Transient Receptor Potential Cation Channels in Pancreatic β Cells

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Abstract There is now overwhelming evidence that TRP channels might play a significant role in the regulation of insulin release from pancreatic β cells, which is until now insufficiently recognized. TRP channels are abundantly expressed on β cells. The focus of this review will be on cation channels from the melastatin TRP subfamily. We will discuss how TRPM channels can influence Ca^{2+} signaling in β cells. Knock out models of TRPM2 and TRPM5, which show a pre-diabetic phenotype, will be illustrative for this purpose. Based on these insights, TRPM5 will be critically evaluated as a potential drug target for diabetes type II therapy, which has received currently a high interest of the pharmaceutical industry. In addition, an unexpected role of the TRP channel TRPM3 as a gatekeeper of zinc, which is required for insulin storage, will be considered. Finally, we will critically discuss the use of mouse models for the unraveling of basic mechanisms of insulin release. The study of the role of TRP channels in the regulation of insulin release is of wide interest for fundamental research, evaluation of molecular mechanisms of disease and exploration of novel drug targets for metabolic diseases.

1 Basic Mechanisms of Insulin Secretion in Beta Cells

The β cell is one of five types of cells present in the pancreatic islets of Langerhans, which are islands of cells distributed throughout the pancreas (Kulkarni 2004). The islet is a complex structure consisting of 5 different cell types: insulin-secreting β cells (which constitute 65–90% of the islet cell population), glucagon-releasing

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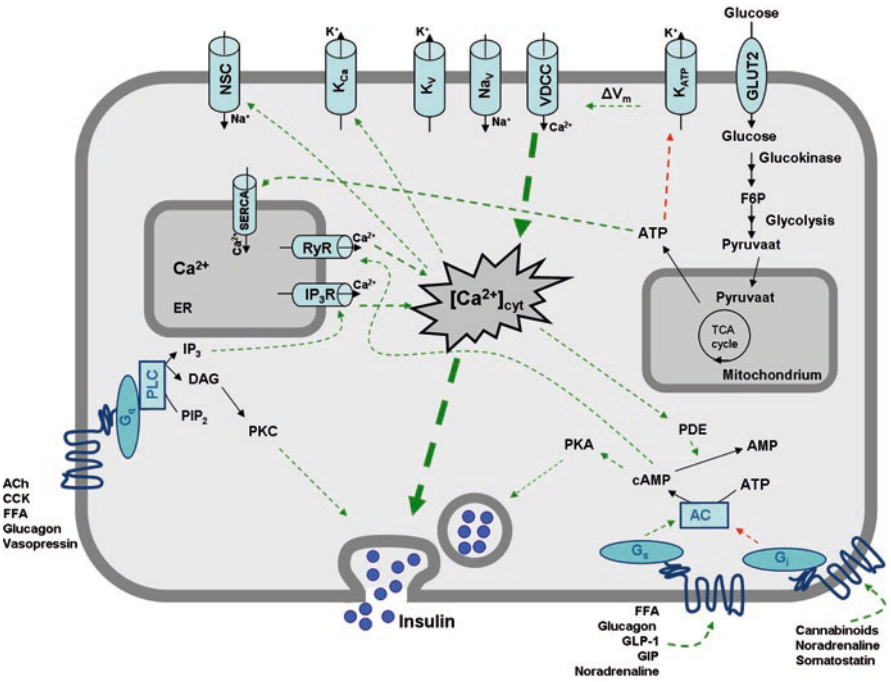

Fig. 1 Stimulus-secretion coupling of the pancreatic β cell. Glucose enters the beta cell and glucose metabolism produces ATP, which closes ATP-sensitive K^+ channels. This leads to a series of events with depolarization of the membrane potential and activation of voltage-dependent Ca^{2+} channels. The resulting Ca^{2+}-influx and increase in cytosolic Ca^{2+} triggers exocytosis of insulin-containing vesicles. Many other ion channels influence the electrical activity and the insulin release can be modulated by many factors, including hormones and neurotransmitters, as indicated. *NSC* non-selective cation channel, K_{Ca} Ca^{2+}-activated K^+ channels, K_V voltage-gated K^+ channels, Na_V voltage-gated Na^+ channels, *VDCC* voltage-dependent Ca^{2+} channel, K_{ATP} ATP-sensitive K^+ channel, *GLUT2* glucose transporter 2, *F6P* fructose-6-phosphate, *SERCA* sarco/endoplasmic reticulum Ca^{2+}-ATPase, IP_3R IP_3 receptor, *RyR* ryanodine receptor, *ER* endoplasmic reticulum, *PDE* phosphodiesterase, *AC* adenlyly cyclase, *FFA* free fatty acids, *GIP* glucose-dependent insulinotropic peptide, *cAMP* cyclic adenosine monophosphate

α cells, somatostatin-producing δ cells, polypeptide-containing PP-cells and ghrelin-secreting ε cells. Insulin is synthesized and secreted into the blood by the β cells mainly in response to glucose but also in response to other nutrients (such as amino acids and fatty acids), hormones (e.g. the incretin hormones GLP-1 and GIP) and neurotransmitters (e.g. ACh) (Newsholme et al. 2010; Winzell and Ahren 2007). Insulin lowers the blood glucose by promoting glucose uptake and nutrient storage in muscle, fat and liver. As it is the only blood glucose lowering hormone and essential for glucose homeostasis, its secretion is a very tightly regulated process that when altered may result in hypoglycemia or hyperglycemia. The latter can result in glucose intolerance and diabetes mellitus (LeRoith 2002).

The secretion of insulin by the pancreatic β cell is a complex process driven by electrical activity and oscillations of the intracellular Ca^{2+} concentration, $[Ca^{2+}]_i$ [see Fig. 1 and (MacDonald and Rorsman 2006)]. Briefly, glucose enters the β cell via

the high K_m GLUT-2 transporter. The rate-limiting glucosensor that determines the characteristic sigmoidal glucose concentration dependence of insulin secretion is the first phosphorylation step in glucose metabolism exerted by the high K_m glucokinase. The metabolism of glucose produces ATP, which closes ATP-sensitive K^+ channels. Consequently, the membrane potential will depolarize, supported by a still unidentified depolarizing conductance (Henquin 2009; Henquin et al. 2009). Indeed, the closure of K_{ATP} increases the input resistance of the β cell, allowing e.g. small inward currents to generate significant depolarizations (Rorsman and Trube 1985). These mechanisms may result in the activation of voltage-dependent Ca^{2+} channels. The ensuing Ca^{2+} increase, together with the resulting Ca^{2+}-induced Ca^{2+} release (Lemmens et al. 2001), causes exocytosis of insulin-containing vesicles. Ca^{2+} stimulates insulin secretion by regulating docking and initiating fusion of secretory granules with the plasma membrane, a process mediated by SNARE proteins (MacDonald and Rorsman 2007).

