



Membrane Potential Dysfunction in Type 2 Diabetes Mellitus: Biological Mechanisms and Biological Perspectives

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Abstract

Type 2 diabetes mellitus (T2DM) is a complicated metabolic illness characterised by insulin resistance, progressive pancreatic β -cell dysfunction, chronic hyperglycaemia, oxidative stress, inflammation and various vascular and neurological consequences. Alterations in glucose and lipid metabolism are fundamental to T2DM pathogenesis, but there is accumulating evidence to suggest that perturbations in cellular membrane potential constitute a key, if relatively underestimated, element of diabetes pathophysiology. Ion concentration gradients across biological membranes give rise to a membrane potential, which is largely maintained by ion channels, pumps and transporters. It controls cellular excitability, calcium signalling, secretion, mitochondrial bioenergetics, vascular tone, neuronal transmission and erythrocyte homeostasis. In pancreatic β -cells, glucose metabolism generally leads to an increase in the ATP/ADP ratio, closure of ATP-sensitive potassium (K/ATP) channels, depolarisation of the plasma membrane, activation of voltage-dependent calcium channels and insulin release. In T2DM, glucotoxicity, lipotoxicity, oxidative stress, mitochondrial dysfunction and changes in ion-channel expression or activity can impair this stimulus-secretion coupling. Similarly, increased reactive oxygen species, altered electron transport, proton leakage and reduced mitochondrial quality control influence the mitochondrial membrane potential. Potassium channel dysfunction and endothelial hyperpolarisation in vascular tissues contribute to decreased vasodilation and vascular consequences. Neuronal ion channel remodelling may influence membrane excitability and contribute to diabetic neuropathy. Erythrocyte Na⁺ + /K⁺ -ATPase abnormalities, membrane fluidity and ion transport may influence red-cell membrane potential and rheological properties. In this study, we focus on the molecular processes of membrane potential malfunction in T2DM and its potential importance as a mechanistic biomarker and therapeutic target. A better understanding of membrane electrophysiology may provide novel insights into the relationship between metabolic derangements and beta-cell failure, vascular and nerve dysfunction, and other diabetic consequences.

Keywords: Type 2 diabetes mellitus; membrane potential; ion channels; potassium channels; calcium signalling; mitochondrial membrane potential; beta-cell dysfunction; oxidative stress; insulin secretion; endothelial dysfunction.

Introduction

Type 2 diabetes mellitus is one of the most common metabolic diseases globally. Pathophysiology involves gradual interplay between insulin resistance, insufficient compensatory insulin secretion, pancreatic beta-cell malfunction, aberrant hepatic glucose generation, adipose-tissue dysfunction and chronic metabolic inflammation. These anomalies at the cellular level are associated with substantial alterations in energy metabolism, redox balance, intracellular signalling and membrane transport. The membrane potential[1] is an important but less emphasised component of these processes. Membrane potential is the electrical potential difference across a biological membrane arising from changes in ionic

concentration and permeability between the intracellular and external compartments. Membrane potential is a key characteristic of excitable cells such as pancreatic β -cells, neurons, cardiac myocytes and vascular smooth muscle cells. Even in cells classically described as non-excitable, such as erythrocytes and endothelial cells, membrane potential plays a role in ion transport, volume regulation, calcium signalling and cellular homeostasis[2].

The membrane potential is determined mainly by the distribution and permeability of potassium (K^+), sodium (Na^+), calcium (Ca^{2+}) and chloride (Cl^-) and the activity of transport proteins such as Na^+/K^+ ATPase. Ion channels provide controlled routes for transport of ions. ATP - dependent ion pumps maintain electrochemical gradients. Thus, changes in cellular metabolism can be translated into electrical changes across the membrane. This makes the membrane potential an essential link between cellular metabolism and physiological function [3].

