



The Role of Potassium and Calcium Ion Channels in Membrane Potential Regulation and Diabetes Mellitus

Udegbulem Daniel Nwanneamaka^{1*}, Nnodim Johnkennedy², Nwodo Divine Akachukwu¹, and Ezeagwuna Chiamaka¹

¹Department of Medical Laboratory Science, Madonna University, Elele Rivers State Nigeria

²Department of Medical Laboratory Science, Imo State University, Owerri

Corresponding Author: Udegbulem Daniel Nwanneamaka

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Department of Medical Laboratory Science, Madonna University, Elele Rivers State Nigeria

ABSTRACT	Review Article
Potassium (K⁺) and calcium (Ca²⁺) ion channels are important regulators of cell electrical activity, membrane potential, intracellular calcium homeostasis, hormone production, vascular tone, neuronal excitability and metabolic function. Their coordinated activity is especially crucial in pancreatic β-cells, where variations in membrane potential act as the electrical coupling between glucose metabolism and insulin release. In healthy β-cells, glucose metabolism increases the intracellular ATP/ADP ratio, closes ATP-sensitive potassium (KATP) channels, depolarises the membrane, activates voltage-dependent calcium channels and increases cytosolic Ca²⁺, which induces insulin granule exocytosis. Potassium channels of several types, including voltage-dependent potassium channels and calcium-activated potassium channels, then regulate the pattern of electrical activity and membrane repolarisation. Thus, calcium channels not only constitute sources of intracellular Ca²⁺ but also play an essential part in the stimulus secretion coupling mechanism. In diabetes mellitus altered expression, activity and control of potassium and calcium channels can affect membrane potential, calcium homeostasis and insulin production. Hyperglycaemia, lipotoxicity, oxidative stress, mitochondrial dysfunction, inflammation and advanced glycation can alter ion-channel function and lead to β-cell failure. Similar channel anomalies are seen in vascular smooth muscle, endothelial cells, neurones and erythrocytes, possibly contributing to vascular dysfunction, diabetic neuropathy and other consequences. The knowledge on the interplay between potassium and calcium channels provides an important basis to explain the cellular mechanisms of diabetes mellitus and may help to create channel-targeted treatments. Key words: Potassium channels; calcium channels; membrane potential; KATP channels; KCa3.1; pancreatic beta-cells; insulin secretion; diabetes mellitus; calcium homeostasis; ion-channel malfunction.	Article History
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INTRODUCTION

Diabetes mellitus is a complicated metabolic disease predominantly characterised by chronic hyperglycaemia caused by insulin deficiency, insulin resistance or a combination of the two. Diabetes is classically regarded as a disease of aberrant glucose metabolism; however, it also causes altered cellular electrical activity, ion transport, membrane integrity, calcium signalling, mitochondrial function and vascular control. Ion channels are crucial to these activities, regulating membrane potential and intracellular signaling [1]. They control the flow of charged particles across biological membranes.

Potassium and calcium channels are particularly essential among the many ion channels expressed in metabolically active tissues. Potassium channels govern resting membrane potential, repolarisation and cellular excitability whereas calcium channels serve as conduits for Ca²⁺ entry and contribute in excitation-secretion coupling, contraction, gene regulation and metabolic signalling. Potassium efflux changes the voltage of the membrane, and therefore affects if voltage-dependent calcium channels open, so the two functions are tightly linked. Calcium influx can then activate calcium dependent potassium channels that can lead to feedback processes that modulate membrane excitability [2].

The pancreatic β -cell is one of the best illustrations of this interaction. Changes in cellular ATP synthesis via glucose metabolism modulate ATP-sensitive potassium channels. These channels close, depolarising the β -cell membrane and activating voltage-dependent calcium channels. The elevation in intracellular calcium that occurs is an important signal for insulin production. Thus, any abnormality of either potassium or calcium channels may interfere with the electrical events necessary for proper insulin release [3].

Experimental and clinical investigations indicate that ion channel malfunction may be involved in the aetiology of diabetes mellitus. Changes in KATP channels, voltage-gated potassium channels, calcium-activated potassium channels and voltage-dependent calcium channels have been correlated with aberrant beta-cell electrical activity and decreased insulin production. Also, alterations in activity of potassium and calcium channels in vascular and neural tissues may be involved in diabetic vascular problems and neuropathy [4].

This review focuses on the significance of potassium and calcium ion channels in the regulation of membrane potential and their relationship with diabetes mellitus, with special emphasis on the physiology of pancreatic β -cells, insulin secretion, calcium homeostasis, vascular function, neuronal activity and the pathomechanisms of metabolic stress through ion-channel dysfunction [5].

