REVIEW

The role of thermosensitive TRP (transient receptor potential) channels in insulin secretion

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Abstract. Insulin secretion from pancreatic β -cells is the only efficient means to decrease blood glucose concentrations. Glucose is the principal stimulator of insulin secretion with the ATP-sensitive K^+ channel-voltage-gated Ca^{2+} channel-mediated pathway being the primary one involved in glucose-stimulated insulin secretion. Recently, several reports demonstrated that some transient receptor potential (TRP) channels are expressed in pancreatic β -cells and contribute to pancreatic β -cell functions. Interestingly, six of them (TRPM2, TRPM4, TRPM5, TRPV1, TRPV2 and TRPV4) are thermosensitive TRP channels. Thermosensitive TRP channels in pancreatic β -cells can function as multimodal receptors and cause Ca^{2+} influx and membrane depolarization at physiological body temperature. TRPM channels (TRPM2, TRPM4 and TRPM5) control insulin secretion levels by sensing intracellular Ca^{2+} increase, NAD metabolites, or hormone receptor activation. TRPV2 is involved not only in insulin secretion but also cell proliferation, and is regulated by the autocrine effects of insulin. TRPV1 expressed in sensory neurons is involved in β -cell stress and islet inflammation by controlling neuropeptide release levels. It is thus clear that thermosensitive TRP channels play important roles in pancreatic β -cell functions, and future analyses of TRP channel function will lead to better understanding of the complicated mechanisms involved in insulin secretion and diabetes pathogenesis.

Key words: Thermosensitive TRP channel, Insulin secretion, Pancreatic β -cell, Glucose tolerance, Intracellular Ca^{2+}

MOST transient receptor potential (TRP) channels are non-selective cation channels. The name TRP comes from the prototypical member in *Drosophila*, where a mutation resulted in abnormally transient receptor potential to continuous light [1]. TRP channels are now divided into seven subfamilies: TRPC, TRPV, TRPM, TRPML, TRPN, TRPP, TRPA, with six subfamilies (all except for TRPN) and 27 channels present in humans. TRP channels are expressed in many tissues and have a wide variety of physiological functions, including detection of various physical and chemical stimuli in vision, taste, olfaction, hearing, touch, and thermosensation [2]. The gene encoding the capsaicin receptor as a noxious heat sensor, which

is now called TRPV1, was isolated from a rodent sensory neuron cDNA library in 1997 and was considered to be a breakthrough for research concerning temperature sensing [3]. Since then, several TRP channels having thermosensitive ability have been identified in mammals, with nine thermosensitive TRP channels reported in mammals to date (Table 1). These channels belong to the TRPV, TRPM, and TRPA subfamilies, and their temperature thresholds for activation are in the range of physiological temperatures, which we can discriminate. TRPV1 and TRPV2 are activated by elevated temperatures, while TRPM8 and TRPA1 are activated by cool and cold temperatures. TRPV3, TRPV4, TRPM2, TRPM4 and TRPM5 are activated by warm temperatures. Thermosensitive TRP channels usually function as 'multimodal receptors' that respond to various chemical and physical stimuli. For example, TRPV1, activated by noxious heat ($> 42^\circ C$), is also a receptor for capsaicin, an active ingredient of chili peppers, and low pH. Activation of these channels could contribute to changes in intracellular Ca^{2+} concentra-

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Table 1 Properties of thermosensitive TRP channels and their expression in pancreatic β -cells

