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Beta-cell Ion Channels and Their Role in Regulating Insulin Secretion

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Abstract

Beta cells of the pancreatic islet express many different types of ion channels. These channels reside in the β-cell plasma membrane as well as subcellular organelles and their coordinated activity and sensitivity to metabolism regulate glucose-dependent insulin secretion. Here, we review the molecular nature, expression patterns, and functional roles of many β-cell channels, with an eye toward explaining the ionic basis of glucose-induced insulin secretion. Our primary focus is on K_{ATP} and voltage-gated Ca^{2+} channels as these primarily regulate insulin secretion; other channels in our view primarily help to sculpt the electrical patterns generated by activated β-cells or indirectly regulate metabolism. Lastly, we discuss why understanding the physiological roles played by ion channels is important for understanding the secretory defects that occur in type 2 diabetes.

Introduction

The islets of Langerhans are endocrine microorgans that are embedded in the larger exocrine pancreas (211). The approximately one million islets that reside within a typical human pancreas constitute a very small percentage of the total volume of the organ [~1%; (102)], while most of the organ is made of acinar and ductal tissue. Within an islet are several different types of endocrine cells. While insulin-secreting β-cells make up the majority (~80% in mice and ~50% in humans), islets also possess glucagon-secreting α-cells (~15% in mice and ~40% in humans), somatostatin-secreting δ-cells (~5% in mice and ~10% in human), ε-cells and PP-cells, which secrete ghrelin and pancreatic polypeptide, respectively (41, 44, 119, 120, 198). Mouse islets, which are a standard experimental model have a β-cell-rich core surrounded by a mantle of mainly α-cells (44, 139, 265). In contrast, human islets have a more random distribution of cells throughout the islet mantle and core (44, 139, 265). As the focus of this article is the pancreatic β-cell, interested readers may wish to consult recent reviews that focus on other islet cell types (95, 229, 297). To be clear, at the onset the focus of this article is not on all β-cell ion channels, but only those which have been shown to play a clear functional role. A list of the ion channels known to be involved

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in β-cell electrical activity and potentially in the control of insulin secretion can be found in Table 1. We also wish to apologize in advance to colleagues whose work is not fully discussed in the present article due to limitations of space.

The β-cell synthesizes and secretes insulin in response to a glucose challenge. Thus, when plasma glucose concentration rises after a meal, for instance, glucose is first transported into the β-cell via specialized glucose transporter(s) molecules [GLUT1 and GLUT2 in humans, GLUT2 exclusively in mice (100, 171, 278)]. Once in the cytosol, glucose is phosphorylated by glucokinase and glycolysis and cellular respiration occur, leading to increased ATP production and, concomitantly, a rise in cytoplasmic ATP/ADP (1, 9, 70, 135). Increased ATP/ADP leads to the closure of ATP-sensitive K^+ channels (K_{ATP}) and subsequently, membrane depolarization, as the conductance of the β-cell plasma membrane to K^+ ions is dominated by the resting K^+ conductance of these channels, gK_{ATP}. Closing K_{ATP} channels, in turn, leads to the opening of voltage-gated Ca^{2+} channels as the membrane potential of the β-cells depolarizes toward −40 mV. The opening of these channels in turn mediates an increase in Ca^{2+} influx due to Ca^{2+}'s strong electrochemical gradient, resulting in a rise in the cytosolic Ca^{2+} concentration. As the exocytosis of insulin granules is Ca^{2+}-dependent, the secretion of insulin results (237, 238).

Insulin is stored within the β-cell in large dense-core secretory granules, in complex with zinc, and there are estimated to be approximately 15,000 granules in a typical β-cell (67, 197). Somatostatin, a hormone which is secreted by islet δ-cells inhibits insulin secretion, while glucagon, which is synthesized and secreted by islet α-cells potentiates insulin secretion by raising cytosolic cAMP (235, 250, 266, 269).

Before discussing the critical role played by different β-cell ion channels in the regulation of insulin secretion, we will digress for a moment to consider some unique aspects of the β-cell as compared to other cells.

In most cells, glucose is metabolized to supply the cell with sufficient chemical energy (in the form of ATP) to fuel general as well as more cell-specific functions. While this also occurs in β-cells, the β-cell not only uses glucose as a *fuel* but as a specific *signal* to trigger insulin secretion. This is very different from the situation in neurons, for instance, where the neuron is stimulated not by fuels but by the release of excitatory neurotransmitters from the presynaptic terminals of neighboring neurons. While β-cells also have cell surface receptors for acetylcholine, ATP, glutamate, and other signaling molecules (these all being "excitatory"), the occupation of these receptors by their ligands is not required for glucose-induced insulin secretion, as glucose itself is the primary β-cell secretagogue. Indeed, the actions of nearly all β-cell modulators are potentiated by elevated glucose (242).

K_{ATP} Channels Are the Primary Ion Channel Regulators of β-cell Electrical Activity

The modulation of ATP-sensitive K^+ channel (K_{ATP}) activity by fuel metabolism is the primary means by which β-cell electrical activity is coupled to glucose-induced changes in intracellular ATP/ADP (5, 190). This is because changes in K_{ATP} conductance, balanced

against the cell's resting ionic leak conductance determines the β-cell membrane potential (59).

When measured in excised membrane patches from β-cells in symmetrical K^+ concentrations, K_{ATP} was shown to be a 50 pS, weakly inwardly rectifying K^+ channel (7, 281). K_{ATP} channel inhibition by increased ATP/ADP is manifested by an increase in mean channel closed time as ATP rises, and a decrease in mean open time as ADP falls (190, 231); there is also a decrease in channel opening frequency as ATP/ADP increases. It is trivial to show that as mean open time (MOT) decreases and mean closed time (MCT) increases, the steady state open probability (Po) is reduced, as Po is equal to MOT/[MCT+MOT]. Thus, reducing Po depolarizes the β-cell away from E_K [e.g. ≈ −70 mV, as set by Nernst; (244)] toward the value of the leak potential, which is more depolarized; it is to this new battery potential that the membrane potential heads when K_{ATP} closes (for full discussion, see Ref. 59). The β-cell leak conductance may in aggregate include open voltage-gated Ca^{2+} channels, activated nonselective cation channels such as TRP or SOCE channels, a resting sodium leak (270), and electrogenic pump currents, as long as they are net depolarizing (5, 20, 59, 84, 104, 141). The depolarizing reversal potential of islet Cl^- channels could also contribute to the overall leak and depolarization to the voltage of the plateau phase (141). Our long experience studying mathematical models of β-cell electrophysiology clearly shows that β-cells are very sensitive to the value of the leak conductance that is chosen. Studying the leak conductance experimentally, however, is difficult because given the high input resistance (or low input conductance) of β-cells, which occurs when K_{ATP} channels are maximally inhibited or closed (11, 219), leak currents can be very small, on the order of 1 pA or less, which is near the limit of resolution of the patch clamp.

Two other considerations are worth noting when discussing the K_{ATP} channels of β-cells. First, calculations made over 30 years ago by Cook and colleagues showed that there are so many K_{ATP} channels in the β-cell plasma membrane that the membrane potential would not be predicted to even *begin* to depolarize (as glucose and ATP/ADP rise) until >90% of the K_{ATP} channels are shut, assuming that a typical β-cell has 15,000 pS of K_{ATP} conductance and 10 pS of leak; these authors called this the "Spare Channel Model" (59). While this simple model did not incorporate ADP activation of K_{ATP} channels (73, 130) or the possibility of ATP subdomains just under the plasma membrane (135), the calculation successfully explained why β-cells would not be persistently depolarized even assuming K_{ATP} channels have an IC50 of 15 μM in excised outside-out patches and are exposed to bulk cytosolic ATP levels in the range of 3–5 mM. The main point of the model was that even when most of the β-cell's K_{ATP} channels were bound by ATP (and thus closed), the cell membrane would still be relatively hyperpolarized nonetheless and that only after closing the last few percent of open K_{ATP} channels would the cells depolarize significantly in response to glucose (59). Barg et al. (15) estimated there are about 7000 KATP channels in a single β-cell, yielding a maximum whole-cell conductance of about 140,000 pS (assuming a single-channel conductance of 20 pS). This suggests that the probability of opening (Po) of K_{ATP} rarely exceeds 0.1.

