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Nutrigenomics of inward rectifier potassium channels

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ABSTRACT

Inwardly rectifying potassium (Kir) channels play a key role in maintaining the resting membrane potential and supporting potassium homeostasis. There are many variants of Kir channels, which are usually tetramers in which the main subunit has two trans-membrane helices attached to two N- and C-terminal cytoplasmic tails with a pore-forming loop in between that contains the selectivity filter. These channels have domains that are strongly modulated by molecules present in nutrients found in different diets, such as phosphoinositols, polyamines and Mg^{2+}. These molecules can impact these channels directly or indirectly, either allosterically by modulation of enzymes or via the regulation of channel expression. A particular type of these channels is coupled to cell metabolism and inhibited by ATP (KATP channels, essential for insulin release and for the pathogenesis of metabolic diseases like diabetes mellitus). Genomic changes in Kir channels have a significant impact on metabolism, such as conditioning the nutrients and electrolytes that an individual can take. Thus, the nutrigenomics of ion channels is an important emerging field in which we are attempting to understand how nutrients and diets can affect the activity and expression of ion channels and how genomic changes in such channels may be the basis for pathological conditions that limit nutrition and electrolyte intake. In this contribution we briefly review Kir channels, discuss their nutrigenomics, characterize how different components in the diet affect their

Abbreviations: ABCC8, ATP binding Cassette Subfamily C Member 8; AMPK, AMP-activated protein kinase; ATS, Andersen-Tawil syndrome; BS, Bartter syndrome; Cl^-, chloride; DAG, diacylglycerol; DASH, dietary approach to stop hypertension; DNA, desoxyribonucleic acid; DM, diabetes mellitus; EAST, epilepsy, ataxia sensoryneural deafness and tubulopathy; FH, familial hyperaldosteronism; H_2O_2, hydrogen peroxide; HbA1c, glycated hemoglobin; HDACI, histone deacetylase inhibitors; HI, hyperinsulinism; HHF, familial hyper insulinemic hypoglycemia; HHS, hyperosmolar hyperglycemic syndrome; IP3, inositol tri-phosphate; IP6, inositol hexa-phosphate; K^+, potassium; KATP, ATP sensitive potassium channel; KCNJ, potassium inwardly rectifying channel subfamily J genes; KD, kidney disease; Kir, inward rectifier potassium channel; K2P, two-pore domain potassium channel; LD, linkage disequilibrium; MIs, Myo-inositosides; MODY, maturity-onset diabetes of the young; mRNAs, messenger RNAs; Msn2, multicopy suppressor of SNF1 mutation proteins 2; Na^+, sodium; NT2DM, permanent neonatal diabetes type 2; NF-y, nuclear transcription factor Y; RNA, ribonucleic acid; ROMK, renal outer medullary potassium channel; OMIM, online mendelian inheritance in man; PIs, phosphoinositosides; PI3K, phosphatidylinositol 3-kinase; PIP_2, phosphatidylinositol-4,5-biphosphate; PKC, protein kinase C; PLC, phospholipase C; PSD-95, postsynaptic protein 95; PUFAs, polyunsaturated fatty acids; SLC12A3, solute carrier family 12 member 3; SNPs, single nucleotide polymorphisms; Sp1, specificity protein 1; Sp3, specificity protein 3; SUR 1, sulfonylurea receptor 1; 2TM, two transmembrane domain potassium selective channels; 4TM, four transmembrane domain potassium selective channels; 6TM, six transmembrane domain potassium selective channels; T2DM, type 2 diabetes mellitus; TNDB, transient neonatal diabetes mellitus; TRPM, transient receptor potential channel melastatin.

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function and expression, and suggest how their genomic changes lead to pathological phenotypes that affect diet and electrolyte intake.

1. Introduction

Ion channels are transmembrane proteins that contain a pore that possesses variable and selective penetration by ions or polar molecules. Such channels usually exhibit extremely fast permeation rates, allowing the passage of these chemical species down their electrochemical gradients [1]. Ion channels are essential for life. Many different processes are regulated by them, such as cell excitability and information transfer in multicellular organisms and tissues, and they are also vital for cell osmotic and volume control, chemical signaling, and maintaining ion concentrations (including pH) in all living cells [1]. Channels are present not only in the plasma membrane but also in intracellular membranes, such as the membranes of the nuclear envelope, endoplasmic reticulum, mitochondria, lysosomes, among others [2]. Because of this, membrane channels play a critical role in intracellular homeostasis [1,2]. Ion channels, along with other membrane transporters and molecules, are a key element of metabolic regulation in every cell and are related to glucose homeostasis, energy production, water and ion fluxes and other important cellular events. Membrane channels are also essential in the control of specialized cells, such as endocrine, kidney, liver, nerve, muscle and other cell types [3].

A recent interdisciplinary science has been developed, termed nutrigenomics. Nutrigenomics integrates genomic science with nutrition, and it recognizes how they influence each other. For example, nutrients can modulate gene expression and processing, as well as initiate genomic changes with different polymorphisms and mutations, and these can, in turn, affect the impact of different nutrients in the bodies of individual living beings [4]. Ion channels, being critical for all the processes related to life and metabolism briefly mentioned above, are thus affected in their gene expression and maintenance by the cellular uptake and composition of various nutrients. Also, different gene polymorphisms and mutations found in a population will have impact on an individual's distinct tolerance to different nutrients (see Fig. 1). For example, potassium channels are ion channels selectively permeant to potassium and are one of the most widely distributed ion

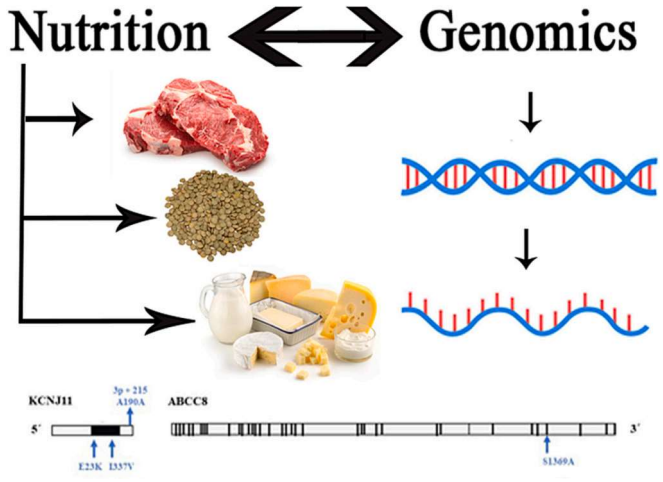


Fig. 1. Schematic view of the reciprocal interaction between nutrition and genomics. The *left panel* shows examples of different nutrients that influence the genetic expression or change protein function. The *right panel* shows nucleic acids, and at the bottom, a schematic representation of the two main genes that encode the KATP channel. The bidirectional arrow between both panels indicates that nutrients can affect the genomic expression and vice-versa, being this the ample topic of nutrigenomics.

channels among different cells and species. They are essential to the control and modulation of many cell functions [2,5]. K^+ channels are glycoproteins that are classified into at least eight major groups, having evolved from ancient two-transmembrane domain potassium selective channels (2TM K channel) that were also the ancestors of the superfamily of S4 channels (most voltage gated cation channels) [6]. However, most of the K channels belong to either 2TM, 4TM (also known as K2P channels) or 6TM main subunit groups [6]. The superfamily of S4 channels are made up of channels that usually have a canonical repeat of one charged amino acid every 3 amino acids in segment 4 of a monomeric main subunit or a repeat domain similar to the monomeric domain, which is the voltage sensor or voltage sensing domain of these channels. They can also contain many auxiliary subunits and exhibit alternative splicing. Both of these different subunits can strongly affect the function of the main subunit [2,5]. The Inward Rectifier Potassium channels (IRK or Kir), are a widespread family of potassium channels, +usually 2 TM, that favors inward over outward potassium fluxes, while K^+ ions flow towards their electrochemical equilibrium potential [7,8].

This review will focus on the interrelationship between various nutrients and the Inward Rectifier Potassium channels (Kir), and how alterations of this relationship may lead to different pathogenic conditions. We will focus first on what is known about how nutrients can affect how these ion channels function and are expressed, and finish with how genomic changes in Kir channels may affect cellular nutrition. In this review we will discuss the genetic basis and pathogenesis of metabolic diseases related to Kir channels and how diet and electrolyte intake can be affected by specific genomic changes in Kir channels.

2. Nutrigenomics of inward rectifier potassium channels

2.1. Overview of Kir channels

There are at least seven subfamilies of the Inward Rectifier Potassium (Kirs) channels, which are assembled as homomers or heteromers, usually with a 2TM main subunit [7,8]. All of the subunits are critical in regulating resting membrane potentials and excitabilities, and their disfunction can be linked to several diseases [7,8]. Functionally they are classified into four groups: a) the classical Kir channels (Kir2.x) which are constitutively active, b) the G protein-gated Kir channels (Kir3.x) which are regulated by G protein-coupled receptors, c) the ATP-sensitive K^+ channels (Kir6.x) which are tightly linked to cellular metabolism, and finally the K^+ transport channels (Kir1.x, Kir4.x, Kir5.x, and Kir7.x) [7,8].

Kir channels are strongly modulated by lipids, particularly phosphoinositosides (PIs). Inward rectifiers are dramatically modulated by PIs, especially phosphatidylinositol-4,5-bisphosphate (PIP_2) [9–11]. Kir channels are usually activated by PIs [11], though different Kir channels show different affinities and dissimilar activation by different PIs [12]. Based on their sensitivities and specificity to modulation by PIs, the Kir channels can be subdivided into three different groups: (a) low sensitivity (Kir 3.1 and 6.1), (b), intermediate (Kir 1.1 and Kir 7.1) and (c) high sensitivity (Kir 2.1 and Kir 4.1) [12]. Interestingly, the sensitivity and specificity of Kir channels to PIP2 cannot be predicted by amino acid sequence, nor by the rectification properties of the channel. For example, the predominantly cardiac Kir2.1 has strong inward rectification, while Kir4.1, found largely in other cells, also possesses high sensitivity and specificity for PIP_2, but does not show a strong inward rectification [13]. Table I shows the different Kir channels that have been identified to date in the human genome and their encoding by 16 *KCNJ* genes.

A subset of the Kir channels (Kir6) exists with quite distinctive

Table I
Inward rectifier potassium channels (K_{ir}) identified in the human genome.

Channel	Gene	Expression site	Functional group
Kir 1.1	*KCNJ1*	Kidney, skeletal muscle, pancreas, spleen, heart, brain, liver	*K^+ transport channels*
Kir 2.1	*KCNJ2*	Heart, skeletal muscle, aortic endothelial cells	*Classical potassium channels*
Kir 2.2	*KCNJ12*	Heart, brain (forebrain, cerebellum), skeletal muscle	
Kir 2.3	*KCNJ4*	Heart, brain (hippocampus, amygdala, caudate nucleus, thalamus).	
Kir 2.4	*KCNJ14*	Retina, pulmonary smooth muscle cells.	
Kir 3.1	*KCNJ3*	Olfactory bulb (piriform cortex), neocortex (layers 2–6), hippocampus (dentate gyrus granule cells), basal ganglia (habenula), thalamus midbrain (inferior colliculus), cerebellum (granule cell layer), brainstem (pontine nucleus).	*G-protein gated potassium channels*
Kir 3.2	*KCNJ6*	Hippocampus, substantia nigra, pontine nucleus, cerebellar granular layer, olfactory bulb, cerebral cortex, septum, amygdala), pancreas.	
Kir 3.3	*KCNJ9*	Pituitary, small intestine, testis, brain, fat, kidney, skeletal muscle, smooth muscle, pancreas.	
Kir 3.4	*KCNJ5*	Heart (atria > ventricle), brain (neurons in the hippocampus - dentate gyrus, globus pallidus, superior colliculus, medial vestibular and dorsal tegmental nuclei, anterior olfactory nuceus and lateral cerebellar nuclei)	
Kir 4.1	*KCNJ10*	Brain (forebrain, cerebellum, cochlea, spinal cord), kidney (distant convoluted tubule), digestive system (gastric parietal cells).	
Kir 4.2	*KCNJ15*	Kidney, pancreas, lung, prostate, testes, leukocytes	*K^+ transport channels*
Kir 5.1	*KCNJ16*	Kidney (convoluted tubule cells), pancreas (acinar and ductal cells), thyroid gland, carotid body (glomus cells, petrosukl ganglion).	
Kir 6.1	*KCNJ8*	Heart, ovary, adrenal grand > skeletal muscle, lung, brain, stomach, colon, testis, thyroid, pancreatic islet cells > kidney, liver, small intestine, pituitary gland.	*ATP-sensitive Potassium channels*
Kir 6.2	*KCNJ11*	Skeletal muscle, heart, pancreatic islets, brain.	
Kir 7.1	*KCNJ13*	Small intestine, stomach, kidney, brain (medulla, hippocampus, corpus callosum, cerebellum, cortex, amygdala, substantia nigra, thalamus), retina (Retinal pigmented epithelium, iris pigmented epithelium)	*K^+ transport channels*

properties. These Kir6 channels (KATP channels) can be inhibited by increasing the intracellular ATP/ADP ratio, and they are constitutively associated with sulfonylurea receptor type 1 (SUR 1) or 2 (SUR 2), which are members of the ATP-Binding Cassette proteins (ABC transporters) [14]. The inhibition of KATP channels in pancreatic β-cells by ATP, which is increased by boosting glucose concentrations, results in inhibition of this potassium channel and promotes membrane depolarization, with subsequent calcium influx and insulin release from intracellular vesicles [15]. KATP channels play a critical role in the pathogenesis of high prevalence disorders, such as cardiovascular diseases and diabetes [14,16]. They were one of the first Kir channels where PIP_2 regulation was recognized as crucial [9]. PIs are necessary for the Kir channels to be inhibited by ATP [17]. Some of these channels can be found in intracellular organelles, such as mitochondria [18].

