TRP-ing Down the Path to Insulin Secretion

Patrick E. MacDonald

The means by which glucose stimulates insulin secretion from pancreatic β-cells has been studied for decades. Yet we still do not fully understand the cellular machinery underlying this process, the complexity of which continues to surprise. The triggering pathway for glucose-induced insulin secretion is generally well described, and the current model, shown on the left-side of Fig. 1, has been accepted for more than 20 years (1,2). However, it is abundantly clear that the ion channels currently included in this consensus model are insufficient to describe the complicated electrophysiological and intracellular Ca^{2+} responses of the β-cell to glucose and other secretagogues. Furthermore, the contribution of an ion channel-based component to the well-known "amplifying" effects of glucose (3) remains unclear. Recent studies, including that of Uchida et al. (4) in the present issue, are beginning to elucidate roles for multiple additional ion channels in the β-cell electrical and intracellular Ca^{2+} responses, particularly the contribution of the transient receptor potential (TRP) channels. Moreover, there are hints that these channels may play a more complex role in β-cells than we suspect.

In mammals there are 28 members of the TRP channel family, and these generally show a selective permeability to cations such as Na^+ and Ca^{2+} (5). Thus, activation of these channels could contribute to β-cell depolarization and intracellular Ca^{2+} responses. TRP channels play exceptionally diverse roles in many different tissues, acting as sensors of signals that include temperature, mechanical stress, pheremones, Ca^{2+}, and intracellular messengers. Several studies have now suggested that numerous TRP channels are expressed in β-cells (6–12). Therefore, TRP channels in the β-cell may integrate a variety of stimuli to modulate glucose-stimulated electrical and Ca^{2+} responsiveness. Recent work has focused on the melastatin-related family of channels (TRPM) and suggested roles for these in the control of islet Ca^{2+} oscillations (12) and responses to steroid hormones (9), intracellular protein kinase A (PKA) and cyclic ADP–ribose (cADPR) (8), and hydrogen peroxide (13) (Fig. 1). Uchida et al. have now examined mice lacking TRPM2, demonstrating impaired glucose homeostasis and reduced islet intracellular calcium concentration and secretory responses to glucose and glucagon-like peptide 1 (GLP-1).

TRPM2 contributes to the intracellular Ca^{2+} response of islets by mediating Ca^{2+} influx, and it is interesting that several potential mechanisms, including metabolic and hormonal signals, may regulate this. The authors' previous work demonstrating that β-cell TRPM2 channels are activated by cADPR and PKA (8) may explain why loss of this channel impairs glucose and GLP-1 stimulated insulin secretion, respectively. Consistent with a metabolic requirement for the involvement of TRPM2, insulin secretion stimulated by tolbutamide was preserved in TRPM2$^{-/-}$ islets. However, the role for TRPM2 may be more complex than first thought, because it could be argued that the reduction in glucose-stimulated insulin secretion is greater than can be accounted for by reduced intracellular Ca^{2+} alone. Furthermore, under conditions designed to "clamp" intracellular calcium concentration with KCl and diazoxide, glucose triggers insulin secretion through activation of an "amplifying" pathway (3,14). This well-known effect is completely lost in the TRPM2$^{-/-}$ islets even though no difference was observed in intracellular Ca^{2+} under these conditions (supplementary Fig. 4 in Uchida et al.). One could possibly invoke a role for TRPM2 modulating Ca^{2+} just under the plasma membrane, which would be undetectable by cytosolic Ca^{2+} measurement. However, a recent article by Gilon and colleagues (15) demonstrates that glucose has no effect on submembrane Ca^{2+} under identical conditions. Thus, the present data are suggestive of a role for TRPM2 that is independent of its ability to mediate membrane depolarization or Ca^{2+} entry!

Such a role for ion channels in hormone secretion, separate from their ability to conduct ions, is not without precedent. It has been known for some time that interaction of Ca^{2+} channels with exocytotic soluble *N*-ethylmaleimide attachment protein receptor (SNARE) proteins acts to localize insulin granules close to sites of Ca^{2+} entry, and that disruption of this interaction impairs insulin exocytosis without affecting Ca^{2+} influx (16). The localization of ATP-sensitive K^+ channels to secretory granules suggests a role in insulin secretion, independent of their plasma membrane K^+ conductance (17). More recently, the voltage-dependent K^+ channel Kv2.1, thought to play an important role in β-cell action potential repolarization (18), is proposed to play a direct role in exocytosis in PC12 and chromaffin cells independent of its K^+ conductance through its interaction with the SNARE proteins (19,20). A role for this in insulin secretion, however, has yet to be shown. Indeed, the related TRPM5 channel has been implicated in the direct control of insulin secretion, distinct from the channel's Na^+ conductance, because arginine-stimulated insulin secretion from islets lacking TRPM5 is reported to be impaired (11). Thus, a novel and perhaps direct function for TRPM2 in glucose-stimulated insulin secretion is indicated by the fact that it appears to play a role under conditions in which it is not affecting either membrane depolarization or Ca^{2+} to any detectable degree.