The linkage of metabolism to the electrical activity of the membrane is particularly significant in pancreatic β -cells. ATP-sensitive potassium (KATP) channels are regulated by the ATP generated by glucose metabolism. Closing these channels depolarises the β -cell membrane, opening voltage-gated calcium channels and increasing intracellular Ca^{2+} to promote insulin granule exocytosis. Thus, electrical activity is an important intermediary between glucose metabolism and insulin production. This highly regulated mechanism may be affected in T2DM. Increased glucose, increased free fatty acids, mitochondrial dysfunction, oxidative stress, advanced glycation end products, inflammation and changed lipid composition can alter ion channels and transporters. The ensuing anomalies of membrane-potential may contribute to faulty insulin production, endothelial dysfunction, aberrant neuronal excitability and altered erythrocyte physiology[4].

The Biology of Membrane Potential

The membrane potential arises from the unequal distribution of charged ions across a selectively permeable biological membrane. An animal cell at rest often has a negative intracellular potential relative to the extracellular environment. Potassium is especially significant since the plasma membrane is generally very permeable to K^+ under resting situations. Na^+/K^+ -ATPase is the principal contributor to the maintenance of ionic gradients. This membrane pump employs ATP to transfer three Na^+ ions out of the cell and two K^+ ions into the cell. In addition to keeping the sodium and potassium gradients, this electrogenic activity adds directly to membrane potential [5].

Ion channels determine how these ionic gradients are converted into electrical activity. Potassium channels normally promote K^+ efflux and hyperpolarisation of the membrane, whereas Na^+ and Ca^{2+} influx might promote depolarisation. The exact effect depends on the electrochemical gradient, channel parameters and physiological factors of the cell in question. Thus, the membrane potential can be considered as a composite readout of cellular energy availability, ion-channel activity, membrane permeability, ATP-dependent pump function, intracellular calcium concentration, mitochondrial activity, oxidative and inflammatory stress, and membrane lipid composition. This makes membrane potential especially relevant for metabolic illnesses such as T2DM [5].

Membrane potential of the pancreatic β -cell and insulin secretion

The pancreatic β -cell is likely the best example of the link between cellular metabolism and membrane electrical activity. KATP channels are generally active at low extracellular glucose concentrations, permitting potassium outflow, and keeping the β -cell relatively hyperpolarised. Increased extracellular glucose leads to β -cell glucose uptake and glycolysis, pyruvate oxidation, and mitochondrial metabolism. This results in an elevated ATP/ADP ratio, which blocks the KATP channels. This inhibition of channels reduces potassium outflow and depolarises the β -cell membrane. This leads to membrane depolarisation and the opening of voltage-gated calcium channels, calcium influx and exocytosis of insulin-containing granules.

This metabolic-electrical coupling is an essential of glucose-induced insulin release. KATP channels, comprising mostly of Kir6.2 and sulfonylurea receptor 1 (SUR1) subunits, act as metabolic sensors that relate intracellular nucleotide levels to β -cell electrical activity. Therefore, their altered control can lead to changes in insulin secretion. The membrane potential also works in close conjunction with the calcium signalling. Voltage-gated calcium channels facilitate calcium entrance into the cell and represent a key trigger for exocytosis of insulin granules. Thus, aberrant β -cell membrane potential can lead to downstream anomalies in intracellular Ca^{2+} dynamics, insulin vesicle docking and insulin release[6].

Membrane Potential Dysfunction in T2DM β -Cells

T2DM is characterised by a gradual defect in β -cell stimulus-secretion coupling. Potassium and calcium channel disruption is an essential mechanism, however the particular electrophysiological abnormalities may vary with illness stage and experimental type. KATP channels are one of the most critical factors of β -cell membrane potential. Changes in channel expression, localisation, nucleotide sensitivity or regulation may affect the electrical response of β -cells to glucose.

In a normal β -cell, glucose-stimulated ATP generation shuts KATP channels and commences membrane depolarisation. Mitochondrial failure in metabolically challenged β -cells can limit ATP production or alter the ATP/ADP ratio. So, glucose can lead to either no membrane depolarisation or to inappropriate depolarisation. Ion-channel anomalies might play a role in deficient glucose-stimulated insulin production in T2DM.

