The COX-2/PGE_2/EP3/$G_{i/o}$/cAMP/GSIS Pathway in the Islet: The Beat Goes On

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Interest in regulation of glucose-induced insulin secretion (GSIS) by arachidonic acid (AA) metabolites began in the early 1970s. The metabolite of primary interest has been prostaglandin E_2 (PGE_2) because it is one of several negative modulators of GSIS yet unique because it is not classified as a hormone, such as epinephrine or somatostatin. Rather, PGE_2 is considered an autocoid because it is a substance whose action takes place in the same cell as its synthesis, which in the case of the pancreatic β-cell suggests PGE_2 is an endogenous modulator of GSIS. This autocoid, produced via cleavage of AA from phospholipid and further metabolism by cyclooxygenase-2 (COX-2), is the most abundant AA metabolite in the β-cell. The article in this issue of *Diabetes* by Neuman et al. (1) takes a fresh look at this pathway by focusing on PGE_3, an alternate prostaglandin formed when eicosapentaenoic acid (EPA) rather than AA is used as the dominant dietary substrate. (Before reading further, it may be helpful to examine Table 1 of the article by Neuman et al., which identifies the players in this complex lexicon.) Clinical relevance of this consideration of the impact of a diet rich in EPA stems from the fact that this polyunsaturated fatty acid is proposed to be beneficial in chronic conditions such as diabetes.

Historically, long before the discovery of prostaglandins, Ebstein (2) reported in 1876 that treatment of his patients with diabetes with oral sodium salicylate reduced urinary glucose levels. It took nearly 100 years for the Nobel prize–winning work of Vane (3) and his colleagues to establish that nonsteroidal anti-inflammatory drugs, such as sodium salicylate, used inhibition of the COX-2 pathway as a major mechanism of action (4). At roughly the same time, several investigative groups were performing experiments in vitro with static incubation of isolated islets or in vivo by infusing PGE_2 in animals and humans (5–8) with variable and sometimes contrary results. The result of our own work found consistently that PGE_2 inhibited first-phase GSIS specifically and did not inhibit first-phase insulin release in response to nonglucose secretagogues (reviewed in Robertson [9]). The mechanism of action for this inhibitory effect was later discovered in 1987 to involve PGE_2-specific binding sites on the plasma membrane of isolated primary mammalian islets as well as the β-cell line HIT-T15, with its postreceptor (EP3) effect of pertussis toxin–sensitive $G_{i/o}$ protein activation and a decline of cAMP levels (10). Eighteen years later, Kimple et al. (11) published work studying PGE_1 rather than PGE_2 action in the Ins-1(832/13) β-cell–derived line and reported that the PGE_1 effect to inhibit GSIS was not pertussis toxin–sensitive. They identified $G\alpha_Z$ as the inhibitory G-protein involved in PGE_1 action in their cell line. More recent information using advanced molecular and genetics-based technology has confirmed the inhibitory effects of PGE_2 on β-cell structure and function (12,13).

The question asked by Neuman et al. (1) was whether shifting plasma membrane polyunsaturated fatty acid composition to favor EPA would alter prostaglandin production toward formation of PGE_3 and thereby diminish PGE_2 signaling and enhance β-cell function. The authors designed an extensive series of experiments featuring methodologies using BTBR wild-type mice, *Leptin*$^{ob/ob}$ (Ob) mice, and NOD mice; EPA-enriched diets; islet isolation and GSIS; lipid extraction and gas chromatography; cDNA synthesis and gene expression; islet imaging; and PGE_2 ELISA. They observed that an AA-enriched diet accelerated the development of diabetes, whereas the EPA-enriched diet shifted prostaglandin production to favor PGE_3 as opposed to PGE_2 and enhanced GSIS. Notably, they reported that both PGE_2 and PGE_3 reduced GSIS from BTBR-Ob islets in a dose-dependent manner but that the IC_{50} for this reduction was 10-fold weaker for PGE_3, the effects of both were fully competed by a specific EP3 antagonist, and the EPA-enriched diet also reduced EP3 gene expression fivefold. Other experiments examined the effects of interleukin-1β (IL-1β) on prostaglandin production in BTBR-Ob islets. The study by Neuman et al. confirmed

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earlier work that showed this cytokine increases COX-2 mRNA levels (14–16) but found uniquely that this effect was diminished by dietary EPA enrichment. The beauty of these experiments lies in the use of dietary manipulation to assess the pathophysiological role of PGE_2 in abnormal β-cell function in animal models of diabetes. This approach is more elegant than previously published work that was dependent on the use of pharmacological agents, such as nonsteroidal inflammatory drugs, which by their very nature are nonspecific tools. Dietary enrichment of EPA depends on substrate-driven enhancement of endogenous prostaglandins, which can be measured to document the magnitude of shift in product without concern for off-target effects of drugs that provide only nonspecific enzyme inhibition. In this sense, the work of Neuman et al. puts to rest any lingering doubt that PGE_2 is an endogenous inhibitor of GSIS.

