

Ion Channels in Endocrine Pancreatic Cells and their Role in Diabetes

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Maintaining glucose homeostasis is an important factor in mammalian physiology, and is controlled to a large extent by the pancreas. Specialized beta cells residing in the Islets of Langerhans sense the blood glucose levels and secrete insulin, which signals these levels to the rest of the body. Ion channels play a major role in many aspects of this cellular process and serve as targets for pharmacological interventions that treat diseases in which glucose homeostasis is impaired. In type-2 diabetes, the tight link between glucose sensing and insulin secretion is impaired due to mutations (as well as other genetic and acquired changes) in a specific K^+ channel and most medications for this condition target this channel. This short review describes the mechanisms underlying the physiology and pathophysiology of insulin secretion with emphasis on the role ion channels play in controlling and modulating it.

The Pancreas

The main function of the pancreas, a gland attached to the intestine, is to control blood glucose levels. However, most of the pancreas is comprised of exocrine tissue, which secretes enzymes into the intestine, while only about 1% of the tissue consists of endocrine cells, which are clustered in the Islets of Langerhans.

Most of the endocrine cells in the islet are called beta cells. These respond to an increase in the plasma glucose level by secreting insulin into the blood circulation, which in turn allows cells (mainly in muscle and liver) to absorb glucose. (For more information see the website mentioned in Ref. 1)

Other cell types in the pancreas further control the plasma glucose levels. Alpha cells secrete glucagon, which stimulates mitochondrial respiration in target cells, when the glucose level is low. Delta cells secrete somatostatin onto the islet, which inhibits both insulin and glucagon secretion. Lambda cells secrete GLP-1, which causes an increase in glucagon and insulin secretion. All these cell types contribute to synchronization in the “whole islet” response.

Cells in the Islet of Langerhans are Excitable

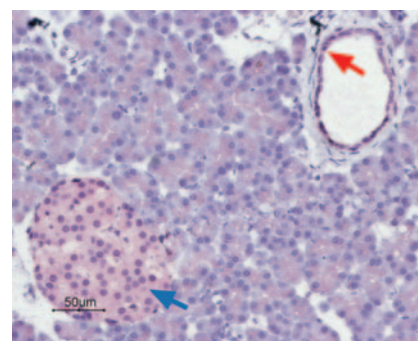
Like neurons, pancreatic endocrine cells respond to their relevant stimulation with plasma membrane depolarization (caused by changes in the activity of ion channels) and action potential firing, which leads to vesicle exocytosis (controlled by elevation of Ca^{2+} concentration, mediated by ion channels) and hormone secretion.²

Thus, glucose stimulation leads to depolarization, which is often oscillatory and is accompanied by oscillations in Ca^{2+} and NADH concentrations and in mitochondrial membrane potential, often leading to oscillatory insulin secretion. Ion channels play a major role in a network of cellular and molecular feedback mechanisms that produce these dynamics.²⁻⁷

Resting Potential and Initiation of Hormone Secretion

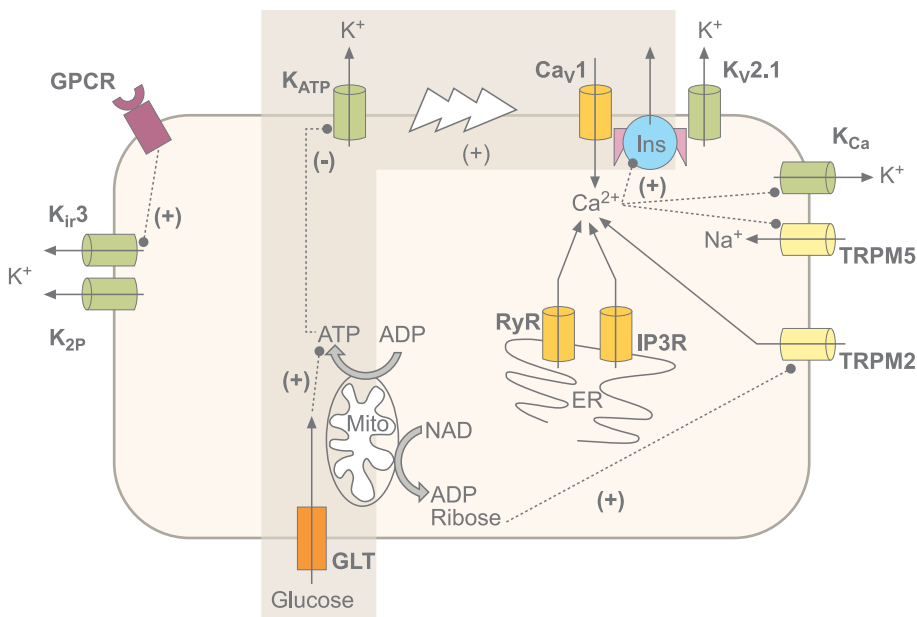
The mechanism that links glucose sensing to hormone secretion has been extensively studied

