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Producing insufficient insulin yet diabetic? Your pancreatic beta-cells have changed the major signaling pathway

Diabetes Mellitus, or simply diabetes, is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Majorly classified as either type1(T1DM) or type 2 (T2DM), the latter accounts for over 90% of all diabetes cases. Insulin is a hormone that regulates blood glucose. It is produced by pancreatic beta (ß) cells of the Islets of Langerhans. Glucose homeostasis is achieved by tight regulation of insulin secretion from pancreatic ß cells in response to various physiological factors, including nutrients and hormonal and neuronal inputs. Of these factors, glucose is the primary initiator of insulin secretion. Glucose-induced insulin secretion (GIIS) occurs through a sequence of precisely regulated events in pancreatic ß cells. Transport of glucose into ß cells and enhanced glucose metabolism increase the ATP/ADP ratio, thereby closing the ATP-sensitive K+ (K_{ATP}) channels. As K_{ATP} channel activity maintains a negative resting membrane potential, closure of the channels causes membrane depolarization and activates voltage-dependent Ca^{2+} channels (VDCCs), thereby leading to insulin release. The K_{ATP} channels thus play a crucial role in linking the ß cell's metabolic status to its electrical activity for the release of insulin. GIIS is amplified by hormones and neurotransmitters. Many of these function by activation of the trimeric G proteins Gs and Gq. Among them, the incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which are released by gut cells following meal ingestion, are critical for preventing postprandial hyperglycemia by amplifying insulin secretion in a glucose concentration–dependent manner. This is called "the incretin effect". In non-diabetic subjects, the incretin effect is responsible for 50-70% of insulin release during oral glucose administration, with GIP contributing about 60% of the direct incretin effect on ß cells. In type 2 diabetes patients, although the incretin effect is impaired and contributes to only 20-35% of the insulin response to oral glucose, the response to GIP is almost completely lost whereas that of GLP-1 is largely preserved. Moreover, Asian T2DM patients, a majority in the world, exhibit retained incretin effect. Using this glucose-dependent effect, and the unique therapeutic potential of GLP-1, incretin-based drugs such as dipeptidyl peptidase-4 (DPP-4) inhibitors and GLP-1 receptor agonists (GLP-1RAs) have been developed and are increasingly used worldwide for diabetes therapy. However, the reason why only GLP-1–based drugs are effective in improving insulin secretion after presentation of diabetes has not been resolved. We generated ß cell–specific K_{ATP} knock out mice (ß*Kcnj11*$^{-/-}$ mice) to enable clarification of the direct role of the ß cell K_{ATP} channel in insulin secretion and glucose homeostasis. These mice exhibited severe glucose intolerance and impaired GIIS, defects that can be corrected by GLP-1, but not by GIP, indicating that the ß*Kcnj11*$^{-/-}$ mouse is a useful model for studying the mechanisms underlying the differential effects of GLP-1 and GIP in insulin secretion in diabetes, as the model presents with features remarkably similar to humans who develop T2DM. In addition to studying ß*Kcnj11*$^{-/-}$ mice, we examined various in vivo and ex vivo models that mimic the inactive state of K_{ATP} channels in ß cells. We found that persistent depolarization induces a switch from Gs to Gq signaling in ß cells in these models and that similar changes are induced in human islets by conditions emulating diabetes. We propose that this switch accounts for the clinical observation that GLP-1 but not GIP is effective in T2DM.