Membrane Potential: The Biological Basis

Membrane potential is the differential in the electrical potential across the plasma membrane caused by an unequal distribution of ions between the intracellular and extracellular compartments. The principal contributors of the membrane potential are potassium, sodium, calcium and chloride. The selective permeability of the plasma membrane to these ions and the activity of ion pumps and transporters define the electrical state of the cell [6].

Potassium plays a very vital role, because the intracellular concentration of potassium is much larger than the external concentration of potassium. Potassium channels open and K^+ flows along its electrochemical gradient, often from the intracellular to the extracellular compartment. This flow of positive charge tends to make the intracellular milieu more negative and hence leads to membrane hyperpolarisation or repolarization [7].

Calcium has a different but complimentary role. As the external Ca^{2+} is significantly more concentrated than free cytosolic Ca^{2+} concentration, the opening of calcium channels allows positively charged calcium ions to flow inward. This usually leads to depolarisation and, more crucially, an increase in intracellular Ca^{2+} which can activate a number of signalling pathways [8].

The potassium and calcium conductances are coupled, and this coupling permits the cell to form complicated electrical patterns. A depolarising stimulation could open calcium channels, raising calcium within the cell. Calcium then can activate calcium-sensitive potassium channels, causing K^+ efflux and membrane repolarisation. This connection is particularly significant in excitable cells such as pancreatic β -cells, neurones and vascular smooth muscle cells [9].

Potassium Channels and Membrane Potential Regulation

Potassium channels are one of the broadest and most diversified groups of ion channels. They affect resting membrane potential, action potential length, cellular excitability, secretion and vascular tone. Their activity is modulated by intracellular metabolites, membrane voltage, calcium concentration and other signalling processes. The ATP sensitive potassium channels or KATP channels in pancreatic beta-cells are of special importance. These channels link metabolism of the cell with its electrical activity. KATP channels are functionally assembled from potassium channel subunits linked with regulatory sulfonylurea receptor subunits. Their activity is regulated by intracellular nucleotides, such as ATP and ADP [10].

When glucose availability is low, KATP channels are relatively active, permitting potassium efflux and maintaining the β -cell membrane in a relatively hyperpolarised state. Hence, the voltage-dependent calcium channels are mostly closed and the insulin release is relatively low.

Increased extracellular glucose stimulates entry of glucose into the β -cell and its conversion to ATP. The resultant increase in ATP/ADP ratio favours the closure of KATP channels. Reduction in potassium efflux promotes membrane depolarisation and activation of voltage gated calcium channels. Calcium then enters the cell and induces insulin granule exocytosis.

Thus, KATP channels serve as a metabolic sensor that couples changes in glucose metabolism to changes in membrane potential. Ashcroft and Rorsman have highlighted the key significance of KATP channels in the coupling between β -cell metabolism and electrical activity and islet hormone release.

Further evidence of the relevance of KATP channels comes from defects in the genes encoding its components. Activating mutations may make the channel too open to allow proper depolarisation of the membrane and secretion of insulin, whereas loss-of-function mutations may leave β -cells inappropriately depolarised and secrete excessive amounts of insulin. These data give substantial evidence that proper modulation of potassium conductance is critical for glucose-responsive insulin secretion [11].

K⁺ channels that depend on voltage

Repolarisation of the β -cell after depolarisation involves voltage-dependent potassium channels. Potassium channels are activated, helping to bring the membrane potential back near the resting potential, once calcium entry has occurred. This process affects the duration and frequency of electrical activity and so indirectly controls calcium entry and insulin secretion.

The operation of voltage-dependent potassium channels may affect the form of electrical oscillations in β -cells. Increased potassium conductance can abbreviate the depolarisation and diminish calcium influx. Either scenario might possibly change the temporal pattern of insulin secretion.

MacDonald and Wheeler emphasised the significance of voltage-gated potassium channels in pancreatic β -cells and their therapeutic potential. Thus, changes in these channels may result in aberrant β -cell excitability and defective insulin secretion [13].

Calcium-Activated Potassium Channels

Intracellular increases in Ca^{2+} activate calcium-activated potassium channels. KCa channels are significant feedback between calcium signalling and membrane potential. An increase in intracellular calcium can activate KCa channels and promote K^+ efflux and lead to either repolarisation or hyperpolarisation of the membrane. One of these calcium-activated potassium (KCa) channels that has been implicated in pancreatic β -cell physiology is the $\text{KCa}_{3.1}$ channel. Experiments have indicated that changes in $\text{KCa}_{3.1}$ activity may affect glucose-dependent insulin secretion. Aberrant activation of these channels can modify the electrical response of β -cells and hence can alter calcium influx and insulin secretion [14].

