

Eicosanoids as Pluripotential Modulators of Pancreatic Islet Function

R. PAUL ROBERTSON

Eicosanoids both negatively and positively modulate glucose-induced insulin secretion. Although the identity of the positive modulator is uncertain, the negative modulator appears to be prostaglandin E₂ (PGE₂), because 1) glucose stimulates PGE₂ synthesis from islet cells; 2) exogenous PGE₂ inhibits glucose-induced insulin secretion; 3) inhibition of β-cell PGE₂ synthesis increases glucose-induced insulin secretion, and this increase is reversed by exogenous PGE₂; and 4) PGE₂ binds to specific β-cell receptors that are coupled to inhibitory regulatory components of adenylate cyclase whose activation decreases cAMP levels. Other possible regulatory effects of eicosanoids on islet function include modulation of islet blood flow and its immune responsiveness. From these considerations, the perspective is offered that eicosanoids are pluripotential modulators of islet function. *Diabetes* 37:367–70, 1988

A scientific perspective is a highly personal concoction of history, established facts, and new observations. It is seasoned with personal experiences, scientific intuition, and occasional flights of fancy. If successful, a perspective is a stimulating brew that reflects what is known and, perhaps less precisely, points to future directions. More simply, it is a sharing of ideas that should be treated as Yeats would have it: "I have spread my dreams under your feet; tread softly because you tread on my dreams."

Eicosanoids is an inclusive term that embraces the oxygenated derivatives of arachidonic acid, including prostaglandins (PGs), thromboxanes, leukotrienes, and HETEs (hydroxy fatty acid derivatives). These substances are reg-

ulators of biologic activity in the cells in which they are synthesized and, in some instances, may have paracrine effects. Although there is evidence in several pathologic states that they may gain access to the circulation and have effects in distant tissues, physiological experiments indicate that eicosanoids do not travel through the systemic circulation as free molecules from one tissue to influence biologic activity in another. Hence, they are autocooids not hormones.

The established effects of eicosanoids on the pancreatic islet are their modulatory effects on hormone secretion. Less verified effects include eicosanoid-receptor-adenylate cyclase interactions, blood flow regulation, and modulation of immune responses. This perspective of the pluripotentiality of eicosanoids as modulators of the islet considers each of these categories in turn.

MODULATION OF HORMONE SECRETION

Evidence that eicosanoids affect pancreatic islet function can be dated as early as 1876, when Ebstein (1) reported that sodium salicylate decreased the amount of glucose appearing in the urine of diabetic patients. One hundred years later, this drug was shown to partially restore absent first-phase insulin secretion in hyperglycemic type II (non-insulin-dependent) diabetic patients (2). Since then, many investigators have reported similar observations with various nonsteroidal anti-inflammatory drugs, although conflicting results have been obtained with indomethacin (for review, see ref. 3). More recently, a great deal of effort has been expended to determine which arachidonic acid products are synthesized by the islet. Although the lists of putative products and the investigators who have found them are long, only a handful of eicosanoids have been unequivocally demonstrated by more than one group of investigators with appropriate methodology. These products are PGE₂, PGF_{2α}, 6-keto-PGF_{1α} (all products of the cyclooxygenase pathway), and 12-HETE (a lipoxygenase-pathway product). For the sake of relevance and brevity, only this group of four products is included in my consideration of eicosanoid effects on islet hormone secretion.

From the Diabetes Center and the Division of Endocrinology, University of Minnesota School of Medicine, Minneapolis, Minnesota. Address correspondence and reprint requests to R. Paul Robertson, MD, Diabetes Center, Box 101, University of Minnesota, Minneapolis, MN 55455. Received for publication 25 November 1987 and accepted 9 December 1987.