There are seven subfamilies of the Kir gene family identified in the human genome. The first column shows the name of the protein encoded by the respective gene family KCNJ (Potassium Inwardly Rectifying channel family). There are at least 15 KCNJ genes. It is evident that there are widely diverse organ and tissue distributions of Kir channels in the human body (Table I). The physiological role of Kir channels is clearly related to their location, and also the subtype of channel. The Kir subfamilies can be classified into four groups based on their functional properties, as shown in the fourth column of Table I: *1) K^+ transport channels (Kir1.x, Kir4.x, Kir5.x, and Kir7.x), 2) Classical K_{ir} channels (Kir2.x), 3) G-protein-gated K_{ir} channels (Kir3.x) and 4) ATP-sensitive K+ channels.* In excitable tissues (heart, skeletal muscle, nervous tissue) inward rectifier currents determined by classical Potassium channels (Kir2.x) are very important in repolarization and in maintaining plasma membrane resting potential. Also, the expression of ATP-sensitive Potassium channels in pancreatic islet beta cells, is essential for the induction of insulin secretion.

Kir channels play a crucial role in coupling nutrient-dependent modulation to cell and tissue function. Kir channels have been implicated in a variety of physiological processes, including insulin secretion, neuronal excitability, and cardiac function [8]. Nutrient-dependent modulation of Kir channels is one potential mechanism by which these channels can couple nutrient sensing to various cellular functions [19]. The coupling between nutrient-dependent modulation and cell or tissue function by Kir channels involves several mechanisms as these channels are involved in maintaining the resting membrane potential of cells and regulating the flow of potassium ions across the cell membrane. By doing so, Kir channels influence various cellular processes and contribute to the overall function of tissues and organs [8].

One way in which Kir channels couple nutrient-dependent modulation to cell and tissue function is through their sensitivity to intracellular factors, including metabolites and signaling molecules that are influenced by nutrient availability [8]. Kir channels can be modulated by the levels of phosphoinositides, which are influenced by dietary intake of phosphoinositide-containing foods. Phosphoinositides directly interact with Kir channels and can modulate their activity, thereby impacting the electrical signaling and function of cells [12].

In addition, Kir channels can be regulated by other nutrient-sensitive signaling pathways. For instance, certain metabolic intermediates, such as ATP, etc.; ions like H^+, Mg^{2+} and Na^+, etc., can modulate Kir channel activity [8,20]. Changes in nutrient availability or metabolic status can alter the levels of these ions and molecules, thereby influencing the activity of Kir channels and subsequently affecting cellular function. For example, one proposed mechanism by which Kir channels may couple nutrient-dependent modulation and cell/tissue function is through the regulation of KATP channels, composed of Kir6.x and sulfonylurea receptor (SUR) subunits [15,21]. They are primarily found in pancreatic beta-cells, where they play a critical role in insulin secretion. Glucose metabolism in pancreatic beta-cells leads to increased ATP levels, which in turn inhibits KATP channels and depolarizes the membrane potential, triggering insulin secretion. In contrast, low glucose levels lead to decreased ATP levels, which increases KATP channel activity and hyperpolarizes the membrane potential, thereby inhibiting insulin secretion [15,21].

Other proposed mechanisms by which Kir channels may couple nutrient-dependent modulation and cell/tissue function include the regulation of intracellular signaling pathways, such as the insulin signaling pathway, and the modulation of ion channel expression and localization. For example, insulin signaling in adipose tissue modulates the activity of phosphatidylinositol 3-kinase (PI3K) and Akt signaling [22]. It is also known that this pathway affects Kir2.1 channels in the vascular tissue of adipose tissue losing its shear sensitivity to blood flow in endothelia from obese rodents [23]. Moreover, Kir channels are expressed in specific cell types and tissues, and their activity is tailored to meet the specific functional requirements of those cells [8]. As an example, in pancreatic beta cells, Kir channels play a crucial role in

glucose-stimulated insulin secretion [15]. The entry of glucose into beta cells leads to an increase in intracellular ATP levels, which in turn closes the Kir channels, leading to membrane depolarization and triggering insulin release [15].

Similarly, in cardiac myocytes, Kir channels contribute to maintaining the resting membrane potential and electrical stability of the heart. Dysregulation of Kir channel function can lead to arrhythmias and cardiac abnormalities [24].

Kir channels act as molecular links between nutrient availability, intracellular signaling, and cellular function. Their modulation by nutrients and metabolic factors allows cells and tissues to respond to changes in nutrient availability and adapt their electrical properties and functions accordingly.

To summarize this, the coupling between nutrient-dependent modulation and cell or tissue function by Kir channels is complex and can involve multiple mechanisms. This coupling between nutrient-dependent modulation and cell/tissue function by Kir channels involves multiple mechanisms and some of the keyways by which this coupling is achieved are the following:

1. Direct modulation of Kir channels by metabolites or nutrients: Kir channels can be directly regulated by metabolites generated during nutrient metabolism. For example, ATP, ADP, and PIP_2 are important modulators of Kir channel activity. Changes in the levels of these metabolites can directly impact Kir channel function and thereby influence cell/tissue function. This is related to modulation by metabolic signaling of pathways by nutrients that can activate and modulate Kir channel function [8]. Kir channels are known to be modulated by intracellular ATP levels, which are regulated by nutrient availability. In pancreatic beta-cells, glucose metabolism activates the PI3K and Akt signaling pathway [25], which, in turn, phosphorylates and inhibits Kir6.2 subunits of KATP channels [22]. This inhibition leads to the closure of KATP channels and subsequent depolarization of the membrane potential, triggering insulin secretion in pancreatic β-cells by glucose metabolism that in turn increases intracellular ATP levels [15].
2. Metabolic regulation of channel expression: Nutrient availability can influence the expression levels of Kir channel subunits. Certain diets or nutrient conditions can affect the expression of Kir channels in different tissues (including trafficking to the membranes). These changes in channel expression can alter the electrical properties of cells and tissues, impacting their function. Different diets and nutrient availability can influence the expression levels of Kir channels in specific cell types or tissues [26].
3. Modulation of membrane potential: Kir channels contribute to setting the resting membrane potential of cells. Nutrient-dependent modulation of Kir channels can alter the membrane potential, which in turn affects various cellular processes. Thus, changes in membrane potential due to Kir channel modulation can influence neuronal excitability, hormone secretion, and muscle contraction [8]. Nutrients, such as glucose, can directly influence Kir channel activity by altering intracellular ATP levels. In pancreatic beta-cells, increased glucose metabolism leads to elevated ATP levels, which inhibit Kir channels and depolarize the membrane potential. This depolarization triggers downstream signaling events, such as insulin secretion [15].
4. Interaction with signaling pathways, crosstalk with signaling pathways and indirect effects of nutrient sensing pathways on Kir channels: Kir channels can interact with intracellular signaling pathways that are regulated by nutrients. Nutrient-dependent modulation of Kir channels can influence the activity of these signaling pathways, thereby affecting cell/tissue function. Kir channels can interact with other signaling pathways and proteins that are involved in nutrient sensing and metabolism. Kir channels can physically associate with and modulate the activity of other ion channels, receptors, or transporters that are involved in nutrient uptake or signaling. Nutrient sensing pathways, such as the AMP-activated protein kinase (AMPK) pathway, can indirectly regulate Kir channel activity [27]. AMPK is activated by an increase in the AMP/ATP ratio, which occurs during energy stress or calorie restriction [28]. AMPK can then activate KATP channels, leading to membrane hyperpolarization and a decrease in insulin secretion [29,30]. Kir channels can also be indirectly regulated by AMPK through downstream effectors such as the transcription factor CREB [27].
5. Feedback regulation: Kir channels can participate in feedback loops that regulate nutrient uptake or metabolism. In certain tissues, Kir channels can modulate glucose uptake by influencing membrane potential and glucose transporter activity. This feedback regulation helps maintain nutrient homeostasis and ensures proper cellular function [31,32].
6. Post-Translational Modifications: Nutrients can also modulate Kir channel activity through post-translational modifications, such as phosphorylation, acetylation, or redox modifications. These modifications can alter the biophysical properties of Kir channels, including their conductance or gating properties, thereby affecting their functional coupling to nutrient sensing [33,34].
7. Epigenetic regulation of Kir channel gene expression: Nutrients can also affect Kir channel expression through epigenetic mechanisms, such as DNA methylation or histone modification [35].

It's important to note that the coupling between nutrient-dependent modulation and cell or tissue function by Kir channels involves a complex interplay between ion flux, metabolic signaling pathways, gene expression regulation, post-translational modifications, and crosstalk with other signaling molecules. These mechanisms collectively allow Kir channels to integrate nutrient sensing and regulate cellular functions in response to changing nutrient conditions. As such, the specific mechanisms by which Kir channels couple nutrient-dependent modulation and cell/tissue function may vary depending on the tissue or cell type involved. The understanding of these mechanisms is still evolving, and further research is needed to uncover the precise details of these coupling mechanisms in different contexts.

To end this overview, we want to mention briefly the role of non-ATP dependent Kir channels in the regulation of metabolism. As it can be observed in Table I, most of the Kir channels are non-ATP dependent Kir channels. Non-ATP-dependent Kir channels have been implicated in the regulation of several metabolic processes. These channels are not activated by ATP but can be regulated by other metabolic factors such as pH, membrane potential, and intracellular signaling molecules [8].

Kir channels are expressed in joint chondrocytes, and it has been suggested that they play role in volume regulation and chondrogenesis [36]. Kir 2.1 channels also play a key role in endothelial cells in the lung and the response to inflammation [37]. Other metabolic processes that are regulated by non-ATP-dependent Kir channels include the regulation of blood pressure and the control of neuronal excitability [8]. These functions given as examples, are related to the metabolism of particular cells in the body, and as such influence the whole metabolism of the body.

In general, a few roles of non-ATP-dependent Kir channels in metabolic regulation are the following:

1. K^+ homeostasis: Non-ATP-dependent Kir channels contribute to maintaining cellular K^+ homeostasis. They facilitate the efflux of K^+ ions, helping to regulate the intracellular K^+ concentration. Proper K^+ balance is essential for normal cellular function, including metabolic processes [38].
2. Insulin secretion: Non-ATP-dependent Kir channels are involved in regulating insulin secretion from pancreatic beta cells. These channels, particularly Kir6.2, form complexes with the sulfonylurea receptor (SUR1) in pancreatic beta cells but there are also non-ATP-dependent Kir channels modulating insulin secretion in not well understood ways. Some of them are Kir 1.1, Kir 2.1, Kir 3.2, Kir 3.3.

There might be some species dependence issue plus other things we still do not understand well [39–41].

3. Glucose metabolism: Non-ATP-dependent Kir channels have been implicated in regulating glucose metabolism in various tissues. In cancer cells, for example, some Non-ATP dependent Kir channels are present and upon glycosylation can affect glucose metabolism. Their activity influences membrane potential and subsequently affects glucose transporter function, thereby regulating glucose utilization by these cells [42].
4. Adipose tissue function: Non-ATP-dependent Kir channels are found in endothelia from adipose tissue. Their dysfunction might be implicated in the pathogenesis of obesity and insulin resistance [43–45].
5. Regulation of neuronal activity: ATP and Non-ATP-dependent Kir channels are expressed in various regions of the brain and play a role in regulating neuronal excitability and neurotransmitter release. Proper neuronal function is crucial for regulating appetite, nutrient intake, energy balance, and overall metabolic control [46,47].