A hallmark of provocative and interesting papers is that they often raise many questions. The work of Uchida et al. succeeds in this respect because it raises several issues

From the Alberta Diabetes Institute and Department of Pharmacology, University of Alberta, Edmonton, Canada.
Corresponding author: Patrick MacDonald, pmacdonald@pmcol.ualberta.ca.
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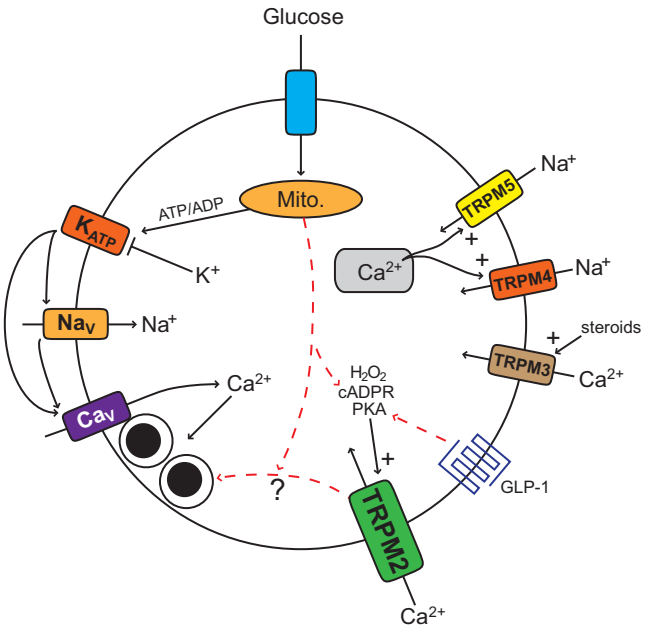

FIG. 1. TRPM channels in insulin secretion. On the left is the consensus triggering pathway for insulin secretion in which a glucose-stimulated rise in the ATP/ADP ratio closes ATP-sensitive K^+ (K_{ATP}) channels, depolarizing the β-cell and activating voltage-gated Na^+ (Na_V) and Ca^{2+} (Ca_V) channels. The latter mediates Ca^{2+} influx that triggers insulin granule exocytosis. On the right are TRPM channels shown to contribute to β-cell Ca^{2+} and insulin responses. TRPM4 and (perhaps to a greater degree) TRPM5 mediate an inward Na^+ current in response to increases in intracellular Ca^{2+}, perhaps through depletion of Ca^{2+} stores, contributing to membrane depolarization and control of Ca^{2+} oscillations. TRPM3 activation by external steroidal signals allows influx of Ca^{2+}. TRPM2 is activated by internal signals that include PKA phosphorylation, cADPR, and hydrogen peroxide (H_2O_2). Uchida et al. demonstrate a role for TRPM2 in glucose and GLP-1 stimulated Ca^{2+} responses and insulin secretion. Also intimated in their data is a role for TRPM2 as a regulator of the "amplifying" effects of glucose independent from the channel's role in mediating Ca^{2+} influx. Putative interactions are shown as red dashed arrows. Mito., mitochondria.

with respect to the role of TRPM2 in insulin secretion. Is this channel activated by GLP-1? Is it regulated by β-cell glucose metabolism, and does cADPR act as a signal for this? Does TRPM2 play a role in the amplifying effects of glucose? If so, is this through some as yet undetected effect on Ca^{2+}, or is it through some unsuspected role independent from its ability to conduct Ca^{2+} ions? These questions can only be answered by a more detailed investigation of the interaction of TRPM2 with the insulin secretory machinery and the regulation of this interaction by intracellular cues. Nonetheless, it is clear that a number of TRP channels are important contributors to pancreatic islet function, and we will continue our "TRP" down the path toward a fuller understanding of the complexity underlying the physiological mechanism of insulin secretion.

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