24 h of incubation. The active cytokine in this crude preparation was subse-

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quently found to be IL-1. Further evidence that IL-1 was responsible for inhibition of insulin secretion in these studies was that either native IL-1 or recombinant IL-1 (rIL-1) reproduced the effects described above on β-cell function.

These inhibitory effects of IL-1 on insulin secretion from pancreatic β-cells have been confirmed by at least three other laboratories in both static and dynamic secretion studies (14–16). In addition to its ability to inhibit insulin secretion, IL-1 can also potentiate agonist-induced insulin release, depending on the parameters of IL-1 concentration and length of exposure to this cytokine (14,15,17). A 15- to 18-h exposure of islets to 0.5 pM IL-1 potentiated glucose-induced insulin secretion (Fig.1). Under the same incubation conditions, a higher concentration of IL-1 (2 nM) profoundly inhibited insulin secretion. Exposure of islets to this concentration of IL-1 (2 nM) for a shorter time (90 min) resulted in potentiation of insulin secretion. An intermediate period of exposure (3 h) of islets to IL-1 (2 nM) resulted in neither potentiation nor inhibition of glucose-induced insulin release (15). Thus, it appears that IL-1 can either potentiate or inhibit glucose-induced insulin secretion depending on the concentration and length of exposure to β-cells. In 15- to 18-h incubations, the inhibitory effect of IL-1 is reversible, and β-cell death does not occur (15). These observations establish that IL-1 can exert potent effects on β-cell function without inducing cell death.

A less clear issue is whether IL-1 can participate in β-cell destruction (cytotoxicity), which might ultimately lead to IDDM. Studies on β-cell cytotoxicity of IL-1 have used prolonged incubation times of 6–7 days in the continuous presence of IL-1 (18; Fig. 1). Morphologic evidence of cell death in such studies has been attributed to a cytotoxic effect of IL-1 (12,13,18). This issue has been reexamined in studies with a quantitative ^{51}Cr-release assay to monitor lysis of rat islet cells maintained in monolayer culture during continuous exposure to various cytokines for 4 days (19). In such studies, IL-1 and IL-2, tumor necrosis factor (TNF), and lymphotoxin (LT) did not influence ^{51}Cr release from islet cells. Simultaneous addition of IL-1 with TNF, LT, or interferon-γ did accelerate islet cell ^{51}Cr release, which is compatible with a cytotoxic effect of IL-1 in the presence of additional cytokine(s). Similar effects were observed with combinations of TNF and interferon-γ or of LT and interferon-γ. The cytotoxic effect of these cytokines acting in concert was also confirmed by phase-contrast microscopy. The observation that IL-1 induced cytotoxicity only in the presence of other cytokines argues against a direct causative effect of IL-1 alone in β-cell destruction. Differences in experimental design in the studies discussed may account for the apparently discrepant findings on this issue.