Calcium Channels and Depolarisation of the Membrane

Voltage-dependent calcium channels are opened by membrane depolarisation. In pancreatic β -cells these channels are the primary means of transducing membrane depolarisation into an intracellular calcium signal. Increase in cytosolic calcium concentration Ca^{2+} entrance through voltage-dependent calcium channels. Calcium then engages the molecular machinery that is involved in the exocytosis of insulin granules. The amount and timing of insulin secretion are dependent on the size, length and spatial distribution of calcium signals. Distinct types of calcium channels may contribute differently to distinct components of β -cell calcium signalling. Thus, insulin secretion can be altered by changes in channel expression, activation or inactivation. Yang, S. N., & Berggren, P. O. (2004). The role of voltage-gated calcium channels in pancreatic β -cell physiology and pathology. Their function underscores the basic idea that electrical activity and calcium signalling are closely connected activities in insulin-producing cells [15].

Potassium and calcium channels in glucose-induced insulin secretion

Glucose-stimulated insulin production requires an integrated sequence of metabolic, electrical and calcium-dependent processes. Glucose intake leads to increased ATP generation via intracellular glucose metabolism. KATP channels close when the ATP/ADP ratio is high. Membrane depolarisation due to reduced K^+ conductivity. At some voltage threshold the membrane will open voltage dependent calcium channels permitting Ca^{2+} inflow. The rise in the cytosolic calcium is the immediate signal for the exocytosis of insulin granules. But the absolute level of intracellular calcium is not the only factor that determines insulin production. The time course of calcium oscillations, membrane depolarisation and channel activation may also have a role in the efficiency and kinetics of insulin release. Subsequently potassium channels are involved in repolarisation and recovery of membrane excitability. The β -cell operates by a dynamic feedback loop of potassium and calcium where potassium channels regulate the electrical conditions for calcium entry, and calcium activates potassium channels to assist in the termination of depolarization [16].

Diabetic Mellitus with Impaired Potassium and Calcium Channel Function

In diabetes mellitus the normal link between metabolism, membrane potential and ion-channel activity may be uncoupled. β -cell dysfunction may be caused by prolonged exposure to high glucose concentrations, increased fatty acids, oxidative stress, inflammatory mediators and mitochondrial abnormalities and altered intracellular signalling. The glucotoxicity caused by chronic hyperglycaemia affects β -cell metabolism and ion-channel control. Long-term exposure to glucose may lead to increased oxidative stress, changes in mitochondrial function and altered cellular signalling pathways [17]. Due to the sensitivity of KATP channels to variations in ATP and ADP levels, abnormalities in mitochondrial ATP synthesis can modify KATP -channel activity. Thus, metabolic failure may translate into aberrant electrical activity. Chronic metabolic stress may also result in a decoupling of the normal link between membrane depolarisation and calcium influx, resulting in impaired insulin secretion. Increased circulating fatty acids and lipid buildup in cells may decrease β -cell activity. Lipotoxicity could change the composition of membrane lipids, mitochondrial metabolism, oxidative balance and activity of ion-channels. Ion channels are embedded in the plasma membrane, and changes in the lipid content of the membrane could affect ion channel performance. Thus, the ability of the potassium and calcium channels to respond properly to metabolic and electrical signals may be impaired by lipotoxicity [18].

Oxidative Stress

Oxidative stress is a crucial pathway linking metabolic dysregulation to cellular damage in diabetes.

Excessive generation of reactive oxygen species can alter proteins, lipids and nucleic acids. Ion channels and their control protein may be the targets for oxidative changes. Oxidative stress can thereby change channel conductance, gating characteristics and cellular signalling.

The importance of oxidative stress is particularly crucial as pancreatic β -cells have relatively low antioxidant defences. Ongoing oxidative stress might thus compromise mitochondrial function, ATP generation and ion-channel processes necessary for insulin secretion [19].

Calcium Homeostasis and Beta-Cell Failure

Calcium is required for insulin release but large or sustained elevations in intracellular Ca^{2+} may be deleterious. Physiological calcium signals are transitory and closely regulated, but chronic increase of calcium may trigger stress pathways and compromise cellular function. Diabetes may lead to disruption of calcium homeostasis due to changes in calcium channels, intracellular calcium storage, calcium binding proteins and calcium extrusion mechanisms. Dysfunctional β -cells may result from altered calcium management and contribute to impaired insulin production. The connection between calcium and potassium channels increases the consequences. Changes in calcium influx affect KCa channels, and potassium conductance sets the membrane potential that drives calcium-channel activation [20].