Ca_v1.2 Expression in Rat Pancreas



Immunohistochemical staining of $Ca_v1.2$ in rat pancreas was visualized using Anti-human $Ca_v1.2$ antibody (#ACC-022) (1:50). Paraffin embedded sections of rat pancreas showing both endocrine (Islets of Langerhans) and exocrine areas. Strong and highly specific staining is evident in both endocrine cells (blue arrow) and arteries endothelium (red arrow). Universal Immunoalkaline-phosphatase Polymer followed by New Fuchsin Substrate (Histofine, Nichirei corp) was used for the color reaction. Counterstain is Hematoxylin.

Fig. 1: Schematic Representation of Ion Channels and their Roles in Pancreatic Beta Cells



In the central shaded area, the principle pathway linking extracellular (blood) glucose levels to insulin secretion is shown. On the right some modulatory links are presented, which include a set of Ca^{2+} permeable as well as Ca^{2+} activated channels.

GPCR= G-Protein Coupled Receptor.
 GLUT= GLucose Transporter.
 Ins= Insulin.
 Mito= Mitochondria.
 ER= Endoplasmic Reticulum.

→ Ionic current
 Influences (the + or - signs in brackets stand for enhancement or inhibition, respectively)
 K^+ channels
 Ca^{2+} channels
 Non-selective (depolarizing) channels
 Synaptic proteins (syntaxin etc.)
 Depolarization

in beta cells and involves the activity of several ion channels at key points in the cascade (for detailed reviews see Refs. 2, 8-9).

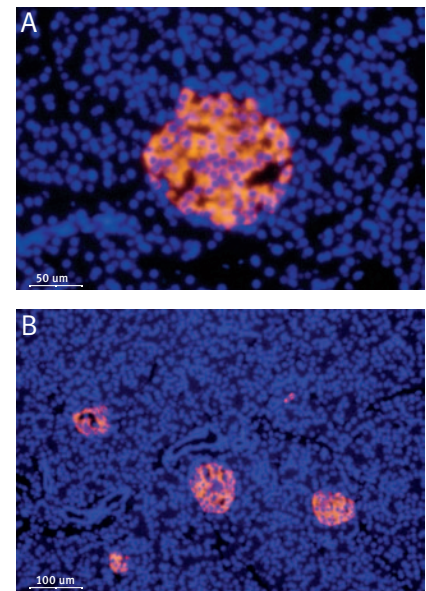
K^+ channels that are sensitive to ATP are plasma membrane protein complexes composed of four $K_{ir}6.2$ (KCNJ11) pore-forming subunits surrounded by four SUR1 (sulphonylurea receptor, of the ABC transporter protein family) auxiliary subunits. These protein complexes sense the amount of glucose entering a beta cell since the activity of K_{ATP} channels depends on the amount of ATP in the cytoplasm, which in turn depends on the amount of glucose absorbed by the beta cell. The activity of K_{ATP} channels is negatively correlated to the amount of ATP, i.e. increases in ATP levels tend to reduce the activity of the channel.⁹

K_{ATP} channels are the main channels that are open during resting conditions and therefore their activity sets the resting membrane potential. Closure of K_{ATP} channels by increased ATP