The observations that PGE inhibits glucose-induced insulin secretion both in vitro and in vivo were published in 1974. Burr and Sharp (4) observed inhibition by PGE of insulin secretion from pancreas perfused with 16.7 mM glucose. Robertson et al. (5) observed inhibition of first-phase insulin responses to intravenous glucose in anesthetized dogs pretreated with α -adrenergic blockade to eliminate possible confounding effects of catecholamine secretion on insulin secretion. Since these initial reports, many others have appeared confirming that PGE inhibits first-phase insulin responses to glucose and, importantly, that PGE₂ reverses the stimulatory effect of cyclooxygenase inhibitors on insulin secretion (6,7). However, insulin responses to non-glucose secretagogues are generally not inhibited by PGE, and PGE itself has been observed to have mild stimulatory effects on insulin secretion when glucose concentrations are held constant at a basal level (for review, see ref. 3). Moreover, glucose has been reported to increase the synthesis of PGE₂ (8), consistent with a PGE₂ counterregulatory effect on glucose-stimulated insulin secretion. Thus, the inhibitory effect of PGE appears to be relatively specific for glucose-induced insulin release.

The published information about effects of PGF_{2 α} on islet function is much less extensive. Reports of experiments with this eicosanoid in humans (9,10) and rat pancreas and islets (11,12) have yielded variable results. 6-Keto-PGF_{1 α} is an

active metabolite of PGI₂ or prostacyclin. PGI₂ also has inconsistent effects on insulin secretion (13–15). 12-HETE by itself has not been demonstrated to affect insulin secretion. However, its precursor 12-HPETE has been observed to augment glucose-induced insulin secretion (16). This observation coupled with multiple reports of inhibition of insulin secretion by lipoxygenase inhibitors suggests that the lipoxygenase pathway positively modulates glucose-induced insulin secretion, although it is uncertain precisely which lipoxygenase product(s) accounts for this positive effect (3). This contrasts with the cyclooxygenase pathway that negatively modulates insulin secretion, primarily through the actions of PGE₂, and allows the potential of dual modulation—both positive and negative—by arachidonic acid metabolism (Fig. 1A). By comparison, little work has been published regarding the effects of eicosanoids on glucagon, somatostatin, and pancreatic polypeptide secretion, although available information suggests that PGE₂ augments glucagon secretion (17–19).

EICOSANOID-RECEPTOR-ADENYLATE CYCLASE INTERACTIONS

More recent observations about eicosanoid modulation of the islet concern efforts to elucidate mechanisms of action. Although reports of PGE binding sites on fat cells appeared as early as 1972, characterization and regulation of eico-