Subsequent to studies functionally characterizing the channel, biochemical and cloning work revealed that two protein subunits constituted the channel: an inward rectifying Kir6.2

subunit (*KCNJ11)* and an ATP-binding cassette transporter family member, called SUR1 for sulfonylurea receptor 1 (*ABCC8*). Structural characterization of the channel showed that it is an octameric complex made up of four pore-forming Kir6.2 subunits and four regulatory SUR1 subunits arranged around a central pore (54, 260). Each SUR1 protein interacts with the first transmembrane domain of Kir6.2 via its amino-terminal transmembrane domain (TMD0), which is connected to the ABC transporter core structure of SUR1. This consists of two transmembrane domains and two nucleotide-binding domains (NBDs) that are connected via an intracellular loop (L0). Recent work from two different groups using cryo-EM has produced an elegant three-dimensional reconstruction of the channel, as described in Refs 157, 169.

Intracellular adenine nucleotides regulate both Kir6.2 and SUR1 activity. In the absence of Mg^{2+}, nucleotides inhibit the K_{ATP} channel activity by binding to a nucleotide-binding pocket formed between the amino and carboxy-terminal domains of two adjacent Kir6.2 subunits (190). In addition, ADP activation of the channel occurs via its interactions with the two Walker consensus domains of SUR1, as well as phosphorylation sites that in turn regulate K_{ATP} activity. Readers interested in a more detailed discussion of K_{ATP} channel gating are referred to Refs 6, 190. Furthermore, both gain and loss of function mutations in K_{ATP} have been linked to persistent hyperinsulinemic hypoglycemia of infancy [or PHHI; (48)] and neonatal diabetes [or NDM; (13, 218)]; details of these mutations are beyond the scope of the present article. However, the impact of these mutations in either SUR1 or Kir6.2 highlights that K_{ATP} is a critical regulator of insulin secretion, as gain of function mutations lead to insufficient insulin secretion and neonatal diabetes, and loss of function mutations produce excessive secretion and hypoglycemia (87, 277). In terms of the clinical significance of K_{ATP} pharmacology to type 2 diabetes, K_{ATP} was shown decades ago to be blocked by sulfonylureas [ligands to the sulfonylurea receptor; (103, 174)] as well as glinides (163), two different classes of oral medications used historically in the case of first-generation sulfonylureas to treat type 2 diabetes because of their powerful actions as insulin secretagogues.

More recent work in the field suggests that besides the acute regulation of K_{ATP} channel gating by changes in cytosolic ATP/ADP due to fuel metabolism, hormones such as leptin (53, 202) or insulin (137) as well as chronic glucose (88) can regulate the number of K_{ATP} channels resident on the β-cell surface. These perturbations have been shown to result from modulation of K_{ATP} trafficking from endosomal sites within the cell to the plasma membrane where they are electrophysiologically active (168). This is an entirely new form of K_{ATP} channel regulation and while it is doubtful that glucose-induced changes in K_{ATP} trafficking supersede in importance the modulation of K_{ATP} channel gating by glucose metabolism and ATP/ADP (98), this is a fascinating new area of K_{ATP} research, and it well justifies more research.

Voltage-gated Ca^{2+} Channels (VGCCs)

In response to β-cell depolarization due to K_{ATP} closure, VGCCs open and electrical bursting commences (68). Bursting consists of spontaneous slow plateau depolarizations with superimposed trains of rapid spikes that are believed to mediate the patterns of Ca^{2+}

entry that drive pulsatile insulin exocytosis. This basic pulsatility is necessary for proper insulin action (238). VGCCs mediate the upstroke of the β-cell spikes and the regularly occurring and Ca-dependent slow plateau depolarizations (57, 60). Furthermore, blocking VGCCs pharmacologically inhibits insulin secretion under most cases (243).

VGCCs can be broadly separated into two different functional classes: high voltage-activated (HVA) channels that open in response to a large membrane depolarization, and low voltage-activated (LVA) channels that are activated by smaller voltage excursions, typically depolarizations not far from the β-cell silent phase potential (47, 97). HVA Ca^{2+} channels can undergo Ca^{2+}- and/or voltage-dependent inactivation, where the channel can enter a refractory gating state wherein it is unable to pass Ca^{2+}. For L-type Ca^{2+} channels, the most typical type of inactivation is where Ca^{2+} entering the cell through the open channel binds to calmodulin residues on the carboxy-terminal of the α subunit, mediating inactivation (105, 123). This type of inactivation occurs over 10s of milliseconds and is strikingly slowed by the replacement of Ca^{2+} with Ba^{2+} as the charge carrier (241).

While the L-type Ca^{2+} channel was the first VGCC to be functionally characterized, later studies using careful pharmacological as well as biophysical dissection of HVA current revealed not only L-type channels, the subtype modified by dihydropyridine drugs such as nifedipine; but N-type channels, which are blocked by omega conotoxin from the snail Conus (282); and P/Q-type, which are blocked by the funnel-web spider toxin, agatoxin-V (161); and an R-type (for “residual”) for which no clear selective blockers have been identified (217), although R-type can be inhibited by SNX-482 along with other Ca^{2+} channels (4, 188). While all of these channels can coexist in the same cell, sometimes in different proportions, and while all of them can bring Ca^{2+} into the cell, the extent of their coupling to insulin granule exocytosis may differ based on their proximity to hormone granule release sites or due to differences in their channel kinetics (243).

In Cav3.2 channels (referred to as LVA or T-type Ca^{2+} channels) replacing Ca^{2+} with Ba^{2+} does not alter the fast inactivation kinetics observed (282), as T-type channel inactivation is a purely voltage-activated process, resembling the inactivation of voltage-gated Na^{+} channels. Here fast inactivation occurs largely because of interactions of charged residues into the pore to occlude channel gating from the inside face of the membrane (107).

The types of Ca^{2+} channels expressed in β-cells depends on the species

In mouse islets, one of the most well-studied experimental preparations, the major high voltage-activated Ca^{2+} channel of β-cells is the L-type channel (237, 258). The L-type channel is closely tied to insulin secretion, as its blockade by dihydropyridines such as nifedipine or nimodipine profoundly suppresses GSIS (106, 192) and blocks or at least largely curtails islet bursting. The L-type channel is also functionally important in rat (83) and human β-cells (36, 227), but besides this channel, rat β-cells express T-type LVA channels. T-type channel activity in the β-cells of these preparations not only bring in Ca^{2+} but also augment the amplitude of membrane depolarization to facilitate the opening of L-type channels (27), likely because of their fast rate of voltage-dependent activation (however, they inactivate more quickly, too) and low activation threshold. However, progress in understanding the detailed role of T-type channels has been hampered by the lack of

sufficiently specific drugs or toxins to target T-type channels). The available evidence suggests that interfering with T-type channels reduces insulin secretion in human and rat β-cells (64, 183).

Molecular structures

L-type channels exist as a complex of several different subunits: a pore-forming α1 subunit, a disulfide-linked $\alpha_2\delta$ dimer, an intracellular β subunit, and a transmembrane γ subunit. The α_1 subunit is composed of four repeating homologous domains (I to IV) each containing six transmembrane segments (S1 to S6), a pore loop (P-loop) between the S5 and S6 segments, and three intracellular linkers (303). The P-loops form the lining of the aqueous pore and contain either four glutamic acid residues (in high voltage-activated VGCCs) or two glutamic acid and two aspartic acid residues (in low voltage-activated VGCCs); these constitute the Ca^{2+} channel selectivity filter (236, 271). The voltage sensors of the VGCCs are made up of charged amino acid residues, primarily within the S4 segment which create charge movement and lead to channel opening in response to depolarization of the membrane potential (303). The auxiliary subunits of the channel are involved in channel trafficking to the cell surface and also modify the biophysical and pharmacological properties of the channel (50). In neurons, the $\alpha_2\delta$ subunit has been shown to regulate Ca^{2+} channel density at the synapse and it also helps promote assembly of the channel (114). Genetic ablation of $\alpha_2\delta{-}1$, the dominant $\alpha_2\delta$ subunit in pancreatic β-cells, causes a 50% reduction in Ca^{2+} current amplitude, reduced insulin secretion, glucose intolerance, and diabetes suggesting an important role for $\alpha_2\delta$ in β-cells (170).

The various HVA VGCCs that play significant roles in GSIS by mediating Ca^{2+} entry include L-type channels (Cav1.2/*CACNA1C* and Cav1.3/*CACNA1D*), P/Q-type (Cav2.1/*CACNA1A*), N-type (Cav2.2/*CACNA1B*), and R-type (Cav2.3/*Cacna1e*). For LVA or T-type VGCCs, Cav3.1/*CACNA1G* and Cav3.2/*CACNA1H* are expressed (303). The relative levels of expression of each of the channel isoforms, and the activity of each varies depending on the species (303). The different VGCCs can be identified and classified by their different biophysical properties and the effects of differential pharmacological inhibitors on their activity.