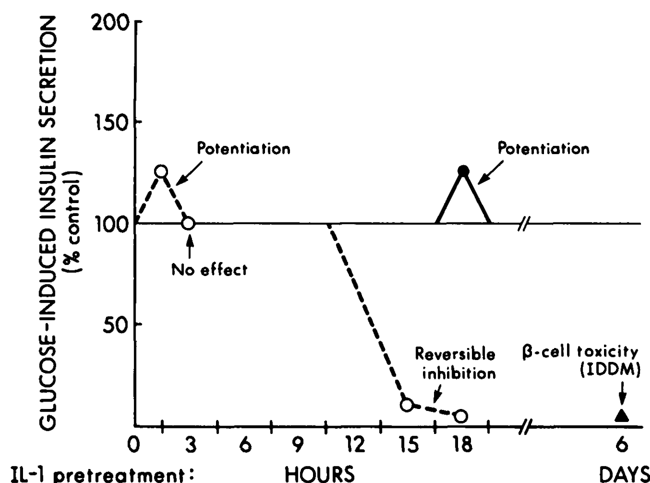

FIG. 1. Effects of rIL-1 pretreatment on glucose-induced insulin secretion: concentration and time dependence. ○, Exposure of islets to 2 nM IL-1 for 90 min results in potentiation of glucose-induced insulin secretion. No effect is observed at 3 h. Inhibition is observed after 15–18 h incubation (15). After 6 days of culture in presence of 20 and 60 U/ml IL-1, β-cell death has been reported (▲; 18). ●, Exposure of islets to 0.5 pM IL-1 for 15–18 h results in potentiation of glucose-induced insulin secretion (15).

In summary, the effects of purified IL-1 and rIL-1 on β-cell function include either potentiation or inhibition of glucose-induced insulin secretion, depending on both the concentration and time of exposure. The inhibitory effects are reversible and are observed with insulin secretion induced by glucose and by other secretagogues (15). It appears that the function of other islet cells, e.g., α- and δ-cells, may also be affected by IL-1 treatment (2). Whether a direct cytotoxic effect of IL-1 is observed appears to depend on the experimental methodology employed.

MECHANISTIC ASPECTS OF EFFECTS OF IL-1 ON β-CELL FUNCTION

Determining the mechanism(s) of the effects of IL-1 and/or other cytokines on β-cell function represents a formidable challenge for future studies. The abilities of IL-1 to potentiate and to inhibit glucose-induced insulin secretion in a reversible manner require clarification. It is not clear whether these effects are mediated by similar or different mechanisms. An understanding of the acute potentiation of insulin secretion by IL-1 within 2 h of exposure may yield insight into the early biochemical events initiated by IL-1. This potentiating effect is, however, relatively weak (~30% increase in insulin secretion) compared with the 80–90% inhibition of insulin secretion after a 15- to 18-h exposure to IL-1 (15). If similar cellular mechanisms are involved in both the stimulatory and inhibitory effects of IL-1 on insulin secretion, closer scrutiny of the inhibitory effect might be more rewarding in clarifying the pathogenesis of IDDM. It is possible, however, that fundamentally distinct biochemical mechanisms underlie the stimulatory and inhibitory effects of IL-1 on insulin secretion. Examination of the early biochemical events in IL-1 action on β-cells may require the utilization of sensitive and quantitative assays of the biochemical parameters in question. The possibility that distinctly different mechanisms may be responsible for the potentiating and inhibitory effects of IL-1 on insulin release has not been clearly addressed.

Investigation of the mechanism(s) for the effects of IL-1 on β-cell secretion would logically involve processes thought to be important in the insulin secretory response to physiologic secretagogues such as D-glucose. As illustrated in Fig. 2, such fundamental processes include *1)* glucose utilization and ATP production; *2)* the generation of phospholipid-derived mediators, including inositol phosphates, diacylglycerol (DAG), and arachidonic acid and its cyclooxygenase and lipoxygenase metabolites; *3)* Ca^{2+} homeostasis by intracellular organelles; *4)* plasma membrane

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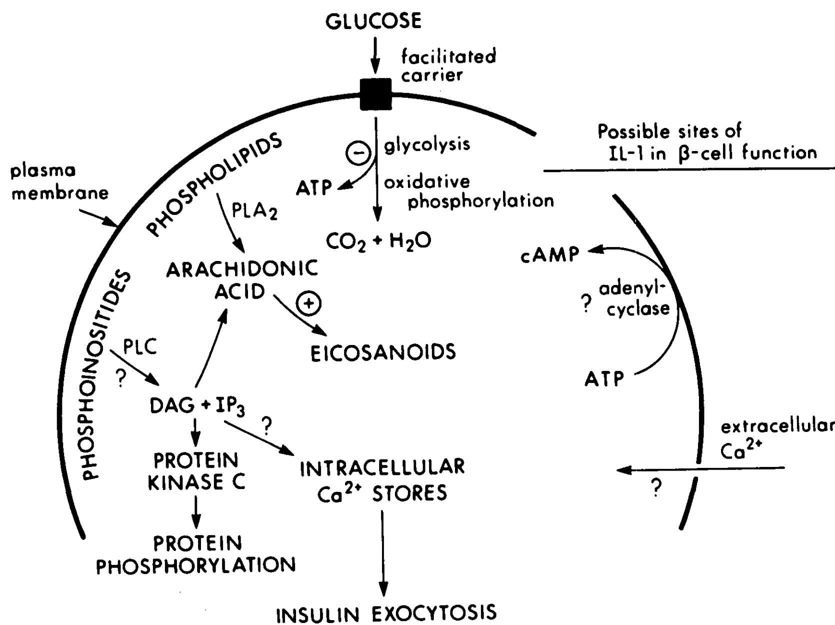