	temperature threshold	tissue distribution	other stimuli	β -cells expression
TRPV1	> 42°C	sensory neuron, brain, skin	capsaicin, proton, shanshool, allicin, camphor, resiniferatoxin, vanillotoxin, 2-APB, propofol, anandamide, arachidonic acid metabolic products (by lipoxygenases), NO, extracellular cation	RINm5F, INS-1, rat islets
TRPV2	> 52°C	sensory neuron, brain, spinal cord, lung, liver, spleen, colon, heart, immunocyte	probenecid, 2-APB, cannabidiol, mechanical stimulation	MIN6, mouse β -cells
TRPV3	> 32°C	skin, sensory neuron, brain, spinal cord, stomach, colon	camphor, carvacrol, menthol, eugenol, thymol, 2-APB	—
TRPV4	> 27–41°C	skin, sensory neuron, brain, kidney, lung, inner ear, bladder	4 α -PDD, bisandrographolide, citric acid, arachidonic acid metabolic products (by epoxygenases), anandamide, hypoosmolality, mechanical stimulation	MIN6
TRPM2	> 36°C	brain, immunocyte etc	(cyclic) ADPribose, β -NAD, H ₂ O ₂ , intracellular Ca ²⁺	INS-1, human islets, RIN-5F, MIN6, rat β -cells, mouse β -cells
TRPM4	warm	heart, liver, immunocyte etc	intracellular Ca ²⁺	INS-1, RINm-5F, Human β -cells, β -TC3, ENG1G9
TRPM5	warm	taste cell	intracellular Ca ²⁺	MIN-6, INS-1, mouse β -cells, human pancreas
TRPM8	< 27°C	sensory neuron	menthol, icilin, eucalyptol	—
TRPA1	< 17°C	sensory neuron, inner cell	allyl isothiocyanate, carvacrol, cinnamaldehyde, allicin, acrolein, icilin, tetrahydrocannabinol, menthol (10–100 μ M), formalin, H ₂ O ₂ , alkalization, intracellular Ca ²⁺ , NSAIDs, propofol/ isoflurane/ desflurane/ etomidate/ octanol/ hexanol	—

Capsaicin (in capsicum), shanshool (in *Zanthoxylum peperitum*, Japanese pepper), allicin (in garlic), camphor (in wood of the camphor laurel), resiniferatoxin (in cactus), vanillotoxin (in tarantula toxin), 2-APB (2-aminomethoxydiphenyl borate), probenecid (an anion transporter inhibitor), carvacrol (in oregano), menthol (in mint), eugenol (in savory), thymol (in thyme), 4 α -PDD (4 α -phorbol 12,13-didecanoate), bisandrographolide (in andrographis), ADP-ribose (adenosine di-phosphoribose), β -NAD (β -nicotinamide dinucleotide), icilin (a super cooling agent), eucalyptol (in eucalyptus), allyl isothiocyanate (in wasabi), cinnamaldehyde (in cinnamon), acrolein (in tear gas), tetrahydrocannabinol (in cannabis plant), NSAIDs (non-steroidal anti-inflammatory drugs), isoflurane/ desflurane/ etomidate/ octanol/ hexanol (all analgesia).

tions ($[Ca^{2+}]_i$) and control of membrane potentials in many cell types.

Insulin secretion from pancreatic β -cells is the only efficient means to decrease blood glucose concentrations. Accordingly, insulin secretion is strictly controlled by glucose, hormones, and autonomic nervous system activity. The trigger pathway for glucose-stimulated insulin secretion is generally described as involving an ATP-sensitive K⁺ (K_{ATP}) channel-voltage-gated Ca²⁺ channel (VGCC)-mediated pathway. In the first step, glucose is transported into β -cells through glucose transporter 2 (GLUT2) to produce a change in the ATP/ADP ratio, which in turn generates membrane depolarization through a direct block of K_{ATP} channels. VGCCs open upon depolarization, leading to $[Ca^{2+}]_i$ increase whereupon oscillations of $[Ca^{2+}]_i$ and membrane potentials drive pulsatile insulin secretion. The main source

for the increase in $[Ca^{2+}]_i$ is Ca²⁺ influx through L-type VGCCs, but recent electrophysiological studies indicated that many ion channels can contribute to Ca²⁺ signaling and changes in membrane potentials, and their relative importance has been examined [4, 5]. Thus, insulin secretion mechanisms are very complicated. Several reports showed that TRPC1, TRPC2, TRPC4, TRPC6, TRPV1, TRPV2, TRPV4, TRPV5, TRPM2, TRPM3, TRPM4, and TRPM5 channels are expressed in pancreatic β -cells [6–12], and that six (TRPM2, TRPM4, TRPM5, TRPV1, TRPV2 and TRPV4) are thermosensitive TRP channels. Interestingly, among the thermosensitive TRP channels expressed in pancreas, four channels are warm temperature-sensitive channels (activated around body temperature) (Table 1), indicating that these channels have functions at physiological body temperature conditions that differ from