L-type Ca^{2+} channels activate near −50 mV and reach maximal activation near 0 mV. They exhibit slow inactivation and are modified by dihydropyridines drugs (DHPs) that alter their gating modes (106, 192), or by phenylalkylamine or benzothiazepine blockers that cause use-dependent channel blockade (111). In β-cells, whole-cell L-type VGCC currents were first reported in cultured neonatal rat pancreatic β-cells (239). Since their initial characterization, VGCCs have been studied in a wide range of insulin-secreting cell lines (115, 243) and primary β-cells from many species (18, 113, 142, 184, 225). The L-type VGCC generally comprises the majority of VGCC current in most of the species where it has been quantitatively examined (237, 258).

Mouse β-cells express two L-type subtypes Cav1.2 and Cav1.3 (186, 251, 298). Cav1.2 has been reported to be the primary L-type isoform for VGCC current as its genetic ablation results in the near complete loss of DHP-sensitive L-type Ca^{2+} current (251). Furthermore, mutant mouse β-cells expressing a DHP-resistant variant of Cav1.2 had no residual, DHP-

sensitive Ca^{2+} current (159, 160). It has been estimated that approximately 60% to 80% of glucose-induced insulin secretion can be attributed to the activation of L-channels (64, 194, 251). Cav1.2 plays an especially prominent role in triggering first phase insulin secretion in mouse islets, as its inhibition drastically reduces first phase secretion (251).

The role of Cav1.3 in β-cells has been more controversial. Some groups have reported that L-type channel blockers have no effect on the residual Ca^{2+} current observed in mouse β-cells lacking Cav1.2, and additionally, had difficulty confirming Cav1.3 immunoreactivity (16, 251). However, in contrast, other groups found that mouse β-cells express Cav1.3 mRNA and protein and that knocking out Cav1.3 resulted in a compensatory overexpression of Cav1.2 and reduced basal insulin secretion (186) that Cav1.3 plays a role in mediating basal insulin secretion, although more work needs to be done to verify this hypothesis. However, other groups have shown that there are more Cav1.3 than Cav1.2 mRNA in human β-cells (36) which, combined with the reported shift in total Ca^{2+} current activation toward more negative voltages (34, 147), suggests that Cav1.3 likely plays a more significant role in human β-cells.

P/Q-type VGCC in β-cells

As stated above, L-type channels carry the majority of Ca^{2+} current in β-cells. However, DHPs and other CCBs do not fully block total Ca^{2+} current in most β-cell preparations (212, 232, 251, 261). P/Q-type channels were reported in mouse β-cells following pharmacological inhibition of competing HVA currents (251). Thus, using a mixture of isradipine, a DHP that blocks L-type VGCCs, and the R-type blocker SNX482, Cav current was reduced by about 80% but was still not fully eliminated. The subsequent addition of ω-agatoxin, a specific inhibitor of P/Q-type channels isolated from the funnel-web spider, blocked nearly all of the remaining Cav current (251). P/Q-type channels rapidly activate near −30 mV, reach a peak amplitude at about +10 mV and exhibit slow inactivation (158). P/Q-type channels are encoded by the *CACNA1A* gene (50).

Rat β-cells and rat-derived insulin-secreting cell lines were found to express functional P/Q-type VGCCs (158) and Cav2.1 is also expressed in human β-cells. P/Q is manifested as a residuum of HVA Cav current in solutions containing both nifedipine and ω-conotoxin GVIA (64, 258). About 25% of human β-cell Cav current appears to be of the P/Q-type, based on its sensitivity to ω-agatoxin (258). The Cav2.1 blocker ω-agatoxin also partially blocks Cav currents in rat β-cells and inhibits the DHP-resistant component of GSIS by about 30% (158). In human β-cells, in contrast, ω-agatoxin inhibits about 65% of human GSIS (258).

N-type VGCC in β-cells

The role of N-type VGCCs encoded by Cav2.2 has been somewhat controversial in β-cells. While it has been reported that mouse and human β-cells do not express functional Cav2.2 as ω-conotoxin GVIA, an N-channel specific neurotoxin from the marine snail *Conus* (195) does not affect β-cell Cav currents (86), there is evidence showing ω-conotoxin GVIA decreases arachidonic acid-induced Ca^{2+} influx in β-cells (216). N-type VGCCs have also been detected in several rat-derived insulin-secreting cells, including hamster insulinoma

tumor (HIT) (243). However, other groups have reported that Ca^{2+} signaling in these lines were insensitive to the actions of ω-conotoxin GVIA (115, 167, 247).

Several studies have shown that ω-conotoxin GVIA has no effect on GSIS in human islets (64, 214), while others reported that ω-conotoxin GVIA reduced HVA Cav current in human β-cells and reduced second phase insulin secretion in rat islets (145). The reduction in second phase secretion, however, has been attributed to a ω-conotoxin-induced reduction of β-cell ATP/ADP, rather than via a direct effect on Ca^{2+} channels (194). This suggests that Cav2.2 could conceivably play a role in regulating glucose metabolism and ATP generation, but the mechanism involved remains obscure (2, 230).

R-type VGCC in β-cells

In other cell preparations, even blocking L, N, and P/Q channels does not completely eliminate all HVA current, suggesting that a possible residual (or "R" current) current persists that is mediated by a separate type of Ca^{2+} channel (217). An R-type VGCC was reported in mouse β-cells and could be inhibited by SNX-482, a high affinity Cav2.3 channel blocking peptide (188). Thus, SNX-482 was observed to reduce isradipine-resistant Cav current by 60% in mouse β-cells (251). SNX-482 sensitive-current could also be detected in INS-1 cells (288). Cav2.3 knockout mice had reduced Cav current, as elicited by depolarizations to −10 mV or more (128), again supporting the existence of R channels in β-cells. Functional R channel current was shown to be due to Cav2.3 gene expression (50).

R-type channels were shown to regulate insulin secretion in both INS-1 cells and mouse β-cells (206, 207, 288, 302). In terms of whole-body responses, Cav2.3 knockout mice had reduced glucose tolerance, reduced insulin secretion, and were hyperglycemic (206). Further studies with Cav2.3 knockout mice and SNX-482 blocking peptide demonstrated that Ca^{2+} entry through Cav2.3 channels appeared to be most strongly coupled to second phase rather than first phase insulin secretion (128). While L-type Ca^{2+} channels are localized close to the exocytotic machinery of the β-cell (31, 243), Cav2.3 appears to be more distant from the exocytosis sites and may instead help recruit insulin-containing granules from the large reserve pool to the more readily releasable pool (128, 302).

T-type VGCC in β-cells

Unlike the other VGCCs, the T-type Ca^{2+} channels are low-voltage-activating, meaning they activate at more negative membrane potentials close to the silent phase potential of oscillating β-cells. T-type channels are rapidly inactivating and have activation thresholds as negative as −60 mV (208, 310). They mediate maximal current at about −30 mV and they are reversibly blocked by amiloride (275), Ni^{2+} (154), and NNC55–3096 (36). The inactivation of T-type Ca^{2+} channels is a voltage-dependent process, exhibiting half-maximal inactivation at −65 mV. T-type channels are expressed in rat and human, but not mouse β-cells (8, 18, 108, 240, 310). However, T-type channels have been reported in β-cells from nonobese diabetic (NOD) mice (295), suggesting that the genes that encode these channels might be disallowed in normal mouse β-cells. In islet α-cells, however, T-type channels are crucial for the secretion of glucagon when the cells are exposed to low glucose concentrations (94, 223). T-type Ca^{2+} channels have been identified in α-cells of guinea pigs

(223) and mice (40), although mouse delta cells may express more T-type channels than α-cells (40).