FIG. 2. Cellular mechanisms involved in glucose-induced insulin release by β-cell that may be affected by IL-1.

ion fluxes; and 5) protein kinase activities. Obviously, this schema is not exhaustive, but it illustrates a number of important cellular processes that in many instances have been documented to be modulated by IL-1 in other cellular models and may be similarly influenced by the action of IL-1 on β-cells.

Sandler et al. (16) have observed that treatment of rat islets for 48 h with IL-1β inhibits both glucose-induced insulin secretion and insulin biosynthesis (16). These effects are accompanied by a 50% reduction in glucose (16.5 mM) oxidation to CO_2. It is not known if this reflects an impairment of the facilitated transport of glucose. Another possibility that requires examination within this experimental design is that glycolysis and/or mitochondrial oxidative phosphorylation may be impaired after 48 h of exposure to IL-1β. An equally important question is whether the observed 50% reduction in glucose utilization results in a fall in ATP concentration. A significant reduction could compromise numerous cellular processes, e.g., ATP-dependent ion fluxes and protein kinase activities.

Rapidly accumulating evidence indicates that signal-transduction processes including phospholipase C–catalyzed hydrolysis of phosphoinositides and the consequent production of inositol phosphates, DAG, and unesterified arachidonic acid are involved in the insulin secretory process (20). Various cells, including IL-1–responsive T-lymphocytes, produce a complex array of inositol phosphate isomers on stimulation with agonists. In studying various aspects of transmembrane signaling during IL-1–dependent T-lymphocyte activation, it has been shown that stimulation with phytohemagglutinin (PHA) resulted in a 3.7-fold increase in total inositol phosphate formation by a murine T-lymphoma line, whereas rIL-1 had no significant modulatory influence on this response, and it did not alter the relative proportions of the various inositol phosphate species released after PHA stimulation (21). In contrast to the effects of IL-1 on T-lymphocyte activation, recent evidence indicates that stimulation of mouse peritoneal macrophages by IL-1 provokes a rapid increase in inositol monophosphate (IP_1), bisphosphate (IP_2), trisphosphate (IP_3), and tetrakisphosphate (IP_4), with IP_2, IP_3, and IP_4 returning to control levels after 1 min (22). These results suggest that the mechanism of IL-1 in receptor activation may be mediated by the rapid hydrolysis of phosphoinositides and the generation of inositol phosphates.

Glucose-induced insulin secretion by islets is accompanied by a rapid increase in the production of 1,4,5-IP_3, 1,3,4,5-IP_4, 1,3,4-IP_3, and 3,4-IP_2 (23). It will therefore be important to examine the effect of IL-1 on glucose-induced inositol phosphate production by islets after both acute and long-term incubations. It will also be important to establish whether the mobilization of intracellular Ca^{2+} from the endoplasmic reticulum by 1,4,5-IP_3, the biologically active IP_3 isomer, is altered in islets exposed to IL-1 (24).

