COMMENTARY

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A TRP channel contributes to insulin secretion by pancreatic β-cells

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The release of insulin by pancreatic β-cells involves a complex interplay of conductances that generate oscillations and drive secretion. A recent report identifies a new player in this process, the ion channel TRPM5. TRPM5 was originally identified in taste cells, where it forms a Ca^{2+}-activated cation channel that is required for sensory responses to bitter and sweet tastes. New research now shows that TRPM5 is expressed within the pancreatic islets of Langerhans, where it regulates the frequency of Ca^{2+} oscillations and contributes to insulin release by β-cells.

Key words: insulin, TRPM5, pancreas, β-cell, Ca^{2+} oscillations, secretion

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The primary sensor regulating blood glucose levels is the pancreatic β-cell, which releases insulin to stimulate entry of glucose into muscle and fat. The cellular events that underlie insulin secretion have been well-described and many of the key molecular components have been identified. In the first step, glucose is transported into the β-cells by the Glut2 transporter, producing a change in the ATP/ADP ratio. This generates membrane depolarization, through a direct blocking effect of ATP on a specific class of potassium channel (KATP) composed of KIR/SUR subunits.[1,2] Voltage-gated calcium channels open upon depolarization, leading to an elevation of intracellular Ca^{2+}. From there, Ca^{2+} levels and the membrane potential oscillate, which drives pulsatile secretion of insulin.[3] This oscillatory behavior is highly complex and still poorly understood. It involves cyclical changes in intracellular Ca^{2+} levels which affect the gating of a number of ionic conductances and the rate of glucose metabolism.[4]

In addition to the known conductances, it has been hypothesized that there must be a Na^+ permeable "background" current in β-cells to drive membrane depolarization upon closure of KATP channels.[5] Such Na^+ permeable currents have been described in pancreatic β-cells and in related cell lines. For example, single channel recordings revealed the presence of a Na^+ and K^+ permeable cation channel that was activated by intracellular Ca^{2+}, referred to as Ca-NS.[6] These channels are characterized by a conductance of 20–25 pS and sensitivity to block by adenine nucleotides. A link between these channels and insulin secretion has been suggested by experiments showing that in β-cells the insulinotropic hormone, glucagon-like peptide-1a activates a nonselective conductance sensitive to Ca^{2+} and cAMP[7,8] and that release of Ca^{2+} from intracellular stores activates a conductance sensitive to maitoxin, a toxin that promotes insulin release.[9] Until now, the molecular identity of these Ca-NS channels was unknown.

Several TRP channels form Ca^{2+}-activated nonselective cation channels and thus are candidates to underlie the Ca-NS current of pancreatic β-cells. Ca^{2+} is considered the physiological activator for two TRP channels, TRPM4 and TRPM5, both of which are permeable to monovalent cations, but impermeable to Ca^{2+}.[10-13] More recently, it has been reported that TRPM2 is activated by intracellular Ca^{2+}.[14,15] TRPM4 is widely distributed and has some of the features of the Ca-NS of pancreatic cells, such as block by adenine nucleotides.[16] However, animals that carry a targeted deletion of TRPM4 do not have any defects in glucose tolerance or insulin secretion.[17] Several other TRP channels have been found in islets, but none has been definitively linked to insulin secretion by β-cells.[18]

Two groups now report, surprisingly, that TRPM5 plays a key role in insulin secretion. TRPM5 is a protein of 1,165 amino acids in human[19] and 1,158 amino acids in mouse[20] with highest homology to TRPM4. It is distantly related to other TRPM channels, such as the cold and menthol receptor TRPM8. Like other TRP channels, TRPM5 is thought to contain 6 transmembrane domains and to assemble as a tetramer.

Expression of TRPM5 was initially reported to be restricted to taste receptor cells,[21,22] although later reports found expression of TRPM5 in other chemosensory cells.[23,24] In taste cells, TRPM5 is required for the sensory response to bitter, sweet and umami.[22] In this system, taste receptors, which are G protein-coupled receptors, signal through phopholipase C (PLC) β2 and the ensuing elevation of intracellular Ca^{2+} gates TRPM5 channels.[25] TRPM5 is activated by micromolar concentrations of intracellular Ca^{2+}; it is ~five times more sensitive to intracellular Ca^{2+} as compared with TRPM4 under the same conditions.[26,27] TRPM5 channels desensitize with prolonged Ca^{2+} elevation, a response that is partially attributed to depletion of PIP_2, a positive regulator of channel gating.[12]