The Na^+ Channels of β-cells

Na^+ channels mediate the classic, fast activating, and inactivating inward current first identified by Alan Hodgkin and Andrew Huxley in the squid giant axon, where they mediate the rapid upstroke of the sodium spike (109, 110). Na^+ channels are expressed in human, rat, and mouse β-cells (36, 71, 213, 308). However, there is a consensus that they play only a minor role in mouse β-cell excitability because their steady state inactivation(or h-infinity curve) is quite left-shifted in mouse β-cells (93, 213); Na^+ current can thus only be elicited by de-inactivating the channels using very negative holding potentials. In mouse islets, the Na^+ channel specific toxin, tetrodotoxin (TTX) clearly blocks Na^+ current elicited from very negative prepotentials but under physiological conditions, TTX is without effect on GSIS (308). However, this is not the case for human or rat β-cells where the channels are more active physiologically (36, 71)

Voltage-gated Na^+ channels (VGSCs) are composed of an α-subunit (Nav1.1-Nav1.9/ *SCN1A-SCN5A*, *SCN8A SCN11A*), which makes up the voltage-dependent pore, and an auxiliary beta-subunit ($beta_{1–4}$/*SCN1B-SCN4B*) which regulates channel trafficking and gating (90, 203). As in VGCCs, the α-subunit is made up of four repeating domains (termed I to IV), each containing six transmembrane segments (S1 to S6), with the S4 segment acting as a voltage sensor. The P-loop between S5 and S6 is the ionic selectivity filter (101).

Mouse β-cells predominantly express Nav1.7 (*Scn9a*), some Nav1.3 (*Scn3a*), and very little Nav1.6 (*Scn8a*) (224). Of the β-subunits, beta1 (*Scn1b*) is expressed at higher levels than beta3 (*Scn3b*) (308). While there is some evidence to support the idea that Na^+ currents may be important for rodent β-cells (308), the topic is controversial, and more work needs to be done to fully understand if Na^+ current affects rodent β-cells and if so, under what conditions.

Human β-cells mainly express Nav1.6 (*SCN8A*) with Nav1.7 (*SCN9A*), Nav1.3 (*SCN3A*), and Nav1.2 (*SCN2A*) making up the remainder (30, 189, 224). Of the beta-subunits, beta1 (*SCN1B*) and beta3 (*SCN3B*) are expressed about equally. Unlike mouse β-cells, human β-cells have large TTX-sensitive Na^+ currents, having half-maximal inactivation at −40 mV, much more positive than mouse (36). Because of this characteristic, Na^+ channels play a more important role in the upstroke of the action potential, and several studies have shown that TTX reduces human β-cell action potential amplitude, as well as glucose-stimulated insulin secretion, although this action is reduced at higher glucose concentrations (10–20 mM) (18, 36).

Transient Receptor Potential (TRP) Channels

Over the years, increased attention has been paid to the possible roles of Transient Receptor Potential channels in islets (reviewed recently in Ref. 122). TRP channels, first identified in the photoreceptors of *Drosophila*, where they are involved in the generation of light-induced receptor potentials (182) are a superfamily consisting of a number of different TRP families

such as TRPC, TRPM, TRPV, TRPML, TRPP, and TRPA channels. Accumulating evidence gathered through molecular as well as functional studies has provided support for TRPC, TRPM, TRPP, and other TRP channels in β-cells, along with various mRNA splice variants (122).

TRP channels are broadly speaking nonselective cation channels, but their Ca^{2+}-permeability in particular and their activation by Ca^{2+} vary by channel type, as do their functional roles. TRP channels that have been shown to have constitutive activity appear well suited to contribute to the "leakage conductance" of the β-cell, whose reversal potential drives cell depolarization when gK_{ATP} is reduced by (say) glucose metabolism. But a further interesting role of TRP channels is their sensitivity to environmental factors such as pH, mechanical perturbation or swelling, odorants and taste stimuli, temperature, and the like. Additionally, these channels are also subject to regulation by cAMP dependent as well as PKC-dependent phosphorylation and activators such as intracellular Ca^{2+}, ADP-ribose, cyclic ADP-ribose, and others (290). We note, however, that the specific types of TRP channels that are expressed in mouse, rat, and human primary β-cells and those present in the range of insulinoma β-cell lines can be controversial and is quite heterogeneous. Thus, caution has to be exerted before assuming that a particular functional attribute of an insulin-secreting cell must necessarily reflect the participation of a TRP channel in the process under study. This situation was not helped, especially in the early days of TRP channel research when the pharmacological agents being employed were limited and often quite nonspecific.

TRP channels have been proposed to play an essential role in β-cell electrophysiology in a number of ways. TRPC1, for instance, has been proposed to be part of the SOCE current along with Orai-1 which activates following ER Ca^{2+} depletion and concomitantly, STIM1 puncta formation (234). Or TRP as has been proposed for TRPC3 channels have been proposed to couple to GCPRs such as the fatty acid receptor GPR40, which can activate the channel due to PKC activation (300). In INS1 cells, TRPC4 may be involved in leptin-induced K_{ATP} channel translocation to the plasma membrane (264).

Relevant to studies of islet electrical oscillations was a study where the role of TRPM5 was examined by genetically deleting its gene in a mouse and studying its isolated islets. Unlike wild type islets that in this study tended to display either fast (period <1 min.), slow (period <5 min.), or mixed fast/slow oscillations in suprathreshold glucose, the islets from the knockout mice tended to show mostly slow oscillations at the expense of fast ones (55). The authors proposed that during the nadir of the bursting phase, TRPM5 channels contribute to a rise in Ca^{2+} that facilitates cell depolarization to the next active phase, increasing burst frequency (55). Consistent with this, TRPM5 null mice were found to be glucose intolerant and had displayed reduced insulin secretion. While these are intriguing results, a complexity of the study was that even the wild-type islets had slow, as well as fast oscillating islets, and the defective secretion that was seen in isolated islets could be due to more direct effects of the *TRPM5* gene (43). It also would have been more convincing if the *TRPM5* deletion was β-cell-specific and not a global one (55).

Due to limitations of space, we cannot discuss in detail many of the other roles that have been proposed for β-cell TRP channels in any detail. However, TRP channels have been implicated in GLP-1 mediated insulin secretion (136, 201, 285), β-cell proliferation (262) and apoptosis (49, 121), the sensitivity of insulin secretion to changes in temperature (134, 284), and responses to cell swelling (245, 246). The contribution of TRP channels to zinc transport in β-cells (294), and a possible role for them in intracellular Ca^{2+} release (151) have also been suggested by experimental work.

Cl^- Channels

The role of Cl^- channels (and anion channels, more generally) in pancreatic β-cell physiology has not been as thoroughly studied as have cation channels. Originally thought to play a passive role, Cl^- was long ago shown to actively accumulate against its electrochemical gradient in rat β-cells and that its channels can therefore mediate Cl^- efflux-induced membrane depolarization (254). A few years later, several studies showed that Cl^- flux could modulate insulin secretion from rat β-cells in a glucose-dependent manner (263, 272). In 1988, Sehlin and Meissner reported that changes in $[Cl^-]_i$ in mouse β-cells could alter voltage-gated Ca^{2+} channel activity, providing the first link between glucose metabolism, altered Cl^- fluxes, and insulin secretion (255).

Since those early studies, several different chloride channels have been reported in pancreatic β-cells, most notably a volume-regulated anion channel (VRAC/SWELL1) (131, 141), the cystic fibrosis transmembrane conductance regulator (CFTR) (78, 96), and Ca^{2+}-activated Cl^- channels (Ano1/2) (78, 148).

VRAC/SWELL1

Volume-regulated anion channels (VRAC) were first described in β-cells by Kinard and Satin (141) and by Best et al (26). These authors found that rodent β-cells exhibit swelling-regulated, outwardly rectifying Cl^- currents that were sensitive to anion channel blockers, although only Satin's group reported that the current was also cAMP activated (141). VRAC activation led to membrane depolarization due to increased Cl^- efflux that in turn could increase insulin secretion (25, 42). In determining whether VRAC was activated by glucose, it was found that increasing glucose similarly activated depolarizing Cl^- currents (22) and it was proposed that this resulted from β-cell swelling in response to increased glucose metabolism; the finding of ATP-dependence is concordant with the glucose sensitivity of the channels (178, 179).

As mentioned earlier, K_{ATP} closure alone is insufficient to depolarize the β-cell membrane because a depolarizing "leak conductance" must also be part of the prevailing circuit. As the reversal potential for Cl^- channels (about −35 mV) is close to the plateau potential (141, 220), Cl^- channels are likely a component for this leak conductance. A VRAC model, by Best and colleagues, incorporated VRAC into the consensus model of insulin secretion as a carrier of the depolarizing leak current (23). In this model, glucose decreases outward K_{ATP} current by raising ATP/ADP while also increasing inward current, which together promote β-cell depolarization and consequently insulin secretion. Best and colleagues proposed that

glucose metabolism can regulate VRAC, depolarizing the β-cell and facilitating insulin secretion (24).