It is important to note that the specific roles and mechanisms of non-ATP-dependent Kir channels in metabolic regulation may vary depending on the tissue or cell type involved. Additionally, there are multiple subtypes of non-ATP-dependent Kir channels, each with its own specific functions and regulatory mechanisms. Further research is still ongoing to fully elucidate the precise contributions of these channels to metabolic regulation in different contexts.

2.2. Nutrients affecting Kir activity and expression

2.2.1. Inositols and phosphoinositosides

The binding site for PIs in Kir and other channels has been structurally identified in mice and chicken by Rod MacKinnon's research team [48,49]. This is considered important, because this lipid is related to the activity of phospholipase C (PLC), which is involved in the synthesis of the second messengers Inositol Tri-Phosphate (IP3) and Diacylglycerol (DAG) [50].

Because PIP_2 is located in the intracellular leaflet of the plasma membrane s and is able to modulate many different intracellular messenger pathways, its concentration is tightly controlled [11,50]. It is estimated that PIP_2 accounts for only about 1 % of the total membrane phospholipids, and therefore its membrane concentration per area can be estimated to be around 5000 to 10,000 molecules per μm^2 [51]. The headgroup of PIs contain s inositol, which is an isomer of hexahydroxycyclohexane [52]. The basic structure of Inositols and PIs are shown in Fig. 2. PIs are formed as the result of phosphorylation of phosphatidylinositol at positions 3, 4 or 5, of the inositol headgroups and are inserted into the cytoplasmic membrane leaflet, by different inositol lipid kinases [53].

In nature, PIs are found in various foods in a variety of different phosphorylation states from IP3 to IP6 [54]. For example, foods with a high content of PIs and inositol are grain and legumes, and the PI-inositol content can vary from 0.4 to 1.2 % of dry weight in beans, peas, peanuts and almonds [54,55]. They are also found in whole grain bread, dried prunes and avocados [54]. Most of the ingested PIs are hydrolized in the guts of animals to inositol before absorption [54].

Inositols are crucial to human nutrition, not only because of their role as precursors of PIs but as messenger molecules by themselves, such as the *Myo*-Inositosides (MI) messengers [52]. It is now becoming clear that MI and its various derivatives play critical roles in several pathological conditions [52]. MIs are present in fresh beans, grains, nuts, dried prunes and fruits, and diets based in these foods can provide up to 1500 mg/day per 1800 KCal [56]. Diets rich in Mis, are reported to be beneficial in various health disorders like Type 2 Diabetes Mellitus (T2DM) and kidney disease (KD), where MI metabolism seems to play a role [54,56]. The mechanisms by which inositol levels might impact Kir channels include direct functional regulation as we have mentioned

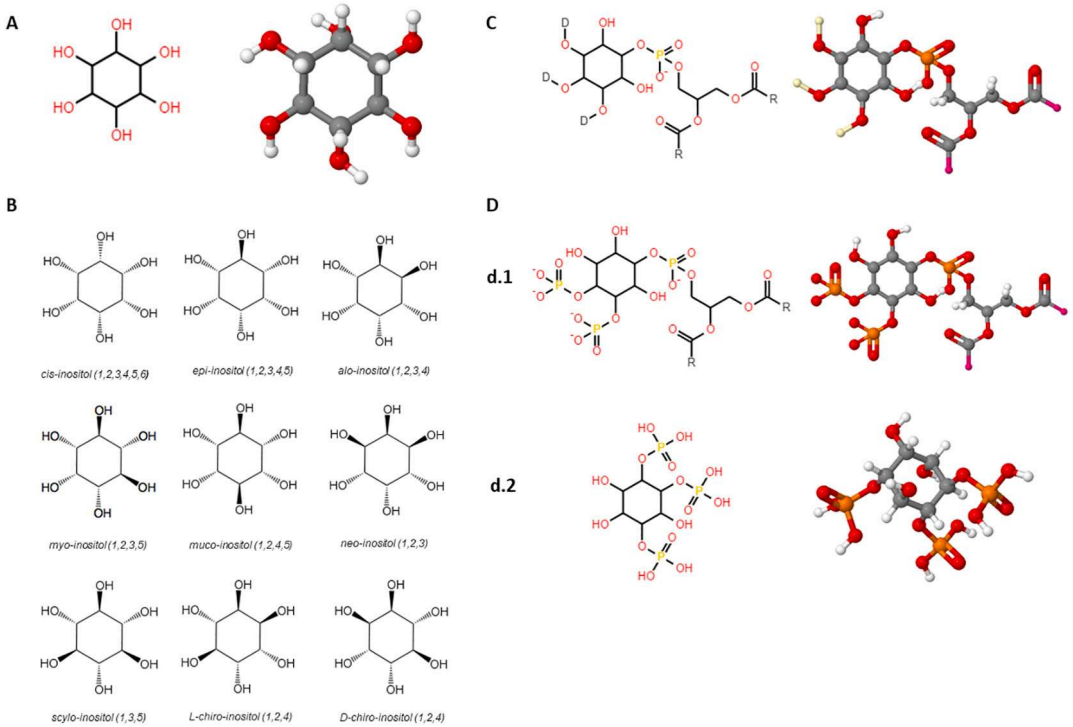


Fig. 2. Basic structure of Inositols and Phosphoinositols.
General molecular structure of Inositol. (B). Inositol stereoisomers. The most frequently found in nature is myo-inositol, considered as a member of the vitamin B complex. (C). General molecular structure of phosphoinositides (PIs). PIs are composed by a diacylglycerol molecule (glycerol bounded to two fatty acids) linked to a phosphate group, which is binded to an inositol. "D" represents the possible phosphorylation sites in the inositol (positions 3, 4 and 5), and "R" the fatty acids hydrocarbonated chains. (D). Examples of important PIs. d.1. Phosphatidylinositol 4,5-bisphosphate (PIP2). d.2. Inositol triphosphate (IP3).

above, but they can also involve modulation of the Kir channel expression, since inositols are also important transcription regulating factors. The critical residues for Kir channel s expression have been found in the N-terminus of Kir 2.1 channels [57], and it is intriguing that Sp1, Sp3 and NF-γ are transcription factors known to be involved in the expression of Kir2.1 channels [58]. Some of these transcription factors are also linked to inositol metabolism as well [59].Inositols, either directly or through the metabolism and the control of different enzymes that are dependent on their presence, may also regulate many other transcription factors that could affect the expression of Kir channels [60,61]. Enzymes related to inositol are also important for the activity of stress response transcription factors like *Mun2*, and thus they could impact the expression of many quite different proteins [62]. However, it remains unknown if several transcription factors known to regulate Kir channel expression in a vital organ like the heart are directly related to inositol metabolism [63].

Inward rectifier potassium channels are essential for vital events like insulin secretion (KATP channels, Kir6.2 with SUR 1) [15] and renal function [38]. These channels may be partially involved in the benefits observed from the use of diets developed and recommended for T2DM and KD [64]. Failures in maintaining inositol levels have also been implicated in other endocrine and metabolic disorders, where the inward rectifier potassium channels and other channels might play a critical role, such as seen in dyslipidemias and polycystic ovary syndrome [64–66].

The three-dimensional transmembrane structure of an inward rectifier (Kir) and the binding site for PIP_2 are shown in Fig. 3A. This figure displays the structure of two subunits of a 2TM Kir channel with the main binding sites of nutrients and modulators discussed in this review. The thick lines represent the boundaries of the lipid bilayer. In Fig. 3B the binding site for PIP_2 in the Kir channel outlined in Fig. 3A is shown at higher relative magnification [12]. Fig. 3C shows how the concentration of PIP_2 in the extracellular medium can modify Kir currents. It is known that Kir channels in the heart are inhibited by low doses (~200 μM), of hydrogen peroxide (H_2O_2), similar to observations reported with other cell types [67]. As shown in Fig. 3D, we demonstrated that the exposure of isolated hearts and ventricular cells from guinea pigs to fusogenic nanomicelles enriched with specific PIs [68,69], can change the membrane voltage and make it more resistant to depolarization when 200 μM H_2O_2 is added to the extracellular medium (*unpublished results*). Although such data are intriguing, additional information will be needed to understand how nutrition and particular foods enriched or depleted in inositols and PIs can affect the function and organ expression of Kir channels and their genes. It will be more daunting to confirm

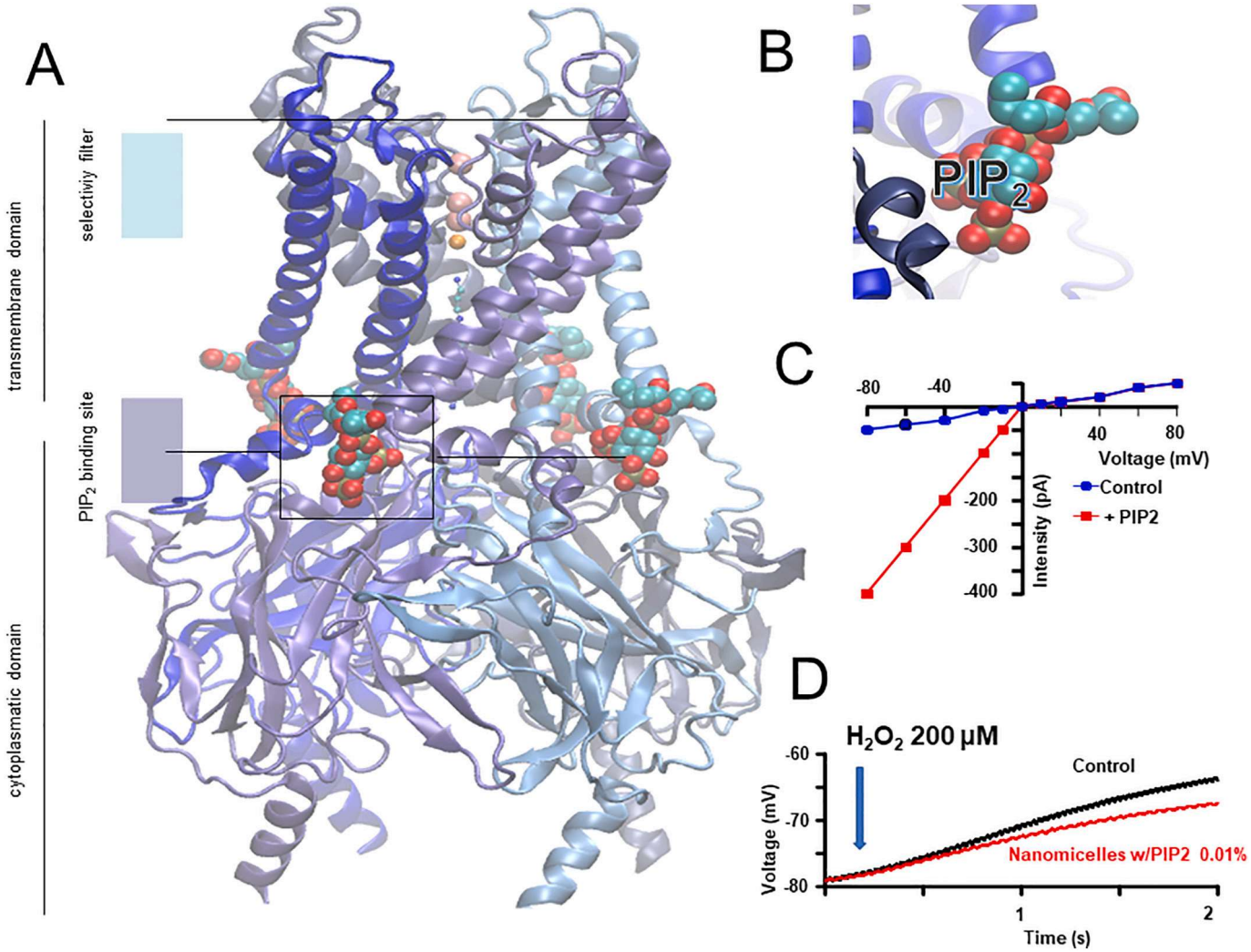


Fig. 3. Structure of an inward rectifier (Kir channel), the binding site for PIP_2 and its functional effects. (A). The three-dimensional structure of a Kir channel, based on the PDB 6XIT. (B). Magnification of the PIP_2 binding site, with coordinates extracted from PDB 6XIT. (C). Inward rectifying effect on curve IV of Kir channels due to the PIP_2 binding. In the absence of PIP_2, decreases in outward and inward currents are observed. Data presented are based on and modified from MacKinnon et al. [48]. (D). The presence of low doses of hydrogen peroxide (approx. 200 μM), inhibits Kir channels and depolarizes cardiomyocytes. This inhibition is prevented by incubation of the cardiomyocytes with fusogenic nanomicelles containing specific PIs, similar to results that have been described for human spermatozoa [69].

whether specific foods or natural supplements containing critical molecules that affect specific membrane channels can prevent or delay the onset or development of certain pathological conditions. Nonetheless, we feel that this approach is highly relevant, since Kir channels are expressed in a wide variety of cells and these channels can affect cell membrane resting potentials and the membrane voltage near the resting potential. Kir channels are not unique in their abilities to be modulated by PIP_2. Ion channel regulation by PIs has been described in several other ion channels and transporters [70].