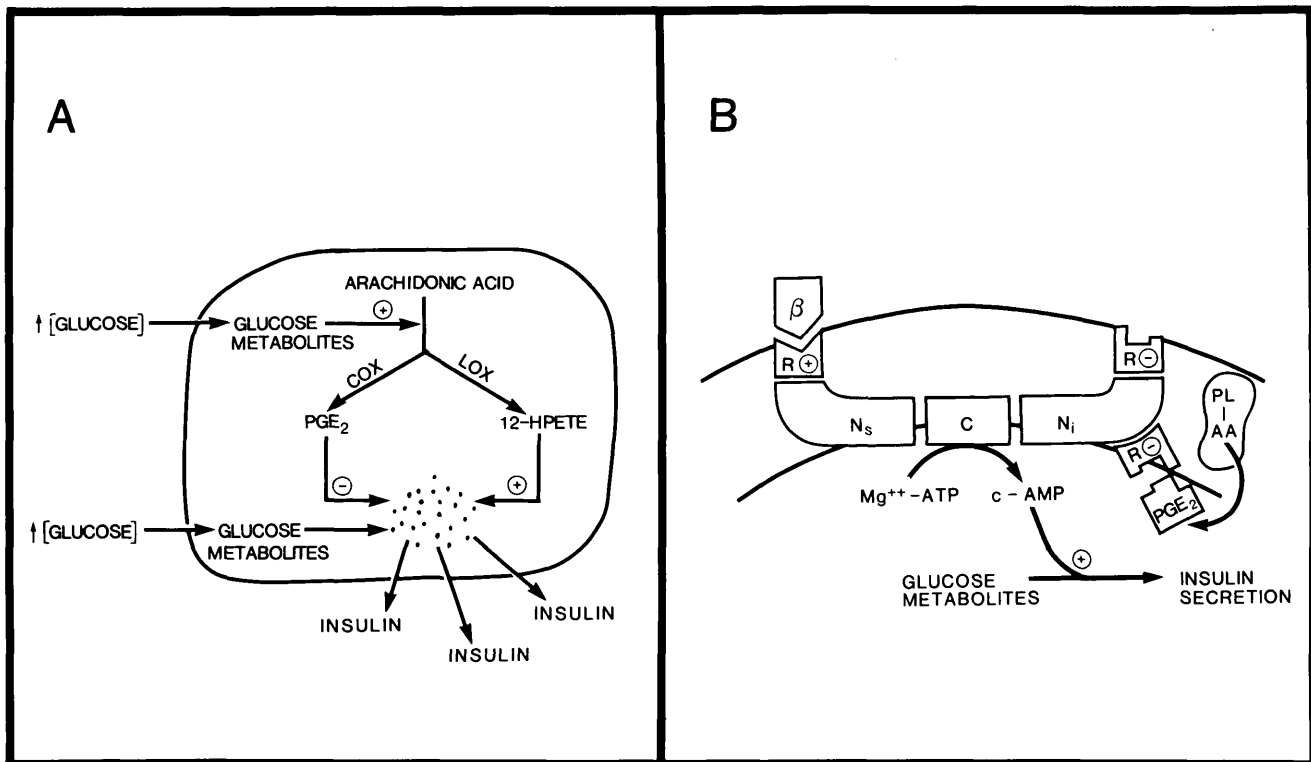


FIG. 1. A: theoretical schema in which glucose promotes pancreatic islet β -cell arachidonic acid (AA) metabolism to form eicosanoids via cyclooxygenase (COX) and lipoxygenase (LOX) pathways. PGE₂ and 12-HPETE are designated as the most likely eicosanoids formed by COX and LOX, respectively, to provide dual negative and positive modulation of glucose-induced insulin secretion. B: theoretical mechanism for PGE₂ action involving islet β -cell plasma membrane receptors and adenylate cyclase. Either net stimulatory or net inhibitory effects on the catalytic component (C) of adenylate cyclase and cAMP generation can result, depending on the relative degree to which stimulatory regulatory (N_s) and inhibitory regulatory (N_i) components are activated by occupancy of stimulatory receptors (R+) and inhibitory receptors (R-), respectively. Example illustrates binding to extracellularly oriented R+ site by β -adrenergic hormone and binding to intracellularly oriented R- site by PGE₂, which is synthesized by metabolism of plasma membrane phospholipid (PL)-derived arachidonic acid. Possibility remains for PGE₂ binding to extracellularly oriented site. Glucose-induced insulin secretion is augmented by net accumulation or turnover of cAMP.

sanoid receptors is still a burgeoning area of research (for review, see ref. 20). It has been established that eicosanoids have binding sites on virtually all cells examined, that these sites are usually on the plasma membrane (although whether on the internal or external side or both has not been ascertained), and that the density of these sites can be up- and downregulated in much the same manner observed with hormone receptors. However, researchers are only on the threshold of delineating the immediate postreceptor consequences of eicosanoid binding to cells.

Some of these consequences appear to involve interactions with both the stimulatory regulatory (N_s) and inhibitory regulatory (N_i) components of adenylate cyclase with resultant modulation of the amount of cAMP synthesized by the cell. For example, we have observed that use of a PGE analogue to downregulate PGE receptors in liver caused heterologous desensitization to various adenylate cyclase agonists, an event shown to be due to decreased availability of N_s (21). A similar observation has been reported in human fibroblasts (22). More recently, we used cultures of a transformed islet β -cell line, the HIT cell (23), to examine postreceptor consequences of PGE binding to β -cells (24,25). This cell line is a particularly attractive investigative tool both because it is comprised of a pure β -cell population and also because it responds with first-phase insulin responses to glucose and, in the presence of 3-isobutyl-1-methylxanthine (IBMX), has second-phase glucose-induced responses (24). Our experiments with HIT cells indicate that they synthesize PGE₂ and that PGE₂ is as effective as somatostatin and epinephrine in inhibiting cAMP generation and glucose-induced insulin secretion (Fig. 2; 25). This inhibition by PGE appears to depend on interactions with a PGE-specific receptor whose postbinding effects are at least partially mediated by N_i components of adenylate cyclase (25).