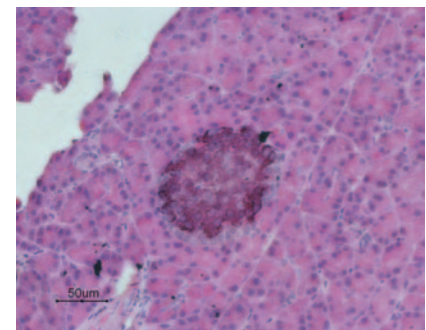
concentration leads to membrane depolarization, which causes opening of voltage dependent Ca_v (Ca_v) channels, leading to Ca^{2+} influx.² The exact molecular make-up of Ca_v channels in beta cells probably differs between species and is still somewhat controversial.¹⁰ However, the main Ca_v channels that control insulin secretion are L-type channels of the Ca_v1 subfamily ($Ca_v1.2$ and/or $Ca_v1.3$).¹¹⁻¹³ In addition, using a $Ca_v1.3$ knockout mouse it was demonstrated that this channel is essential for the normal development of the pancreas.¹⁴ Other Ca_v channels, members of the Ca_v2 (P/Q, N and R types) channel subfamily have been detected in these cells and in several cases their functional contribution was demonstrated.¹⁵⁻¹⁷ Members of the Ca_v3 (T-type) channels were also detected in some beta cells preparations.¹⁰

The mechanism of coupling between depolarization and secretion is very similar in beta cells and in neuronal synaptic transmission. Further emphasis on the major role played by

$Ca_v1.3$ Expression in Rat Pancreas



Immunofluorescent staining of $Ca_v1.3$ in rat pancreas was visualized using Anti- $Ca_v1.3$ antibody (#ACC-005) (1:50). Paraffin embedded sections of rat pancreas showing both endocrine (Islets of Langerhans) and exocrine areas. Strong and highly specific staining is evident only in endocrine cells (red). Secondary antibody is goat anti-rabbit Alexa 555 (1:400). Counterstain is Hoechst 33342 (blue). (A) 200x (B) 100x



Immunohistochemical staining of $Ca_v1.3$ in rat pancreas was visualized using Anti- $Ca_v1.3$ antibody (#ACC-005) (1:50). Paraffin embedded sections of rat pancreas showing both endocrine (Islets of Langerhans) and exocrine areas. Color reaction was obtained with DAB after incubation with a peroxidase-conjugated second antibody. Counterstain is H&E.

Ca_v1 channels in insulin secretion is given by demonstrations of physical and functional interaction of Ca_v channels with synaptic proteins (such as syntaxins and SNAP-25) that control vesicle exocytosis.¹⁸⁻²⁰

The above-mentioned channels and pathways comprise the principle route for transduction of the blood glucose level into blood insulin signal (Fig. 1). However, many more channels are involved in fine-tuning and regulation of this

Fig. 2: Effects of Ca_v Channel Modulators on Ca_v Currents and $[Ca^{2+}]_i$ in RIN Cells



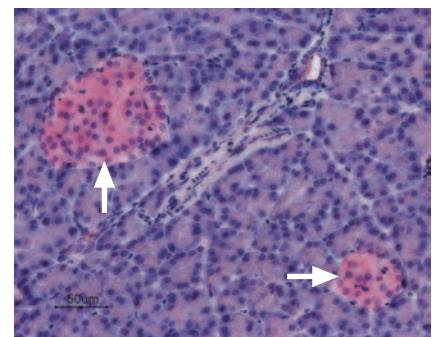
signal transduction pathway and these are briefly described below.