2 Role of Ion Channels: The Classical View

The activity of ATP-sensitive K^+ channels, voltage-dependent Ca^{2+} channels and other ion channels results in a typical pattern of electrical activity of the beta cell, consisting of slow waves of depolarized plateaus on which bursts of action potentials are superimposed (Ashcroft and Rorsman 1989; Drews et al. 2010) and separated by electrically silent intervals. The oscillating process regenerates as long as the glucose concentration is elevated and is glucose-dependent: with increasing glucose concentration, burst phases are prolonged and interburst phases are shortened until continuous activity is reached at glucose concentrations above ~25 mM. This typical pattern of electrical activity is accompanied by simultaneous oscillatory changes in $[Ca^{2+}]_i$. The origin of this characteristic pattern is a complex interplay between different ion channels, intracellular Ca^{2+} levels ($[Ca^{2+}]_{cyt}$) and the cellular metabolism of the beta cell (Bertram et al. 2007). After closure of ATP-sensitive K^+ channels as a result of glucose metabolism and ATP production, the membrane potential depolarizes with the help of an unidentified depolarizing background conductance. The activation of voltage-dependent Ca^{2+} channels causes the initiation of the electrical activity and is responsible for the fast upstroke of the action potentials on top of the burst. The repolarizing phase of the action potential is caused by activation of delayed-rectifier and Ca^{2+}-dependent K^+ channels. These channels close at around −40 mV, which is the origin of the plateau potential (Ashcroft and Rorsman 1989).

Why do β cells generate an oscillatory pattern of $[Ca^{2+}]_i$ during constant glucose stimulation? The pattern results mainly from an equilibrium between hyperpolarizing K^+ conductances and depolarizing Ca^{2+} conductances and the following course of events has been proposed (Ashcroft and Rorsman 1989; Drews et al. 2010; MacDonald and Rorsman 2006). While the depolarizing component dominates at the beginning of the burst, this decreases during the burst of activity due to Ca^{2+}-dependent inactivation of VDCC. Furthermore, Ca^{2+}-dependent K^+ channels and ATP-sensitive K^+ channels will be activated during the burst as a result of the

increase in intracellular Ca^{2+} and a lowering of the ATP/ADP ratio (due to an increased Ca^{2+}-ATPase activity and depolarization of the mitochondrial potential $\Delta\Psi$) respectively. As a result, the V_m hyperpolarizes and the burst terminates. During the interburst interval, the intracellular Ca^{2+} concentration lowers which results in a decrease of Ca^{2+}-dependent K^+ channel activity, a decrease in the activity of Ca^{2+}-ATPase, a hyperpolarization of the mitochondrial potential $\Delta\Psi$ and a resulting increase in ATP production and finally a recovery of the voltage-dependent Ca^{2+} channels from inactivation. All these events result in a depolarization of the membrane potential, an increase in intracellular Ca^{2+} concentration and the initiation of the next burst. The duration of the interburst interval is proposed to be determined by the rate of recovery of voltage-dependent Ca^{2+} channels from inactivation (Santos et al. 1991).

This glucose-induced electrical activity and insulin release can be modulated by several factors, including several hormones, neurotransmitters and nutrients like amino acids (see Fig. 1). The incretin hormone GLP-1 enhances glucose-induced insulin secretion and is suggested to depolarize the Vm in several ways, including closure of K_{ATP} channels, activation of yet unidentified nonselective cation currents and Ca^{2+}-mobilization from intracellular stores (Miura and Matsui 2003; Holst 2007; Winzell and Ahren 2007). The neurotransmitter ACh enhances insulin secretion by acting via the PLC pathway and by activation of a Na^+ current. The latter mechanism is still unclear, but might be due to activation of the NALCN leak channel via a G-protein independent pathway (Gilon and Rorsman 2009). Finally, the hormones glucagon and somatostatin, released by α and δ cells from the pancreatic islet, can respectively stimulate and inhibit insulin release in a paracrine manner.

3 Expression of TRP Channels in Pancreatic β Cells

The consensus model of glucose-induced insulin release attributes the depolarization of the membrane potential towards the initiation of electrical activity to the closure of ATP-sensitive K^+ channels. However, this event needs the presence of an additional inward background current that can bring the membrane potential away from the equilibrium potential of K^+. Because of the increased input resistance of the β cells by closure of K_{ATP}, only small currents are required to bring about depolarization. At this point, the identity of this current is still unclear (Gilon and Rorsman 2009; Henquin 2009; Henquin et al. 2009). In theory, the current could be produced by an efflux of Cl^- or a cation influx. TRP channels were often regarded as interesting candidates for this background depolarizing current (Drews et al. 2010; Jacobson and Philipson 2007).

Transient receptor potential (TRP) channels form a large group of cation channels with 28 mammalian members that can be subdivided into six main subfamilies based on amino acid homology (see Fig. 2): TRP canonical (TRPC; TRPC1-7, with *Trpc2* being a pseudo gene in humans), TRP vanilloid (TRPV; TRPV1-6), TRP melastatin (TRPM; TRPM1-8), TRP polycystin (TRPP; TRPP2, TRPP3 and