Voltage-gated calcium channels are also critical for β -cell function. These channels are activated by membrane depolarisation and lead to Ca^{2+} influx into the β -cell and insulin granule exocytosis. Chronic glucotoxicity and lipotoxicity may affect calcium handling by influencing channel function, calcium storage and calcium-dependent signalling. Calcium also plays a role in β -cell metabolism, gene transcription, endoplasmic-reticulum function and cellular stress responses. Therefore, prolonged calcium dysregulation may further jeopardise β -cell viability. Thus, membrane potential dysfunction and calcium dysregulation may constitute a self-amplifying pathogenic cycle in T2DM[7].

Membrane electrical dysfunction and glucotoxicity

Chronic hyperglycaemia is one of the major causes of cellular dysfunction in T2DM. Excess intracellular glucose enhances the metabolic fluxes through the polyol pathway, protein kinase C pathway, hexosamine pathway, and advanced glycation end-product pathways. These mechanisms induce oxidative stress and change protein function. Ion channels and membrane transporters may be especially vulnerable in this regard, as their activity depends on the protein structure, the membrane lipid environment, phosphorylation and redox status[8]. Hence, sustained hyperglycaemia may result in increased reactive oxygen species production, lipid peroxidation, protein glycation, altered phosphorylation of ion channels, changes in membrane lipid composition, mitochondrial dysfunction and decreased ATP production. These perturbations can subsequently alter membrane potential and cellular excitability. Thus prolonged hyperglycaemia may influence electrical activity not only through direct effects on ion channels but also through its effects on cellular metabolism, mitochondrial function and membrane structure [9].

Lipotoxicity and the Membrane Potential

Another key hallmark of IR and T2DM is increased circulation free fatty acids. Long term exposure of pancreatic β -cells to saturated fatty acids can lead to impairment of mitochondrial activity, increased ER stress and oxidative damage. In addition, lipid accumulation may directly modulate physical characteristics of cellular membranes. Changes in the composition of phospholipids, membrane fluidity and cholesterol may impact the activity of membrane proteins such as ion channels, pumps and receptors.

The erythrocyte is the evidence for this concept. Studies have shown changes in erythrocyte membrane composition, lipid peroxidation and Na^+/K^+ -ATPase activity in T2DM. Thus, diabetes can change the biochemical environment necessary for proper membrane function. Lipotoxicity may consequently affect membrane potential indirectly via mitochondrial and oxidative processes and directly through alterations in membrane[10] architecture. Membrane Potential Dysfunction and Oxidative Stress.

Oxidative stress is a major mechanism linking metabolic problems to membrane dysfunction in T2DM. Mitochondria are an important source of reactive oxygen species. Under healthy conditions, mitochondrial electron transport generates a proton gradient across the inner mitochondrial membrane. This electrochemical gradient generates the mitochondrial membrane potential ($\Delta\Psi_m$) which is required for ATP production.

Damage to mitochondrial membrane lipids, respiratory-chain proteins, mitochondrial DNA, ion channels, ATP synthase, antioxidant enzymes and membrane transport systems results from overproduction of reactive oxygen species in the case of defective mitochondrial electron transport. Oxidative stress in pancreatic β -cells can initiate uncoupling pathways and increase proton leakage and decrease ATP production. Thus, mitochondrial failure may disturb the ATP-dependent control of KATP channels, thereby affecting β -cell membrane potential.

The association could be interpreted as a pathogenic process where hyperglycaemia and lipotoxicity provoke mitochondrial oxidative stress, leading to changes in mitochondrial membrane potential and decreased ATP generation. Reduced ATP availability disrupts KATP channel regulation leading to aberrant beta cell membrane potential, poor calcium entry and ultimately faulty insulin secretion. This is a crucial molecular relationship between metabolic stress and β -cell dysfunction[11].

Mitochondrial Membrane Potential in T2DM

Special attention should be paid to mitochondrial membrane potential since mitochondria are not only energy producing organelles but also significant regulators of intracellular signalling and cell survival. In mitochondria, the electron transport chain pumps protons from the matrix into the intermembrane space, creating an electrochemical gradient that ATP synthase uses to make ATP.