In summary, PIs are a group of phospholipids that play important roles in many cellular processes, including signal transduction, membrane trafficking, and cytoskeletal dynamics [71]. They are also known to modulate the activity of several ion channels, including Kir channels [70], which have a key role in setting the resting membrane potential of cells [8].

As we have discussed in this section, studies have shown that PIs can directly interact with Kir channels and modulate their activity. Specifically, phosphatidylinositol 4,5-bisphosphate (PIP_2) is a key phosphoinositide that binds to Kir channels and regulates their gating properties [48]. PIs can also activate other proteins that modulate Kir channels like Protein kinase C (PKC), which can phosphorylate Kir channels and alter their function [72]. In addition to direct binding and protein modulation, PIs can also affect Kir channels through changes in membrane lipid composition. For example, diets rich in PIs can lead to changes in the lipid composition of the cell membrane, which can affect the interaction between Kir channels and other membrane proteins or lipids, changing indirectly the activity of Kir channels [73].

There is some evidence to suggest that diets rich in PIs may affect Kir channel activity or expression, by altering the levels of PIP_2 in cells. PIs can be found in high concentrations in certain foods, such as soybeans, peanuts, and sesame seeds [73].The impact would be different depending on the specific types of PIs consumed and the levels of these lipids in the body [74]. It is also important to note that diet is not the only factor that can affect phosphoinositide levels in the body as other factors, such as exercise and stress, can also modulate postprandial glycemia, insulin resistance and phosphoinositide levels [75]. Obese mice fed with a diet high in myoinositol showed increased Kir channel activity in cardiac myocytes and restored cardiac function leading to changes in heart rate and cardiac electrical activity [76]. In mice it was also found that a diet supplemented with inositol increased the expression of Kir2.1 channels in cardiac tissue [77]. PIs also play a role in the modulation of Kir channel activity in neurons, and altering the levels of PIs could affect the excitability of these cells [70]. These studies suggest that consuming foods with higher levels of PIs may lead to increased Kir channel activity and expression, even though we are still just beginning with these type of nutrigenomics approach underpinning these channels.

In conclusion, the available evidence suggests that diets rich in PIs like that with liver, soybean, seeds, legumes and nuts, may affect the expression and function of Kir channels, although the exact mechanisms underlying these effects are not yet fully understood. It is important to note that the effects of PIs on Kir channels are complex and context-dependent, because the effects of PIs on Kir channels can be modulated by other factors, such as membrane potential and the presence of other channel modulators. Also, diets rich in PIs can affect Kir channels through multiple mechanisms. The exact nature of these effects can depend on the specific type of phosphoinositide and the Kir channel subtype involved. More research is needed to determine the balance of different types of dietary PIs on channel activity as not all of them would produce the same final effects and have the same strength on the channels. The available results so far indicate that diets rich in PIs affect the activity and expression of Kir channels, but the precise effects would depend on a variety of factors and would need to be studied further in specific contexts. Further research is needed to elucidate the molecular pathways involved in these processes, to fully understand the complex interplay between PIs and Kir channels, and determine the potential health implications of diets rich in PIs to get a clearer picture of their precise implications for human health.

2.2.2. *Polyamines*

Similar to the properties of inositol and PIs, polyamines in the diet can affect Kir channel activity and also change their level of genomic expression. Polyamines are stable, ubiquitous polycations that are usually present as low molecular weight aliphatic amines, with two or more amino groups [78,79]. The basic structures of a few common polyamines are shown in Fig. 4. Since their discovery in 1678, they have been found in almost all living cells. Due to their positive charges, they can interact with many different charged molecules, such as proteins, DNA and RNA [79]. Because of these interactions, they are related functionally to cell growth and differentiation, and they also exhibit antioxidant and anti-inflammatory properties [78,79]. Polyamines are especially important in tissues that have high cell replacement rates, such as the small intestine [78,80]. There is evidence that a diet deficient in polyamines results in hypoplasia of the intestinal mucosa, whereas diets containing excess polyamines are associated with tumor growths in the rat intestine [78,80,81]. Due to their antioxidant and anti-inflammatory properties polyamines have been found to be useful nutrients for the prevention of cardiovascular diseases [82]. They are also important in maintaining the gut microbiota, and they have been implicated in obesity and age-related diseases [83]. The most abundant cellular polyamines are spermine, spermidine and putrescin, and their dietary requirements change during life. During the early years of life where there are rapid rates of cell proliferation and differentiation, such as in neonates, there is a high demand for polyamines [79]. During the aging process the synthesis of polyamines in organisms can decrease dramatically, and there is again a high demand for polyamines from dietary sources [79],

In their relation to Kir channels, intracellular polyamines play a critical role in their inward rectification properties, and hence, in the function of these channels [84,85]. Due to their polycationic nature and the structure of Kir channels intracellular polyamines exert strong voltage dependent rectification of potassium outward currents, thus favoring inward currents [84,85]. In Fig. 5A the three-dimensional structure of a Kir channel and the binding site for polyamines is represented. The binding site is shown at a relatively higher amplification in Fig. 5B. In Fig. 5C the data obtained from the Nichols group regarding current voltage relationships (IV curves) in excised patches is presented [84]. Dib et al. have found that extracellular polyamines can block Kir channels [86]. As a consequence of polyamine binding, the Kir channels are open at the membrane resting potential, but they are blocked during the depolarization of an action potential. A consequence of this process can be seen in cardiac action potentials during their “plateau” or phase 2 stage [84,85]. The affinities for polyamines at the intracellular surfaces of Kir channels varies among distinct Kir channels and different polyamines [85]. Polyamines have also been reported to exert effects in several other types of ion channels [87,88].

Polyamines in organisms are provided from three different sources: endogenous sources (*de novo* biosynthesis in cells), intestinal sources (microorganisms), and exogenous sources (nutrients in the diet) [89,90]. When they are provided by an endogenous source, they are usually synthesized by ornithine decarboxylase and are then converted to different polyamine forms [78–80]. When they are from exogenous sources, they are either from the bacterial metabolism of intestinal microbiota, and/or from the diet [78–80]. Quantitatively, the most important source is dietary nutrients [91]. Dietary polyamines are important not only as an exogenous source but also as a major modulator of endogenous production [91]. Polyamines are particularly abundant in breast milk, where they are important for the intestinal maturation of neonates [92].

Polyamines present in nutrients are generated from amino acids like arginine and ornithine that are precursors that undergo decarboxylation by putrefactive bacteria [90]. This is the reason for their abundance in

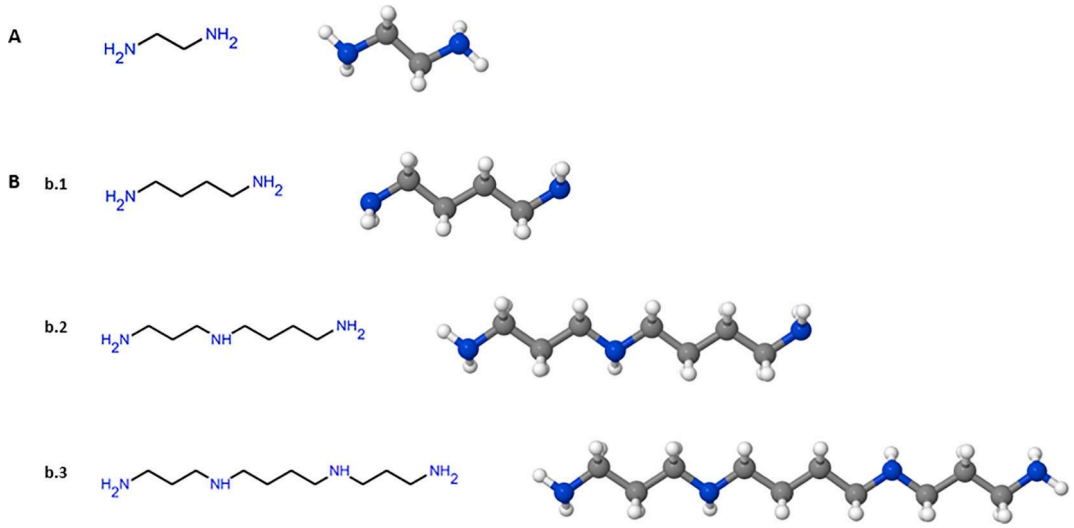


Fig. 4. Structure of polyamines. (A) The basic minimal structure of all polyamines having at least two primary amino groups is shown. The *left panel* shows a planar representation whereas the *right panel* shows the tridimensional appearance of these positively charged molecules. In (B), the structures of the most common polyamines found in nature and diets are shown in planar (*left panels*) and tridimensional arrangements (*right panels*). The structures shown are b.1. Putrescine. b.2. Spermidine. b.3. Spermine.

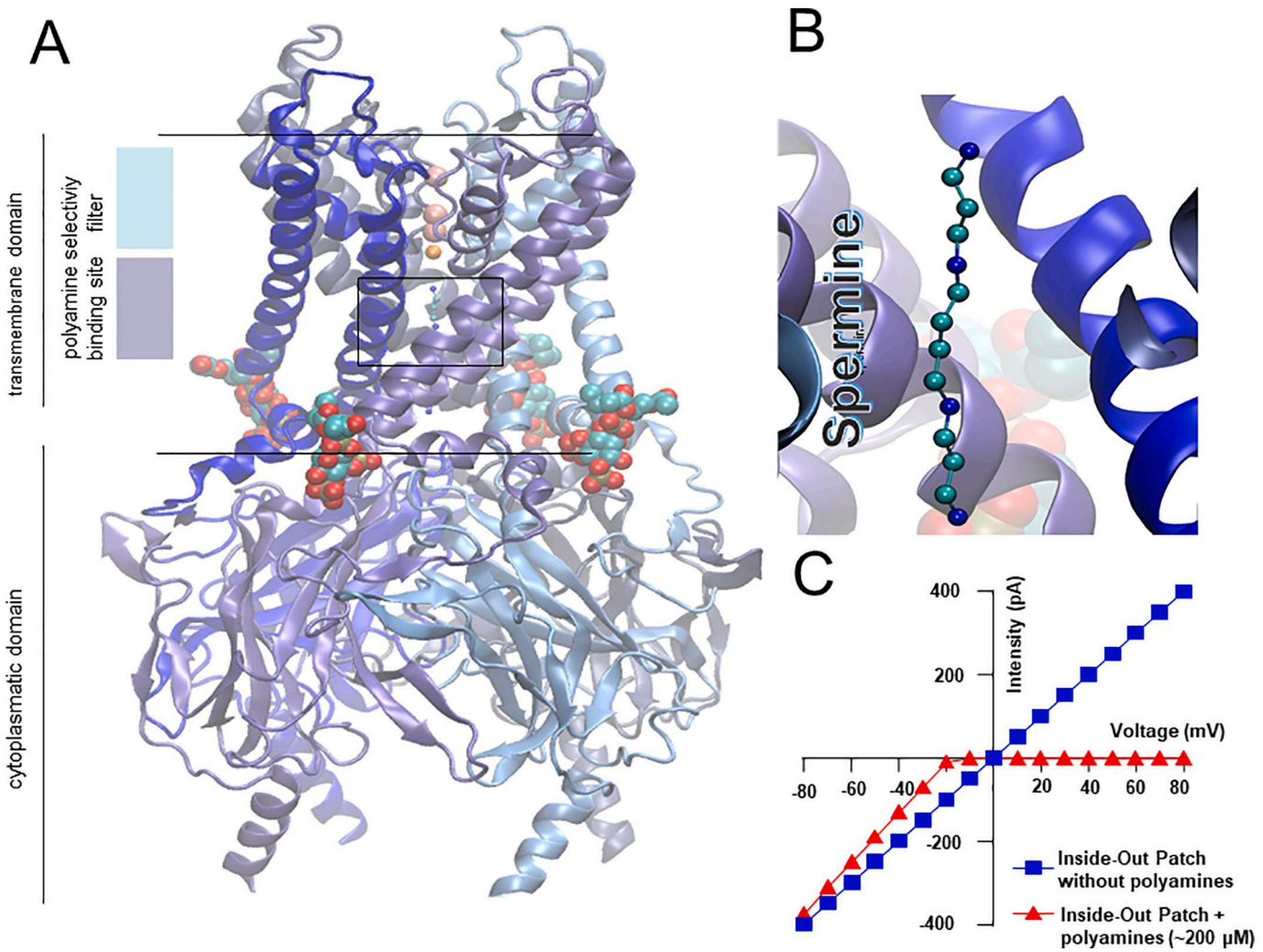


Fig. 5. Structure of the inward rectifier, polyamine binding site and its functional effect. (A). Three-dimensional structure of the Kir, based on the PDB 6XIT. (B). Magnification of the polyamine binding site, coordinates 2WLK (PDB). C. Rectification of the current in excised patches through the Kir channels in the presence of intracellular polyamines, vs. the membrane potential. Data based and modified from Lopatin et al., 1994 [84].

fermented foods from various origins (most cheeses, sauerkraut, etc.), and this also explains why they are found mostly in plants that experience osmotic stress during their growth–like some species of beans [93]. They can be obtained from various foods, such as fruits, meats, cheeses and some vegetables [92]. The mean dietary intake of polyamines varies between 250 and 550 μmol/dl [94]. Interestingly, Mediterranean diets usually result in longer lifespans of individuals and provide approximately 700 μmol/dl of polyamines, and this has been associated with the antioxidant properties of polyamines, preventing chronic diseases in elderly populations [95]. In fact, appropriate dietary levels of polyamines have been linked with better management of the aging process and reductions in several chronic diseases [96]. Certain foods, such as cheese and fruits, are abundant in polyamines like putrescin, whereas products derived from meat and vegetables are rich in spermidine and spermine [90].