environmental temperature sensing. In this review, we focus on the involvement of thermosensitive TRP channels (TRPM2, TRPM4, TRPM5, TRPV1, TRPV2 and TRPV4) in pancreatic β -cell functions, especially in insulin secretion, development of type-1 diabetes, and the autocrine effects of insulin.

TRPM2

TRPM2 is a highly Ca^{2+} -permeable cation channel that is activated by nicotinamide adenine dinucleotide (NAD), adenosine 5'-diphosphoribose (ADPR), hydrogen peroxide (H_2O_2), and intracellular Ca^{2+} . TRPM2 is predominantly expressed in the brain and has also been detected in the bone marrow, spleen, heart, liver, lung, and immunocytes [13-15]. Some reports have shown that TRPM2 plays a role in processes such as chemokine release and cell death [15, 16]. While searching for a novel thermosensitive TRP channel, we found that TRPM2 has thermosensitivity and is activated by cyclic ADPR (cADPR) at body temperature [17]. Furthermore, our group and others found that TRPM2 is also expressed in pancreatic β -cells (Table 1) [17-20]. To clarify the physiological function of TRPM2 in pancreatic β -cells, we analyzed TRPM2 knockout (TRPM2-KO) mice [21]. In TRPM2-KO mice, glucose clearance was impaired with an accompanying reduction in plasma insulin levels. An oral glucose tolerance test in TRPM2-KO mice revealed that plasma insulin levels, which are believed to reflect the action of incretin hormones on food intake, were significantly reduced shortly after glucose administration. Insulin secretion stimulated by glucose and incretin hormones was also reduced in TRPM2-deficient islets. Furthermore, TRPM2-deficient pancreatic β -cells showed a blunted increase in $[\text{Ca}^{2+}]_i$ in response to glucose stimulation and incretin hormones (Fig. 1). While activation of TRPM5 causes depolarization leading to L-type VGCC activation and subsequent $[\text{Ca}^{2+}]_i$ increases needed for insulin secretion (see below), TRPM2 activation induces both Ca^{2+} influx (through TRPM2 channel pores) and depolarization, the latter of which could activate L-type VGCCs. However, TRPM2 action may be more complicated because TRPM2-KO islets did not show glucose-stimulated insulin secretion under $[\text{Ca}^{2+}]_i$ clamp conditions when incubated with KCl and the K_{ATP} channel agonist diazoxide [21]. As such, insulin secretion *via* TRPM2 may involve Ca^{2+} influx-independent mechanisms.

Glucose and incretin stimulate TRPM2 activation but the precise mechanism for modulation of TRPM2 activity remains unclear. cADPR, reported to be involved in glucose-stimulated insulin secretion [22], is a candidate TRPM2 activator (Fig. 1). Furthermore, the fact that NAD also activates TRPM2 indicates that NAD and its metabolites in concert may activate TRPM2 at body temperature. Protein kinase A (PKA), which is involved in insulin secretion downstream of incretin receptors, potentiates TRPM2 activity [17], suggesting that PKA acts as a modulator of TRPM2 activity, likely through phosphorylation (Fig. 1). Increased $[\text{Ca}^{2+}]_i$ resulting from several mechanisms may further activate TRPM2 [23]. TRPM2 is also known to be activated by H_2O_2 , with several reports showing that Ca^{2+} influx through TRPM2 activation is induced by H_2O_2 and that tumor necrosis factor α (TNF- α) causes cell death in pancreatic β -cell lines [15, 19, 20]. Oxidative stress is known to activate TRPM2 through ADPR-dependent and -independent mechanisms [24] using ADPR synthesized in the nucleus and mitochondria. From these reports, it is possible that TRPM2 activation can lead to either insulin secretion or β -cell death depending on the extent of its activation.