This points to the need of a healthy mitochondrial membrane potential for oxidative phosphorylation, ATP synthesis, calcium buffering, management of reactive oxygen species, control of apoptosis, and cellular metabolic signalling. Mitochondrial malfunction of β -cells is closely correlated with failure in T2DM. An excess of reactive oxygen species can uncouple mitochondria, resulting in proton leakage and reduced ATP synthesis. Reduced availability of ATP in β -cells impairs the metabolic signal needed for proper closure of KATP channels.

Vascular endothelial cells and other tissues subjected to persistent hyperglycaemia may also exhibit mitochondrial membrane-potential anomalies. Mitochondrial dysfunction is now increasingly being recognised as an essential player in the diabetic endothelial damage. Thus, mitochondrial membrane potential may be a key link between cellular metabolism, oxidative stress and the development of diabetes complications[12].

Calcium Homeostasis Membrane Potential

Membrane potential and calcium homeostasis are intimately interrelated. The driving power for calcium entry is determined by the electrical gradient across the plasma membrane. Depolarisation of membrane opens voltage-gated calcium channels. In general, hyperpolarisation of membrane decreases the chance of opening of numerous voltage-dependent calcium channels.

The result of this interaction is cell type dependent. In pancreatic beta-cells, membrane depolarisation leads to calcium influx and insulin release. Depolarisation of the membrane in vascular smooth muscle facilitates calcium influx and contraction. Membrane depolarisation is a prerequisite for action potential production and neurotransmitter release in neurones. Generalised perturbations in membrane potential might therefore affect several physiological systems at the same time.

This link is particularly relevant in T2DM where dysregulated calcium handling has been related with β -cell malfunction and decreased insulin secretion. Thus, calcium signalling disturbances may act both downstream and upstream of membrane-potential anomalies, establishing reciprocal interactions that may contribute to progressive cellular dysfunction[13].

Dysfunction of Vascular Membrane Potential

Vascular dysfunction is one of the most important consequences of T2DM. Hyperglycaemia, insulin resistance, oxidative stress and inflammation inhibit endothelial nitric oxide generation and vascular relaxation. Vascular membrane potential is regulated by potassium channels. Several kinds of potassium channels are expressed in endothelial cells and vascular smooth muscle cells, including voltage-gated potassium channels, calcium-activated potassium channels, ATP-sensitive potassium channels and inwardly rectifying potassium channels.

Membrane hyperpolarisation from opening of endothelial potassium channels This procedure may enhance calcium entry into endothelial cells and boost nitric oxide and endothelium-derived hyperpolarisation signalling. Membrane hyperpolarisation in vascular smooth muscle decreases voltage-gated calcium-channel activity and facilitates vascular relaxation. Diabetes may interfere with these activities because hyperglycaemia-induced reactive oxygen species, protein kinase C activation, lipid abnormalities and inflammatory signalling can change vascular ion channels and impede membrane-potential-dependent vasodilation[14].

More recently, evidence has emerged for the role of vascular potassium-channel remodelling in diabetic vascular disease. Thus, ion-channel modulation might be a significant therapeutic target for the prevention or therapy of diabetic vascular dysfunction.

KCa channels in diabetic vascular dysfunction

Calcium-activated potassium channels play a crucial role in vascular physiology. KCa2.3 and KCa3.1 channels are involved in the hyperpolarisation of the endothelium and the endothelium-dependent vasodilation. Dysfunction of these channels has been described in cardiovascular diseases such as diabetes. Interestingly, KCa3.1 channels are also present in pancreatic islets where they contribute to membrane-potential oscillations. Thus, altered expression under glucolipotoxic circumstances may contribute to decreased insulin secretion and pancreatic inflammation. One of the fundamental biological concepts is that the same class of ion channels is involved in pancreatic and vascular physiology. Membrane channels do not operate in isolation inside specific organs but their dysregulation can influence numerous physiological systems at the same time. Thus, aberrant potassium channel function may be a common mechanism linking metabolic inefficiency and vascular complication in T2DM[15].

Diabetes Neuropathy and Membrane Potential

Electrical activity of the membrane is essential for the nervous system. Chronic hyperglycemia can change expression and function of voltage-gated sodium, potassium and calcium channels in peripheral sensory neurones. Voltage-gated sodium channels are critically involved in the initiation and propagation of action potentials. Altered sodium-channel

expression and gating may contribute to aberrant neuronal excitability in diabetes-associated oxidative stress, inflammation and metabolic damage.