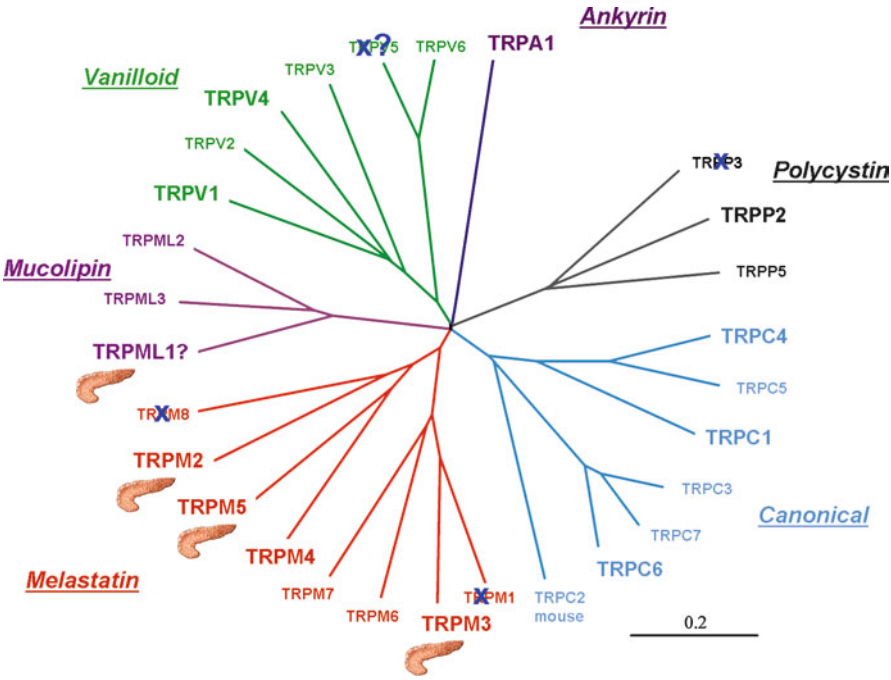

Fig. 2 Phylogenetic tree of the mammalian TRP superfamily. TRPC (canonical), TRPM (melastatin), TRPV (vanilloid), TRPA (ankyrin), TRPP (polycystin), and TRPML (mucolipin). *Trpc2* is a pseudogene in humans. TRP channels with a probably high functional impact are indicated by a *logo*, *larger letter type* indicates high expression but lack of a functional impact, *small letter type* indicates low expression. TRPM2, TRPM5 and TRPM3 are considered as the most important TRP channels in regulating insulin release. In our own assays, TRPML1 and TRPP2 are the channels with the highest expression (Colsoul B., Nilius B., Vennekens R. unpublished).The role of the highly expressed intracellular channel TRPML1 might be related to endo/exocytosis. TRP channels marked by a *cross* are probably not present in β cells

TRPP5), TRP mucolipin (TRPML; TRPML1-3) and TRP ankyrin (TRPA; TRPA1) (Pedersen et al. 2005). Topologically, all TRP channels are membrane proteins with six putative transmembrane segments (S1–S6) and a cation permeable pore-forming loop between S5 and S6. Most TRP channels are non-selective Ca^{2+} permeable channels, although the permeability ratios P_{Ca}/P_{Na} vary considerably, ranging from 0.3 for TRPM2 to >100 for TRPV5 and TRPV6 (Owsianik et al. 2006). TRPM4 and TRPM5 are the only two TRP channels that are impermeable to Ca^{2+} and exclusively permeable to monovalent cations. The gating of TRP channels is very diverse (Nilius et al. 2005a, 2007a; Rohacs and Nilius 2007; Voets and Nilius 2007) and TRP channels can be activated by a plethora of stimuli, including ligand binding, voltage, cell swelling or temperature. Due to this diversity of stimuli, TRP channels can act as polymodal cellular sensors in many cell types: they measure changes in the environment to initiate adequate cell, organ and behavioral responses, e.g. taste/pain transduction and temperature sensing. They contribute to changes in the

cytosolic free Ca^{2+} concentration either by acting as Ca^{2+} entry pathways in the plasma membrane or by influencing the membrane potential, in this way modulating the driving force for Ca^{2+} entry mediated by alternative pathways. Thus, TRP channels influence a plethora of Ca^{2+}-dependent cell functions such as gene transcription, migration, cell death and exocytosis and are implicated in human diseases (Nilius et al. 2005b, 2007b).

Interestingly, more and more TRP channels are being described in primary beta cells or insulin-secreting cell lines [see Table 1, Fig. 1 and (Jacobson and Philipson 2007)]. Indeed, TRPV2, TRPV4, TRPC1, TRPC4, TRPC6, TRPM2, TRPM3, TRPM4 and TRPM5 are identified in insulinoma cell lines such as MIN6 (mouse) or INS-1 (rat). Many of these channels have also been described in primary tissue with expression of TRPV2, TRPV4, TRPC1, TRPM2, TRPM3, TRPM4 and TRPM5 reported in mouse islets and TRPM2, TRPV5, TRPC1 and TRPC4 in rat islets or beta cells. Interestingly, no expression could be found in mouse islets for TRPV5 [which contrasts with earlier reports demonstrating expression in rat islets (Janssen et al. 2002)], TRPM1, TRPM8 or TRPP3, whereas TRPML1 and TRPP2 are highly expressed (Colsoul B., Nilius B., Vennekens R., unpublished). Not much is known yet about expression of TRP channels in human tissue: TRPV5 and TRPV6 are detected in human pancreas and TRPM2, TRPM4 and TRPM5 are specifically reported to be expressed in human islets. In the next sections, we describe the current knowledge of the function of these TRP channels in insulin release.

4 Modulation of Insulin Release by TRP Channels

4.1 TRP Canonicals

TRPC channels are non-selective Ca^{2+} permeable cation channels, with the selectivity ratio P_{Ca}/P_{Na} varying significantly between the different family members (Gees et al. 2011). TRPC channels are widely expressed and their characterization is complicated by the possible occurrence of heterotetramers. TRPC1 mRNA could be detected in INS-1 cells and rat beta cells and at high levels in mouse islets and MIN6 cells, whereas it could not be detected in another mouse insulinoma cell line βTC3. (Sakura and Ashcroft 1997; Li and Zhang 2009). Four transcripts for mouse TRPC1 RNA, representing different splice variants, have been found in mouse islets and the beta cell line MIN6 (Sakura and Ashcroft 1997). However, the influence of TRPC1 on insulin release still needs to be determined.

Not much is known about other TRPC channels in insulin release. Although TRPC4 could be detected in βTC3 and INS-1 cells and in rat beta cells and mouse islets (Roe et al. 1998; Freichel et al. 2004; Li and Zhang 2009), analysis of blood glucose homeostasis by glucose tolerance tests did not reveal differences between WT and *Trpc4*-deficient mice both regarding basal glucose levels under fasting conditions as well as following intraperitoneal glucose challenge (Freichel et al. 2004). Since TRPC4 is activated by phospolipase C pathways, it cannot be excluded that

Table 1 Overview of the TRP channels that are shown to be expressed in endocrine pancreas and their proposed function

TRP	Expression in pancreas	Method	General features and activation mechanisms	Proposed function in β cells	Reference
TRPV1	Controversy: expression shown in Sprague-Dawley rat islets and β cell lines (RIN and INS-1); no expression detected in mouse islets or ZDF rat islets	RT-PCR; western blot; immuno-fluorescence	Heat (≥43°C), capsaicin	Unknown	Caterina et al. (1997), Hayes et al. (2000), Akiba et al. (2004), Voets et al. (2004), Razavi et al. (2006), Gram et al. (2007)
TRPV2	MIN6; mouse islets	RT-PCR	Noxious heat (>53°C); translocation to plasma membrane by IGF-1 and insulin	Insulin-induced enhancement of insulin secretion	Caterina et al. (1999), Beech et al. (2004), Hisanaga et al. (2009), Vennekens et al. (2008)
TRPV4	MIN6; mouse pancreas	RT-PCR	Moderate heat (>23°C); cell swelling; 4α-PDD; EETs; shear stress, arachidonic acid	hIAPP-induced Ca^{2+} elevation and apoptosis	Chung et al. (2003), Suzuki et al. (2003), Casas et al. (2008), Masuyama et al. (2008), Everaerts et al. (2010)
TRPV5	Rat pancreatic islets (localization to secretory granules); human pancreas	RT-PCR; immunohis-tochemistry	Highly Ca^{2+}-selective; constitutively active	Ca^{2+} efflux pathway from secretory granules	Muller et al. (2000), Hoenderop et al. (2001, 2003, 2005), Janssen et al. (2002), Nijenhuis et al. (2003a)
TRPV6	Human pancreas	RT-PCR	Highly Ca^{2+}-selective; constitutively active	Unknown	Muller et al. (2000), Hoenderop et al. (2001, 2003, 2005), Nijenhuis et al. (2003a, b)
TRPC1	MIN6; mouse islets; INS-1; rat beta cells (no detection in βTC-3)	Northern blot; RT-PCR	G_q-PLC pathways (PLC); store depletion	Unknown	Sakura and Ashcroft (1997), Roe et al. (1998), Hofmann et al. (2000), Kim et al. (2003), Liu et al. (2003), Rychkov and Barritt (2007), Li and Zhang (2009)