Voltage dependent K^+ (K_v) channels also sense the depolarization initiated by K_{ATP} closure and their delayed activation leads to repolarization and termination of exocytosis. In beta cells, $K_v2.1$ channels were demonstrated to be the main K_v channel that mediates this termination,²¹⁻²⁶ which in part is based on their interactions with synaptic proteins.^{27,28} Other K_v channels (see below) are expressed in beta and other endocrine cells but their exact functional role is still not fully resolved.^{23,26}

Ca^{2+} activated K^+ channels open in response to intracellular Ca^{2+} ($[Ca^{2+}]_i$) elevation and in turn cause repolarization of the membrane potential, often leading to attenuation of the $[Ca^{2+}]_i$ signal. Via such a feedback loop, K_{Ca2} and/or K_{Ca3} channels (of the small/intermediate conductance protein family) contribute to oscillations in membrane potential and $[Ca^{2+}]_i$.^{29,30} The presence of $K_{Ca1.1}$ (large conductance, BK, Slo) channels was confirmed but they did not contribute to glucose induced electrical activity.³¹

Several K_{ir3} (GIRK or G protein activated inward rectifier K^+ channels) which are structurally similar to the $K_{ir6.2}$ subunit of K_{ATP} , were detected in islet cells. K_{ir3} (mainly $K_{ir3.4}$ but also $K_{ir3.2}$, GIRK4 and GIRK2) channels were found in alpha as well as beta cells. These G-protein activated K^+ channels contribute to hyper and/or repolarization of the membrane potential, once they are opened. Their exact role is not completely resolved, but they probably contribute to reduction in

$K_{ir3.4}$ Expression in Rat Pancreas



Immunohistochemical staining of $K_{ir3.4}$ in rat pancreas was visualized using Anti- $K_{ir3.4}$ antibody (#APC-027) (1:50). Paraffin embedded sections of rat pancreas showing both endocrine (Islets of Langerhans) and exocrine areas. Strong and highly specific staining is evident only in endocrine cells (arrow). Universal Immuno-alkaline-phosphatase Polymer followed by New Fuchsin Substrate (Histofine, Nichirei corp) was used for the color reaction. Counterstain is Hematoxylin.

insulin release, in response to hormones and transmitters such as Ach, epinephrine and somatostatin.³²⁻³⁵

In addition, a few K_{2p} channels have been detected in the whole pancreas at the RNA level (PCR). $K_{2p}5.1$ (TASK-2) was found to be expressed in the islet as well as exocrine tissue, and $K_{2p}10.1$ (TREK-2) is expressed in the insulinoma cell line MIN6.³⁶

TRP channels are sensitive to various stimuli and their activation modulates both $[Ca^{2+}]_i$ and membrane potential, therefore contributing to regulation of secretion. The TRPM5 channel, which is permeable to monovalent cations and gated by internal Ca^{2+} is expressed in the pancreas, where it might contribute to membrane potential oscillations.³⁷ Recently, the involvement of the Ca^{2+} permeable TRPM2 in insulin secretion was reported. It involves ADP ribose activation of this channel as well as temperature dependence.³⁸ The activation by ADP ribose might be related to oscillations in NADH concentration that have been reported to occur in beta cells in response to glucose activation. In addition, two splice variants of TRPC4 which were cloned from mouse insulinoma cell lines have been suggested to act as heteromeric (with other TRPC) Ca^{2+} channels.^{39,40}

Intracellular RyR and/or IP_3R channels on the ER membrane contribute to shaping Ca^{2+} signals and therefore, insulin secretion.^{7,41} These channels release Ca^{2+} from ER into the cytoplasm and are linked to $[Ca^{2+}]_i$ oscillations possibly via interaction with TRP channels.⁴¹

Some evidence suggests that islet cells may under certain conditions (low glucose for example) respond to ATP (which may have been co-released with insulin) via P2X channels.⁴² Such a mechanism would further increase secretion, as these ATP receptors respond to ATP binding by opening a Ca^{2+} permeable pore. However, expression of P2 receptors in the pancreas is developmentally regulated, and for example, P2X7 (in alpha cells) is expressed only in adults and might be related to aging.⁴³ This might be in correlation to the suggested role for this channel in supporting apoptosis.