TRPM4 and TRPM5

TRPM4 and TRPM5 are monovalent cation-permeable channels expressed in pancreatic β -cells that are activated by intracellular Ca^{2+} , although they are not Ca^{2+} permeable (Table 1) [25-28]. In pancreatic β -cells, $[\text{Ca}^{2+}]_i$ increase is needed for exocytosis of insulin-containing vesicles. The main source of the increased $[\text{Ca}^{2+}]_i$ is Ca^{2+} influx through VGCCs activated by membrane depolarization resulting from a direct blocking of K_{ATP} channels. As shown above, TRPM2 activation induces both Ca^{2+} influx and depolarization, with the latter activating L-type VGCCs. In contrast, TRPM4 and TRPM5 could be activated by increasing $[\text{Ca}^{2+}]_i$ and this activation causes membrane depolarization by Na^+ influx through the channels (Fig. 1).

TRPM4 is expressed in the heart, prostate, colon and other tissues in addition to the pancreas, and some reports indicate that TRPM4 is involved in the immune response and cardiac activity [29, 30]. In a rat pancreatic β -cell line (INS-1), glucose-stimulated insulin secretion was suppressed by expression of dominant negative TRPM4. Furthermore, impaired insulin secretion was also observed upon treatment with the

Fig. 1 Thermosensitive TRP channel-mediated insulin secretion.

The main triggering pathway for glucose-stimulated insulin secretion is the ATP-sensitive K⁺ (K_{ATP}) channel-voltage-gated Ca²⁺ channel (VGCC)-mediated pathway shown on the left. Glucose uptake in β -cells through a glucose transporter 2 (GLUT2) causes an increased ATP/ADP ratio that closes K_{ATP} channels, causing membrane depolarization (depo.), followed by Ca²⁺ influx through VGCCs. TRPM2 is activated by cyclic adenosine 5'-diphosphoribose (cADPR) at body temperature (body temp.), protein kinase A (PKA) phosphorylation, and intracellular Ca²⁺. TRPM2 is involved in Ca²⁺ responses and insulin secretion stimulated by glucose, and this response is further potentiated by incretin hormones. TRPM4 and TRPM5 are intracellular Ca²⁺-activated monovalent cation-permeable channels. Activation of these channels by intracellular Ca²⁺ increases (can be through many pathway shown as dashed arrows) induces membrane depolarization, causing activation of VGCCs, which is important for forming Ca²⁺ oscillations. TRPV2 is mainly distributed in the cytoplasm, especially in the endoplasmic reticulum under unstimulated conditions. Insulin secreted by glucose stimulation causes TRPV2 translocation and subsequent increases in intracellular Ca²⁺ concentrations. These autocrine effects of insulin induce further insulin secretion and β -cell proliferation. Mit., mitochondria.

Gq-coupled receptor agonist arginine vasopressin [25]. TRPM4 activity could be modulated by membrane depolarization, increased Ca²⁺ from the extracellular space through VGCCs and from intracellular Ca²⁺ stores, or activation of the PLC/PKC pathway. However, glucose clearance and insulin secretion were recently reported to be normal in TRPM4 knockout (TRPM4-KO) mice and glucose-stimulated insulin secretion from TRPM4 deficient islets was also found to be intact [29]. On the other hand, TRPM5 knockout (TRPM5-KO) mice exhibit impaired glucose clearance resulting from reductions in insulin secretion [28, 31], suggesting that among the two Ca²⁺-activated monovalent cation-permeable TRP channels, TRPM5 could predominantly contribute to pancreatic functions. TRPM5 shows a relatively restricted expression pattern compared with TRPM4 (i.e. mainly expressed in taste cells, pancreatic β -cells and some intestinal epithelial cells) [32]. Colasoul *et al.* showed that TRPM5 is expressed in pancreatic β -cells and that glucose-induced oscillations in membrane potentials are impaired