After ingestion, polyamines are rapidly absorbed from the intestinal lumen, mainly in the duodenum and the proximal jejunum [92,97,98]. Subsequently, with slower kinetics, they reach the portal circulation [97]. The transport of polyamines from the intestinal lumen to the circulation is not well characterized in mammals [97]. Absorption mechanisms that have been proposed include polyamine carriers and paracellular absorption [92,98]. Absorption through the epithelial cell membrane is affected by temperature, pH (highest absorption occurs at physiological pH, when polyamines are fully charged), and saturation [98]. Transport kinetics seem to indicate that polyamines bind rapidly to the outer surface of the cell membrane and are then slowly transported through the lipid bilayer by specific carriers [98]. Transport across the contralateral membrane is also mediated by high-affinity carriers [98]. This mechanism allows that even though polyamines quickly disappear from the intestinal lumen, plasma concentrations remain relatively constant and within the limits necessary to meet all of the needs of cell proliferation [98]. On the other hand, it has been observed that the presence of polyamines in the intestinal lumen can improve and facilitate the absorption of some drugs, thus giving polyamines a possible therapeutic value [99,100].

The effect of polyamines on proliferation and differentiation are partially explained by their binding to DNA and regulation of gene expression, for example, stimulating the translation of histone acetyltransferase mRNAs. This is one of the proposed mechanisms of epigenetic regulation of gene expression [101]. The inhibition of the deacetylation of histones by histone deacetylase inhibitors, such as HDACI, has been shown to induce potassium channel atrial remodelation in the heart [102]. This might partially explain the phenomenological link between obesity (with higher levels of histone deacetylase inhibitors) and atrial fibrillation [103]. A similar result was also observed with the expression of potassium channels in the heart [103,104].

The epigenetic and cell-specific modulation of ion channels through nutrients like polyamines, seems to be implicated in many of the activities attributed to polyamines [105]. There are several foods known to contain HDACIs, and this is an active area of research in nutrigenomics, such as the proposals that HDACI are important epigenetic regulators [106–108].

Polyamine compounds are present in various chemical forms and are found in foods like berries, onions, wines, apples, tomatoes, citrus, tea, and grapes [108]. They have been implicated in the prevention of cardiac remodeling during heart failure [108]. Ion channels, and in particular potassium channels, play a key role in cardiac remodeling, and they would be important targets of polyamines [109,110]. With regard to Kir channels, polyamines are important nutrients that can modify the activity of *this type* of channel, and also the epigenetic control of its expression. Further research is needed to establish the relationship between the intake of polyamines and ion channels expression.

In summary, polyamines are organic compounds, usually small positively charged organic molecules that are essential for various cellular functions, including cell growth, proliferation, gene expression, protein synthesis, ion channel regulation, and differentiation. They are naturally present in many foods, and a diet rich in polyamines can influence the function of Kir channels [111].

There is evidence to suggest that a diet rich in polyamines may affect the function and expression of Kir channels [112]. The exact impact of a diet rich in polyamines on Kir channel function may depend on various factors, including the specific types and concentrations of polyamines consumed, as well as the cell or tissue type in which the Kir channels are expressed [113]. Polyamines can exert both direct and indirect effects on Kir channels, and their presence in the diet can influence the electrical activity and function of cells and tissues where these channels are expressed [85]. It's worth noting that the specific effects of polyamines on Kir channel function may vary depending on the cell or tissue type and the specific Kir channel subtype involved [85]. Furthermore, the concentration and duration of exposure to polyamines may also influence their effects on Kir channels [85]. While the direct effects of a diet rich in polyamines on Kir channel expression have not been extensively studied, some research suggests that polyamines can modulate the expression of ion channels, including Kir channels, through their effects on gene regulation and cellular signaling pathways [85,111,113]. Polyamines have been found to modulate Kir channel activity through multiple mechanisms. One such mechanism is the direct interaction of polyamines with Kir channels. Studies have shown that polyamines can modulate the activity of Kir channels through direct binding to the channel protein, so polyamines can bind to specific sites on Kir channel proteins and modify their gating properties. Polyamines such as spermine and spermidine have been shown to block the activity of Kir channels in the heart, contributing to the regulation of heart rhythm avoiding arrhytmias [8,85]. In the pancreas, polyamines have been shown to regulate insulin secretion through modulation of Kir channels in beta cells [15,114,115]. In the brain, polyamines have been implicated in the regulation of neuronal excitability through modulation of Kir channels in various cell types [8,85]. Additionally, polyamines can also indirectly affect Kir channel function by modulating intracellular signaling pathways. Polyamines can influence the activity of enzymes, such as protein kinases and phosphatases, which can in turn regulate Kir channel activity [113]. Some of them can act as cofactors of PIP_2 activating Kir channels [116]. Polyamines can also affect the activity of PKC [117] and protein phosphatase 2A (PP2A) [118], both of which can modulate Kir channel function [119,120]. Polyamines can interact with specific receptors or ion channels on the cell surface, leading to the activation of intracellular signaling cascades [121]. These signaling pathways can then modulate the activity or expression of Kir channels, thereby affecting their function [85]. Polyamines can also influence Kir channel function through their interactions with other cellular components. For example, polyamines can interact with phospholipids, proteins, or nucleic acids, which can indirectly affect Kir channel activity [111,113,122]. These interactions may alter the lipid composition of cell membranes or modify the conformation or stability of proteins involved in Kir channel regulation [85]. Additionally, polyamines have been shown to interact with intracellular nucleotides, such as ATP and GTP, which are known modulators of Kir channels [8]. By affecting the intracellular levels of these nucleotides, polyamines can indirectly influence Kir channel activity [85].

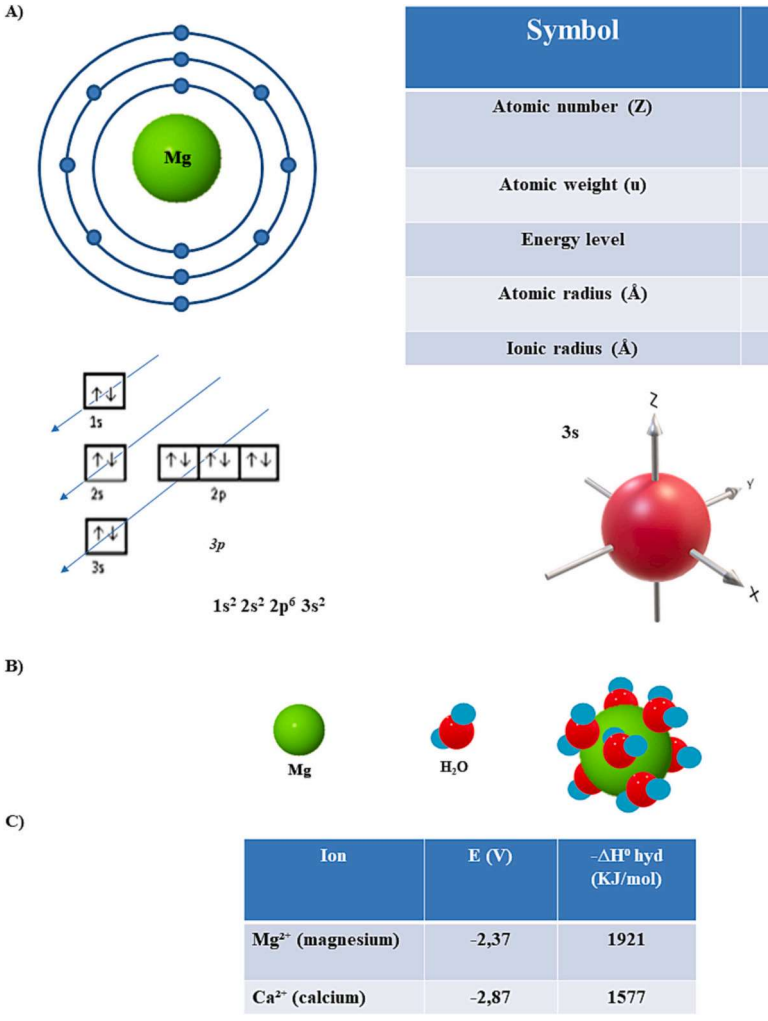
Polyamines have been shown to influence gene expression by interacting with DNA, RNA, and proteins involved in transcriptional regulation and histone acetyltransferase mRNAs [101,123]. They can affect the activity of transcription factors, alter chromatin structure, and modulate the binding of transcriptional regulators to gene promoters [39,124]. Furthermore, polyamines have been shown to regulate gene expression through their interaction with DNA and chromatin [124]. They can influence the binding of transcription factors to gene promoters, affecting the transcriptional regulation of target genes, including ion channels [111]. Therefore, a polyamine-rich diet could potentially impact Kir channel expression by modulating the transcriptional machinery involved in their regulation. Polyamines can influence

the expression and function of ion channels through various mechanisms, including transcriptional regulation, post-transcriptional modifications, and direct interactions with channel proteins [113]. However, the specific impact of polyamines on Kir channel expression may vary depending on the specific channel subtype, cell type, and experimental conditions. Through these mechanisms, polyamines could potentially influence the expression of Kir channels or other ion channels involved in potassium homeostasis. Additionally, polyamines can affect cellular signaling pathways that regulate protein synthesis and degradation. They can modulate the activity of protein kinases and phosphatases [117,125], as well as the synthesis and stability of specific proteins. These signaling pathways may indirectly influence the expression and function of Kir channels. It's important to note that the effects of polyamines on Kir channel expression may depend on various factors, including the specific type of Kir channel, the cell or tissue type, and the overall metabolic context. Further research is needed to fully understand the mechanisms by which a diet rich in polyamines may affect Kir channel expression and function.

In conclusion, while the exact mechanisms are not fully understood, a diet rich in polyamines may indirectly influence Kir channel function through various signaling pathways and interactions with cellular components. Further research is needed to elucidate the specific effects and underlying mechanisms of polyamines on Kir channels. A diet rich in polyamines may affect Kir channel function through any mechanism of modulation of channel activity, which in turn could impact various physiological processes such as insulin secretion, heart rhythm and neuronal excitability. Regarding expression of Kir channels, a diet rich in polyamines can affect the expression of Kir channels in different tissues, which may have important implications for cellular and physiological function [85]. However, more research is needed to fully understand the mechanisms by which polyamines regulate Kir channel expression and activity, as well as to understand the mechanisms underlying this relationship and the potential health implications. It's important to note that the specific effects of a polyamine-rich diet on Kir channel expression would depend on various factors, including the overall polyamine concentration, the duration of the diet, and the individual's metabolic state. We are just beginning to understand the nutrigenomics of polyamines concerning Kir channel expression and function in health and disease.