(continued)

Table 1 (continued)

TRP	Expression in pancreas	Method	General features and activation mechanisms	Proposed function in β cells	Reference
TRPC4	βTC-3; INS-1; rat beta cells; mouse islets	Northern blot; RT-PCR	G_q-PLC pathways	Unknown	Roe et al. (1998), Freichel et al. (2001, 2004), Qian et al. (2002), Tiruppathi et al. (2002), Cavalie (2007), Li and Zhang (2009)
TRPC6	βTC-3	Northern blot	G_q-PLC pathways (DAG)	Unknown	Roe et al. (1998), Hassock et al. (2002), Estacion et al. (2004), Li and Zhang (2009)
TRPM2	Several cell lines; rat beta cells; human and mouse islets (localization to plasma membrane and lysosomes)	RT-PCR; immunoblot; immunofluorescence	ADP-ribose; cADPR; NAD; heat; H_2O_2; Ca^{2+}	Glucose-, heat- and GLP-1-induced insulin release; H_2O_2-mediated cell death	Uchida et al. (2011), Qian et al. (2002), Inamura et al. (2003), Kraft and Harteneck (2005), Kuhn et al. (2005), Togashi et al. (2006), Lange et al. (2009), Li and Zhang (2009)
TRPM3	INS-1; mouse islets	RT-PCR; northern blot; western blot	Steroid hormones (PS); hypotonic cell swelling	PS-induced Ca^{2+}-increase; zinc influx	Wagner et al. (2010), Grimm et al. (2003), Lee et al. (2003), Wagner et al. (2008)
TRPM4	Several beta cell lines; mouse and human islets	RT-PCR, immunoprecipitation; western blot; immunofluorescence	Ca^{2+}-impermeable; activation by IC Ca^{2+}, PKC, heat, PIP_2; inhibition by ATP; voltage dependent	Controversy	Cheng et al. (2007), Vennekens et al. (2007), Marigo et al. (2009), Launay et al. (2002), Ullrich et al. (2005)
TRPM5	INS-1; MIN6; mouse and human islets	RT-PCR; immunofluorescence	Ca^{2+}-impermeable; activation by IC Ca^{2+}, heat, PIP_2; voltage dependent	Positive regulation of glucose-stimulated insulin secretion	Brixel et al. (2010), Colsoul et al. (2010), Hofmann et al. (2003), Liu and Liman (2003), Prawitt et al. (2003), Ullrich et al. (2005)

the channel is involved in ACh- or glucagon-induced amplification of insulin release. Finally, TRPC6 transcripts have been detected, although to a low level, in βTC-3 insulin-secreting cells. Thus, it is clear that more research is needed in order to clarify the possible function of TRPC channels in the insulin release of the pancreatic beta cell. It has been suggested that TRPC channels mediate the unknown depolarizing current that account for the Ca^{2+}-release activated cation current characterized earlier in βTC3 cells (Roe et al. 1998).

4.2 TRPM2

TRPM2 is a non-selective Ca^{2+} permeable cation channel with unique gating properties that is fused C-terminally to an enzymatic ADP-ribose pyrophosphatase domain (Perraud et al. 2001). The channel is shown to be expressed in insulin-secreting cell lines, such as the rat cell lines CRI-G1 and RIN-5F, and in human and mouse pancreatic islets (Hara et al. 2002; Qian et al. 2002; Inamura et al. 2003; Togashi et al. 2006). Moreover, the channel co-expresses with insulin but not with glucagon, indicating expression in beta cells (Togashi et al. 2006).

TRPM2 is shown to be activated by various stimuli, including adenine dinucleotides (ADPR, cADPR, NAADP, β-NAD), reactive oxygen species (ROS) such as H_2O_2 and OH^-, and intracellular Ca^{2+} (Perraud et al. 2001; Sano et al. 2001; Hara et al. 2002; Du et al. 2009). In the rat insulinoma cell line CRI-G1, a current with TRPM2-like properties (such as the need of intracellular Ca^{2+} for current activation, an intermediate Ca^{2+} permeability ratio and activation by ADPR and β-NAD) could be detected (Inamura et al. 2003). Furthermore, ADPR elicited rapid activation of linear currents with biophysical and pharmacological characteristics typical of TRPM2 in INS-1 cells and primary mouse beta cells. In *Trpm2*$^{-/-}$ primary beta cells, no ADPR-elicited current could be detected, suggesting that TRPM2 is natively expressed and forms a functional channel in beta cells (Lange et al. 2009).

TRPM2 is important in beta cell apoptosis, a feature linked to the activation of the channel by H_2O_2 and OH^-. These ROS, that are produced by oxidative stress, are thought to play a central role in beta cell death and the consequent development of type 1 and type 2 diabetes (Mandrup-Poulsen 2003; Rhodes 2005). Indeed, activation of TRPM2 by H_2O_2 has been shown to mediate Ca^{2+} influx and beta cell death in a rat beta cell line RIN-5F that natively expresses TRPM2 (Hara et al. 2002; Ishii et al. 2006). Moreover, INS-1 cells with suppressed TRPM2 expression are 72% less affected by H_2O_2-induced cell death (Lange et al. 2009). The H_2O_2-induced Ca^{2+} influx is thought to be mediated by increasing levels of NAD^+, that binds directly to the Nudix motif in the cytosolic C terminal of TRPM2 (Hara et al. 2002). Furthermore, the H_2O_2-induced Ca^{2+} increase is reduced when the cells are treated with scavengers of the hydroxyl radical (Ishii et al. 2006), indicating that H_2O_2 acts by generation of free radicals in the cell interior. TRPM2 activation by H_2O_2 can also be mediated by release of ADP-ribose, a metabolite of NAD^+, from the mitochondria. ADP-ribose directly binds the Nudix motif and in this way activates TRPM2 (Perraud et al. 2001).