in TRPM5-deficient islets [28]. In TRPM5-KO mice, glucose tolerance was impaired and insulin secretion was reduced after oral or intraperitoneal glucose administration [28, 31]. Ca²⁺ oscillation in wild-type islets can be classified into three patterns: fast (frequency > 0.015 Hz); slow (frequency < 0.015 Hz); and mixed. Interestingly, the fast type oscillation was not observed in TRPM5-deficient islets. Furthermore, the fast oscillation of membrane potentials is almost abolished in TRPM5-deficient islets [28]. One proposed model is that these fast oscillations are controlled by ion channel activity during persistent high glycolytic activity [33]. TRPM5 could be the relevant ion channel because it can control oscillation of cytosolic Ca²⁺ levels and membrane potentials in pancreatic β -cells.

TRPV1, TRPV2 and TRPV4

TRPV1 is a highly Ca²⁺-permeable cation channel and is dominantly expressed in unmyelinated primary sensory neurons. Many reports revealed that TRPV1 is

involved in sensing noxious heat and other nociceptive stimuli (Table 1) [3, 34, 35]. Although there is evidence for TRPV1 expression in a rat pancreatic β -cell line (RIN-5F) and that capsaicin treatment of rat pancreatic β -cells or systemically injected into rats was reported to cause insulin secretion [7], it is not generally accepted that TRPV1 is expressed in pancreatic β -cells. Instead, TRPV1 is well expressed in primary sensory neurons innervating the pancreas and TRPV1 activity might contribute to maintenance of islet inflammation and insulin resistance [36]. Razavi *et al.* found that elimination of TRPV1-positive sensory neurons (TRPV1⁺ neurons) by injection of capsaicin reduced diabetes progression in type-1 diabetic model mice (NOD mice). Furthermore, islet infiltration and the proportions and absolute numbers of CD8⁺ and activated CD8⁺CD69⁺ effector T lymphocytes in pancreatic lymph nodes were reduced in TRPV1⁺ neuron-eliminated NOD mice. Mutations of the TRPV1 gene were also found in NOD mice and capsaicin responses were reduced both in *in vivo* and *in vitro* analyses of these mice, suggesting that polymorphisms may affect TRPV1 function. Accumulation of substance P in nerve endings was also observed in NOD mice. If reduction of substance P release is critical for islet pathology in NOD mice, increased substance P levels should affect pathogenic processes. As predicted, intra-arterial injection of substance P to the pancreas improved islet infiltration, blood glucose levels, and insulin resistance. From these results, a feedback model is proposed (Fig. 2). In normal mice, insulin from islet β -cells controls not only blood glucose levels but also the levels of substance P released from TRPV1-expressing sensory neurons. Neuropeptides including substance P maintain pancreatic β -cell physiology. This feedback balances levels of insulin and substance P in an optimal range. In the case of NOD mice, TRPV1 expressing sensory neurons failed to release neuropeptides due to TRPV1 mutation, although insulin is normally secreted from pancreatic β -cells. Disruption of this balance leads to insulin resistance and β -cell stress. Furthermore, T lymphocyte infiltration is also enhanced in islets. As a result, islet β -cell death is facilitated, leading to development of type-1 diabetes. Although this model is quite interesting, few additional supporting studies have appeared since its initial report.

TRPV2 is also a Ca²⁺-permeable cation channel and is expressed in many tissues and cells, including neurons. TRPV2 is reported to be involved in axon out-

Fig. 2 A feedback mechanism between TRPV1-positive sensory neurons and pancreatic β -cells.

