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The role of the prostaglandin PGE2 in pancreatic β-cell death in the context of type 2 diabetes

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Abstract

Type 2 diabetes (T2DM) could be a complex disease characterized by β-cell failure within the setting of insulin resistance. The underlying causes of β-cell failure are complex and result from the interplay between genetic and environmental factors. Consumption of foods high in saturated fatty acids (FFAs) and also the elevation of circulating FFAs are implicated as a crucial causative link among obesity, insulin resistance and β-cell dysfunction. Moreover, cumulative evidence indicates that there's a decrease in β-cell mass thanks to β-cell death in T2DM patients. FFAs can induce β-cell death by apoptosis, even within the absence of high glucose, whereas unsaturated fatty acids are usually protective. Several mechanisms are implicated in palmitate-induced β-cell death, including ceramide formation resulting in altered lipid partitioning, oxidative stress, and inflammation. Mild inflammation has been suggested to play a job within the pathogenesis of T2DM. Another family of molecules involved in inflammation is prostaglandins, but their role within the development of T2DM is poorly understood. this research aims at understanding the impact of prostaglandins (PGE2) on β-cell death.

We show that PGE2-induced apoptosis is mediated by p38MAPK. To further elucidate the downstream signaling pathway of prostaglandins in β-cells, we studied the differential expression of PGE2 receptors (EP1-EP4) and located that the EP3 receptor is differentially upregulated in islets from T2DM patients. the importance of this receptor in β-cell apoptosis was tested by using EP3 specific siRNA or EP3 antagonist, and located that they led to a big rescue of those cells from apoptosis. In comparison to the opposite PGs, the role of PGE2 in β-cell function has been studied in greatest detail. this might stem from early reports demonstrating that the AA metabolite chargeable for decreased insulin secretion was PGE2 (Robertson 1988). However, several groups have called into question the solely inhibitory effect of PGE2 on insulin secretion. There are numerous lines of evidence in support of an inhibitory role of PGE2 on β-cell function in β-cell lines, isolated islets, and in vivo. In vitro studies have demonstrated that PGE2 treatment decreases GSIS in several different β-cell lines, including the HIT-T15, βHC13, and INS-1 (832/3) lines (Kimple et al. 2013; Meng et al. 2009; Robertson et al. 1987; Seaquist et al. 1989). Early studies within the HIT line demonstrated that the action of PGE2 to inhibit GSIS is mediated by a pertussis toxin (PTx)-sensitive mechanism leading to decreased cAMP levels (Robertson et al. 1987; Seaquist et al. 1989). PTx blocks the action of inhibitory G proteins, excluding GαZ, by ADP-ribosylation on a critical cysteine residue (Fields and Casey 1997). PTx was originally called islet-activating protein (IAP) because of its ability to reverse α-adrenergic inhibition of cAMP and to boost insulin secretion from islets (Yajima et al. 1978). Since EP3 is that the only PGE2 receptor that couples to Gi proteins, these data suggest that EP3 is that the receptor chargeable for this negative regulation of GSIS. PGE2 also facilitates the inhibitory effect of IL-1β on GSIS in vitro (Tran et al. 1999), providing further evidence in support of an inhibitory role of PGE2 on insulin secretion. Two structurally different COX-2 inhibitors were ready to reverse the decreased GSIS in response to IL-1β treatment in HIT-T15 and βHC13 lines partly by decreasing PGE2 production. When exogenous PGE2 was added back to those cells, GSIS was yet again decreased. The mechanism of action wasn't determined but the authors predicted that PGE2 signaling through the EP3 receptor is to blame for the observed decrease in GSIS (Tran et al. 1999).

Many of the in vitro data described above are mirrored in in vivo settings and in isolated islets. Intravenous infusion of PGE2 decreased circulating insulin levels and GSIS in vivo in early studies using animal models and humans (Giugliano et al. 1983; Robertson et al. 1974; Sacca et al. 1975). As discussed previously, Burr and Sharp demonstrated that PGE1 inhibited both first and second phases of GSIS in isolated rat islets in 1974 (Burr and Sharp 1974). PGE2 differs from PGE1 in terms of side chain unsaturation: PGE1 contains one covalent bond whereas PGE2 has two double bonds (Speroff and Ramwell 1970); both PGE1 and PGE2 can act as agonists for the EP receptors (Breyer et al. 2001). the consequences of PGE on insulin secretion were confirmed in later studies within which isolated rat islets (Meng et al. 2009; Meng et al. 2006; Metz et al. 1981; Sjoholm 1996; Tran et al. 2002) or mouse islets (Meng et al. 2009; Parazzoli et al. 2012) were incubated within the presence of PGE2 and demonstrated again that PGE2 treatment decreases GSIS. In rat islets, treatment with anodyne, a anti-inflammatory drug, decreased PGE2 production and augmented GSIS (Metz et al. 1981). However, in

contrast to what was observed in cell lines, inhibition of GSIS by PGE2 wasn't reversed upon PTx treatment (Sjoholm 1996). this could be explained by PGE2 signaling through the PTx-insensitive inhibitory G protein, GαZ, discussed in additional detail below. PGE2 also mediates the negative effect of IL-1β on GSIS in isolated rat islets (Tran et al. 2002), as was described in β-cell lines above. Here, treatment of isolated islets with pain pill blocked the IL-1β-induced decrease in GSIS (Tran et al. 2002). PGE2 also affects β-cell function in vivo in mice. Increased production of PGE2 in vivo leads to hyperglycemia and impaired glucose homeostasis during a transgenic mouse model (Oshima et al. 2006).

When COX-2 and therefore the microsomal PGE2 synthase-1 (mPGES-1) were overexpressed in mouse β-cells as how to induce PGE2 production, homozygous mice developed chronic hyperglycemia beginning at six weeks old (Oshima et al. 2006). Heterozygous mice were euglycemic but displayed impaired glucose homeostasis because of a decrease in plasma insulin levels during an IP-GTT (Oshima et al. 2006). Thus, in many various experimental paradigms, PGE2 decreases GSIS.

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