The molecular identity of VRAC was recently determined. VRAC is composed of a hexameric complex of leucine-rich repeat-containing protein 8 (LRRC8A-E), with LRRC8A (commonly called SWELL1) being essential for channel function (69, 146). Knocking down SWELL1 in MIN6 cells and primary mouse β-cells using CRISPR/Cas9 reduces swelling- and glucose-induced Cl^- current and blunts insulin secretion (131, 268). Stuhlmann et al. have shown that all five VRAC subunits are expressed in mouse islets, with *Lrrc8a*, *Lrrc8c*, and *Lrrc8d* attaining the highest expression levels (268). Interestingly, VRAC containing LRRC8D channels are also permeable to taurine, *myo*-inositol, GABA, and lysine, which can also affect insulin secretion (162). Indeed, when cells expressing VRAC are exposed to hypotonic solutions that activate VRAC by causing cell swelling, taurine, inositol, and other molecules can be shown to efflux the cells (118, 249).

CFTR

Cystic fibrosis transmembrane conductance regulator (CFTR) is a member of the ATP-binding cassette superfamily of proteins (ABCC7), whose open/closed gating allows anions to flow down their electrochemical gradient. CFTR is made up of two sets of transmembrane domains, each containing six membrane-spanning α-helices and two cytoplasmic nucleotide-binding domains (309). CFTR also contains an important regulatory (or R) domain that allows for PKA-mediated phosphorylation that regulates channel gating. Functional studies have demonstrated that the open probability of CFTR is increased by cAMP-dependent phosphorylation. In terms of its electrophysiological properties, CFTR exhibits a linear IV relationship, with a single-channel conductance of approximately 6 to 11 pS (19).

The presence of CFTR in β-cells has been very controversial as the very low levels of expression cast doubt on their functional relevance for islets. A lack of signal found with RNAseq has been interpreted as evidence that *Cftr* is not expressed in mouse β-cells (224). However, other studies have detected expression of *Cftr* (30), possibly due to contamination by high levels of CFTR expression from residual exocrine tissue (252).

Whether CFTR plays a functional role in insulin secretion is similarly controversial, as several studies support (78, 96) while others dispute (99, 196) such a role for the channel. Despite its low level of expression, CFTR has been demonstrated to play a role in regulating $[Cl^-]_i$ in neurons (185, 199), supporting the idea that even low levels of CFTR expression may be sufficient. As a significant percentage of cystic fibrosis patients develop CF-related diabetes (96), this remains an important and clinically relevant question.

However, CFTR may not necessarily influence insulin secretion and β-cell function directly via channels in the β-cell plasma membrane. In several cell types, CFTR is active in the trans-Golgi network (14), endosomes and lysosomes (28), and in acidic organelles and granules (149). Several studies suggest that CFTR may play a role in insulin processing and the exocytosis of insulin-containing granules via the acidification of the insulin granule, and hence not directly through an action on the electrophysiology of the β-cell (65, 77).

The classic interpretation of the role of CFTR in CF diabetes attributes its action in acinar cell function whereby defective CFTR regulation leads to poor mucus secretion from the pancreatic acini, ductal malfunction, and concomitant inflammation, and islet damage (81, 99).

Ca^{2+}-activated Cl^- channels (CaCCs)

CaCCs were first described in guinea pig β-cells as mediating a current which reverses at −22 mV, assuming an internal Cl^- concentration of 65 mM, which is higher than predicted from passive distribution of the anion (148). This current is functionally similar to that mediated by the anoctamin channels Ano1 and Ano2 (204), which have been suggested to play a role in insulin secretion (61, 78). Ano1 is expressed in mouse and rat β-cells and its inhibition by T-AO1, tannic acid, or Ano1-specific antibodies, reduces glucose-stimulated insulin secretion, the rate of action potential firing, and results in the partial repolarization of the β-cell membrane potential (61). Ano1 is expressed as well in human β-cells and siRNA-mediated silencing of Ano1 or T-AO1 inhibits insulin secretion (78, 127, 299). While the above studies support Ano1's involvement in insulin secretion, other studies have failed to find expression of Ano1 or Ano2 in mouse or human β-cells and have concluded that they play a minimal role (224). Clearly, this issue needs to be reexamined more thoroughly.

Role of β-cell Cl^- channels in autocrine regulation

Besides insulin, pancreatic β-cells contain several other substances which are co-released with insulin in response to glucose. Several of these substances have been proposed to be autocrine and/or paracrine regulators of islet cell electrical or secretory activity (35, 301). Two substances which could regulate Cl^- channel activity, and therefore β-cell excitability, are GABA and glycine.

Pancreatic β-cells contain two types of GABA receptors: ionotropic $GABA_A$ receptors and metabotropic $GABA_B$ receptors. $GABA_A$ receptor activation in human β-cells depolarizes the cell membrane toward the Cl^- equilibrium potential [ca. −35 mV (35)] due to the prevailing intracellular Cl^- concentration and can increase insulin secretion (35). Inhibiting $GABA_A$ receptors using a $GABA_A$ receptor antagonist such as SR95531 prevents insulin secretion (35). Activation of the metabotropic $GABA_B$ receptor, however, has been shown to inhibit insulin secretion when activated (33, 38) while $GABA_B$ antagonists such as CGP55485 stimulate secretion (274), suggesting that GABA can both stimulate and inhibit insulin secretion depending on the receptor type engaged. Because pancreatic β-cells contain high levels of GABA (276), it is possible that GABA could act as an autocrine and/or paracrine signal to neighboring cells. GABA has been shown to be released from both rodent (85) and human (37) β-cells via exocytosis (35, 39) or via nonvesicular release, possibly through bestrophin-1 (BEST1) channels (155) although more work needs to be done to understand the details of GABA release.

Glycine is also stored inside the β-cell secretory granule and is co-released with insulin (301). Glycine receptors are found on the membranes of both rodent and human β-cells and have been shown to result in membrane depolarization in response to glycine (156, 296, 301). Antagonizing the glycine receptor with strychnine has been shown to reduce

glucose-sensitive insulin secretion in human islets (301). Yan-Do et al. (301) proposed that β-cells use glycine as an autocrine positive feedback signal to stimulate insulin secretion.

Ca^{2+}-dependent K^+ Channels

Potassium channels that are activated by a rise in intracellular Ca^{2+} concentration or KCa channels have been of interest in the β-cell field for a long time, from even before the advent of the patch clamp and the subsequent discovery of K_{ATP} channels. This was the case because the presence of KCa channels in β-cells was a logical way in which to link voltage-dependent Ca^{2+} influx into the β-cell by VGCCs to subsequent membrane repolarization during bursting, a simple type of negative feedback mechanism. The identification of potential KCa channel blockers increased the attractiveness and testability of this hypothesis. Thus, the idea took hold that the cyclic activation of KCa following a phase of Ca^{2+} influx could periodically terminate bursts of spikes in β-cells by repolarizing the membrane potential (10, 12). We now know that there are two main types of KCa channels in β-cells: a voltage-insensitive, small conductance K^+ channel named SK (273, 307) and a larger, highly voltage- and Ca^{2+}-sensitive K channel, called BK (58, 150).

Along with K_{ATP}, the KCa channels play specific roles in β-cell physiology. For SK channels, there are three different SK channel isoforms and all three are expressed in β-cells (72, 126, 273). SK channels slowly activate as cytosolic Ca^{2+} rises during spiking or bursting, they have a unitary conductance of 9 to 10 pS (293) and they have a distinctive pharmacology; the classic SK inhibitor is apamin, a component of bee venom (307). A major step forward in our understanding of slowly activating KCa (likely SK) was the development of a burst waveform voltage-clamp protocol by Göpel and Rorsman (92) who found they could isolate slow KCa current by subjecting the β-cell membrane to this physiological clamp command. In response to the imposed waveform, KCa slowly rises following the rise in Ca^{2+} creating an “envelope current” that reaches a peak by the end of the pulse burst, a phase corresponding to the voltage plateau of a burst. Once the spike-like voltage command pulses subside, a slow tail current of KCa occurs as Ca^{2+} falls to a low value corresponding to the holding phase potential. While the envelope and slow tail currents evoked by this protocol may include contributions from multiple types of KCa currents, there is also evidence that K_{ATP} channels can also contribute to the current (133). We note that the burst wave protocol described here has been used productively by other labs, including our own in other studies (89, 307).

A large amount of work has been done in neurons to identify the role of SK and other K^+ channels mediating slow K^+ currents like those underlying spike after-hyperpolarization of hippocampal neurons (205), and a number of compounds have been identified as putative SK selective blockers (29). Work with these compounds applied to β-cells suggests that the slow KCa tail current is likely carried by SK3 (307) or possibly SK4 (72) or a combination thereof. Regardless, the KCa current due to SK likely is important in regulating slow bursting when K_{ATP} is not mediating the majority of negative feedback (20). We will discuss this point further in the Modeling Section below.