Repertoire of Ion Channels in Different Types of Endocrine Cells

Alpha cells respond to glucose by decreasing glucagon secretion. This might be achieved by glucose acting on beta cells to release GABA, which in turn activates GABA(A)R on alpha cells and causes inhibition of glucagon secretion. However, once the glucose level is low, GABA is not released from beta cells and alpha cells go on secreting glucagon.⁴⁴ Another proposed mechanism involves insulin secreted from beta cells, which reduces the alpha cell K_{ATP} channels' sensitivity to ATP inhibition. This means that glucose is now less effective in inducing glucagon secretion from alpha cells.⁴⁵

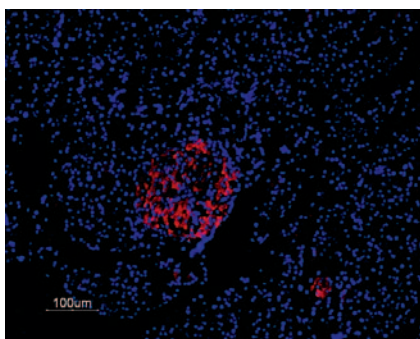
In comprehensive studies that have addressed this issue, alpha cells are reported to express

the following channels: $K_v3.1$, the silent subunits $K_v6.1$ and possibly $K_v9.2$.²⁶ At the level of a single cell RT-PCR and electrophysiology experiments have suggested the following Ca^{2+} and Na^+ channels as mediators of voltage dependent inward currents in alpha cells: $Ca_v1.2$ and $Ca_v1.3$ (L-type), $Ca_v2.1$ (P/Q-type), $Ca_v2.3$ (R-type) and $Na_v1.7$ (TTX-sensitive).¹⁷

Beta cells respond to increase in glucose concentration by insulin secretion. Beta cells are reported to express the following K_v channels: $K_v2.1$, $K_v3.2$ and the silent subunits $K_v6.2$ and $K_v9.3$.²⁶ Reports that $K_v11.1$ (erg1) is also expressed and is involved in glucose induced insulin release are based on PCR and some pharmacology.⁴⁶ *Shaker* type K_v1 channels were found along with K_v2 channels, but these probably do not contribute to secretion.²³ RT-PCR and electrophysiology experiments at the level of the single cell suggested that the following Ca^{2+} and Na^+ channels mediate voltage dependent inward currents in beta cells: $Ca_v1.2$ (L-type), $Ca_v2.1$ (P/Q-type), $Ca_v2.2$ (N-type), $Ca_v2.3$ (R-type) and $Na_v1.7$ (TTX-sensitive).¹⁷

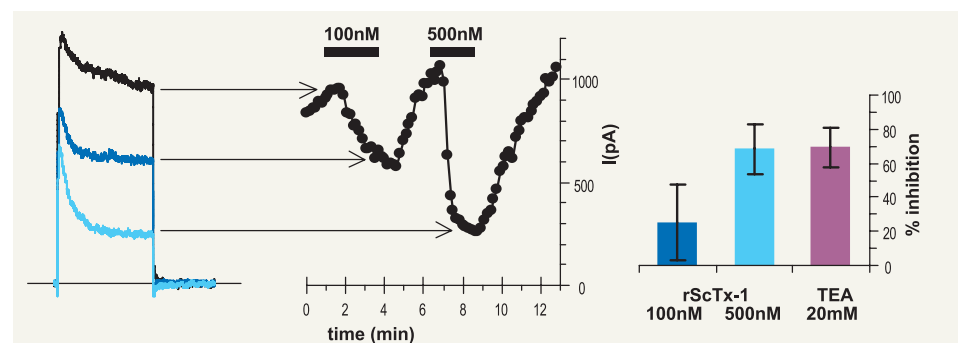
Delta cells secrete somatostatin, which inhibits both alpha and beta cell secretion. One possible mechanism for this inhibitory action is via inhibition of oxidative respiration in beta cells.⁴⁷ Another proposed mechanism is the activation of K_v3 channels by somatostatin receptors on alpha and beta cells.³³ Delta cells are reported to express $K_v2.2$ and possibly the silent $K_v9.2$.²⁶ Another report implies that the $K_v3.4$ channel acts as the major delayed rectifier and shows electrical activity following glucose stimulation and Na_v

$K_v2.1$ Expression in Rat Pancreas



Immunofluorescent staining of $K_v2.1$ in rat pancreas was visualized using Anti- $K_v2.1$ antibody (#APC-012) (1:50). Paraffin embedded sections of rat pancreas showing both endocrine (Islets of Langerhans) and exocrine areas. Strong and highly specific staining is evident only in endocrine cells (red). Secondary antibody is goat anti-rabbit Alexa 555 (1:400). Counterstain is Hoechst 33342 (blue).