Unesterified arachidonic acid is another phospholipid-derived mediator that is liberated during the insulin secretory process. Arachidonate may be liberated by the action of phospholipase A_2 or by the sequential actions of phospholipase C and neutral lipases. It has been clearly established by stable-isotope dilution mass-spectrometric measurements that glucose induces a significant increase in the islet accumulation of unesterified arachidonic acid. The temporal profile of glucose-induced arachidonate accumulation parallels that of insulin release (25). The cyclooxygenase metabolite prostaglandin E_2 (PGE_2) and the lipoxygenase metabolite 12-HETE are the most abundant arachidonate metabolites produced in islets, and both compounds have been implicated in the insulin secretory process (26). Several reports suggest that IL-1 enhances PGE_2 production in other cells (27,28). Recent studies in our laboratory have shown that exposure of islets to rIL-1 for 18 h results in an approximately sixfold increase in PGE_2 production as determined by enzyme-linked immunoassay procedures. The possible role that the metabolites of arachidonic acid may play in

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mediating the potent effects of IL-1 on insulin secretion by the β-cell is clearly an area of significant importance. Quantitation of arachidonate metabolites produced by both the cyclooxygenase and lipoxygenase pathways after the acute (90-min) and long-term (15- to 18-h) exposure of islets to IL-1 will clearly require sensitive methods. Radiochemical studies with ^{3}H-labeled arachidonate may be insufficient alone to establish the effects of IL-1 on islet arachidonate release and metabolism, because some glucose-sensitive islet pools of arachidonate are difficult to label with exogenous [^{3}H]arachidonate. Direct mass measurements of these metabolites by radioimmunoassay or mass spectrometry may be the preferable approach (26). There have been no reports directly linking the effects of IL-1 on islet eicosanoid production with either potentiation or inhibition of glucose-induced insulin secretion.

TNF has recently been reported to induce a rapid increase in phospholipase A_2 activity and the synthesis of a phospholipase A_2–activating protein (PLAP) in endothelial cells. Phospholipase A_2 activation and the synthesis of metabolites of [^{3}H]arachidonate in this study required both RNA and protein synthesis and were temporally associated with the accumulation of PLAP (29). Interestingly, IL-1 also induces an increase in PLAP synthesis in a murine EL4 T-lymphocyte cell line (30), which is similar to the effect of TNF on endothelial cells. The effect of IL-1 on the de novo synthesis of PLAP and other proteins that may alter signal-transduction processes has been demonstrated in various cells sensitive to IL-1. Recently, IL-1 has been shown to stimulate fibroblast cyclooxygenase synthesis after 12–16 h of treatment. This is followed by an increase in PGE_2 production, suggesting that IL-1 mediates the latter effect via induction of cyclooxygenase synthesis (31). The effects of IL-1 on the synthesis of proteins other than insulin, like PLAP or cyclooxygenase at either the transcriptional or translational level, have not yet been defined in islets after either acute or long-term incubations with this cytokine.

Studies over the past two decades have clearly established a second-messenger role for Ca^{2+} in the insulin secretory process. Both mobilization of Ca^{2+} from intracellular sequestration sites, e.g., the endoplasmic reticulum, and the movement of extracellular Ca^{2+} through voltage-dependent channels in the plasma membrane appear to participate in insulin secretion (32). Methods such as patch clamping, intracellular Ca^{2+} measurements with fluorescent indicators, and image analysis and in vitro preparations of permeabilized cells provide new approaches for examining the effects of IL-1 on β-cell Ca^{2+} homeostasis. A rise in cytosolic Ca^{2+} is believed to be an important signal for granule exocytosis in neutrophils. It has been shown recently that exposure of human neutrophils to IL-1 resulted in an immediate rise in intracellular Ca^{2+} as measured with quin 2 (33). Additional studies have indicated that IL-1 induces the mobilization of cell membrane–associated Ca^{2+}, which may contribute to the rise in Ca^{2+}. Clearly, similar changes in intracellular Ca^{2+}, if shown to occur in β-cells after IL-1 exposure, would have significant implications relevant to the potentiating effect of IL-1 on glucose-induced insulin secretion. In terms of the inhibitory effect on insulin secretion after longer exposure to IL-1, the effect of this cytokine on the passive permeability of the islet cell plasma membrane to the 10, 000-fold gradient of extracellular to intracellular Ca^{2+} concentrations also warrants examination. For example, a slow increase in Ca^{2+} influx through the plasma membrane from extracellular sources could eventually render the cell incapable of regulating intracellular Ca^{2+} concentration and thereby impair the secretory process. A sufficiently sustained elevation in intracellular Ca^{2+} might ultimately result in cell death.