Besides SK channels, large conductance (e.g. 200 pS), voltage-, and Ca^{2+}-activated "BK" channels are a second class of KCa channel in β-cells, as first described by Cook and Hales in isolated inside-out patches (58). Unlike the KCa channels of red blood cells or SK channels, the steep voltage dependence of these channels, their Ca^{2+} sensitivity, and their rapid speed of activation and deactivation are hallmarks (129, 152). The gene encoding the BK channels is known as *KCNMA1* (56, 91).

Because of its dynamics and voltage dependence, BK channels are rather poorly equipped to mediate islet bursting (unlike K_{ATP} or SK) and it is believed by most workers in the field that their main role is to contribute to the repolarization of fast action potentials in the β-cell (116, 126, 241), likely in concert with K_v channels (see below). BK channels are quite sensitive to blockade by toxins such as charybdotoxin (248), iberiotoxin (187), or paxillin (116), as well low dose tetraethylammonium (TEA). In response to BK blockade, the amplitude of the β-cell action potentials is potentiated, as is insulin secretion (116). However, inhibiting these channels has no pronounced effect on the pattern or kinetics of islet bursting (116).

Voltage-dependent K^+ Channels

Pulse depolarizations applied in voltage clamp not only activate BK current as the membrane depolarizes and Ca^{2+} enters the cell, but also a voltage-dependent delayed rectifier K^+ current, which activates with a delay and usually inactivates slowly, if at all (227, 228). In β-cells, the current carried by these channels strongly overlaps current mediated by BK channels; this delayed activating current is referred to as K_{dr} (delayed rectifier) or K_v current, and channel expression is encoded by the gene *KCNB1* (K_v2.1) (164, 165). Progressively depolarizing the β-cell membrane from −30 to +50 mV results in an outward current that turns on with a characteristic delay and then smoothly activates further; with progressive depolarization, the current grows in amplitude and activates more rapidly. Blockers of the current include the classic inhibitors such as TEA, quinidine, and aminopyridines but also dendrotoxin (32, 117, 164, 222). We believe that the main role of this current is to repolarize the action potential in concert with BK current, although overexpression of K_v2.1 does reduce insulin secretion, rendering the mice glucose intolerant (210).

Inward Rectifying K^+ Channels Besides Kir6.2

KIR channels are expressed in a variety of tissues, including β-cells. Their role is to help maintain the resting membrane potential near their reversal potential and to regulate the intrinsic excitability of electrically active cells. As their name suggests, KIR channels display inward rectification, with conductance that increases with hyperpolarization. Under physiological conditions, KIR channels mediate a large inward current at potentials negative to E_K and small outward current at potentials positive to it (97). This rectification is due to blockade of the channel by polyamines or intracellular cations such as Mg^{2+} when the cell membrane is depolarized; the block is relieved by hyperpolarization and so conductance increases (191). The most important KIR channel in the β-cell is Kir6.2, the pore-forming

subunit of K_{ATP}. However, other KIR channels have also been suggested to play a role in regulating insulin secretion.

Using sulfonylureas to inhibit K_{ATP} currents allows other KIR channels to be studied. In human β-cells, hyperpolarizing voltage steps applied from −70 mV cause progressively increasing, tolbutamide-resistant inward current that showed inward rectification (221, 227). Blockade of the current using Ba^{2+} or Cs^{+} (both of which inhibit KIR channels) resulted in membrane depolarization. However, this type of functional study was unable to identify which KIR channel likely was contributing to the current observed.

G protein-coupled inward-rectifying K^{+} (GIRK) channels, a type of inward rectifier that is activated in a G-protein-dependent manner have been shown to be present in mouse β-cells, where they mediate epinephrine- and somatostatin-induced hyperpolarization (124, 226).

Another type of KIR channel that has recently been studied in β-cells is Kir2.1, which is encoded by *KCNJ11*. Interestingly, in SUR1 knockout mice lacking functional K_{ATP} channels, islets still exhibit electrical bursting, although the bursting seen is no longer glucose- or tolbutamide-sensitive (253). Moreover, mice lacking K_{ATP} exhibit relatively normal blood glucose levels unless they are metabolically stressed or age (177, 253). A very similar phenotype is seen in Kir6.2 knockout mice (256). We proposed that to compensate for their loss of K_{ATP}, SUR1−/− β-cells upregulate Kir2.1 (304). Our model is based on the report that Kir2.1 contains several phosphorylation sites for protein kinase A (PKA) and that phosphorylation of these ser/thr sites results in potentiation of Kir2.1 current (79, 233, 305). Recent studies using Förster resonance energy transfer (FRET) and total internal reflection fluorescence (TIRF) microscopy show that elevated glucose induces oscillations in cAMP in mouse β-cells (76, 279). As PKA activity is cAMP-dependent, we proposed that changes in intracellular cAMP concentrations may regulate Kir2.1 channel activity and give rise to electrical oscillations in the absence of K_{ATP} (304). However, more work needs to be done to more completely prove that this occurs.

Two-pore-domain K^{+} (K2P) Channels

Two-pore-domain K^{+} channels (K2P) are small conductance K^{+} channels that are active at all membrane potentials and can serve as resting “leak” channels. K2P channels are formed as dimers having two α-subunits, each containing four transmembrane domains and two pore domains (180). They have been proposed to primarily serve to stabilize the plateau potential during glucose-induced electrical bursting (63). However, the conductance of these channels is significantly less than that of K_{ATP} (62, 291). Thus, it is believed that K2P channels have a more prominent role in the regulation of membrane potential when K_{ATP} is largely inhibited.

The existence of several K2Ps has been reported in mouse and human β-cells, most notably TALK1 (encoded by *KNCK16*), TWIK1 (encoded by *KCNK1*), and TASK1 (encoded by *KCNK3*) (125). TALK1 is an outwardly rectifying, and very small (about 1pA/pF) K^{+} current that is detectable at voltages above −45 mV and which has a reversal potential near −50 mV (291). Islets isolated from TALK1-deficient mice have more depolarized

β-cells, reduced interburst duration, and elevated second phase GSIS (291). How TALK1 is regulated is not completely clear as yet. Interestingly, a GOF polymorphism in TALK1 (A277E) has been linked to increased risk of T2D (289). This is a gain-of-function polymorphism that increases TALK1 channel open probability, resulting in membrane hyperpolarization, decreased β-cell Ca^{2+} influx, and reduced in insulin secretion. TALK1 is also pH sensitive, with increased channel activity observed under alkaline conditions and decreased activity under acidic conditions (132). TALK1 has also been shown to be activatable by nitric oxide (74).

The two-pore-domain acid-sensitive K^+ channel called TASK-1 is highly expressed in human and rodent β-cells and localizes to the plasma membrane, where it resembles an outwardly rectifying, noninactivating K^+ current that is active at all physiological membrane potentials (66, 75, 140). In both human and mouse β-cells, blockade of TASK-1 using the inhibitor A1899 depolarizes the membrane in high glucose (14 mM) and has been shown to increase GSIS (63).

Modeling β-cells

As islet oscillations result from coordinated and highly complex interactions between β-cell ion channels, mechanisms for handling cytosolic Ca^{2+}, and cell fuel metabolism such complexities require the construction of predictive quantitative models to probe the underlying mechanisms of islet oscillations. Our group has thus worked for many years to develop and test increasingly sophisticated and powerful β-cell models, culminating in the Integrated Oscillation Model or IOM (as reviewed in Ref. 20). The IOM, a variant of our previous Dual Oscillator Model [DOM; (21)] predicts that both autonomous glycolytic oscillations (AGOs), resulting from the autocatalytic activity of phosphofructokinase, and passive glycolytic oscillations (PGOs) due to Ca^{2+}-driven ATP consumption leading to K_{ATP} activation can predominate during different conditions. The model is uniquely suited for determining islet glucose responses to a range of conditions, and most importantly how islets can account for fast oscillations, slow oscillations, and mixed or compound oscillations (20). While a full discussion of the mathematical details of these models is beyond the scope of the present article, all of the models to date going back to the seminal model of Chay and Keizer (52) involve two key subsystems: a fast feedback loop involving Ca^{2+} and K^+ channels of the voltage-dependent and/or Ca^{2+}-activated variety, and a slower feedback loop where a slow variable drives the slow plateau depolarizations that are observed in response to suprathreshold glucose. By plotting the behaviors of the model with its fast and slow components on the phase plane, a representation of the solutions of the many equations that compose the model one can readily predict the expected dynamics of the oscillations and/or stability of the complete model.