Next to the involvement in oxidative stress sensing, TRPM2 has been suggested to contribute to insulin release induced by heat, glucose and incretin hormones (Uchida et al. 2011; Togashi et al. 2006). Indeed, forskolin- (an activator of adenylyl cyclase) and exendin-4- (a GLP-1 receptor agonist) induced insulin release from rat pancreatic islets was significantly reduced in si-TRPM2-treated islets (Togashi et al. 2006). Furthermore, 2-aminoethoxydiphenyl borate (2-APB), a rapid and reversible inhibitor of TRPM2, inhibits both heat- and exendin-4- evoked insulin release from rat pancreatic islets (Togashi et al. 2008). These pharmacological data are confirmed in studies using the *Trpm2*$^{-/-}$ mouse: insulin secretion induced by glucose and GLP-1 was seriously impaired in *Trpm2*-deficient islets, whereas the response to tolbutamide, a K_{ATP} channel inhibitor, was unchanged (Uchida et al. 2011). This impairment of insulin secretion is caused by reduced increases in intracellular Ca^{2+}, indicating that TRPM2 mediates Ca^{2+} influx during glucose- and/or GLP-1 stimulation. However, the situation might be more complex, since glucose-stimulated insulin secretion evoked under conditions of glucose, diazoxide and high K^+ (conditions designed to "clamp" intracellular Ca^{2+}), was lost in *Trpm2*-deficient islets. Since the intracellular Ca^{2+} under these conditions was not altered, these data suggest that TRPM2 mediates insulin secretion independent of its role as a Ca^{2+} entry channel (Uchida et al. 2011).

Finally, TRPM2 has been reported to have an additional role as an intracellular Ca^{2+} release channel in pancreatic beta cells (Lange et al. 2009). Indeed, internally applied ADPR gives rise to a single Ca^{2+} transient both in INS-1 and in primary mouse beta cells and this effect was completely abolished in *Trpm2*$^{-/-}$ primary mouse beta cells. Furthermore, TRPM2 colocalizes with lysosome-associated membrane protein-1 (LAMP1), a specific marker for lysosomes. In agreement with this, ADPR-induced intracellular Ca^{2+} release was abolished in INS-1 cells treated with bafilomycin A, a macrolide antibiotic that empties lysosomal Ca^{2+} stores without affecting ER stores (Bowman et al. 1988). These data indicate that ADPR-dependent TRPM2-mediated Ca^{2+} release occurs predominantly from a lysosomal store. In addition, it is suggested that TRPM2-mediated Ca^{2+} release contributes to H_2O_2-induced apoptosis (Lange et al. 2009). Indeed, H_2O_2 induces significant cell death in INS-1 cells in the absence of extracellular Ca^{2+}, albeit with a reduced severity. This effect was reduced in cells with reduced TRPM2 expression, indicating that not only Ca^{2+} influx through plasma membrane TRPM2 but also TRPM2-dependent lysosomal Ca^{2+} release plays a critical role in H_2O_2-mediated beta cell death (Lange et al. 2009).

4.3 TRPM3

TRPM3 is a member of the melastatin subfamily of TRP channels with limited homology to the heat-sensitive TRPV channels. The TRPM3 gene encodes for the largest number of different TRPM3 isoforms due to alternative splicing and exon usage, leading to channels with divergent pore and gating properties (Oberwinkler et al. 2005). Interestingly, TRPM3 is so far the only TRP channel which hosts a microRNA gene (intron 8 encodes miR-204), which may regulate a variety of target genes at the

transcriptional level (Weber 2005; Oberwinkler and Phillipp 2007). Theoretically, the number of possible variants due to alternative splicing is indeed huge. We refer here only to the (probably most common) variant TRPM3α2 (1709 amino acids: the pore lacks 12 aa in comparison to the longest form TRPM3α1 of 1721 aa).

TRPM3 is expressed in a variety of neuronal and non-neuronal tissue (Oberwinkler and Phillipp 2007), including whole pancreas (Grimm et al. 2003; Fonfria et al. 2006), INS-1 cells and mouse pancreatic islets (Klose et al. 2011; Wagner et al. 2008). TRPM3 channels are directly activated by the neuro-steroid hormone pregnenolone-sulphate (PS). Pancreatic beta cells and INS-1 cells express PS-sensitive channels that share several pharmacological and biophysical properties of recombinant TRPM3 channels [such as sensitivity to nifedipine and block by monovalent cations (Wagner et al. 2008)]. Moreover, PS elicits a large Ca^{2+} increase in INS-1 cells and pancreatic islets, an action dependent on TRPM3 expression. This PS-induced Ca^{2+} increase could be blocked by the selective and potent TRPM3 blocker mefenamic acid in INS-1E cells and mouse pancreatic islets (Klose et al. 2011). Remarkably, mefenamic acid did not block glucose- or tolbutamide- induced Ca^{2+} increase, indicating that TRPM3 is not involved in the K_{ATP}-dependent Ca^{2+} signaling of the beta cell. PS did increase however glucose-induced insulin secretion from pancreatic islets, an effect abolished by mefenamic acid (Klose et al. 2011; Wagner et al. 2008). Thus, TRPM3 is present in pancreatic β cells and activation of the channel increases insulin release via intracellular Ca^{2+} increase although the channel does not seem to influence glucose-induced insulin secretion. Interestingly, PS activation of β cells (via TRPM3 and voltage-gated Ca^{2+} channels) induces the biosynthesis of a gene regulatory protein, the zinc finger transcription factor Egr-1, and in this way leads to increased biosynthesis of insulin (Mayer et al. 2011). However, as the pharmacological concentrations of PS (50 μM) used to demonstrate enhancement of insulin secretion do not occur in vivo, it seems unlikely that PS has an important role in the direct regulation of insulin secretion. It is possible that TRPM3 plays a role in certain conditions where elevated plasma PS levels and changes in glucose homeostasis co-occur (like pregnancy or 21-hydroxylase-deficiency).