It is generally believed that an increase in β-cell cytoplasmic Ca^{2+} concentration after agonist stimulation somehow results in the translocation of insulin secretory granules to the plasma membrane and exocytosis. Both protein kinase C and a Ca^{2+}- and calmodulin-dependent protein kinase are also thought to participate in these processes, as is a cAMP-dependent protein kinase (34). The identity of the endogenous substrates of these protein kinases and their role in insulin secretion have been subjects of intense investigation. They are believed to be components of the effector limb of insulin exocytosis. Any specific alterations of protein kinase activities induced by IL-1 may be important in deciphering the complex effects of this cytokine on the β-cell. IL-1 activates certain T-lymphocyte cell lines by a process that appears to involve activation of protein kinase C (35). Analogous effects of IL-1 on islet protein kinase C activity have not been demonstrated but may occur.

In addition to the diverse effects of IL-1 on the β-cell described above, recent studies suggest important interactions between the neuroendocrine system and IL-1. For example, IL-1 stimulates the secretion of ACTH from the anterior pituitary and corticotropin-releasing factor from the hypothalamus (36–38). Because IL-1 influences the function of both the pancreatic β-cell and the neuroendocrine system, there may be a physiological role for the immune system in the regulation of endocrine function that is not yet understood.

CONCLUSION

Experimental data suggest a potential role for IL-1 and other cytokines in regulating insulin secretion by the pancreatic β-cell. Several questions concerning the significance of the in vitro effects of exogenous IL-1 on β-cell function remain unanswered, but these effects may reflect physiological modulation of insulin secretion in vivo by IL-1 or may relate to the etiology of IDDM. The cellular mechanism(s) underlying the effects of IL-1 on the β-cell clearly warrants careful examination. Studies are beginning to be directed at cellular mechanisms that may be responsible for mediating the diverse effects produced by IL-1 on β-cell function. Key cellular mechanisms that have been well characterized in the insulin secretory process (e.g., glucose metabolism; the production of phospholipid-derived mediators, i.e., IP_3, DAG, and arachidonic acid and its metabolites; the regulation of intracellular Ca^{2+}; and protein kinase activities) will probably represent prime targets for IL-1. Such mechanistic information may clarify the role of IL-1 in modulating β-cell function and may yield insight into cellular mechanisms operable in other target cells sensitive to IL-1.