A. In normal mice, insulin from islet β -cells controls not only blood glucose levels but also the levels of neuropeptides released from TRPV1-expressing sensory neurons. Neuropeptides maintain pancreatic β -cell physiology. B. In NOD mice carrying TRPV1 mutations, TRPV1-expressing sensory neurons fail to release neuropeptides, including substance P, although insulin is secreted normally from pancreatic β -cells. Disruption of this balance leads to insulin resistance and T lymphocyte infiltration in islets.

growth in developing neurons [37], intestinal movement [38], and immune responses [39]. This channel is also detected in MIN6 cells and mouse pancreatic β -cells [8, 40]. TRPV2 function in pancreatic β -cells is unique compared with those of other thermosensitive TRP channels. Under unstimulated conditions, TRPV2 is mainly distributed in the cytoplasm, especially in the endoplasmic reticulum (ER). High glucose concentrations induce TRPV2 translocation to the plasma mem-

brane, and this translocation can be inhibited by nifedipine, diazoxide and somatostatin, agents known to block glucose-stimulated insulin secretion. Exogenous insulin also caused TRPV2 translocation. Intracellular Ca^{2+} increases were also observed upon TRPV2 activation [8]. This translocation is mediated by PI3kinase downstream of insulin receptor activation [40]. Furthermore, tranilast, a TRPV2 antagonist, and reductions of TRPV2 expression levels by shRNA impaired glucose-stimulated insulin secretion. Inhibition of TRPV2 activation by tranilast also impaired cell proliferation in MIN-6 cells [8]. Thus, TRPV2 appears to be regulated by insulin and is involved in the autocrine actions of this hormone in pancreatic β -cells (Fig. 1).

In contrast to TRPV1 and TRPV2, TRPV4 is dominantly expressed in epithelial cells where it participates in skin barrier functions and detecting bladder extension [41, 42]. In addition, TRPV4 mutations have been found to cause several genetic disorders [43-45]. TRPV4 can be activated by physical stimuli, including volume changes, osmolality, and mechanical stimuli. One report showed that TRPV4 is also expressed in the mouse pancreatic β -cell line MIN-6 [9]. In MIN-6 cells, aggregated human islet amyloid polypeptide (hIAPP) interacts with the plasma membrane and increases $[\text{Ca}^{2+}]_i$ by activating TRPV4. This $[\text{Ca}^{2+}]_i$ increase causes ER stress and impaired cell viability [9]. Although there is little evidence for TRPV4 involvement in insulin secretion, $[\text{Ca}^{2+}]_i$ increases in β -cells may occur through TRPV4 activation caused by cell volume changes upon glucose uptake [46, 47].

Perspectives

Thermosensitive TRP channels act not only as ambient temperature sensors, but also as modulators of cell functions such as insulin secretion in pancreatic β -cells. In particular, TRPM channels (TRPM2,

TRPM4 and TRPM5) control insulin secretion levels by sensing intracellular Ca^{2+} increases, NAD metabolites or activation of hormone receptors. Therefore, it is possible that these TRP channels interact with each other through changes in $[\text{Ca}^{2+}]_i$. Increases in $[\text{Ca}^{2+}]_i$ following TRPM2 activation could cause further membrane depolarization leading to TRPM4 and TRPM5 activation. The next question is whether these channels are involved in the development of diabetes. In addition, does TRPM2 activation worsen pathological conditions that accompany diabetes or improve insulin secretion? Further studies with diabetic models and TRP channel-KO mice will provide the answers to these questions. TRPV1 expressed in sensory neurons was found to be involved in β -cell stress and islet inflammation through control of neuropeptide release levels as described above. There are reports indicating that TRPA1- and TRPV4-expressing sensory neurons are involved in pancreatitis-related pain sensation [48, 49], suggesting that not only TRPV1 but also other thermosensitive TRP channels expressed in sensory neurons (TRPV2, TRPM8, TRPA1 and possibly TRPV4) could also be involved in pancreatic β -cell functions. TRPM3 has recently been found to be sensitive to noxious heat [50], although it is not clear whether TRPM3 can also be classified as a thermosensitive TRP channel. Given the report that TRPM3 is expressed in pancreatic β -cells and is involved in insulin secretion as a steroid receptor [12], thermosensitive TRP channels could comprise a larger family than was generally thought and may contribute to many physiological functions in the pancreas. In any case, it is clear that thermosensitive TRP channels play important roles in pancreatic β -cell functions and future analyses of TRP channels will lead to a better understanding of the complicated mechanisms of insulin secretion and diabetes pathogenesis.

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