4.4 TRPM4

TRPM4 is a Ca^{2+}-activated nonselective monovalent cation channel that is impermeable to divalent cations. The channel has been proposed to control insulin secretion in a rat insulinoma cell line INS-1, where TRPM4 protein is abundantly expressed (Cheng et al. 2007). TRPM4 expression and TRPM4-like channel activity could be detected in the beta cell lines INS-1, HIT-T15, RINm5F, β-TC3 and MIN-6 and the alpha cell line INR1G9 (Cheng et al. 2007; Marigo et al. 2009). Inhibition of TRPM4 decreases the magnitude of the Ca^{2+} signal and insulin release in response to glucose, AVP (arginine-vasopressin, a Gq-coupled receptor agonist in β-cells) and glyburide (glibenclamide) in INS-1 cells (Cheng et al. 2007; Marigo et al. 2009). These data suggest that depolarizing currents generated by TRPM4 are an important component

in the control of intracellular Ca^{2+} signals necessary for insulin secretion. Furthermore, it is suggested that TRPM4-containing vesicles are translocated to the plasma membrane via Ca^{2+}-dependent exocytosis, which may represent a regulatory mechanism by which beta cells regulate electrical activity (Cheng et al. 2007; Marigo et al. 2009). However, all these studies have been performed on cell lines. Although TRPM4 protein expression could be found within insulin-producing human beta cells and mouse pancreatic islets (Marigo et al. 2009), studies on *Trpm4*$^{-/-}$ mice revealed no difference in glucose-induced insulin secretion from freshly isolated pancreatic islets (Vennekens et al. 2007). Moreover, these mice did not suffer from an impaired glucose tolerance after an intraperitoneal injection of glucose. These data suggest that TRPM4 is probably not involved in the signal mechanism following glucose stimulation. On the other hand, this does not exclude a possible role for TRPM4 in G_q- or G_s-receptor-coupled signaling pathways, for example during stimulation with e.g. glucagon or GLP-1. Additionally, TRPM4 is proposed to be involved in glucagon secretion from the pancreatic alpha cell line αTC1-6 (Nelson et al. 2011): TRPM4 inhibition decreased the magnitude of intracellular Ca^{2+} signals and glucagon secretion in response to several agonists such as the G_q–protein coupled receptor agonist AVP and high K^+ (Nelson et al. 2011).

5 TRPM5 as a Modulator of Ca^{2+} Oscillations

TRPM5, like its closest homologue TRPM4, is a Ca^{2+}-activated nonselective monovalent cation channel that is impermeable to divalent cations (Hofmann et al. 2003). The channel is expressed in β cells from pancreatic islets, as its expression colocalizes with insulin. A Ca^{2+}-activated non-selective monovalent cation channel could be measured in β cells and was largely reduced in *Trpm5*$^{-/-}$ mice, indicating that TRPM5 is an important constituent of the Ca^{2+}-activated cation current in β cells (Colsoul et al. 2010). The TRPM5-dependent current is of a small magnitude, ~2pA/pF at −80 mV and 1.5 μM $[Ca^{2+}]_i$ (Colsoul et al. 2010), suggesting that the channel can only influence the electrical activity of β cells under conditions of high electrical resistance. Indeed, whereas no difference could be detected in V_m or intracellular Ca^{2+} in non-stimulatory (low glucose, high K_{ATP} activity) conditions of low electrical resistance, TRPM5 seems to influence electrical activity during glucose stimulation (a condition with low K_{ATP} activity and consequently a high electrical resistance). Whereas normal wild type islets respond to glucose stimulation with three types of oscillations (slow, mixed or fast), *Trpm5*$^{-/-}$ islets displayed specifically a lack of fast glucose-induced oscillations in V_m and Ca^{2+} (Colsoul et al. 2010). TRPM5 contributes to the slow depolarization in the slow interburst interval of the glucose-induced electrical activity, in this way shortening the interburst interval and leading to faster glucose-induced oscillations in V_m and Ca^{2+}. Why TRPM5 is only functionally relevant in a (fast-oscillating) subpopulation of the islets remains unclear but it might be that the weight of TRPM5-mediated depolarization is coupled to the glycolytic rate in the cell. According to the dual oscillator model (Bertram et al. 2007), fast oscillations are

characterized by a high glycolytic rate (and a resulting high ATP production). This situation would make TRPM5 activity able to depolarize V_m in the interburst interval, as the hyperpolarizing K_{ATP} current is largely inactive at that point. This is in contrast with the situation in slow oscillating islets, where the oscillating glycolytic rate and the resulting high activity of K_{ATP} in the interburst interval would make TRPM5 insufficient to depolarize V_m. Fast Ca^{2+} oscillations are shown to be more efficient than slow oscillations in triggering exocytosis of secretory vesicles and insulin release (Berggren et al. 2004). In line with this, glucose-induced insulin release was reduced in isolated pancreatic islets from *Trpm5*$^{-/-}$ mice.

6 Lessons Form Knock-Out Models: TRPM2 and TRPM5

It is clear that many TRP channels are proposed to be involved in insulin release, but the majority of evidence comes from insulinoma cell lines. In order to define the role of TRP channels in insulin release and glucose homeostasis, it is necessary to study their function in vivo. So far, 2 knock out animals display dysfunctions in their glucose homeostasis. Studies on the *Trpm2*$^{-/-}$ mouse confirmed that TRPM2 is involved in insulin secretion stimulated by glucose and that further potentiated by incretins (Uchida et al. 2011). The *Trpm2*$^{-/-}$ mice exhibit higher basal glucose levels and an impaired glucose tolerance caused by lower plasma insulin levels (Uchida et al. 2011). These data suggest that TRPM2 might be a new target for diabetes therapy. Two independent laboratories have described a similar phenotype for the *Trpm5*$^{-/-}$ mice. TRPM5 is involved in glucose-induced insulin release and *Trpm5*-deficient mice display an impaired glucose tolerance during oral and intraperitoneal glucose tolerance tests (Brixel et al. 2010; Colsoul et al. 2010), caused by lower plasma insulin levels. These data suggest that *Trpm2*- and *Trpm5*- deficient mice display a prediabetic phenotype, caused by beta cell dysfunction. The relevance of this prediabetic phenotype during conditions of higher insulin demand (such as pregnancy, obesitas, ageing, etc.) remains to be shown.

7 An Intestinal TRPM5 Connection: Incretins

Interestingly, TRPM5 might influence glucose homeostasis indirectly via the incretin effect. The channel is detected in enteroendocrine cells of the gut, a population of intestinal solitary cells that is believed to play a role in chemosensation and releases hormones such as glucagon-like peptide 1 (GLP-1). GLP-1 is released from L cells and is, together with glucose-dependent insulinotropic hormone (GIP) released from K cells, responsible for the so-called incretin effect: an increase in the release of insulin even before plasma glucose levels have increased (Burcelin 2005). Interestingly, enteroendocrine cells show similarities to the taste cells of the taste bud. The function of TRPM5 in the taste transduction of sweet, bitter and umami tastes is well described (Zhang et al. 2003). Binding of taste compounds to