Does this now mean that no work is left to be done in the research area of prostaglandins and islet function? Not at all. Quite the contrary. Development of therapeutic agents for humans with diabetes and abnormal β-cell function that will suppress inhibitory prostaglandins has not been robust. As illustrated in Fig. 1, there are many attack points that could be used to develop new β-cell–specific therapeutic agents that interrupt PGE_2 synthesis or antagonize the postreceptor actions of EP3, especially in states of inflammation that involve IL-1β and perhaps other cytokines that can harm islets. Further laboratory work with islets is needed to better characterize enzymatic pathways in the AA cascade to verify that the islet does or does not conform to conventional thinking about regulation of prostaglandin production. Very little is known about the final step in PGE_2 synthesis. In most cells, a set of proteins termed prostaglandin synthases are responsible for the final fine-tuning of the regulation of prostaglandins. Work in this area has indicated that generally regulation of PGE_2 in the basal state is regulated by the enzyme cPGES, whereas mPGES-1 regulates cytokine-stimulated PGE_2 production. However, we reported in a recent publication the unanticipated discovery that mPGES-1 mRNA and protein is absent in mouse, rat, and human islets (17). This leaves COX-2 itself as the sole regulator of PGE_2 synthesis, which carries the implication that drug discovery efforts designed to block PGE_2 synthesis should not focus on inhibiting mPGES-1 activity. Rather, pharmacological development of specific inhibitors of β-cell COX-2 that do not affect COX-2 in other cells is a goal that is much more likely to provide a drug that will benefit people with type 2 diabetes and intrinsically impaired GSIS as well as that induced by cytokines. So, I invite you to listen to this developing story as the beat goes on.

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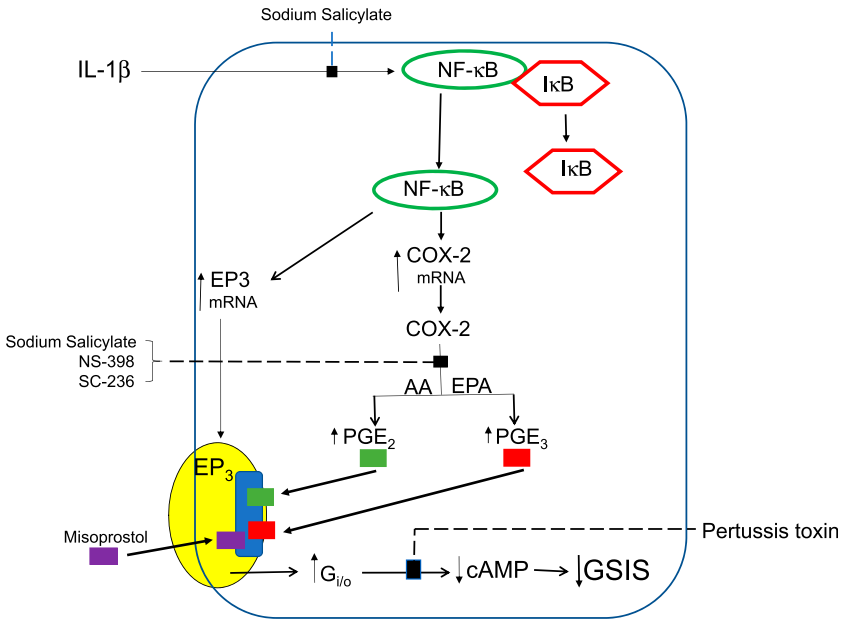

Figure 1—The COX-2/PGE_2/EP3/$G_{i/o}$/cAMP/GSIS pathway in the β-cell. The mechanism for IL-1β stimulation of PGE_2 synthesis is via increasing COX-2 mRNA and protein levels, which in the presence of AA increase synthesis of PGE_2, which in turn binds to its receptor EP3. The postreceptor mechanism of action for EP3 is mediated by an increase in $G_{i/o}$ activity, which in turn decreases intracellular cAMP levels with a consequent decrease in GSIS. When EPA rather than AA is the dominantly available substrate, PGE_3 rather than PGE_2 synthesis is favored. PGE_3 has only one-tenth of the PGE_2 efficacy to decrease GSIS (1). NS-398 and SC-236 are COX-2 inhibitors. Misoprostol is an EP3 agonist. Information taken from Robertson et al. (10), Tran and colleagues (14,15), and Seaquist and colleagues (18,19). IκB, inhibitor of κB; NF-κB, nuclear factor-κB.