2.2.3. *Intracellular magnesium*

Magnesium (and its ion, Mg^{+2}) is an important divalent cation in every living organism. It is the most frequent cation found in the extracellular medium, and after potassium (K^{+}) it is the second most frequent cation present in the intracellular medium. Magnesium is an abundant alkaline earth metal with an atomic number of 12 and an electronic configuration of *1 s2 2s2 2p6 3 s6*, (Fig. 6A) [126]. It has a low density, low melting point, and a high reactivity but in nature it is almost always oxidized to its +2 state [126]. This high rate of oxidation can be explained by its very low redox potential (see Fig. 6, C, E(V)). The energy needed to lose its two outer s electrons is not that high, being around 15 eV (electronvolts). Mg is smaller than Calcium (Ca), another crucial divalent cation important for life (Fig. 6B and C, radius). Calcium is critical for ion- dependent inactivation processes in ion channels [127,128]. However, the hydration properties for Ca^{+2} and Mg^{+2} are



Symbol	Mg
Atomic number (Z)	12
Atomic weight (u)	24,312
Energy level	3
Atomic radius (Å)	1,60
Ionic radius (Å)	0,65

Ion	E (V)	$-\Delta H^{0}$ hyd (KJ/mol)
Mg^{2+} (magnesium)	-2,37	1921
Ca^{2+} (calcium)	-2,87	1577

Fig. 6. A. Mg elemental characteristics. Atomic features of the atom of Magnesium. (A) The *left panel*, shows the Bohr atomic model for Mg, which brings a visual representation of electrons orbiting around a small nucleus containing 12 protons and 12 neutrons. The last electron shell contains the valence electrons, which are two in this case (Mg valence 2+). That is why Mg gets easily ionized and oxidized as +2. The *right panel* shows some relevant atomic features such as atomic number (Z), atomic weight, energy level, atomic radius and ionic radius (both in Å). As happens with Ca^{2+}, Mg^{2+} also belongs to the group of alkaline earth metals but it is smaller than Ca^{2+}. *Below the atomic model, to the left,* the Moeller diagram with the corresponding electronic configuration for Mg and the electrons spin ($s = + - ½$) for each orbital are shown. *To the right*, a spatial representation of the "3 s" orbital, corresponding to the one with the higher level of energy that its lost during ionization, is shown. (B). Graphic representations of Mg cation (Mg^{2+}) hydrated with water molecules. This is the most common form of Mg in nature as it is usually heavily hydrated. The left panel represents the hydrated form of Mg^{+2}, which is the form that ions are in aqueous medium such as biological systems. In both parts, Mg^{2+} is painted in green following the CPK color scheme convention. (C). Comparison between Ca^{2+} and Mg^{2+}regarding redox potential (E) and hydration enthalpy ($-\Delta H^{0}$ hyd). Values and sizes are quite different between both ions, which might explain why one is usually a fast modulator of biological processes (Ca^{2+}), while the other is a slow modulator or blocker (Mg^{2+}). Both ions are critical electrolytes needed in our diet.

different and because of their different radii, Mg^{+2} has a higher enthalpy dehydration than Ca^{+2} (Fig. 6C, enthalpy). This, in turn, makes the reactions of Mg^{+2} with water or similar protein pockets and environments, slower than those of Ca^{+2}. Because of this, Mg^{+2} is a critical cation in long term homeostatic control s mechanisms (such as blocking channels or activating ATPases), although Ca^{+2} can act as a fast, homeostatic control cation through calcium release events that affect the assembly, and activation of many enzymatic pathways (for example, calmodulin). Mg^{+2} is a commonly used cation cofactor in many intracellular enzymes, because it has specific physicochemical properties that make it well-suited for its role. Those properties include its charge, size, coordination, versatility, and availability. These properties are what makes Mg^{2+} different from other cationic divalent cations like those of heavy metals that can also affect channels and are often toxic [129,130]. Mg^{+2} is a cofactor in many enzymatic processes involving the transfer, storage, and use of metabolic energy. The daily requirement of Mg^{2+} is around 5–7 mg/kg/day [131,132]. Magnesium cation plays many crucial roles in the body, such as supporting muscle and nerve function and energy production. Low Mg^{2+} levels usually don't cause symptoms. However, chronically low levels can increase the risk of high blood pressure, heart disease, type 2 diabetes and osteoporosis [133]. This cation is obtained from the diet, from foods such as green vegetables, meats, and nuts, as well as magnesium-enriched foods, such as flour or water [131,132]. Approximately 50 % of the magnesium ingested in the diet is absorbed; of this percentage, the majority is absorbed in the proximal jejunum and ileum. Each day approximately 40 mg of Mg^{+2} are secreted by the intestine, and only half of this is reabsorbed in the colon and rectum [131].

There are two main mechanisms of Mg^{2+} transport. A transcellular, passive and non-saturable pathway, which is responsible for 80–90 % of the Mg^{+2} that is absorbed daily, and an active and saturable pathway that occurs through the transient receptor potential channel melastatin member 6 (TRPM6) and 7 (TRMP7) [131,134]. TRPM6 was found expressed mainly in the distal small intestine and colon, while TRPM7 is ubiquitously expressed [134]. Although the fraction of Mg^{2+} absorbed by these two pathways is very small, it is important; in fact, the pathogenic mutation of TRMP6 is responsible for familial hypomagnesemia, a rare autosomal recessive disease that manifests as hypomagnesemia associated with other hydroelectrolytic disorders [134,135]. Since magnesium participates in a key way in the intestinal, active transport of calcium and potassium through cell membranes, it is responsible for both their absorption and for the physiological functions that these ions fulfill, such as electrical conduction, muscular contraction, vasomotor tone, heart rate, among other functions [134].

Another factor that affects the absorption of magnesium, decreasing its bioavailability, is the pH of the digestive tract. The suppression of the secretion of hydrochloric acid in the stomach by drugs, such as proton

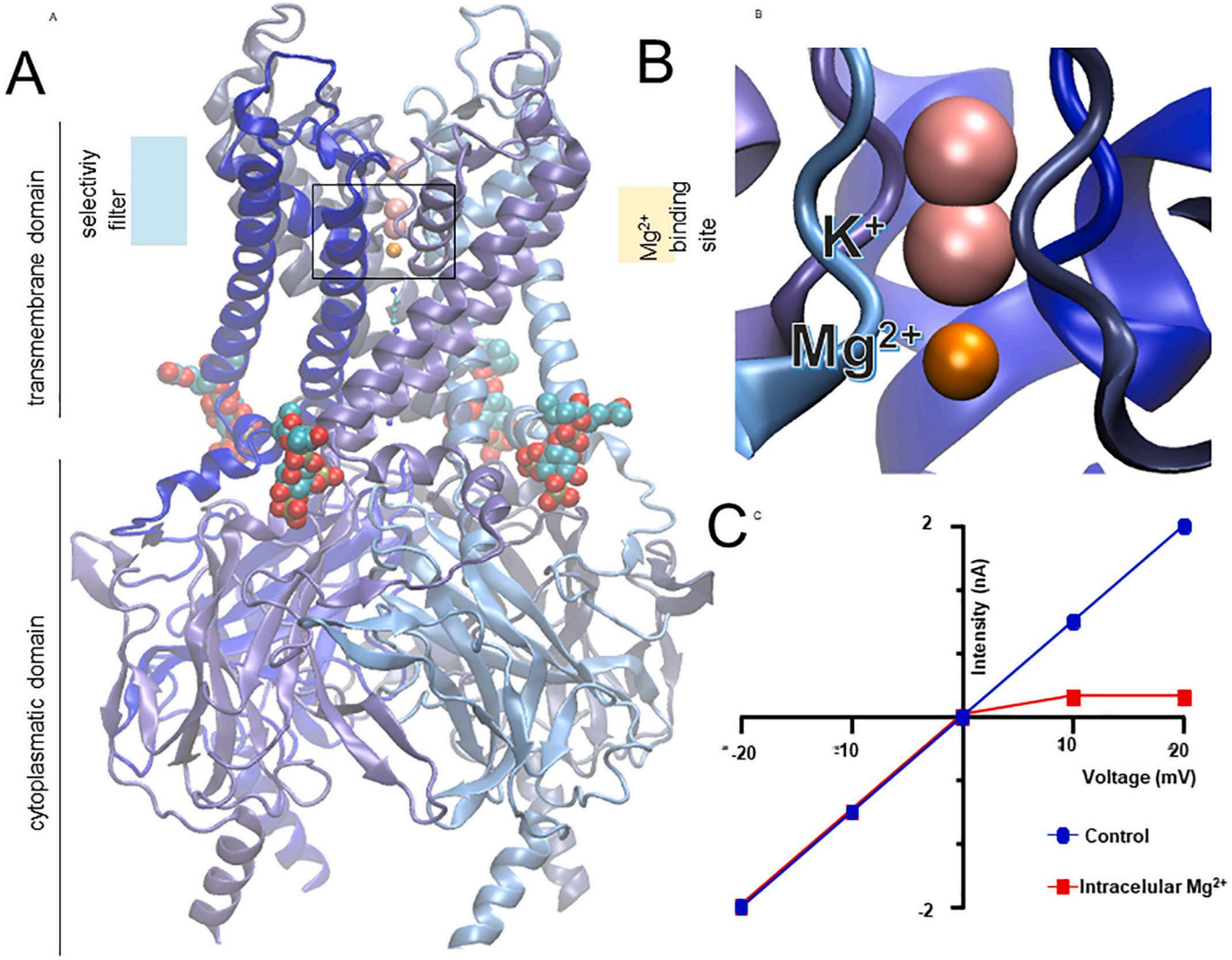


Fig. 7. Structure of the inward rectifier, binding site for magnesium and its functional effect. (A). Three-dimensional structure of the Kir, based on the PDB 6XIT. (B). Zoom in of the Mg^{+2} binding site, located at the intracellular side of the channel pore, coordinates 1XL4 (PDB). (C). Effect on the IV curve of the presence of intracellular Mg^{2+}.In the absence of Mg^{2+}, suppression of inward rectification is observed, data modified from Matsuda et al. [137].

pump inhibitors, will decrease the absorption of magnesium, and this can result in hypomagnesemia if such drugs are administered for long periods of time [132,134,136]. On the other hand, diets abundant in sodium, calcium, protein, alcohol or caffeine can alter the absorption of Mg^{2+}, either by reducing its bioavailability or by interfering with its absorption mechanisms [132]. Although no hormone has been identified as a regulator of magnesium homeostasis, several hormonal factors can affect it, such as insulin, parathyroid hormone, and catecholamines [132].

Kir channels are strongly modulated by the presence of intracellular Mg^{2+} [137–139]. Since the early research of Matsuda and Vandenberg in the 1980s, it was known that the presence of intracellular Mg^{+2} is largely responsible for its inward rectifying properties, since it can block the channel pore in a voltage- and flux-dependent manner against depolarized membrane potentials [137–139]. Fig. 7A shows the structure of a Kir channel with the Mg^{2+} binding site. The binding site has been amplified in Fig. 7B. Fig. 7C shows the IV curve for Kir channels in control without Mg^{2+} and blocked by intracellular Mg^{2+}. This effect is responsible for inward rectification, and it is synergic with the action of other intracellular cations such as polyamines [140,141]. The presence of extracellular Mg^{+2} also produces a direct blockage of the channel at higher concentrations, which can be eliminated by removing a negative charge on the external face of the pore [138]. The increase in the extracellular concentration of K^+ can decrease this blockage [138]. A slow modulation of Kir channels has also been described, as the mechanism responsible for the IRK3 current, which mediates the response to muscarinic receptors. This current can be removed by divalent ion chelators, such as EDTA, but not by EGTA, so Mg^{+2} has been proposed to be its effector [139]. This modulation would allow a long-term adjustment of the cell membrane potential, and would be independent of the pore blockade previously described [139]. Thus, the alterations in the Mg^{+2} pool can affect the biological functions in which the K^+ currents given by these channels are involved.

Chronic Mg^{+2} deficiency produces a moderate loss of intracellular Mg^{+2}. When this loss reaches 35 %, the expressions of Kir 2.1 and Kv4.2 are downregulated, and consequently a reduction of IK1 and Ito currents occurs, causing a prolongation of the QT interval that can be easily observed [142,143]. Mg^{+2} deficiency is mainly seen in patients with T2DM, because insulin is an important modulator of Mg^{+2} homeostasis, as it activates the renal Mg^{+2} channel TRPM6, that determines the final urinary excretion of Mg^{2+} [144]. Also, the concentration levels of Mg^{+2} regulates Kir 6.1, which is a channel associated with insulin secretion, modulating the phosphorylation of the peripheral insulin receptor and having a direct role in peripheral insulin resistance [143,144]. Thus, similar to PIP_2 and polyamines, Mg^{2+} can also exert s direct effects on Kir channels, but in addition it is also able to modulate their function indirectly through allosteric mechanisms that might involve the channel expression [8]. These effects are reversed with oral Mg^{+2} supplementation, after the correction of Mg^{+2} deficiency in these patients [143,144].