Fig. 3: Stromatoxin-1 Inhibits K_v Currents in RIN Cells



Inhibition of K_v currents in RIN Beta cells by rStromatoxin-1 (rScTx-1).

Left: Traces recorded using the whole cell patch clamp technique from RIN cells before (black) and during perfusion of 100 nM (blue) and 500 nM (cyan) rScTx-1 (#RTS-350). Arrows point to the middle section to illustrate the current trace origin.

Middle: Time course of the experiment that is shown on the left. Stimulating pulses were delivered every 5 sec from holding potential of -60 mV to +50 mV for 40 ms. Periods of toxin perfusion are marked with horizontal bars. Note that the toxin effect is reversible upon wash.

Right: Percentage of current inhibition of different rScTx-1 concentrations (n=3 and n=6, for 100 and 500 nM respectively) and TEA (n=4 for 20 mM TEA) on K_v currents in RIN cells.

(TTX-sensitive) as well as Ca_v channel activity.⁴⁸

Lambda cells secrete GLP-1, which promotes glucagon and insulin secretion. GLP-1 probably acts on beta cells via GPCR dependent mechanisms, which involves elevation of cAMP that increases the L-type Ca_v current and inhibits K_v channels.⁴⁹

Use of Specific Channel Modulators and Neurotoxins in the Study of Endocrine Physiology

K_{ATP} channel blockade leads to insulin secretion while openers of K_{ATP} block insulin secretion; both approaches are used clinically to tackle diabetes and hyperinsulinism, respectively. Extensive reviews cover this important topic and it will not be discussed here in detail.^{8,50,51}

Pharmacological manipulation of Ca_v1 (L-type) channels modulate secretion. DHPs (DiHydroPyridines) are widely used, relatively specific L-type modulators. **(±)-Bay K 8644** is a potent enhancer of L-type current and is often used to induce $[Ca^{2+}]_i$ elevations and insulin secretion.¹² Several snake venom toxins, **TaiCatoxin**, **Calciclude**, **Calciseptine** and **FS-2** are specific and potent inhibitors of L-type channels, some of which have been shown to be effective in beta cells (Figure 2).⁵²

As mentioned before, the main Ca_v channel involved in insulin secretion is one of the Ca_v1 family members. However, although other Ca_v channels have been detected in beta cells, their role is not fully resolved. The role played by these channels might be to regulate and/or fine tune the release process. A nice example is illustrated by an experiment in which **SNX-482**, a specific $Ca_v2.3$ channel blocker, was shown to inhibit only the second phase of insulin release.¹⁶

In accordance with its major role in depolarization and termination of exocytosis, $K_v2.1$ channel blockade increases secretion. This was demonstrated with a few spider toxins such as **Hanatoxin** and **Guangxitoxin**, which are specific blockers of this channel.^{21,22} We demonstrate that

rStromatoxin-1 (rScTx-1) is a potent inhibitor of K_v currents recorded in RIN insulinoma cells (Fig. 3).

Synaptic neurotoxins have been used to affect secretion. **α-Latrotoxin** application induced both ion channel modulation (in a direction favoring increased exocytosis) as well as direct enhancement of insulin containing vesicle exocytosis.^{52,53} We demonstrate that α-Latrotoxin potently affects Ca^{2+} dependent enzyme phosphorylation in RIN cells (Fig. 4).

