

Ion Channels as Targets for Treatment of Type II Diabetes Mellitus

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Abstract

Ion channels have been successful targets for intervention of therapeutic agents for decades. As an example, the modulators of a particular potassium channel, ATP-sensitive potassium channel (KATP), have been the mainstay of oral treatment for type II diabetes mellitus. Increasing evidence has demonstrated that modulation of some of the voltage-gated potassium channels and the voltage-gated calcium channels may yield anti-diabetic indications. In recent years, the knowledge into ion channel structures and the technologies for ion channel functional screening have been significantly improved which provides us exciting opportunities of finding novel ion channel targets. In this review, the author has summarized the existing anti-diabetic ion channel targets, and the recent findings that support other ion channels as potential therapeutic targets for treatment of type II diabetes mellitus.

Introduction

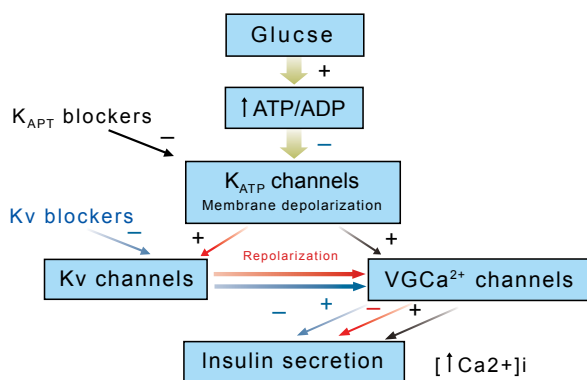
Type II diabetes mellitus (previously called noninsulin-dependent diabetes) is widespread throughout Western society. It affects approximately 15 million people in the United States and accounts for about one sixth of all expenditures for health care. The mortality rate in patients with diabetes may be up to 11 times higher than in persons without the disease⁽¹⁾. From pathophysiological standpoint, type II diabetes mellitus causes abnormal carbohydrate, lipid and protein metabolism associated with insulin resistance and impaired insulin secretion. It usually begins as insulin resistance, a disorder in which the cells do not use insulin properly. As the need for insulin rises, the pancreas gradually loses its ability to produce it. Insulin resistance is a major contributor to progression of the disease and to complications of diabetes. Type II diabetes is a chronic, progressive disease that cannot be cured now. However, it can be treated using the non-pharmacological approaches including diet modification, weight control and regular exercise, and pharmacological approaches when the blood glucose levels can not be controlled with diet and exercise. There are five classes of diabetes medicines used in the United States: sulfonylureas, meglitinides, biguanides, thiazolidinediones, and α -glucosidase inhibitors which work in different ways to lower blood glucose levels via one of the following mechanisms: increase of insulin secretion, decrease of glucose absorption, improvement of insulin sensitivity or increase glucose clearance via kidneys. The blockade agents of KATP, for example, are mediated with increase of insulin secretion. The physiological importance of KATP channels in insulin secretion was established more than 20 years ago⁽²⁾. Many the

anti-hyperglycemic agents, such as sulfonylureas, repaglinide, nateglinide are the modulators of K_{ATP} channels. Since last five years, increasing findings have demonstrated that modulation of other ion channels such as voltage-gated potassium (Kv) channels including Kv1.3, Kv1.4, Kv2.1, and voltage-gated calcium channels including Ca_v2.2 and L-type Ca channel showed antidiabetic indications which may lead to discovery of novel pharmacologic agents to treat type II diabetes mellitus.

1. ATP-sensitive potassium (K_{ATP}) channels

The K_{ATP} channel is a hetero-octamer consisting of 4 subunits of sulfonylurea receptor (SUR) and 4 subunits of channel protein (Kir6). Kir6 is a member of the Kir channel family. SUR has three transmembrane domains (TMD0, TMD1, TMD2), and TMD2 is a member of the ATP-binding cassette (ABC) protein family. In the pancreatic β -cells, the K_{ATP} channels play an essential role in coupling membrane excitability with glucose-stimulated insulin secretion^(3,4). As illustrated in Figure 1,

K_{ATP} Dependent Glucose -stimulated Insulin Secretion



increase of circulating glucose leads to increase of intracellular [ATP]/[ADP] ratio, producing changes in cytosolic nucleotide concentrations that cause K_{ATP} channel closure resulting in membrane depolarization. Consequent activation of voltage-dependent Ca²⁺ channels causes Ca²⁺ influx and a rise in [Ca²⁺]_i, which triggers insulin release. Conversely, a decrease in the metabolic signal is to open K_{ATP} channels and suppress the electrical trigger of insulin secretion. Many currently marketed therapeutic agents, such as sulfonylureas, nateglinide and repaglinide promote insulin secretion by binding to the regulatory sulfonylurea receptor subunit (SUR1 or SUR2) and inhibiting K_{ATP} channel currents⁽⁶⁾. Some other drugs act as potent stimulators of insulin secretion from direct closure of K_{ATP} channels mediated via Kir6.2 subunit^(6,7).