GPCR in these cells results in activation of the GTP-binding protein α-gustducin, functional interaction with PLCβ2, formation of IP_3 and release of Ca^{2+} from intracellular stores. Consequently, TRPM5 is activated by the resulting increase in intracellular Ca^{2+} and causes depolarization of the membrane potential (Huang and Roper 2010). It is hypothesized that a similar pathway leads to GLP-1 release in enteroendocrine cells. Several reports describe expression of TRPM5 and other taste signaling molecules (taste receptors, α-gustducin and PCLβ2) in enteroendocrine cells and involvement of this pathway in the release of GLP-1 (Jang et al. 2007; Rozengurt and Sternini 2007; Kokrashvili et al. 2009b). E.g. *α-gustducin*$^{-/-}$ mice showed no significant rise in plasma concentrations of GLP-1 and a delayed rise in plasma insulin after glucose gavage (Jang et al. 2007; Kokrashvili et al. 2009a, b). Next, *T1r3*-(sweet taste receptor) deficient mice failed to release GLP-1 from their duodenal cells after glucose injection into the intestine. These data indicate that sweet receptors in enteroendocrine cells couple to heterotrimeric gustducin to detect extracellular glucose or other components and respond with secretion of GLP-1. The exact role of TRPM5 in this process has to our knowledge not been investigated yet. However, since the channel is expressed in enteroendocrine cells, it is conceivable that it plays a role in the sweet tastant-induced release of GLP-1 or other hormones. Bitter tastants are also shown to release gastrointestinal hormones such as CCK, GLP-1 and ghrelin (Janssen et al. 2011; Chen et al. 2006; Jeon et al. 2008), but the functional impact on insulin release or glucose homeostasis (and a possible role for TRPM5) remains to be shown (Fig. 3).

8 TRPM3: A Zinc Connection

As mentioned above, all TRP channels are cation channels with varying permeabilities for Ca^{2+} and Na^{+}. Most of these channels are important in different cell types either as Ca^{2+} channels or as Na^{+} entry channels and activation of TRP channels causes membrane depolarization and/or Ca^{2+} entry. However, TRPM3 channels are proposed to constitute a regulated Zn^{2+} entry pathway in pancreatic beta cells (Wagner et al. 2010). Zinc is important for insulin release as it is packed into co-crystals with insulin in the exocytotic vesicles. The formation of insulin crystals in beta cells depends amongst others on the ZnT8 transporter, which contributes to the packaging efficiency of stored insulin (Lemaire et al. 2009). Since Zn^{2+} ions are co-released with insulin, pancreatic beta cells need to continuously replenish their Zn^{2+} stores by taking up Zn^{2+} ions from the extracellular space. Insufficient Zn^{2+} uptake may lead to impaired insulin synthesis and aggravate diabetic symptoms (Chausmer 1998). Interestingly, TRPM3 channels in beta cells have been shown to be highly permeable for Zn^{2+} and capable of mediating Zn^{2+} uptake under physiological conditions through their own ion-conducting pore. The depolarization caused by the activation of TRPM3 channels leads to the activation of voltage-dependent Ca^{2+} channels and increases the Zn^{2+} influx through these channels (Gyulkhandanyan et al. 2006; Wagner et al. 2010). Thus, TRPM3 channels provide a novel regulated Zn^{2+} entry pathway in β cells and might in this way contribute to an improved insulin synthesis.

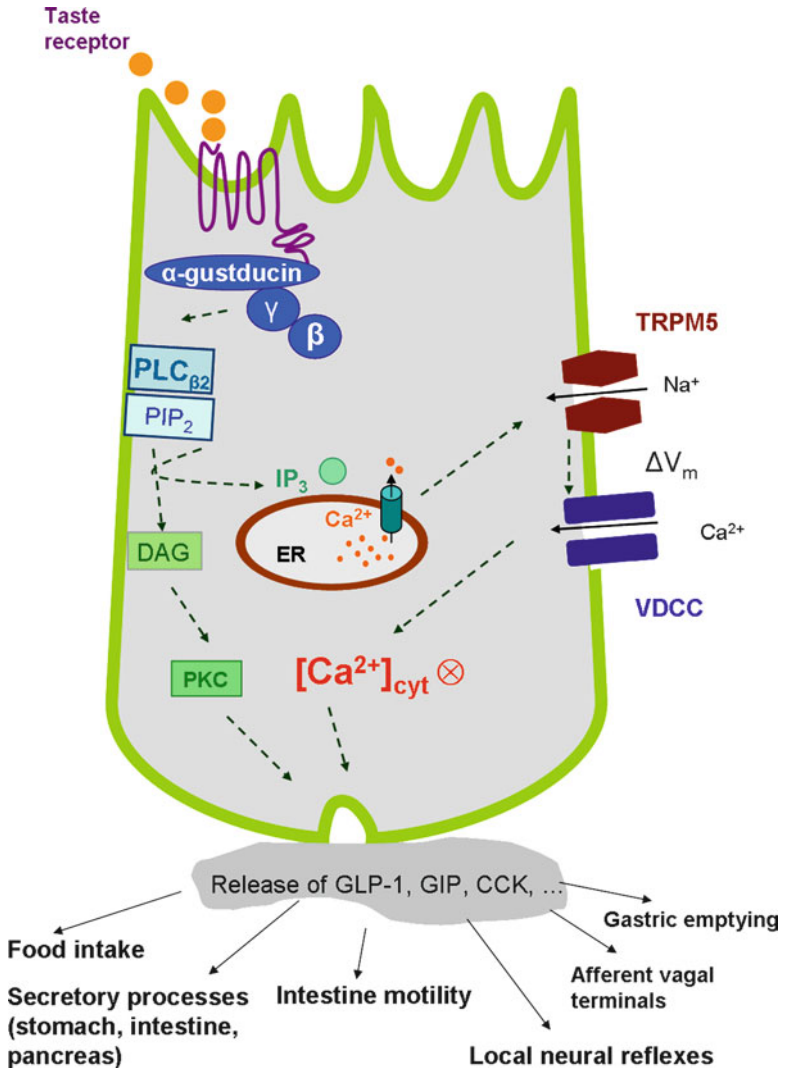

Fig. 3 Putative pathways triggered by sweet taste stimuli in gastrointestinal enteroendocrine cells. Sugar and other nutrients bind to sweet taste receptors in the apical portion of the enteroendocrine cell. This engages α-gustducin and PLCβ2, leading to intracellular Ca^{2+} release, activation of TRPM5, membrane depolarization and activation of voltage-dependent Ca^{2+} channels (VDCC). The resulting increase in intracellular Ca^{2+}, in combination with DAG-mediated activation of PKC, triggers the release of gastro-intestinal peptides such as GLP-1 and CCK. These peptides act in a paracrine or endocrine manner in order to exert diverse effects, among which amplification of glucose-induced insulin release. See also (Rozengurt and Sternini 2007)