Channelopathies Related to Diabetes

Mutations and polymorphism in K_{ATP} channel components cause a few congenital as well as acquired conditions (via increased susceptibility).^{8,50,51}

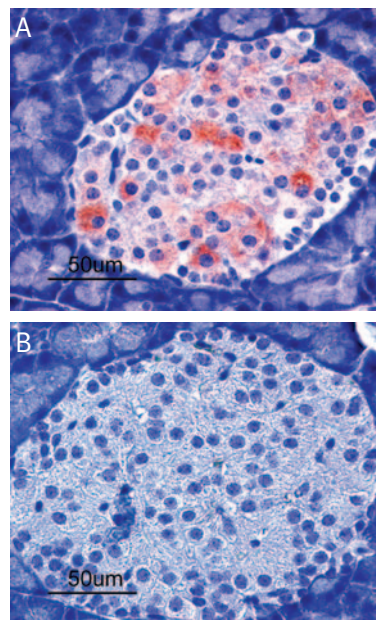
Gain of function mutations usually make K_{ATP} less sensitive to ATP blockage, resulting in increased channel activity, decreased insulin release and diabetes.

Loss of function mutations either eliminate K_{ATP} channels from the plasma membrane or increase their sensitivity to ATP block. This causes decreased channel activity, leading to increased insulin secretion, hyperinsulinism and hypoglycemia. This depolarized beta cell state may eventually lead to apoptosis, beta cell death and diabetes.

Recently two gain of function mutations in $Ca_v1.2$ (Timothy syndrome)⁵⁴ and in $Na_v1.7$ (familial erythralgia)⁵⁵ were described, as these two channels are expressed in islet cells, mutations in their coding might influence the normal functioning of the pancreas.

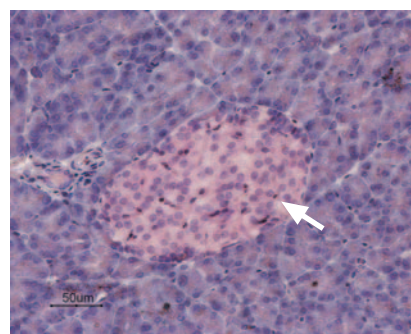
For humans, the consequences of glucose imbalance might be severe. Currently the principle way to tackle such conditions in the clinic is with pharmacophores that bind to K_{ATP} and shift their ATP sensitivity. However, many ion channels participate in the control of secretion in pancreatic endocrine cells and therefore, in the maintenance of glucose homeostasis. Therefore, the fact that the modulation of secretion can be fine tuned renders it amenable to many possible interventions.

$K_{ir}6.2$ Expression in Rat Pancreas



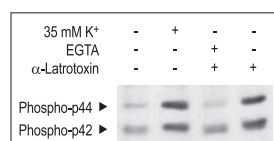
Immunohistochemical staining of $K_{ir}6.2$ in rat pancreas. Paraffin sections of rat pancreas were visualized by Anti- $K_{ir}6.2$ antibody (#APC-020) (1:100). (A) Strong granular staining in a number of cells within the Islets of Langerhans is readily detected (red). (B) The negative control slide shows no staining.

$K_{2p}5.1$ (TASK-2) Expression in Rat Pancreas



Immunohistochemical staining of $K_{2p}5.1$ in rat pancreas was visualized using Anti- $K_{2p}5.1$ antibody (#APC-037) (1:50). Paraffin embedded sections of rat pancreas showing both endocrine (Islets of Langerhans) and exocrine areas. Strong and highly specific staining is evident only in endocrine cells (arrow). Universal Immuno-alkaline-phosphatase Polymer followed by New Fuchsin Substrate (Histofine, Nichirei corp) was used for the color reaction. Counterstain is Hematoxylin.

Fig. 4: Activation of p42/44 by α-Latrotoxin



α-Latrotoxin promotes activation of p42/44 MAP Kinase by inducing Ca^{2+} influx in RIN insulinoma cells. Cells were treated for 15 min with 35 mM K^+ or 2 nM α-Latrotoxin (#LSP-130) in presence or absence of 5mM EGTA. The picture presents Western blot analysis of active p42/p44 MAP Kinase probed with a phospho p42/p44 MAPK antibody.