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References

1. Neuman JC, Schaid MD, Brill AL, et al. Enriching islet phospholipids with eicosapentaenoic acid reduces prostaglandin E_2 signaling and enhances diabetic β-cell function. Diabetes 2017;66:1572–1585

2. Ebstein W. Zur therapei des diabetes mellitus insbesondere uber die anwendung des salicylsauren natron bei demselben. Klin Wochenschr 1876;13: 337–340

3. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol 1971;231:232–235

4. Metz SA, Robertson RP, Fujimoto WY. Inhibition of prostaglandin E synthesis augments glucose-induced insulin secretion is cultured pancreas. Diabetes 1981;30:551–557

5. Bressler R, Vargas-Cord M, Lebovitz HE. Tranylcypromine: a potent insulin secretagogue and hypoglycemic agent. Diabetes 1968;17:617–624

6. Spellacy WN, Buhi WC, Holsinger KK. The effect of prostaglandin F 2 and E 2 on blood glucose and plasma insulin levels during pregnancy. Am J Obstet Gynecol 1971;111:239–243

7. Johnson DG, Fujimoto WY, Williams RH. Enhanced release of insulin by prostaglandins in isolated pancreatic islets. Diabetes 1973;22:658–663

8. Robertson RP, Chen M. A role for prostaglandin E in defective insulin secretion and carbohydrate intolerance in diabetes mellitus. J Clin Invest 1977;60: 747–753

9. Robertson RP. Arachidonic acid metabolite regulation of insulin secretion. Diabetes Metab Rev 1986;2:261–296

10. Robertson RP, Tsai P, Little SA, Zhang HJ, Walseth TF. Receptor-mediated adenylate cyclase-coupled mechanism for PGE_2 inhibition of insulin secretion in HIT cells. Diabetes 1987;36:1047–1053

11. Kimple ME, Nixon AB, Kelly P, et al. A role for G_Z in pancreatic islet β-cell biology. J Biol Chem 2005;280:31708–31713

12. Oshima H, Taketo MM, Oshima M. Destruction of pancreatic β-cells by transgenic induction of prostaglandin E2 in the islets. J Biol Chem 2006;281: 29330–29336

13. Meng Z, Lv J, Luo Y, et al. Forkhead box O1/pancreatic and duodenal homeobox 1 intracellular translocation is regulated by c-Jun N-terminal kinase and involved in prostaglandin E2-induced pancreatic β-cell dysfunction. Endocrinology 2009;150:5284–5293

14. Tran POT, Gleason CE, Poitout V, Robertson RP. Prostaglandin E(2) mediates inhibition of insulin secretion by interleukin-1beta. J Biol Chem 1999;274: 31245–31248

15. Tran PO, Gleason CE, Robertson RP. Inhibition of interleukin-1β-induced COX-2 and EP3 gene expression by sodium salicylate enhances pancreatic islet β-cell function. Diabetes 2002;51:1772–1778

16. Heitmeier MR, Kelly CB, Ensor NJ, et al. Role of cyclooxygenase-2 in cytokine-induced beta-cell dysfunction and damage by isolated rat and human islets. J Biol Chem 2004;279:53145–53151

17. Parazzoli S, Harmon JS, Vallerie SN, Zhang T, Zhou H, Robertson RP. Cyclooxygenase-2, not microsomal prostaglandin E synthase-1, is the mechanism for interleukin-1β-induced prostaglandin E2 production and inhibition of insulin secretion in pancreatic islets. J Biol Chem 2012;287: 32246–32253

18. Seaquist ER, Walseth TF, Nelson DM, Robertson RP. Pertussis toxin–sensitive G protein mediation of PGE_2 inhibition of cAMP metabolism and phasic glucose-induced insulin secretion in HIT cells. Diabetes 1989;38:1439–1989

19. Seaquist ER, Neal AN, Shoger KD, Walseth TF, Robertson RP. G-proteins and hormonal inhibition of insulin secretion from HIT-T15 cells and isolated rat islets. Diabetes 1992;41:1390–1399