There has been increasing evidence that excessive insulin release might be closely associated with development of type II diabetes, and relative insulin hypersecretion causes the β cell to become exhausted resulting in a reduced ability to respond to glucose stimuli and subsequent degeneration. Reduction of insulin secretion improves β cell function⁽⁸⁾. Thus, inhibition of insulin secretion via activation of K_{ATP} channels has become a new approach for the treatment and prevention of type II diabetes. Although the relationship between hyperinsulinemia has been known for decades, only a few inhibitors of insulin release have been characterized in vitro and in vivo. K_{ATP} openers, such as diazoxide and NN414 have been shown to protect β cells and preserve function of islets^(9,10,11)

2. Voltage-gated potassium (Kv) channels

Kv channels belong to the six-transmembrane family of K⁺ channels consisting of Kv1 to Kv11 subfamilies⁽¹²⁾ and regulate cell membrane potential by controlling the rate of K⁺ exit from the cell. Kv channel was found to be the dominant Kv current of β -cells⁽¹³⁾. Inhibition of the β -cell Kv current prolongs the action potentials, sustains the opening of voltage-dependent Ca²⁺ channels, and thereby enhances glucose-induced insulin release. Such a therapeutic strategy would be expected to pose a lower risk for hypoglycemic events comparison with sulphonylurea K_{ATP} channel blockers. Thus, the β cell Kv channel has attracted much attention as a potential therapeutic target for treatment of type II diabetes^(14,15).

2.1. Kv1.3

Kv1.3 is expressed in a number of insulin sensitive tissues, including fat and skeletal muscle. Gene inactivation or pharmacological inhibition of Kv1.3 increases peripheral glucose homeostasis and insulin sensitivity by stimulating glucose uptake in adipose tissue and skeletal muscle⁽¹⁶⁾. The mechanism of this indication is thought that inhibition of Kv1.3 facilitates the translocation of the glucose transporter, GLUT4 to the plasma membrane which increases the amount of GLUT4 at the plasma membrane. It is well known that GLUT4 is the major insulin-responsive transporter that is predominantly restricted to adipose and skeletal muscle tissues. Insulin-stimulated glucose uptake in adipocytes and muscle is mediated with rapid movement of GLUT4 from intracellular storage sites to the plasma membrane⁽¹⁷⁾. In addition, studies have confirmed that mutations in the Kv1.3 gene exist in humans which are associated with alterations of glucose homeostasis. Five single-nucleotide polymorphisms in the promoter region (T-548C, G-697T, A-845G, T-1645C, and G-2069A) were identified with allelic frequencies of

the minor allele of 26, 23, 9, 41, and 16%. A variant in the promoter of the Kv1.3 gene is associated with impaired glucose tolerance and lower insulin sensitivity⁽¹⁸⁾. Therefore, Kv1.3 is a promising target for the development of drugs for the improvement of insulin resistance that is a major contributor to progression of the disease and to complications of diabetes.

2.2. Kv1.4

A recent study has identified a link between Kv1.4 and GIP (glucose-dependent insulinotropic polypeptide). GIP is one of the major intestinal hormones involved in the stimulation of insulin secretion during a meal^(19,20). GIP reduces A-type peak current amplitude of Kv1.4 via activation of protein kinase A (PKA). Using mutants of Kv1.4 with Ala-Ser/Thr substitutions in a potential PKA phosphorylation site, C-terminal phosphorylation was shown to be linked to GIP-mediated current amplitude decreases. GIP treatment results in similar decreases in A-type potassium current peak amplitude to those in HEK293 cells expressing Kv1.4⁽²⁰⁾. These results strongly support an important novel role for GIP in regulating Kv1.4 cell surface expression and modulation of A-type potassium currents, which is likely to be critically important for its insulinotropic action. Therefore, Kv1.4 channel could represent a candidate gene as a therapeutic target for type II diabetes.