Altered sodium, potassium, calcium and transient receptor potential channels may be involved in spontaneous neuronal firing and aberrant sensory signalling in painful diabetic neuropathy. Thus, ion-channel dysfunction has become a significant component of diabetic neuropathic pain. This may thus assist explain how a metabolic illness leads to an electrical abnormality of the peripheral nervous system via membrane-potential dysfunction[16].

Erythrocyte Membrane Potential Impairment in T2DM

Mature erythrocytes do not include nuclei and mitochondria, but do have transmembrane ion gradients and other membrane transport mechanisms. Erythrocyte ionic homeostasis depends on Na⁺/K⁺-ATPase and other ion transport pathways. Diabetes may change the erythrocyte membrane composition, fluidity, lipid peroxidation and ATPase activity. Significantly, altered erythrocyte transmembrane potential has been described in diabetes. Experimental data have related hyperpolarisation of diabetic erythrocyte membranes to oxidative stress and have shown the possibility of partial normalisation of the aberrant electrical state by antioxidant and antiglycation treatment. These changes may have physiologic implications since erythrocyte deformability, membrane stability and ion homeostasis are important for microvascular blood flow.

In the diabetic microcirculation, erythrocyte membrane abnormalities may add to reduced oxygen delivery when combined with endothelial dysfunction and modified blood rheology which already limit tissue perfusion. Therefore, erythrocyte membrane disruption may be another mechanism via which systemic metabolic abnormalities lead to tissue injury[17].

Na⁺/K⁺-ATPase Dysfunction

Of particular importance is the Na⁺/K⁺-ATPase because it couples the cellular energy metabolism to the membrane electrical activity. The pump is ATP driven and any circumstance that lowers cellular ATP availability can disturb sodium and potassium gradients. In contrast, the modification of the membrane lipid composition, the oxidative stress and the glycation could directly affect the activity of the pump.

Studies on erythrocytes of diabetic patients have shown alterations in Na⁺/K⁺-ATPase activity and membrane fluidity. In T2DM these alterations have been related with hyperglycaemia, altered lipid composition and oxidative stress. Reduced Na⁺/K⁺-ATPase activity in neurones can interfere with the resting membrane potential and may result in aberrant excitability. Diabetic neuropathy has also been connected with changes in the salt pump. Thus, Na⁺/K⁺-ATPase failure is a putative common mechanism linking metabolic stress and membrane electrical instability[18].

Advanced Glycation Endproducts (AGEs) and Membrane Dysfunction

Advanced glycation end-products (AGEs) are produced by the nonenzymatic reaction of reducing sugars or reactive carbonyl compounds with proteins and lipids. Chronic hyperglycaemia may lead to the accumulation of AGEs, which may change membrane proteins and alter their structure and function. AGE-RAGE signalling can potentially activate inflammatory and oxidative pathways.

These pathways may contribute to ion-channel alteration, changed Na⁺/K⁺-ATPase activity, increased reactive oxygen species, membrane lipid peroxidation, endothelial dysfunction, neuronal damage and decreased cellular signalling via advanced glycation. AGE-mediated alteration is thus another way by which prolonged glucose exposure translates into membrane-potential anomalies.

Membrane Potential and Inflammation

T2DM has been increasingly recognised as a chronic low-grade inflammatory disease. Cytokines such as tumour necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β) and interleukin-6 (IL-6) can modulate the expression, phosphorylation and membrane trafficking of ion channels. It may also indirectly affect membrane potential by increasing reactive oxygen species generation and impairing mitochondrial activity.

Chronic inflammation may worsen glucotoxic/lipotoxic damage in pancreatic β -cells. Vascular inflammation leads to endothelial dysfunction and alterations in vascular ion-channel activity. Inflammatory mediators modulate ion channels involved in nociception and neuronal excitability in peripheral nerves. Thus, membrane potential disruption may be seen as part of a more integrated network of metabolism, inflammation and oxidative stress rather than an isolated electrophysiological abnormality[19].