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REFERENCES

1. Maclaren NK: Autoimmunity and diabetes. In *The Islets of Langerhans*. Cooperstein SJ, Watkins D, Eds. New York, Academic, 1981, p. 453–66
2. Nerup J, Mandrup-Poulsen T, Molvig J: The HLA-IDDM association: implications for etiology and pathogenesis of IDDM. *Diabetes Metab Rev* 3:779–802, 1987
3. Durum SK, Schmidt JA, Oppenheim JJ: Interleukin-1: an immunological perspective. *Annu Rev Immunol* 3:263–87, 1985
4. Dinarello CA: Interleukin-1. *Rev Infect Dis* 6:51–95, 1984
5. Gery I, Gershon RK, Watsman BH: Potentiation of the T-lymphocyte response to mitogens. *J Exp Med* 136:128–42, 1972
6. Dinarello CA, Wolff SM: Molecular basis of fever in humans. *Am J Med* 72:799–819, 1982
7. Kampschmidt RF, Upchurch HF, Eddington CL, Pulliam LA: Multiple biological activities of a partially purified leukocyte endogenous mediator. *Am J Physiol* 224:530–33, 1973
8. Furutani Y, Notake M, Yamayoshi M, Yamagishi J, Nomura H, Ohue M, Furuta R, Fukui T, Yamada M, Nakamura S: Cloning and characterization of the cDNAs for human and rabbit interleukin-1 precursor. *Nucleic Acids Res* 13:5869–82, 1985
9. March CJ, Mosley B, Larsen A, Cerretti D, Braedt G, Price V, Gillis S, Henney C, Kronheim S, Grabstein K, Conlon P, Hopp T, Cosman D: Cloning, sequence and expression of two distinct interleukin-1 complementary DNAs. *Nature* (Lond) 315:641–47, 1985
10. Auron P, Webb A, Rosenwasser L, Mucci S, Rich A, Wolff S, Dinarello C: Nucleotide sequence of human monocyte interleukin-1 precursor cDNA. *Proc Natl Acad Sci USA* 81:7907–11, 1984
11. Dower S, Kronheim S, Hopp T, Cantrell M, Deeley M, Gillis S, Henney C, Urdal D: The cell surface receptors for interleukin-1α and interleukin-1β are identical. *Nature* (Lond) 324:266–68, 1986
12. Mandrup-Poulsen T, Bendtzen K, Nielsen JH, Bendixen G, Nerup J: Cytokines cause functional and structural damage to isolated islets of Langerhans. *Allergy* 40:424–29, 1985
13. Mandrup-Poulsen T, Bendtzen K, Nerup J, Egeberg J, Nielsen JH: Mechanisms of pancreatic islet-cell destruction: dose-dependent cytotoxic effect of soluble blood mononuclear cell mediators on isolated islets of Langerhans. *Allergy* 41:250–59, 1986
14. Zawalich WS, Diaz VA: Interleukin 1 inhibits insulin secretion from isolated perifused rat islets. *Diabetes* 35:1119–23, 1986
15. Comens PG, Wolf BA, Unanue ER, Lacy PE, McDaniel ML: Interleukin 1 is potent modulator of insulin secretion from isolated rat islets of Langerhans. *Diabetes* 36:963–70, 1987
16. Sandler S, Andersson A, Hellerstrom C: Inhibitory effects of interleukin 1 on insulin secretion, insulin biosynthesis, and oxidative metabolism of isolated rat pancreatic islets. *Endocrinology* 121:1424–31, 1987
17. Spinas GA, Mandrup-Poulsen T, Molvig J, Baek L, Bendtzen K, Dinarello CA, Nerup J: Low concentrations of interleukin-1 stimulate and high concentrations inhibit insulin release from isolated rat islets of Langerhans. *Acta Endocrinol* 113:551–86, 1986
18. Mandrup-Poulsen T, Bendtzen K, Nerup J, Dinarello CA, Svenson M, Nielsen JH: Affinity-purified human interleukin 1 is cytotoxic to isolated islets. *Diabetologia* 29:63–67, 1986
19. Pukel C, Baquerizo H, Rabinovitch A: Destruction of rat islet cell monolayers by cytokines: synergistic interactions of interferon-γ, tumor necrosis factor, lymphotoxin, and interleukin 1. *Diabetes* 37:133–36, 1988