The theme running through these experiments is that PGE, and perhaps other eicosanoids, interact through specific receptors coupled to adenylate cyclase complexes (Fig. 1B) and thereby modulate secretory activity within the cell, which leads to the unanswered question of whether the binding site is on the external or the internal surface of the plasma membrane. Intuitively, it seems more plausible for such a site to be on the internal surface if it is to receive a locally synthesized eicosanoid. However, external binding sites might exist to receive eicosanoids transported to it by circulating cells, e.g., platelets or lymphocytes, which can synthesize eicosanoids. Such a hypothetical event needs to be carefully distinguished from the improbable one of eicosanoids reaching the external surface of the cell as free molecules within the systemic circulation. The concept of eicosanoid receptors having binding sites with orientations both outside and inside cells has also been advanced by investigators studying renal tubules (26). Whether intracellular PGE production and possible interactions with intracellularly oriented PGE receptors might play a role in amplifying the effects of other inhibitors of insulin secretion is another area for speculation. However, such a possibility is supported by an earlier report that drugs inhibiting prostaglandin synthesis can prevent the inhibitory effects of epinephrine on glucose-induced insulin secretion in human subjects (27).

Having touched on some of the newer information, much

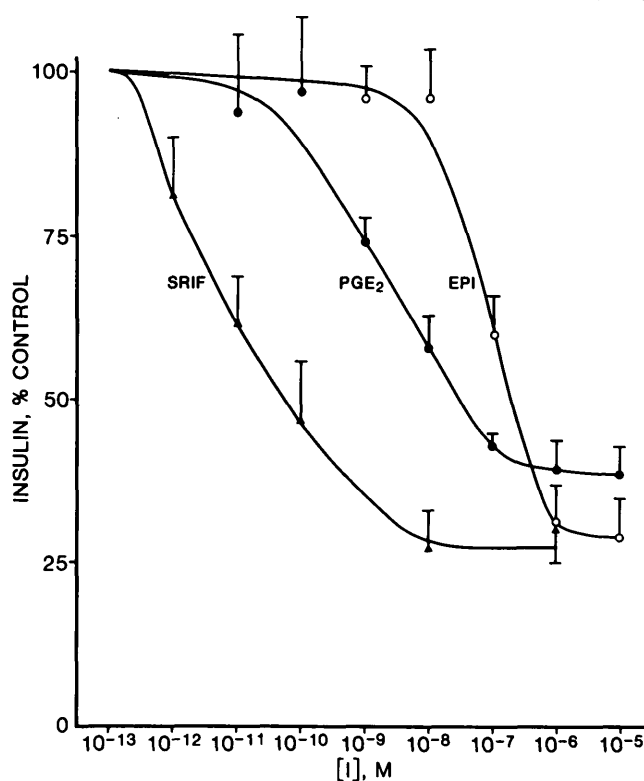


FIG. 2. Comparison of inhibitory effects of somatostatin (SRIF), PGE₂, and epinephrine (EPI) on glucose-induced insulin secretion from HIT cells, a clonal cell line of glucose-responsive transformed islet β -cells (25).

still unverified by separate groups of investigators, I direct my focus toward ideas that are strictly intuitive.

MODULATION OF BLOOD FLOW AND IMMUNE RESPONSES

I indicated that pancreatic islets have been reproducibly demonstrated to synthesize PGE₂, PGF_{2 α} , 6-keto-PGF_{1 α} , and 12-HETE. However, the data supporting modulating effects of PGF_{2 α} and PGI₂ on islet hormone secretion are not convincing. Are there other functions these two eicosanoids might serve? The former is known to cause vasoconstriction, whereas the latter causes vasodilation (as does PGE₂) in many different tissues. It therefore seems that vasoactive eicosanoids might modulate blood flow through the islets and thereby influence the rate of delivery of blood-borne substances to islet cells. Perhaps certain eicosanoids are preferentially synthesized by islet cells in specific situations to either augment or decrease the arrival and/or clearance of substrates, fuels, signals, hormones, and cells of the immune system. This consideration need not be limited to eicosanoids synthesized by islet cells. Other vasoactive eicosanoids not made by islets but brought to the islet by circulating cells potentially could have regulatory effects on blood flow to and within islets.