In summary, Mg^{2+} is an essential mineral that plays a critical role in many cellular processes, including the regulation of ion channels [145]. It has been shown that Mg^{2+} can modulate the activity of Kir channels by directly interacting with the channel proteins [8]. In addition to its effects on Kir channels, Mg^{2+} is also known to regulate other ion channels and transporters in cells, including Ca^{2+} channels, Na^+ channels, and the Na^+/K^+ ATPase. These effects are thought to be due to Mg^{2+}'s ability to modulate intracellular signaling pathways and gene expression [145].

A diet enriched in high Mg^{2+} foods potentially has several effects on Kir channels. Dietary Mg^{2+} is found in a variety of foods, including green leafy vegetables, whole grains, legumes, nuts, and seeds [146]. Therefore, consuming a diet enriched in high Mg^{2+} foods could increase the levels of Mg^{2+} in the body and thus affect the activity of Kir channels [147].

Firstly, increased Mg^{2+} intake enhances the activity of Kir channels by increasing their sensitivity to intracellular Mg^{2+}. This could lead to a decrease in membrane excitability and potentially reduce the risk of arrhythmias and other cardiovascular disorders [148]. Consistently with this, it has been found that increasing the extracellular Mg^{2+} concentration caused a decrease in Kir channel activity, which in turn reduced the electrical activity of the heart cells [147,149]. Also rats fed with a high- Mg^{2+} diet for four weeks had increased Kir channel activity in their cardiac myocytes compared to rats fed a normal diet [147]. This increase in Kir channel activity was associated with a decrease in the resting membrane potential of the cardiac myocytes, which could have implications for the electrical activity of the heart [147]. This suggests that diets rich in Mg^{2+} may have a suppressive effect on Kir channel activity, which could have implications for cardiovascular health [150]. This situation is cell-dependent as in other cells different than heart with other types of Kir, Mg^{2+} will have different resulting activities on Kir channels, suggesting that the effects of a Mg^{2+} – rich diet on Kir channels may depend on the concentration of Mg^{2+} consumed [8]. The effects of Mg^{2+} on Kir channels will vary in different cells that express different Kir channel subtypes with different sensitivities to Mg^{2+} [8].

Secondly, Mg^{2+} deficiency has been associated with an increased risk of diabetes [132], and Kir channels are involved in insulin secretion [15]. Therefore, a diet rich in Mg^{2+} could potentially improve glucose homeostasis by enhancing the in the correct way the activity of Kir channels involved in insulin secretion.

Thirdly, Mg^{2+} has been shown to have anti-inflammatory effects [151,152], and inflammation can affect Kir channel activity [153]. Therefore, a diet enriched in high Mg^{2+} foods could potentially reduce inflammation and improve Kir channel function.

Fourthly, varying levels of Mg^{2+} in the diet affect Kir channel expression. Mg^{2+} deficiency in animal models causes transcriptional downregulation and expression of Kir channels in the heart, resulting in a prolongation of the QT interval, a long QT syndrome with increased susceptibility to arrhythmias and sudden cardiac death [143]. There is a strong link between the dietary intake of Mg^{2+} and cardiovascular health [154]. The phenomenological cause of this link could be explained in part by the strong modulatory effect of Mg^{2+} in the activity and expression of Kir channels in heart, vessels and kidneys [8].

In conclusion, a diet enriched in high Mg^{2+} foods seem to have several beneficial effects on Kir channel expression, activity and physiology, with potential implications for the regulation of membrane potential and electrical signaling in the cells. Moreover, the available evidence suggests that diets enriched in high Mg^{2+} foods may have complex effects on Kir channel activity, with potential implications for cardiovascular health. However, more research is needed to fully understand the mechanisms underlying these effects in different systems in the body and also to determine the optimal Mg^{2+}intake levels for different populations, as excessive Mg^{2+} intake can lead to adverse effects, such as diarrhea, and nausea.

2.2.4. *Cholesterol*

Cholesterol, a major component of the plasma membrane, is known to have important effects on the structure and function of cell membranes, including the lipid bilayer that surrounds Kir channels [155]. Cholesterol has been shown to influence Kir channels, which are important in regulating membrane excitability. The impact of cholesterol on different Kir channels can be the opposite, with some channels being suppressed and others being enhanced [156]. Most of the Kir channels are down-regulated by cholesterol, but some Kirs are up-regulated [156–158]. A CD loop of the cytosolic domain of the channels seems to play an important role as a domain mediating cholesterol sensitivity in Kir channels because mutations in this region can affect the cholesterol sensitivity of Kir channels across different subfamilies [159]. In Kir 2.1 channels, the interactions at the interface between the channel's N- and C- termini, which couple the intracellular domains of its four subunits during gating, seem to play an important role in the inhibition of the channel by cholesterol [160]. While Kir 2.1 channels are inhibited by cholesterol, Kir 3.2 and 3.4 channels are stimulated [158].

Despite having opposite effects on both channels, putative cholesterol binding sites placed in similar domains in the three channels were described in slightly different locations and/or orientations [158]. These sites are i) non-annular and transmembrane, ii) located between α-helices of two adjacent channel subunits, and iii) they involve aromatic and hydrophobic residues [158]. In addition, a molecular switch in Kir 3.4 channels seems to determine whether cholesterol up-regulates or down-regulates the channels [161]. It was reported that a single point mutation can invert the effect of cholesterol on Kir channels, indicating that subtle differences determining how cholesterol distributes in the proximity of these channels or transmembrane proteins in general, may have important effects on their function [161]. The mechanisms responsible for the cholesterol sensitivity of Kir2 channels have also been studied and characterized, being regulated by specific lipid-protein interactions. Molecular dynamic simulations using Kir 2.2, established that there are four discrete binding sites located within previously located cholesterol-sensitive regions of the channel with multiple cholesterol molecules interacting with the channel at short and long-range interactions [162]. More recent research shows that there is cholesterol-induced decoupling among Kir2.2 subunits upon cholesterol binding to the channel [163]. The degree of decoupling depends on the number of cholesterol molecules bound. Specific residues for this interaction have been identified, whose mutations promote the loss or reversal of modulation by cholesterol [163].

Decreasing cholesterol at the membrane, increases Kir2 channel activity [162]. Of pathogenic relevance is the inhibition of these channels by high plasma membrane cholesterol as it happens during atherogenesis in blood vessels [164]. Their inhibition makes more difficult vessel relaxation. Studies have also demonstrated that enriching cells with cholesterol decreases the density of Kir currents while depleting cells of cholesterol increases the density of these currents [165]. The substitution of cholesterol by its optical isomer, epicholesterol, increases the density of Kir currents [165]. These authors proposed that the interaction between cholesterol and Kir channels ought to be mediated by specific cholesterol-protein interactions [165]. Cholesterol has been found to bind to cholesterol-rich GM1 lipids, which are associated with Kir channels [166]. However, the localization of Kir channels can be dynamic, as they can move between cholesterol-rich and cholesterol-poor domains [166]. Some of the actions of cholesterol could be related to variations and displacement of the previous metabolites of their binding sites and most importantly, to variations in the physicochemical properties of the bilayer surrounding the Kir channels affecting their activity [155]. For example, while PIP2 stimulates the activity of Kir channels, cholesterol suppresses its activity [167]. These two membrane lipids, PIP2, and cholesterol, can stabilize Kir2 channels in a preferred open or closed state, respectively, conferring different hemodynamic sensitivity while linking these findings on Kir channels to circulation in blood vessels in health and disease [167] Thus, the surrounding membrane lipid environment plays a role in modulating the activity of Kir channels [167]. This is particularly important in the context of the role of Kir channels in cardiovascular diseases.

In summary, some ways in which cholesterol can affect Kir channels are the following:

1. Modulation of channel activity: Cholesterol can directly modulate the activity of Kir channels, most of them are down-regulated, and some are up-regulated. Studies have shown that an appropriate level of cholesterol is necessary for optimal channel function. Cholesterol can affect the gating properties of Kir channels, such as their open probability and sensitivity to intracellular factors [161,168,169].
2. Stabilization of channel structure: Cholesterol plays a role in maintaining the integrity and stability of cell membranes, including the lipid environment surrounding Kir channels. It can interact with the surrounding lipids and proteins to form microdomains or lipid rafts, which can impact the organization and function of Kir channels. Cholesterol can stabilize the structure of Kir channels and promote their proper localization within the membrane enriching or depleting the membrane of Kir channels [156,161,165].
3. Modulation of membrane fluidity: Cholesterol influences the fluidity and rigidity of the lipid bilayer. It can decrease the fluidity of the membrane, which can impact the movement and conformational changes of Kir channels. This, in turn, can affect their gating properties and overall activity [170].
4. Interactions with regulatory proteins: Cholesterol can interact with various proteins that regulate Kir channel activity. For example, cholesterol can bind to specific protein domains involved in channel modulation, such as caveolin-1, and modulate their interaction with Kir channels. These interactions can affect the localization, trafficking, and functional properties of Kir channels [171].

It is important to note that the exact mechanisms by which cholesterol affects Kir channels can vary depending on the specific Kir channel subtype and cellular context. Changes in dietary cholesterol intake can affect the physical properties of cell membranes and alter Kir channel activity in different ways in different Kir channels, thus, dietary cholesterol levels can impact the regulation of Kir channels. As we have mentioned, this is of particular relevance regarding the nutrigenomics of Kir channels and cardiovascular diseases [164,167]. Further research is needed to elucidate the precise details of how cholesterol influences Kir channel function in the whole body and impacts health through Kir channel nutrigenomics.

2.2.5. Conclusions regarding the modulation of Kir channels by different diets and nutrients

In conclusion, Kir channels can be differentially regulated in their activity, function and expression by different diets. A diet can influence the levels of various nutrients, metabolites, and signaling molecules in the body, which can in turn impact the activity and regulation of Kir channels. A few summarized examples are the following:

1. High-fat and/or high sugar diet: Kir channels are sensitive to the lipid composition of the cell membrane, including cholesterol levels [156]. Diets high in saturated fats and cholesterol have been associated with increased membrane cholesterol content, which can affect the function of Kir channels [156]. A high-fat diet can lead to changes in the expression and function of Kir channels in various tissues, including the heart and vessels [172–174]. Feeding rats or mice with a high-fat diet for several weeks resulted in decreased expression of Kir2.1 channels, which may contribute to the development of hypertension and other circulation diseases [175,176]. In the heart, a high-fat diet in mice has been shown to increase the risk of arrhythmias disrupting several ion channels [177]. On the other hand, other dietary factors, such as polyunsaturated fatty acids (PUFAs), have different effects on Kir channels that may depend on age and type of cell [178,179]. It is thought that a diet rich in PUFAs could change the expression of Kir channels in the heart in addition to other ion channels, which may have a cardioprotective effect [180,181]. Elevated cholesterol levels have been shown to impair Kir channel activity in certain tissues, such as the heart and the brain [182]. Regarding high sugar diets, in rats it was found that a high-sugar diet changed the pharmacological sensitivity of Kir6.2 channels in pancreatic beta cells, which may contribute to the development of particular conditions for the pharmacological treatment of T2DM and metabolic syndrome [174].
2. Potassium intake and high salt diets: Kir channels are responsible for maintaining potassium homeostasis in cells. Kir channels in the kidneys play a crucial role in regulating potassium reabsorption and maintaining electrolyte balance. A high-salt diet has been shown to change the activity of Kir4.1/Kir5.1 channels in the kidney, which can lead to changes in Na^+ and water reabsorption, coupling with the Na^+/Cl^- cotransporter and the development of hypertension [38,183]. The coupling between these Kir channels and the Na^+/Cl^-

cotransporter is strongly modulated by dietary K^+ intake, which can influence the activity and expression of all of these proteins [184]. Low K^+ diets and intake can modulate the activity of these proteins to enhance K^+ reabsorption in the kidneys and conserve K^+ [184]. Excessive sodium intake can affect the function of these channels and lead to altered potassium handling and development of high blood pressure [185].

3. Metabolic factors: Diet-related metabolic factors, such as insulin and glucose levels, can affect the regulation of Kir channels. High glucose levels, as seen in diets rich in carbohydrates, inhibit KATP channel activity in pancreatic beta cells, impairing insulin secretion [186]. Insulin itself can also modulate Kir channel activity in various tissues, including skeletal muscle and the heart [187]. Related to this topic, caloric restriction and fasting have been associated with changes in Kir channel expression and activity in different tissues and it has been recommended for the treatment of epilepsy [188]. These dietary interventions can impact cellular metabolism and ion homeostasis, which can influence Kir channel function. Another related issue here is the hormonal regulation. Diets can affect hormonal balance in the body, and hormonal signals can influence Kir channel activity. Insulin, which is released in response to carbohydrate intake, can directly interact with Kir channels and modulate their function. Changes in insulin levels due to different diets can, therefore, impact Kir channel activity [189].
4. Modulation by other dietary compounds: Certain dietary compounds, such as polyphenols and flavonoids found in fruits, vegetables, and teas, have been shown to modulate Kir channel activity [190]. These compounds can interact with Kir channels directly or indirectly through signaling pathways, leading to altered channel function [190]. Some phytochemicals have been shown to enhance Kir channel activity and promote potassium efflux [190]. These are known as phytochemical-rich diets. Related to this issue is the global macronutrient composition that has been already discussed, The composition of macronutrients in the diet, such as carbohydrates, proteins, and fats, can impact Kir channel function. We have already discussed the impact of high fat and high carbohydrate diets. Finally, the micronutrient status. Deficiencies or excesses of certain micronutrients like Mg^{2+}, can affect Kir channel regulation (already discussed). An excess of Zn^{2+} can inhibit Kir channel function, while low Zn^{2+} can enhance them [191].
5. Modulation by pathological states such as oxidative stress and inflammation: Diets rich in antioxidants, such as fruits and vegetables, can have a protective effect against oxidative stress and inflammation. Kir channels can be influenced by these factors, as oxidative stress and inflammation can modulate their expression and activity [192].