20. Turk J, Wolf BA, McDaniel ML: The role of phospholipid-derived mediators including arachidonic acid, its metabolites, and inositoltrisphosphate and of intracellular Ca^{2+} in glucose-induced insulin secretion by pancreatic islets. *Prog Lipid Res* 26:125–81, 1987
21. Abraham RT, Steffan NH, Barna TJ, McKean DS: Transmembrane signaling during interleukin 1-dependent T cell activation. *J Biol Chem* 262:2719–28, 1987
22. Wijelath ES, Kardasz AM, Drummond R, Watson J: Interleukin-one induced inositol phospholipid breakdown in murine macrophages: possible mechanism of receptor activation. *Biochem Biophys Res Commun* 152:392–97, 1988
23. Turk J, Wolf BA, McDaniel ML: Glucose-induced accumulation of inositol trisphosphates in isolated pancreatic islets: predominance of the 1,3,4-isomer. *Biochem J* 237:259–63, 1986
24. Wolf BA, Comens PG, Ackermann KE, Sherman WR, McDaniel ML: The digitonin permeabilized pancreatic islet model: effect of *myo*-inositol 1,4,5-trisphosphate on Ca^{2+} mobilization. *Biochem J* 227:965–69, 1985
25. Wolf BA, Turk J, Sherman WR, McDaniel ML: Intracellular Ca^{2+} mobilization by arachidonic acid: comparison with *myo*-inositol 1,4,5-trisphosphate in isolated pancreatic islets. *J Biol Chem* 261:3501–11, 1986
26. Turk J, Colca JR, Kotagal N, McDaniel ML: Arachidonic acid metabolism in isolated pancreatic islets. I. Identification and quantitation of lipoxygenase and cyclooxygenase products. *Biochim Biophys Acta* 794:110–24, 1984
27. Dinarello CA, Marnoy SO, Rosenwasser LS: Role of arachidonate metabolism in the immunoregulatory function of human leukocytic pyrogen/lymphocyte-activating factor/interleukin 1. *J Immunol* 130:890–95, 1983
28. Newton RC, Covington M: The activation of human fibroblast prostaglandin E production by interleukin 1. *Cell Immunol* 110:338–49, 1987
29. Clark MA, Chen M, Crooke ST, Bomalaski JS: Tumor necrosis factor (cachectin) induces phospholipase A_2 activity and synthesis of a phospholipase A_2-activating protein in endothelial cells. *Biochem J* 250:125–32, 1988
30. Clark MA, Conway TM, Shorr RGL, Crooke ST: Identification and isolation of a mammalian protein which is antigenically and functionally related to the phospholipase A_2 stimulatory peptide melittin. *J Biol Chem* 262:4402–406, 1987
31. Raz A, Wyche A, Siegel N, Needleman P: Regulation of fibroblast cyclooxygenase synthesis by interleukin-1. *J Biol Chem* 263:3022–28, 1988
32. Wolf BA, Colca JR, Turk J, Florholmen J, McDaniel ML: Regulation of Ca^{2+} homeostasis by islet endoplasmic reticulum and its role in insulin secretion. *Am J Physiol* 254:E121–36, 1988
33. Smith RJ, Epps DE, Justen JM, Sam LM, Wynalda MA, Fitzpatrick FA, Yein FS: Human neutrophil activation with interleukin-1, a role for intracellular calcium and arachidonic acid lipoxygenation. *Biochem Pharmacol* 36:3851–58, 1987
34. Rasmussen H: The calcium messenger system. *N Engl J Med* 314:1094–101, 1986
35. Zlotnik A, Daine B: Activation of IL 1-dependent and IL 1-independent T cell lines by calcium ionophore and phorbol ester. *J Immunol* 136:1033–37, 1986
36. Bernton EW, Beach JE, Holaday JW, Smallridge RC, Fein HG: Release of multiple hormones by a direct action of interleukin-1 on pituitary cells. *Science* 238:519–21, 1987
37. Sapolsky R, Rivier C, Yamamoto G, Plotsky P, Vale W: Interleukin-1 stimulates the secretion of hypothalamic corticotropin-releasing factor. *Science* 238:522–24, 1987
38. Berkenbosch F, Oers JV, Rey AD, Tilders F, Besedovsky H: Corticotropin-releasing factor-producing neurons in the rat activated by interleukin-1. *Science* 238:524–26, 1987

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