In the DOM, K_{ATP} oscillations that are driven by pulses of FBP produce oscillations in pyruvate that, once amplified by mitochondria, drive slow oscillations in ATP/ADP, V_m and Ca^{2+}. Fast oscillations largely result from negative feedback of Ca^{2+} on K^+ channels interacting with the slow oscillator (21). In the IOM, a rise in Ca^{2+} facilitates glycolytic flux by activating mitochondrial PDH and depleting the F6P pool while increasing mitochondrial

ATP production (173). The ATP rise, in turn, increases Ca^{2+} pumping, which hydrolyzes ATP.

To help understand how each of the main ion channels participates in β-cell bursting, Figure 1 shows the predictions of the IOM model for each current that activates in islets under steady state conditions and 11 mM glucose. The left-hand column corresponds to slow bursting, while the one on the right shows the case for fast bursting.

During slow bursting, L-type Ca^{2+} current activates quickly at the beginning of the burst plateau and spikes of inward current correspond to each of the fast action potentials triggered during the plateau. A small amount of Ca^{2+} current decline occurs during the train of action potentials, corresponding to the decline in activation voltage, and the Ca^{2+} current shuts off promptly after plateau repolarization.

Voltage-dependent K^+ current plays a minor role during the interburst period but then activates rapidly during each action potential to help repolarize them. In contrast, IK(Ca) has much slower kinetics, as these channels (most likely mediated by SK type isoform) follow changes in cytosolic Ca^{2+}, IK(Ca) slowly ramps up during the burst and mainly reaches its peak by the end of the active phase. Notably, a slow KCa tail current is clearly visible during the interburst period.

The K_{ATP} current grows slowly during the burst active phase due to an increase in the total channel conductance brought about by a slow decline in the ATP:ADP ratio. It quickly falls at the end of an active phase due to a rapid decline in the K^+ driving force, but slowly rises as the membrane depolarizes throughout the interburst period.

Qualitatively similar patterns are seen for most of the currents during fast bursting (right-hand column). A particularly notable exception to this is IK(Ca), which more rapidly activates at the initiation of the active phase and then declines instead of continually growing.

Thus, the model can be used to understand how ion currents can contribute to the bursting process and the predictions of these models can be tested in a laboratory. A particularly interesting and important aspect of our models has been their ability to predict unexpected islet behaviors that were subsequently verified by experiment. Three examples will be discussed here.

First, modeling predicted that increasing the cytoplasmic concentration of fructose2,6 bisphosphate (FBP2), an allosteric activator of PFK1 should increase the frequency while decreasing the amplitude of islet Ca^{2+} oscillations. We tested this experimentally by manipulating the expression of PFK2/FBPase2 mutants, which allowed us to either increase or decrease FBP2 levels. In both cases, the model predictions were verified (175).

As a second example, the model predicted that the abolition of islet metabolic oscillations seen following the application of diazoxide, which hyperpolarizes the β-cell membrane by opening K_{ATP} channels should be reversed by the addition of KCl (in the continual presence of diazoxide) to depolarize the membrane and restore Ca^{2+} influx. This novel prediction was

verified experimentally by measuring endogenous NAD(P)H fluorescence (193) or more recently measuring FBP with our PKAR probe (176).

As a last example, it was predicted that individual mouse β-cells exhibiting repetitive spiking but not bursting should be capable of being converted to a more islet-like bursting pattern by increasing their voltage-dependent Ca^{2+} conductance. Using the dynamic clamp technique, whereby a computer-generated ion conductance is calculated in an iterative manner in real time and then injected into the cell in response to changes in the cell's own membrane potential we confirmed that injection of such a conductance indeed was able to convert the cell to bursting (306). These examples, and others, have convinced us over many years that models are not only useful for accounting for the interactions between many variables in a complex dynamical system but that they can make novel yet experimentally testable predictions.

Conclusion and Future Directions

The plethora of ion channels identified in pancreatic β-cells has provided investigators with a robust palette of elements that can be combined in expected as well as unexpected ways to mediate glucose-induced islet electrical bursting and its modulation by not only metabolizable fuels but also neurohormonal modulators and mediators to produce a wide spectrum of electrical behaviors and, in turn, patterns of secretion. The more well-understood roles that classic ion channels play in other cell types typically serve as starting points in our understanding of β-cells, as once these channels are modified by metabolism, or Ca^{2+}, a much wider range of behaviors become possible. Hence, our work has emphasized the importance of mathematical models in understanding how ion channels interact with one another and with metabolism to mediate the range of oscillatory phenomena observed in islets.

Future endeavors in this field will need to build on new work describing the importance of the heterogeneity in channel expression that has been observed, and the recent use of RNAseq combined with patch clamp electrophysiology (45, 46) to decipher the molecular basis of β-cell ion channel heterogeneity is encouraging. Furthermore, extending these studies into understanding human islets, a relatively new development, as well as islet behavior *in vivo*, should be even more illuminating and will likely lead to increasingly clinically relevant findings.

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Didactic Synopsis

Major teaching points

- Understanding the physiology of pancreatic β-cell ion channels is important for understanding how glucose metabolism is coupled to insulin secretion.
- The K_{ATP} channel is the primary regulator of β-cell electrical activity by coupling metabolism to changes in membrane potential.
- Voltage-gated Ca^{2+} channels (VGCCs) are responsible for triggering and sustaining insulin secretion by regulating Ca^{2+} influx across the plasma membrane in response to changes in membrane potential.
- While K_{ATP} and VGCCs are the main ion channels which control insulin secretion, other channels also play a role in modulating secretion.
- Understanding the role of different ion channels in regulating insulin secretion allows for the better design of complex dynamical models to account for β-cell oscillations and hence pulsatile insulin secretion.

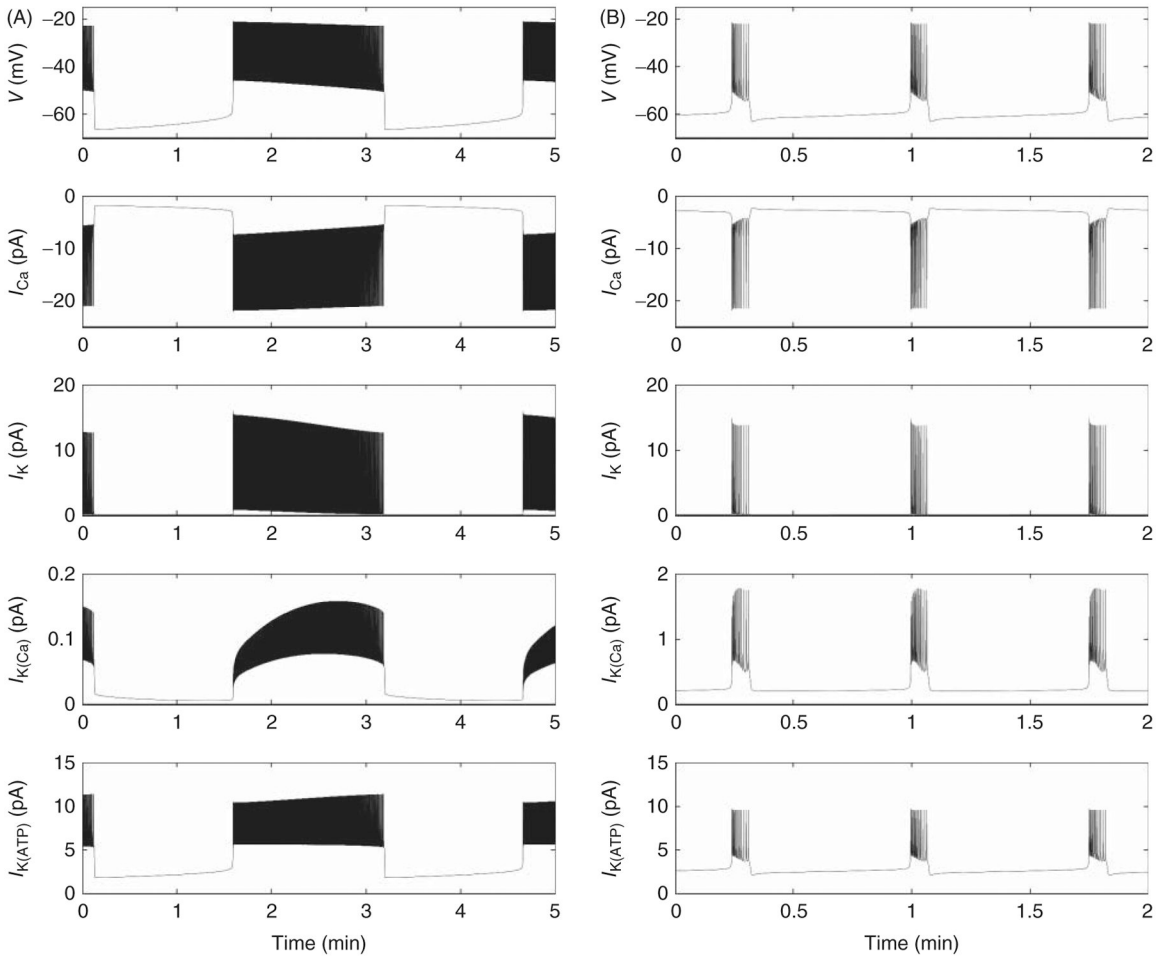

Figure 1.