INTERACTIONS BETWEEN EICOSANOIDS AND CIRCULATING CELLS

Finally, there have been many reports that PGs and leukotrienes cause direct inflammatory effects and that the activity of other inflammatory substances may be mediated by ei-

cosanoids (for review, see ref. 28). It has been speculated by many investigators that PGE release from mitogen-stimulated lymphocytes may serve to provide counterregulation of lymphocyte function, because exogenous PGE can suppress mitogen stimulation of lymphocytes. On the other hand, reports that effects of interleukins and other cytokines may depend on local eicosanoid synthesis seem to be more frequent (29,30). Considering the increasing appreciation of the role of the immune system in the pathogenesis of diabetes, it is appropriate to wonder whether eicosanoids produced within the islet, or brought to it by circulating cells, might play diverse roles in autoimmune-related pancreatic islet β -cell injury in type I (insulin-dependent) diabetes mellitus. Such a hypothesis should not exclude possible roles of eicosanoids in type II diabetes mellitus. As mentioned in the beginning, drugs that inhibit synthesis of cyclooxygenase products partially restore absent first-phase glucose-induced insulin responses in type II diabetic patients. In the absence of evidence for interactions with cytotoxic lymphocytes or for an immune component to the pathogenesis of type II diabetes, this hypothesis would posit local overproduction or hypersensitivity to local eicosanoids in the pathogenesis of this syndrome.

CONCLUSION

Eicosanoids are synthesized by the pancreatic islet and by transformed β -cells. Products of the cyclooxygenase and lipoxygenase pathways, respectively, negatively and positively modulate glucose-induced insulin secretion. A putative mechanism of action for PGE₂ involves specific β -cell receptors coupled to N_i components of adenylate cyclase, whereby PGE₂ negatively modulates cAMP generation and glucose-induced insulin secretion. Theoretical functions of eicosanoids as regulators of islet blood flow and modulators of lymphocyte and cytokine activities in the islet have yet to be evaluated. My perspective is that eicosanoids are potentially important intracellular modulators of islet function. The inescapable challenge is to discover whether they play important roles in the pathophysiological condition known clinically as diabetes mellitus.