New evidence from two groups now extends the distribution of TRPM5 to include pancreatic β-cells and its function to include a role in insulin secretion.[28,29] Previous work had shown that TRPM5 could be detected in the pancreas and in insulinoma cell lines by PCR;[13] the new report by Colsoul and collaborators now shows that TRPM5 immunoreactivity colocalizes with insulin immunoreactivity in islets of Langerhans,[29] demonstrating that TRPM5 is expressed by β-cells. Colsoul and collaborators also provide definitive evidence for functional TRPM5-like channels, by comparing responses of cells from wildtype animals and $TRPM5^{-/-}$ animals to elevation of intracellular Ca^{2+}, an approach previously used to characterize TRPM5 channels in native taste cells.[25] A component of the Ca^{2+}-activated current recorded from islet cells was significantly reduced in cells isolated from $TRPM5^{-/-}$ animals, indicating that this component constituted the TRPM5-dependent current. Interestingly, the TRPM5-dependent current was of a very small magnitude—just a few tens of pA at -80 mV with maximal Ca^{2+} stimulation, indicating that it likely contributes to the membrane potential only under conditions when other conductances are inactive.

Definitive evidence for a role of TRPM5 in insulin secretion comes from studying the response of $TRPM5^{-/-}$ animals to glucose challenge. In this paradigm, the animal is stimulated with a high concentration of glucose either by i.p. injection (IPGTT) or by oral administration (OGTT) and blood glucose and insulin levels are measured over the next 1–2 hrs. Remarkably, both groups report a decrease in insulin secretion and a reduced glucose clearance (tolerance) in $TRPM5^{-/-}$ as compared with WT mice.[28,29] Corroborating this observation, both groups also report that isolated islets from $TRPM5^{-/-}$ animals show a reduced level of insulin release to glucose challenge.

Thus, it can be concluded that TRPM5 is one of a small group of finely tuned conductances that contribute to insulin secretion. But precisely what role does it play in electrical excitability? The two recent reports provide some hints. Colsoul and collaborators report no change in the action potentials recorded from $TRPM5^{-/-}$ islet cells, indicating that TRPM5 does not contribute to the bursting phase of the response. Instead they report a dramatic change in the frequency of oscillations in $TRPM5^{-/-}$ islet cells.[29] In islet cells, oscillations of Ca^{2+} and membrane potential are complex, consisting of both a slow component (on the order of 4–6 minutes) and a fast component (1–2 minutes) which can occur in isolation or can be superimposed.[4] A "dual oscillator model", has been proposed which posits that the fast oscillations are due to the interplay of ionic conductances while the slow oscillations are due to feedback of Ca^{2+} onto the glylcolytic machinery. According to this model, the burst is terminated both by the elevation of intracellular Ca^{2+} which feeds back onto Ca^{2+}-activated K^+ channels and by a decrease in the concentration of ATP, which relieves block of KATP channels. As Ca^{2+} levels decline during the silent phase and ATP levels recover, both types of K^+ channels close, allowing the membrane to again depolarize. Interestingly, $TRPM5^{-/-}$ islet cells retain slow oscillations but are completely devoid of fast oscillations. This has led the authors to propose that TRPM5 functions to depolarize the membrane at the end of the silent phase of the cycle. How might this occur? One possibility is that at the end of the silent phase, Ca^{2+} levels may gradually begin to creep up as voltage-gated channel recover from inactivation.[5] This elevation of Ca^{2+} may provide the stimulus to open TRPM5 channels, leading to a rapid depolarization. Indeed, mathematical modeling by Colsoul and collaborators supports this possibility. However, things may not be so simple, as Brixel et al. find that insulin secretion in $TRPM5^{-/-}$ islet cells is reduced in response to stimulation with argine, which passively depolarizes the cells without changing metabolic status. Under these conditions, KATP channels should be open and TRPM5 currents should be ineffective. Based on this result, Brixel and collaborators propose that TRPM5 plays a direct role in insulin secretion, possibly forming part of the secretory machinery. Clearly more work will be needed to determine the precise role of TRPM5 in insulin secretion.

Regardless of mechanism, the remarkable convergence of results from two labs provides strong evidence that TRPM5 is an important regulator of insulin secretion by pancreatic β cells. Deregulation and impaired insulin secretion contribute to type 2 diabetes, a widespread and debilitating disorder. Could TRPM5 be a target for the treatment of diabetes? With work already underway by pharmaceutical companies to identify agents that modulate TRPM5, it may not be too long before we know the answer.

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