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Related Products

Compound	Product #
Antibodies to Ion Channels	
Anti-Ca _v 1.2	ACC-003
Anti-human Ca _v 1.2	ACC-022
Anti-Ca _v 1.2a	ACC-013
Anti-Ca _v 1.3	ACC-005
Anti-Ca _v 2.1	ACC-001
Anti-Ca _v 2.2	ACC-002
Anti-Ca _v 2.3	ACC-006
Anti-Ca _v 3.1	ACC-021

Anti-Ca _v 3.2	ACC-025
Anti-Ca _v 3.3	ACC-009
Anti-Ca _v pan α1	ACC-004
Anti-Ca _v α2δ-1	ACC-015
Anti-Ca _v β3	ACC-008
Anti-Ca _v γ2	ACC-012
Anti-Na _v 1.7	ASC-008
Anti-K _v 6.2	APC-020
Anti-K _v 3.2	APC-006
Anti-K _v 3.4	APC-027
Anti-K _v 5.1	APC-037
Anti-K _v 10.1	APC-055
Anti-K _v 2.1	APC-039
Anti-K _v 2.2	APC-028
Anti-K _v 2.3 (N-term)	APC-025
Anti-K _v 2.3 (C-term)	APC-103
Anti-K _v 3.1	APC-064
Anti-K _v 2.1	APC-012
Anti-K _v 3.1b	APC-014
Anti-K _v 3.2	APC-011
Anti-K _v 3.4	APC-019
Anti-IP ₃ R1	ACC-019
Anti-TRPC4	ACC-018

Antibodies to Ligand Gated Channels

Anti-GABA (A) α1	AGA-001
Anti-GABA (A) α2	AGA-002
Anti-GABA (A) α3	AGA-003
Anti-GABA (A) α6	AGA-004
Anti-GABA (A) γ2	AGA-005
Anti-P2X1	APR-001
Anti-P2X2	APR-003
Anti-P2X3	APR-016
Anti-P2X4	APR-002
Anti-P2X5	APR-005
Anti-P2X6	APR-013
Anti-P2X7 (extracellular)	APR-008
Anti-P2X7 (extracellular)-FITC	APR-008-F
Anti-P2X7	APR-004

Antibodies to G-Protein Coupled Receptors

Anti-Somatostatin Receptor Type 1	ASR-001
Anti-Somatostatin Receptor Type 2	ASR-006
Anti-Somatostatin Receptor Type 3	ASR-003
Anti-Somatostatin Receptor Type 4	ASR-004

Antibodies to Exocytotic Machinery (Synaptic) Proteins

Anti-SNAP-25	ANR-001
Anti-Syntaxin 1	ANR-002
Anti-Syntaxin 2	ANR-008
Anti-Syntaxin 3	ANR-005
Anti-Syntaxin 4	ANR-004
Anti-Synaptotagmin I	ANR-003
Anti-VAMP-2	ANR-007

Voltage-Gated Ca²⁺ Channel Blockers

ω-Agatoxin IVA	A-500
ω-Agatoxin TK	A-530
Calcicludine	C-650
Calciseptine	C-500
ω-Conotoxin GVIA	C-300
ω-Conotoxin MVIIA	C-670
ω-Conotoxin MVIIIC	C-150
ω-Conotoxin SVIB	C-570
FS-2	F-700
ω-Grammotoxin SIA	G-450
SNX-482	S-500
TaiCatoxin	T-800

Voltage-Gated Ca²⁺ Channel Activator

(±)-Bay K 8644	B-350
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K⁺ Channel Blockers

Apamin	A-200
BDS-I	B-400
BDS-II	B-450
rMaurotoxin	RTM-340
rScyllatoxin	RTS-370
rStromatoxin-1 (rScTx-1)	RTS-350

rTamapin	RTT-400
Tertiapin	T-250
rTertiapin-Q	RTT-170

Voltage-Gated Na⁺ Channel Blockers

QX-222 (Chloride salt)	Q-200
QX-314 (Bromide salt)	Q-100
QX-314 (Chloride salt)	Q-150
Tetrodotoxin (citrate free)	T-500
Tetrodotoxin (with citrate)	T-550

Voltage-Gated Na⁺ Channel Activators

Anthopleurin-C (APE 2-1)	A-400
APE 1-2	A-470
ATX II	A-700

Neurotoxins

α-Latrotoxin	LSP-130
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Cell Ca²⁺ Signaling

Imperatoxin A	I-300
Ryanodine	R-500
Thapsigargin	T-650