Potassium and Calcium Channels in Vascular Dysfunction

Ion channels in diabetes are not only in pancreatic β -cells. Channels for potassium and calcium are important regulators of vascular smooth muscle and endothelial function. Potassium channels in vascular smooth muscle cells regulate voltage-dependent calcium-channel activity by altering the membrane potential. Hyperpolarisation occurs due to increased potassium efflux. This results in decreased calcium entry promoting relaxation. In contrast, a reduction in potassium channel activity may lead to depolarisation, increased calcium entry and increased vasoconstriction. Calcium is consequently a primary factor of vascular smooth muscle contraction. Potassium channels indirectly regulate vascular tone by modulating the electrogenic conditions that influence calcium entry. Endothelium-dependent hyperpolarisation is another major mechanism of vascular relaxation. Potassium-channel activity of endothelial cells may hyperpolarise and convey this to vascular smooth muscle to cause relaxation. Diabetes can interfere with these systems via oxidative stress, diminished nitric oxide bioavailability, inflammation and alterations in ion channel function. Such anomalies may lead to endothelial dysfunction, increased vascular resistance and diabetic vascular consequences [21].

Vascular Tone and KCa Channel Regulation

Calcium-activated potassium channels are important in vascular physiology because they relate intracellular calcium concentrations to membrane potential. KCa channels are activated by a rise in intracellular calcium concentration in vascular cells, resulting in potassium efflux and membrane hyperpolarisation. It may lower the influx of calcium through voltage-dependent calcium channels and induce vascular relaxation. Thus, disruption of KCa-channel activity may lead to increased vascular tone. In diabetes, oxidative stress and metabolic derangement may affect this regulating mechanism and lead to vascular dysfunction [22]. This provides yet another illustration of the importance of potassium-calcium coupling. Calcium activates potassium channels, and the activity of potassium channels feeds back to limit calcium entrance.

Diabetic neuropathy: Potassium and calcium channels

Potassium and calcium channels are also critical for the electrical excitability of the nervous system and for neurotransmission. Action-potential generation, propagation and neurotransmitter release are based on voltage-gated sodium, potassium and calcium channels. Diabetes causes metabolic stress that can alter the function of ion channels in peripheral nerves. Abnormal neuronal excitability may involve oxidative stress, mitochondrial malfunction, disturbed calcium homeostasis and alterations in channel expression. Voltage-gated calcium channels promote the release of neurotransmitters by enabling Ca^{2+} influx into presynaptic terminals. Potassium channels are responsible for repolarisation and determine the duration of electrical activity of neurones. Thus, abnormal control of any channel type can alter neural signalling. These pathways may contribute to impaired sensory function and discomfort in diabetic peripheral neuropathy [23].

Erythrocyte Membrane and Ion Homeostasis in Diabetes

Maintenance of ionic and structural integrity of erythrocytes also requires membrane transport pathways. Diabetes may alter erythrocyte membrane composition, fluidity, enzyme activity and ion transport. Erythrocytes from diabetic people have been described to have changes in the sodium-potassium pump and Na^+/H^+ exchanger. Altered ion transport and intracellular ionic concentrations can lead to changes in membrane characteristics. Although erythrocytes lack the excitable electrical machinery that is characteristic of pancreatic β -cells or neurones, the membrane potential and ion gradients are nonetheless vital for cellular homeostasis. Oxidative stress and glycation associated with diabetes might affect membrane proteins and lipids, thereby contributing to aberrant erythrocyte function [24].

Ion channel dysfunction and advanced glycation

Advanced glycation end products (AGEs) are generated by non-enzymatic interactions between

proteins, lipids or nucleic acids and reducing sugars. Accumulation of these is a prominent characteristic of chronic diabetes. AGEs can change proteins and extracellular frameworks and turn on cellular receptors that encourage oxidative stress and inflammation. These processes can directly or indirectly influence ion channels and regulatory proteins. AGE-mediated oxidative and inflammatory signalling may thus lead to changes in potassium and calcium channel function. In vascular tissues this may contribute to decreased endothelial function and altered vascular tone. Chronic metabolic stress may affect electrical activity and insulin secretion in pancreatic β -cells [25].