The existing evidence supports an integrated hypothesis in which insulin resistance, persistent hyperglycaemia and increased free fatty acids are producing mitochondrial overload and metabolic stress. Reactive oxygen species, oxidative stress and endoplasmic-reticulum stress are generated from these disruptions. Ion channels, Na⁺/K⁺-ATPase activity and mitochondrial function can be altered by the resultant lipid peroxidation, protein glycation and inflammatory signalling.

These alterations alter the plasma membrane potential and the mitochondrial membrane potential, leading to aberrant calcium signalling.

The effects are widespread in many tissues. Pancreatic β -cell membrane and calcium disorders may impede insulin production and hasten β -cell failure. In vascular tissues they may inhibit endothelial function and vascular relaxation. In peripheral nerves they can contribute to neuronal hyperexcitability and neuropathic symptoms. In erythrocytes they can modify membrane stability, deformability and microvascular blood flow. Thus, membrane potential may be a convergent biological endpoint of several key pathogenic processes involved in T2DM.[20]

The idea of membrane potential malfunction provides many interesting directions for future diabetes research. Conventional clinical assessment of T2DM is generally based on glucose concentration, glycated haemoglobin, insulin, lipid profiles and indicators of organ damage. However, membrane potential measurements might provide potentially further information on cellular dysfunction. For the characterisation of diabetic cellular dysfunction, research approaches such as fluorescent membrane potential probes, electrophysiological techniques and mitochondrial bioenergetic assays should be explored. However, the membrane potential should now be viewed more as a research and mechanistic measure than an established regular clinical biomarker[21].

Ion channels are also appealing therapeutic targets because of their direct modulation of cellular excitability. Pharmacological modification of KATP channels to regulate insulin secretion is a well recognised clinical example of sulfonylureas. Future techniques will incorporate more targeted manipulation of KATP channels, voltage-gated calcium channels, calcium-activated potassium channels, voltage-gated potassium channels, mitochondrial ion channels and neuronal sodium channels. Many of these channels are however expressed in multiple tissues and tissue specificity will be required to minimise detrimental effects

Another possible therapeutic target is mitochondrial membrane potential. Strategies to improve mitochondrial quality control, to limit excessive reactive oxygen species production or to prevent pathological mitochondrial depolarisation may assist preserve β -cell function. Mitochondrial ion channels are of particular importance since they are involved in energy production, calcium signalling and cell survival. Hence the therapeutic potential of these agents in T2DM is of rising scientific interest.

Given the strong association between oxidative stress and membrane dysfunction, therapies that enhance redox balance may also indirectly protect membrane potential. Mitochondrial and endothelial function may be affected by lifestyle adjustment, improved glycaemic control and known antidiabetic treatments. However, antioxidant therapy is challenging since reactive oxygen species are also involved in normal cellular signalling. Therefore, future therapies should be directed not just to the elimination of reactive oxygen species, but to the restoration of adequate redox homeostasis[22].

Conclusion

Dysfunction of membrane potential is a key physiologic aspect of type 2 diabetes mellitus. The membrane potential is more than an electrical property of cells, it is a dynamic interface combining cellular metabolism, ion transport, calcium signalling, mitochondrial activity and intercellular communication. Disruption of the glucose-ATP-KATP-membrane potential- Ca^{2+} pathway in pancreatic beta cells may be a direct contributor to decreased insulin secretion. Mitochondrial membrane potential anomalies may limit ATP generation and increase oxidative stress. Aberrant potassium-channel activity and dysfunctional endothelium hyperpolarisation in vascular tissues result in reduced vascular tone and endothelial dysfunction. Altered sodium, potassium and calcium channels can cause aberrant excitability and diabetic neuropathic pain in peripheral neurones. Additional erythrocyte membrane modifications indicate that diabetes may influence membrane transport and electrical characteristics of non-classically excitable tissues. The emerging biological view is hence that T2DM is not only a disease of glucose metabolism. It is also a disease of cellular bioenergetics, ion homeostasis and membrane signalling. Understanding how metabolic stress relates to membrane electrophysiology could offer new indicators and therapeutic targets and may provide a common explanation for the development of many diabetes problems.

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