REFERENCES

1. Ebstein W: Zur Therapie des Diabetes Mellitus, insbesondere über die Anwendung des salicylsauren Natron bei demselben. *Klin Wochenschr* 13:337-40, 1876
2. Robertson RP, Chen M: A role of prostaglandin E in defective insulin secretion and carbohydrate intolerance in diabetes mellitus. *J Clin Invest* 60:747-53, 1977
3. Robertson RP: Arachidonic acid metabolite regulation of insulin secretion. *Diabetes Metab Rev* 2:261-96, 1986
4. Burr IM, Sharp R: Effects of prostaglandin E₁ and of epinephrine on the dynamics of insulin release in vitro. *Endocrinology* 94:835-39, 1974
5. Robertson RP, Gavareski DJ, Porte D Jr, Bierman EL: Inhibition of in vivo insulin secretion by prostaglandin E₁. *J Clin Invest* 54:310-15, 1974
6. Metz SA, Robertson RP, Fujimoto WY: Inhibition of prostaglandin E synthesis augments glucose-induced insulin secretion in cultured pancreas. *Diabetes* 30:551-57, 1981
7. Giugliano D, Di Pinto P, Torella R, Frascolla N, Saccomanno F, Passariello N, D'Onofrio F: A role for endogenous prostaglandin E in biphasic pattern of insulin release in humans. *Am J Physiol* 245:E591-97, 1983
8. Turk J, Colca JR, Kotagal N, McDaniel ML: Arachidonic acid metabolism in isolated pancreatic islets. II. The effects of glucose and of inhibitors of arachidonate metabolism on insulin secretion and metabolite synthesis. *Biochim Biophys Acta* 794:125-36, 1984
9. Giugliano D, Torella R, Improta L, D'Onofrio F: Effects of prostaglandin E₁ and prostaglandin F_{2 α} on insulin and glucagon plasma levels during the intravenous glucose tolerance test in man. *Diabetes Metab* 4:187-91, 1978
10. Spellacy WN, Bui WC, Holsinger KK: The effects of prostaglandin F_{2 α} and E₂ on blood glucose and plasma insulin levels during pregnancy. *Am J Obstet Gynecol* 111:239-43, 1971
11. Landgraf R, Landgraf-Leurs MMC: The prostaglandin system and insulin release: studies with the isolated perfused rat pancreas. *Prostaglandins* 17:599-613, 1979
12. Pek S, Tai T-Y, Elster A: Stimulatory effects of prostaglandins E-1, E-2, and F-2-alpha on glucagon and insulin release in vitro. *Diabetes* 27:801-809, 1978
13. Dembinska-Kiec A, Kostka-Trabka E, Grodzinska L, Zmuda A, Bieron K, Kedzior A, Ochmanski W, Zelazny T: Prostacyclin and blood glucose levels in humans and rabbits. *Prostaglandins* 21:113-21, 1981
14. Patrono C, Pugliese F, Ciabattini G, Di Blasi S, Pierucci A, Cinotti GA, Maseri A, Chierchia S: Prostacyclin does not affect insulin secretion in humans. *Prostaglandins* 21:379-85, 1981
15. Heaney TP, Larkins RG: The effect of prostacyclin and 6-keto-prostaglandin F_{1 α} on insulin secretion and cyclic adenosine 3',5'-monophosphate content in isolated rat islets. *Diabetes* 30:824-28, 1981
16. Metz S, Van Rollins M, Strife R, Fujimoto W, Robertson RP: Lipoxygenase pathway in islet endocrine cells. *J Clin Invest* 71:1191-205, 1983
17. Pek S, Tai TY, Elster A, Fajans SS: Stimulation by prostaglandin E₂ of glucagon and insulin release from isolated rat pancreas. *Prostaglandins* 10:493-502, 1975
18. Sacca L, Perez G: Influence of prostaglandins on plasma glucagon levels in the rat. *Metabolism* 25:127-30, 1976
19. Giugliano D, Torella R, Sgambato S, D'Onofrio F: Effects of alpha and beta adrenergic inhibition and somatostatin on plasma glucose, free fatty acids, insulin, glucagon, and growth hormone responses to prostaglandin E₁ in man. *J Clin Endocrinol Metab* 48:302-308, 1979
20. Robertson RP: Characterization and regulation of prostaglandin and leukotriene receptors: an overview. *Prostaglandins* 31:395-411, 1986
21. Garrity MJ, Andreasen RJ, Storm DR, Robertson RP: Prostaglandin E-induced heterologous desensitization of hepatic adenylate cyclase. *J Biol Chem* 258:8692-97, 1983
22. Kassis S, Fishman PH: Different mechanisms of desensitization of adenylate cyclase by isoproterenol and prostaglandin E₁ in human fibroblasts. *J Biol Chem* 257:5312-18, 1982
23. Santerre RF, Cook RA, Crisel RMD, Sharp JD, Schmidt RJ, Williams DC, Wilson CP: Insulin synthesis in a clonal cell line in simian virus 40-transformed hamster pancreatic beta cells. *Proc Natl Acad Sci USA* 78:4339-43, 1981
24. Hill RS, Boyd AE III: Perfusion of a clonal cell line of simian virus 40-transformed beta cells: insulin secretory dynamics in response to glucose, 3-isobutyl-1-methylxanthine, and potassium. *Diabetes* 34:115-20, 1985
25. Robertson RP, Tsai P, Little SA, Zhang H-J, Walseth TF: Receptor-mediated adenylate cyclase-coupled mechanism for PGE₂ inhibition of insulin secretion in HIT cells. *Diabetes* 36:1047-53, 1987
26. Garcia-Perez A, Smith WL: Apical-basolateral membrane asymmetry in canine cortical collecting tubule cells. *J Clin Invest* 74:63-74, 1984
27. Metz SA, Robertson RP: Prostaglandin synthesis inhibitors reverse alpha-adrenergic inhibition of acute insulin response to glucose. *Am J Physiol* 239:E490-500, 1980
28. Goetzl EJ, Scott WA III: Regulation of cellular activities by leukotrienes. *J Allergy Clin Immunol* 74:309-448, 1984
29. Kettelhut IC, Fiers W, Goldberg AL: The toxic effects of tumor necrosis factor in vivo and their prevention by cyclooxygenase inhibitors. *Proc Natl Acad Sci USA* 84:4273-77, 1987
30. Remick DG, Larrick JW, Nguyen DT, Kunkel SL: Stimulation of prostaglandin E₂ and thromboxane B₂ production by human monocytes in response to interleukin-2. *Biochem Biophys Res Commun* 147:86-93, 1987