Ion-channel regulation and inflammation

A key characteristic of type 2 diabetes is chronic low-grade inflammation. Pro-inflammatory cytokines can affect intracellular signalling cascades, oxidative metabolism and membrane proteins. Inflammatory mediators may modify the expression or activity of ion channels and consequently influence membrane potential and cellular excitability. Inflammatory stress can lead to decreased insulin secretion and eventual β -cell failure in the pancreas. Inflammation may also be caused by oxidative stress and mitochondrial malfunction. The interaction between these pathways implies that alterations of the ion channels in diabetes are unlikely to be due to a single cause. Rather, they are the outcome of interconnected metabolic, inflammatory, oxidative and mitochondrial abnormalities.

A Unified Model of Potassium and Calcium Channel Dysfunction in Diabetes

Potassium (K^+) and calcium (Ca^{2+}) ion channels have a function in diabetes as an interconnected physiological network linking cellular metabolism to membrane excitability and insulin release. Under normal conditions, the increase in glucose metabolism causes an increase in the intracellular ratio ATP/ADP, which leads to the closure of ATP-sensitive potassium (K_{ATP}) channels. This lowers K^+ outflow and leads to membrane depolarisation that activates voltage-dependent Ca^{2+} channels. Subsequent Ca^{2+} influx increases insulin secretion. Activation of Ca^{2+} -dependent and voltage-gated K^+ channels participates in membrane repolarisation and control of further electrical activity.

In diabetes, especially during sustained hyperglycaemia and lipotoxicity, oxidative stress and mitochondrial dysfunction might affect ATP generation, ion-channel activity and intracellular Ca^{2+} handling. Therefore, aberrant K^+ conductance can influence the membrane potential and cause abnormal Ca^{2+} entry and disturbed intracellular Ca^{2+} balance. These anomalies may lead to impaired insulin secretion and contribute to increasing β -cell failure. Similar mechanisms may be operating in other tissues. Altered K^+ channel activity in vascular cells may alter the membrane potential and consequently affect Ca^{2+} channel activity resulting in

poorer vascular contraction and relaxation. Metabolic and oxidative impairments impacting K^+ and Ca^{2+} channels in neurones may alter neuronal excitability and neurotransmission, and may contribute to diabetic neuropathic dysfunction. Thus K^+ and Ca^{2+} channels are not stand-alone entities but interlinked modulators of cellular electrical activity, Ca^{2+} signalling, insulin production and metabolic homeostasis.

Therapeutic Implications

The significance of potassium and calcium channels in diabetes has prompted interest in channel-targeted treatments. K_{ATP} channels are of clinical importance as the sulfonylureas operate on the K_{ATP} -channel complex to affect insulin secretion. The genetic association of K_{ATP} channels with diabetes has also shown that it is possible to therapeutically address the channel abnormalities. The understanding of how individual mutations change channel activity has helped to lead to precision therapies for some kinds of diabetes. Other potassium channels include voltage-dependent potassium channels and KCa channels have been studied as possible therapeutic targets. However, systemic modulation of ion channels should be performed with caution, as the same channels may affect cardiovascular, neurological, and other physiological systems. Calcium channels are potentially possible therapeutic targets. However, 100% blockage of calcium entrance would not be desired since calcium is required for optimal insulin secretion and many other cellular activities. Thus, future efforts may need to focus on selective modulation instead of entire channel obstruction. It is therefore a crucial therapeutic principle to restore the physiological channel activity rather than a simple enhancement or suppression of channel function. The best intervention may depend on the individual channel subtype, tissue, disease stage and underlying metabolic imbalance [26].

CONCLUSION

Potassium and calcium ion channels have a vital function in control of membrane potential and pathogenesis of diabetes mellitus. In pancreatic β -cells, K_{ATP} channels represent the essential metabolic link between glucose metabolism and membrane depolarisation, while voltage-dependent calcium channels translate depolarisation into intracellular calcium signals that activate insulin release. Voltage-gated and calcium-activated potassium channels then regulate membrane repolarisation and electrical activity duration. In diabetes mellitus these carefully regulated mechanisms can be disturbed by chronic hyperglycaemia, lipotoxicity, oxidative stress, mitochondrial dysfunction, inflammation and advanced glycation. The ensuing anomalies in potassium and calcium channel function may influence membrane potential, calcium homeostasis and insulin production, ultimately contributing to β -cell dysfunction. The relevance of these channels reaches further than the pancreas. Abnormalities in potassium and calcium conductance may affect arterial tone, endothelial

function, neuronal excitability and erythrocyte membrane physiology and so contribute to the multisystem problems of diabetes. To summarise, potassium and calcium channels should be seen as essential molecular interfaces connecting cellular metabolism, electrical activity of membranes, and diabetes-associated tissue damage. Better understanding of these interconnections may enhance our understanding of diabetes aetiology and create potential for development of innovative channel-targeted diagnostic and treatment approaches.

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