9 TRP Channels and a Possible Role in Diabetes Type II

Disorders of glucose homeostasis can lead to diabetes mellitus, a group of metabolic diseases with the common feature hyperglycemia. Type 1 diabetes, the so-called "Insulin-Dependent Diabetes Mellitus", is caused by an autoimmune destruction of the β cells which subsequently leads to a lack of insulin production. This is in striking contrast to type 2 diabetes, where the β cells can still produce and release insulin, but cannot compensate for the increased demand due to e.g. ageing or obesity. Type 2 diabetes is a polygenic disease, acknowledged to result from a combination between peripheral insulin resistance and a genetically determined susceptibility to β cell dysfunction. It has been proposed that individuals at risk of type 2 diabetes carry one or more polymorphisms in genes encoding ion channels or in genes that regulate ion channel function, membrane targeting or expression, resulting in small changes in β cells electrical activity and consequently in reduced insulin secretion (Ashcroft and Rorsman 2004). Indeed, mutations in K_{ATP} channel genes are not only shown to result in congenital hyperinsulinism and neonatal diabetes, but also suggested to be associated with type 2 diabetes mellitus (Ashcroft 2005; Hattersley and Ashcroft 2005; Proks et al. 2005; Chistiakov et al. 2009). In this regard, it might be that gene variations of TRP channels known to influence insulin release in animal models play a role in the pathophysiology of type 2 diabetes mellitus. One study reports a negative association of beta cell function with three TRPM2 variants (rs2838553, rs2838554 and rs4818917) although no evidence for an association with type 2 diabetes mellitus could be found (Romero et al. 2010).

Interestingly, *Trpm5* expression is negatively correlated with blood glucose concentrations in the small intestine from diabetic patients (Young et al. 2009). Moreover, a recent study reports an association of TRPM5 variants with prediabetic phenotypes in subjects at risk for type 2 diabetes, including insulin secretion, insulin sensitivity and plasma glucose and GLP-1 levels (Ketterer et al. 2011). Indeed, TRPM5 SNP rs2301699 was significantly associated with insulin secretion and associated with lower GLP-1 levels during an oral glucose tolerance test. Furthermore, three TRPM5 SNPs (rs800344, rs800345 and rs2301699) were significantly associated with glucose levels during OGTT. Surprisingly, these SNPs were also associated with OGTT-derived insulin sensitivity (Ketterer et al. 2011). How these TRPM5 variants might affect insulin sensitivity remains elusive, since *Trpm5*$^{-/-}$ mice showed a normal insulin tolerance test (Colsoul et al. 2010). Furthermore, the functional impact of these mutations on the TRPM5 channel has not been clarified yet. However, these data indicate a possible link between TRPM5 and type 2 diabetes mellitus.

10 TRPM5 as a Drug Target

The involvement of TRPM5 in the insulin release and its link with type 2 diabetes suggest that TRPM5 might be a good drug target in the treatment of type 2 diabetes mellitus. A disadvantage of sulphonylureas (a frequently used medicine against

diabetes mellitus type 2) is that, by closing the K_{ATP}-channels regardless of the glucose concentration, they bypass the normal metabolic regulation of the beta cell. Thus, insulin secretion continues even when plasma glucose has fallen to abnormally and dangerously low levels. TRPM5 activators would only increase insulin release at high blood glucose levels and in this way avoid the risk of hypoglycemia attacks. As TRPM5 is also implicated in transduction of sweet taste, activators of TRPM5 might be expected to increase sweet sensation and in this way reduce intake of e.g. sugars. Moreover, GLP-1 secretion might increase as a result of activation of TRPM5, resulting in an amplification of insulin release. Thus, an activator of TRPM5 has many potential benefits. However, this requires selective and efficient modulators of TRPM5. So far, only blockers of TRPM5 have been described. Flufenamic acid (FFA), a non-steroidal anti-inflammatory agent, is shown to inhibit TRPM5 but the compound is non-specific since several other cation channels (e.g. the closest homologue TRPM4) are also inhibited by FFA (Ullrich et al. 2005). Recently, triphenylphosphine oxide (TPPO) was identified as a selective and potent inhibitor of TRPM5 (Palmer et al. 2010). Indeed, it inhibits both human and mouse TRPM5 with an IC_{50} of 12 and 30 μM respectively and has no effect on TRPA1, TRPV1 or TRPM4. Clearly, the functional impact of all these TRPM5 modulators (and possible newcomers) should be critically tested in insulin release assays in isolated islets as well as in vivo (OGTT, IPGTT).

11 A Critical View: From Mouse to Man

In spite of the growing evidence of the function of TRP channels in mouse islets, no functional role for any TRP channel in human islets has been shown yet. What's more, expression data of TRP channels in human pancreatic islets and beta cells are often lacking. So far, TRPV5 and TRPV6 are detected in human pancreas (without any specification about expression in endocrine or exocrine cells) (Muller et al. 2000) and expression is shown specifically in human islets for TRPM2, TRPM4 and TRPM5 (Prawitt et al. 2003; Marigo et al. 2009). Concerning a functional role of these channels in nutrient-induced Ca^{2+} signalling and stimulus-secretion coupling, one can only speculate.

It is evident that human and mouse β-cells differ in many respects and that data obtained from rodent islets cannot be extrapolated to human islets without verification. E.g. whereas voltage-gated Na^+ channels are inactive in rodent islets at physiological potentials and play no role in the bursting behavior, $Na_v1.6$ and $Na_v1.7$ channels are shown to participate in the action potential shaping during intermediate glucose-induced signaling and insulin secretion in human β cells (Barnett et al. 1995; Asensio et al. 2004). Human islets have been shown to respond to glucose and sulphonlyureas with Ca^{2+} oscillations that are synchronous throughout the islet and whose duration is modulated by glucose (Kindmark et al. 1994; Martin and Soria 1996). Even subjects with impaired glucose tolerance had islets that responded with oscillations in intracellular Ca^{2+} upon glucose stimulation (Kindmark et al. 1994). A detailed characterization of voltage-gated ion channels in human islets from

non-diabetic donors revealed that voltage-gated T-type and L-type Ca^{2+} channels as well as Na^{+} channels participate in glucose-stimulated electrical activity and insulin secretion, whereas Ca^{2+}-activated BK channels are required for rapid membrane repolarization and Ca^{2+}-influx through P/Q-type Ca^{2+} channels triggers exocytosis of insulin-containing granules (Braun et al. 2008). This is in many aspects different from the situation in rodent islets, confirming the fact that precaution must be taken when extrapolating data.

The study of ion channels in human islets requires selective and potent blockers. This is problematic for TRP channels, as many of the compounds known to modulate these channels also influence other ion channels. Furthermore, TRP channels would be expected to modulate insulin secretion in a subtle manner, a feature that makes the investigation towards their function in human islets a challenging task. However, as these channels are implicated in many human diseases and channelopathies (Nilius and Owsianik 2010; Nilius et al. 2007b), it is not inconceivable that mutations or dysfunctions of TRP channels contribute to the onset or progress of type 2 diabetes mellitus. In this regard, understanding how these channels influence insulin release from human islets might be a first step towards the development of new drugs against this disease.

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