2.3. Kv2.1

It has been found that Kv2.1 forms the predominant component of repolarizing currents in mouse and human β cells. Dominant-negative “knockout” of Kv2.1 in islet decreases Kv2.1 current by 60-70%. Hanatoxin (HaTx), a specific Kv2.1 blocker (0.1 μ M), inhibits total Kv currents by 65% in human islet^(21,22). Inhibition of Kv2.1 enhances first- and second-phase insulin secretion from perfused mouse pancreas. Hanatoxin induces slow intracellular Ca²⁺ concentration oscillations in human and mouse cells stimulated with glucose. A novel inhibitor of Kv2.1/Kv2.2 channels, guangxitoxin -1 broadens the β cell action potential, enhances glucose-stimulated intracellular calcium oscillations, and enhances insulin secretion from mouse pancreatic islets in a glucose-dependent manner⁽²³⁾. These data supports a mechanism for specific enhancement of glucose-dependent insulin secretion by Kv2.1 blockers, which may provide a new opportunity for the treatment of type II diabetes.

3. Voltage-gated calcium (Cav) channels

Structurally, Cav channels are composed of at least three subunits, the α 1, α 2- δ , and β subunits. The α 1-subunit is a pore-forming component, and is capable of generating Ca²⁺

channel activity⁽²⁴⁾. Molecular cloning studies have revealed that CaV1.1, CaV1.2, CaV1.3, CaV2.1, CaV2.2, and CaV2.3 genes encode the α 1 subunits of L-, P/Q-, N-, R-, and T-type Ca²⁺ currents, respectively^(25,26,27,24). As shown in Fig.1, Cav channels play crucial roles in stimulus-secretion coupling in pancreatic β cells.

3.1. L-type Cav channels

In the voltage-gated L type Ca²⁺ channel, β subunit is believed to play a key role in the assembly/expression of the channel complex and modulate Ca²⁺ currents through α 1 subunits^(28,29,30). It has been well documented that inhibition of L-type Cav channels reduces insulin secretion^(31,32,33). But, surprisingly, knock-out of L-type Cav channel β 3 subunit showed an increase of glucose-stimulated insulin secretion. The β 3 subunit knock-out mice appeared having a more efficient glucose homeostasis compared to wild-type mice⁽³⁴⁾. The mechanism is thought that removal of Ca²⁺ channel β 3 subunit enhances Ca²⁺ oscillation frequency via a modulation of InsP3-induced Ca²⁺ release. It is known that an oscillatory increase of free Ca²⁺ concentration [Ca²⁺]_i in pancreatic β cell, is a key feature in glucose-induced insulin release⁽³⁴⁾. Since the increase in insulin release was manifested only at high glucose concentrations, blocking the β 3 subunit in the beta cell may constitute the basis for a novel diabetes therapy.

3.2. N-type Cav channels

The voltage-gated N-type Ca²⁺ channel is localized in the plasma membrane of insulin-releasing β cells and glucagon-releasing α cells in the pancreatic islets. Electrophysiological and pharmacological studies have shown that glucagon secretion from α cells in the islets is a Ca²⁺-dependent process, and a N-type Ca²⁺ channel blocker partially blocks the Ca²⁺ influx in alpha cells^(35,36). Glucagon, a 29-amino-acid hormone activates the glycogenolytic and gluconeogenic pathways, thereby increasing hepatic glucose production. The actions of insulin and glucagon are thought to be essential in maintaining fasting and postprandial glucose homeostasis. The N-type Cav knock-out mice showed lower plasma glucagon and a higher glucose clearance rate in glucose tolerance test. These results suggested that N-type Cav channels play a role in glucagon release⁽³⁷⁾. Thus, N-type Cav channel blockers might be candidate antidiabetic agents that could treat type II diabetic patients via decrease of glucose production.

Summary

Targeting ion channels has been a major approach for the treatment of type II diabetes. Blockers of KATP channels remain the main agents used to treat type II diabetic patients.

Opening of KATP channels has been recognized as a new approach to preserve β cells in the islets. Blockers of Kv1.3, Kv1.4 and Kv2.1, N-type Cav channels and L-type Cav β subunit could become promising opportunity for the treatment of type-II diabetes in the future. Growing knowledge of ion channel structures and improvement of functional electrophysiological screening technologies will facilitate drug discovery in ion channels.

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