Shows a simulation performed using the Integrated Oscillator Model [IOM; (20)] of β-cell bursting in the steady state (e.g. in 11 mM glucose) to show the respective contributions of voltage-gated Ca^{2+} channels (I_{Ca}), voltage-dependent K^+ channels (I_K), slow Ca^{2+}-activated K^+ channels ($I_{K(Ca)}$) and ATP-sensitive K^+ channels ($I_{K(ATP)}$) to slow (A) versus fast (B) bursting electrical activity (V_m). Simulations were performed by Dr. Isabella Marinelli, to whom we are grateful.

Table 1

Ion Channels in Pancreatic β-cells Involved in Insulin

Family	Channel	Gene	Function in the β-cell	Activators	Blockers	References
Inward-rectifying K^+ channels	Kir2.1	*Kcnj2/KCNJ2*	Spike repolarization?	Zacopride	ML133, Ba^{2+}	(221, 304, 305)
	Kir3.2 (GIRK2)	*Kcnj6*	Spike repolarization in response to hormones and neurotransmitters	Noradrenaline, somatostatin, galanin	Atomoxetine, Tertiapin, Ba^{2+}	(80, 144)
	Kir6.2/SUR1 (K_{ATP})	*Kcnj11/KCNJ11 Abcc8/ABCC8*	Mediates membrane potential and its coupling to metabolism	Diazoxide	Sulfonylureas, ATP/ADP ratio, glinides	(103, 163, 174)
Voltage-gated Ca^{2+} channels	Cav1.2 (L-type)	*Cacna1c/ CACNA1C*	Mediates Ca^{2+} influx during electrical activity	(*S*)-(-)-Bay K8644	Dihydropyridines, benzothiazepines, phenylalkylamines	(153, 186, 251, 298)
	Cav1.3 (L-type)	*Cacna1d/ CACNA1D*	Mediates Ca^{2+} influx during electrical activity	(*S*)-(-)-Bay K8644	Dihydropyridines, benzothiazepines, phenylalkylamines	(153, 186, 251, 298)
	Cav2.1 (P/Q-type)	*Cacna1a/ CACNA1A*	Triggering exocytosis of insulin granules	–	ω-Agatoxin IVA	(36, 161)
	Cav2.2 (N-type)	*Cacna1b/ CACNA1B*	Spiking?	–	ω-Conotoxin GVIA	(282)
	Cav2.3 (R-type)	*Cacna1e*	Spiking?	–	SNX482	(188, 288)
	Cav3.1 (T-type)	*Cacna1g/ CACNA1G*	Low threshold spiking	–	Amiloride, $NiCl_2$, NNC55-3096	(36, 154, 275, 282)
	Cav3.2 (T-Type)	*Cacna1h/ CACNA1H*	Low threshold spiking	–	Amiloride, $NiCl_2$, NNC55-3096	(36, 154, 275, 282)
Voltage-gated Na^+ channels	Nav1.3	*Scn3a/SCN3A*	Upstroke of action potential	Batrachotoxin, veratridine	Tetrodotoxin, saxitoxin	(18, 30, 36, 189)
	Nav1.6	*Scn8a/SCN8A*	Upstroke of action potential	Batrachotoxin, veratridine	Tetrodotoxin, saxitoxin	(18, 30, 36, 189)
	Nav1.7	*Scn9a/SCN9A*	Upstroke of action potential	Batrachotoxin, veratridine	Tetrodotoxin, Saxitoxin	(18, 30, 36, 189)
Volume-regulated Cl^- channels	VRAC/SWELL1	*Lrrc8a/LRRC8A*	Membrane depolarization and response to swelling; volume regulation	Cell swelling, cAMP	DCPIB, DIDS, NPPB, niflumic acid, glyburide	(131, 141)
Ca^{2+}-activated Cl^- channels	Anoctamin-1	*Ano1/ANO1*	Membrane depolarization	Ca^{2+}	T-AO1, tannic acid, niflumic acid	(61, 78, 204)
	Anoctamin-2	*Ano2/ANO2*	Membrane depolarization	Ca^{2+}	T-AO1, tannic acid, niflumic acid	(61, 78, 204)
Other Cl^- channels	CFTR	*ABCC7*	Acidification of insulin-containing granules	PKA phosphorylation	NPPB, niflumic acid	(65, 77)

Family	Channel	Gene	Function in the β-cell	Activators	Blockers	References
Calcium-activated K^+ (Kca) channels	BK (KCa1.1)	*Kcnma1/ KCNMA1*	Spike repolarization	Ca^{2+}, membrane depolarization	Charybdotoxin, iberiotoxin, paxillin, TEA	(58, 116, 150, 187)
	SK1 (KCa2.1)	*Kcnn1/KCNN1*	Modulates Ca^{2+} oscillations, repolarization of the plateau potential	Ca^{2+}, 1-EBIO, GW542573	Apamin, UCL 1684	(29, 112, 273, 307)
	SK2 (KCa2.2)	*Kcnn2/KCNN2*	Modulates Ca^{2+} oscillations, repolarization of the plateau potential	Ca^{2+}, 1-EBIO, CyPPA	Apamin, UCL 1684	(29, 112, 273, 307)
	SK3 (KCa2.3)	*Kcnn3/KCNN3*	Modulates Ca^{2+} oscillations, repolarization of the plateau potential	Ca^{2+}, 1-EBIO, CyPPA	Apamin, UCL 1684	(29, 112, 273, 307)
	SK4 (IK, KCa3.1)	Kcnn4/KCNN4	Modulates Ca^{2+} oscillations, repolarization of the plateau potential	Ca^{2+}, 1-EBIO, SKA-111	TRAM-34	(29, 72, 112, 273, 307)
Voltage-dependent K^+ channels	Kv2.1	*Kcnb1/KCNB1*	Spike repolarization	–	TEA, quinidine, aminopyridines, and dendrotoxin	(32, 117, 164, 222)
TRP channels	TRPC1	*Trpc1/TRPC1*	Mediation of store-operated Ca^{2+} channels	–	La^{3+}, Gd^{3+}, 2-APB	(166, 234, 267, 311)
	TRPC3	*Trpc3*	β-Cell development and GPR40-induced membrane depolarization	GSK1702934A, artemisinin	Pyr3	(143, 287, 300)
	TRPC4	*Trpc4*	K_{ATP} trafficking	leptin, (−)-englerin	M084, ML204	(3, 181, 257, 264)
	TRPM2	*Trpm2/TRPM2*	Mediates Ca^{2+} influx induced by glucose and GLP-1	Ca^{2+}, Adenosine 5′-diphosphate ribose, forskolin, exendin-4	*N*-(*p*-amylcinnamoyl) anthranilic acid, curcumin, JNJ-28583113	(17, 82, 138, 172, 201, 280, 283)
	TRPM5	*Trpm5/TRPM5*	Mediates glucose-induced oscillation	Arachidonic acid, steviol glycoside, GLP-1	Flufenamic acid, TPPO	(55, 200, 209, 259, 286)
	TRPV2	*Trpv2*	Membrane depolarization	Cell swelling, cannabidiol	SET2	(51, 215, 246)
Two-pore-domain K^+ channels	TALK1	*Knck16/KNCK16*	Resting “leak” conductance	pH (alkaline), nitric oxide	pH (acidic)	(74, 132, 291)
	TASK1	Kcnk3/KCNK3	Resting “leak” conductance	pH (alkaline)	pH (acidic), A1899, ML365	(63, 74, 292)