In summary, the specific regulation and effects of Kir channels by different diets is complex and varies depending on the tissue and the specific Kir channel isoform involved, tissue, and overall physiological and metabolic context. The mechanisms underlying the diet-induced regulation of Kir channels are still being studied and are not fully understood. Further research is needed to fully understand the intricate relationships between diet and Kir channel regulation of their function and expression.

2.3. Genetic changes in Kir channels affecting metabolism

2.3.1. Mutations in Kir channels that are not KATP can affect the intake of nutrients and/or electrolytes

The normal functions of Kir channels are to maintain K^+ homeostasis and the resting membrane potentials of cells. Critical mutations in portions of the Kir genetic sequence can alter Kir channel functions, and this can result in the onset of a variety of diseases that can affect the heart, kidneys, pancreas, eyes and the nervous system. Such critical mutations are particularly important when they are located in specific "hotspots", such as in nucleotide sequences encoding the Kir protein pore (or peptide sequences adjoining the pore), the ion selectivity filter and the C-terminal tail. Mutations in these regions can affect normal Kir channel function [193]. Most Kir channels that are not KATP channels are strongly expressed in the kidneys, and mutations in Kir channels expressed in the kidneys can have profound effects on electrolyte balance. Because Kir channels are also expressed in the brain and heart, similar mutations are often associated with neurological and cardiological symptoms or problems in development. Kir channels are modulated by PIP_2 found in the intracellular leaflet of the membrane lipid bilayer [48]. The binding of phosphoinositosides, such as PIP_2, to the Kir channel receptor domain is primarily mediated by electrostatic forces, and the binding site has been localized as discussed previously (Fig. 3B) [194,195]. A peptide with a group of positively charged basic amino acids with a Proline in between, known as the *bPbbb* cluster, is located at the beginning of the C-terminal tail of the Kir channel. This seems to be a "hotspot" for mutations that have an impact on Kir channel function [196]. Mutations in this region also appear to affect nutrient intake.

Bartter syndrome (BS) is a group of autosomal recessive disorders characterized by poor salt reabsorption in the thick ascending loop of Henle with salt depletion, hypokalemic metabolic alkalosis, and hypercalciuria [197]. The overall incidence of the BS in the general population is around 1 in 100,000 to 1,000,000 individuals [197], which is less than another salt wasting nephropathy, the Gitelman syndrome (incidence 1 in 40.000), caused mostly by mutations in the Na^+ and Cl^- transporter [*SLC12A3]* [197]. At least 7 genomic variants of the disease have been found, and one of them (Type II, OMIM 241200) has been associated with more than 40 mutations in a region located close to but upstream of the "hotspot" group of amino acids in the C-terminal tail of Kir1.1 channels (encoded by the *KCNJ1* gene) [193,197]. These mutations cause loss of function of Kir1.1 or ROMK channels. Most of the mutations are misssense/nonsense mutations in exon 2, producing truncated or deficient channels that are poorly expressed or unexpressed [197]. BS patients with these mutations usually have an onset before birth and require severe treatments [193,197]. A diagnosis in this type must be suspected in polyhydramnios patients with elevated blood levels of Cl^- and aldosterone. Of course, any diagnosis of BS must confirmed by molecular genetics [197].

A nutritional approach for treating or supporting BS patients is essential. Along with special care, patients have to careful about water and salt intake. These individuals have an increased appetite for salty foods (containing excess sodium, potassium and chloride), and supplementation with magnesium should be encouraged, unless there are other complications that preclude this [197]. The treatment and nutritional approaches are essentially the same for BS and Gitelam's syndrome, an autosomal recessive, salt-losing tubulopathy characterized by renal potassium wasting, hypokalemia, hypocalciuria, hypomagnesemia, and hyperreninemic hyperaldosteronism [197]. In addition to liquids, and foods enriched in potassium and magnesium, dietary supplements have to be considered in the treatment of these syndromes [198]. Because the intake of magnesium chloride is poorly tolerated as (it causes abdominal pain and diarrhea), liposomes filled with magnesium have been proposed as a more tolerable approach for increasing the intake and replenishment of magnesium pools [198,199]. The dietary approach to treat these syndromes is quite important and well-tolerated. Nutritional counseling with close follow up of blood electrolyte concentrations, is recommended in these patients [198,199].

Another syndrome, Andersen-Tawil syndrome (ATS), is a rare inherited disorder that was recognized in the 1970s, that affects only a few hundred people worldwide [200]. This syndrome is characterized by periodic paralysis and cardiac arrhytmias (a long QT syndrome) that can lead to ventricular fibrillation and alterations in skeletomuscular development in fingers (such as clinodactily or syndactyly), low set ears, widely spaced eyes, small mandible, short stature and scoliosis [200]. ATS has related mutations in the *KCNJ2* inward rectifier gene that encodes the Kir 2.1 channel that lead to a loss-of-function of the channel

[200,201]. These mutations can be found anywhere in the hydrophilic region of the channel, especially in what is known as its channelosome or its interactosome (N-terminus, P-loop and C-terminus) [202]. It appears that physical activity and diets disbalanced in K^+ content s can trigger paralysis or arrhytnias in these patients, though the results are not conclusive. Diets low in carbohydrates and Na^+ are recommended in some cases [203].

Mutations in the *KCNJ5* gene is one of the most significant genetic causes of the familial hyperaldosteronism (FH) [204]. FH is a group of inherited, autosomal dominant conditions in which the adrenal glands produce too much aldosterone, resulting in high blood pressure with hypertension [205]. Because of the mutations in the *KCNJ5* gene, the Kir 3.4 channel becomes less selective to K^+ over Na^+, and the increased intake of Na^+ can depolarize cells, which in turn promotes Ca^{2+} entry and the constant secretion of aldosterone linked to proliferation of the adrenal cells [206]. The mutations in Kir 3.4 described thus far usually take place in the pore region or in the C-terminus or N-terminus regions near the pore region, and this can change the selectivity filter, rectification or conductance of the channel [207–211]. The ultimate result is hypertension, and because of this the diets and daily routines must be highly restrictive for hypertensive patients. For example, DASH diets (Dietary Approach to Stop Hypertension) are highly encouraged, because these diets include foods rich in K^+, Ca^{2+} and Mg^{2+}, which are important in controlling blood pressure. Such diets also limit s foods that are high in Na^+ (1500 to 2300 mg/day maximum), saturated fat and added sugars [212].

Mutations in the *KCNJ10* gene encoding the Kir4.1 channel, which is expressed in various tissues, including brain, inner ear, eye, and kidney, can result in multiple symptoms [213,214]. Diseases caused by *KCNJ10* mutations manifest as autosomal recessive conditions with epilepsy, deafness of sensorineural origin, ataxia, and EAST syndrome (Epilepsy Ataxia Sensoryneural deafness and Tubulopathy). Because the Kir4.1 channel is expressed in the loop of Henle, among other parts of the kidney, it produces the salt wasting tubulopathy known as EAST syndrome [215]. This was first described by Bockenhauer and coworkers, and most of the reported mutations in Kir4.1 channels are in the pore or close to the pore. These mutations cause changes in pH sensitivity and promote loss of function of the channel [215–217]. The resulting electrolytic imbalance is similar to the Gitelman syndrome with hypokalaemic and hypochloraemic metabolic alkalosis combined with hypomagnesaemia and hypocalciuria [215]. The clinical management of this tubulopathy is similar to the Gitelman syndrome [215]. NaCl, K^+, Ca^{2+} and Mg^{2+} should be monitored in these patients, and diets and liquids enrichened in these electrolytes are recommended [215].

The *KCNJ12* gene encodes for the Kir 2.2 channel. Mutations in this gene seem to behave like those mutations found in Kir 2.6, below, and produce mostly paralysis. It is unclear if there is any benefit to supplementation with nutrients or liquid electrolytes [218].

The *KCNJ15* gene is a paralog of the *KCNJ10* gene that it is highly expressed in kidney, lung and brain. It is located in regions of chromosome 21 that are associated with Down Syndrome [219]. High levels of expression of the *KCNJ10* gene have been found in the pancreas of patients with an increased risk of T2DM. This gene has also been described as linked to Kir 4.2 channel polymorphisms, especially in Asian populations [40].

The *KCNJ16* gene encodes the Kir 5.1 channel, and this gene is expressed mostly in the kidney and pancreas [220]. Derst and coworkers have characterized the expression of the *KCNJ16* gene in the kidney, particularly in the proximal tubule, the thick ascending limb, and the cortical collecting duct, and also in the brain [221]. Another interesting observation reported in this contribution is that this gene shares 40 % homology with the gene that encodes Kir 2.x channels and that their expression patterns frequently overlap s [221]. These channels can form heteromers with other channel subunits, changing pH sensitivities, but they can also be expressed as homomers forming complex associations with other proteins, like the PSD-95 protein (poststnaptic protein 95) [222]. Recently, mutations that cause loss-of-function in this channel have been described, such as mutations that yield a hypokalemic tubulopathy with deafness [223]. The dietary guidelines for these conditions are similar to other conditions that cause hypokalemic electrolyte imbalances, as described below for *KCNJ18* mutations.

The *KCNJ18* gene encodes the Kir 2.6 channel, which is expressed in skeletal muscle and is regulated by the thyroid hormone. Mutations in this gene have been linked to thyrotoxic hypokalemic and periodic paralysis [224]. The dietary guidelines for mutations in the *KCNJ18* gene should include ample amounts of high potassium-containing foods that are low in carbohydrates, including avocados, nuts and assorted dried fruits, cheeses, eggs, brussel sprouts, cauliflowers, pumpkins, tomatoes, spinach, asparagus, cabbage, broccoli, and mushrooms. Patients with these mutations should avoid alcohol [225,226].

Table II summarizes the mutations found in the OMIM database, that affect the functions of Kir channels (that are not KATP channels) and that do affect nutrition or electrolyte balance.

BP: Base pair ALA: alanine ARG: arginine ASN: asparagine ASP: aspartic acid CYS: cysteine GLN: glutamine GLU: glutamic acid GLY: glycine HIS: histidine ILE: isoleucine LEU: leucine LYS: lysine MET: metionine PHE: phenylalanine PRO: proline SER: serine THR: threonine TRP: tryptophan TYR: tryptophan VAL: valine.

2.3.2. Genetic changes in KATP channels related to metabolic diseases

2.3.2.1. Mutations in KATP channels or auxiliary subunits. KATP channels are ATP sensitive potassium channels that are gated by intracellular nucleotides like ATP and ADP. These channels are constructed from inward rectifier Kir6.x channels plus a sulfonylurea receptor (SUR.x) [15,227]. Though most of channels are found in the plasma membrane, some are found in intracellular membranes, such as membranes from mitochondria or nuclei [227]. The activities of KATP channels are linked to the intracellular levels of ATP and ADP, and this makes them particularly relevant in the coupling of the variations in membrane potentials to metabolic activities. Channelopathies of human KATP channels are connected to diseases of metabolic homeostasis [228]. For example, insulin secretion from pancreatic islet β- cells is dependent on this particular type of inward rectifier channels or ATP sensitive (KATP) channels [15]. Because of the central role of KATP channels in insulin secretion, genetic variations in these channels have dramatic effects on metabolic diseases and the uptake of nutrients [21]. Mutations and polymorphisms in the gene encoding this channel have been linked to diabetes and other disorders related to insulin secretion.

Some inherited diseases in neonates with hyperinsulin disorders are related to mutations in the genes encoding the SUR1 subunit and the Kir6.2 protein that abolishes KATP channel activity. This can result in Familial Hyper-insulinemic Hypoglycemia (FHH) (MIM:601820 for Kir 6.2, and 256,450 for SUR1). In this review we will refer mostly to features of the main subunit, except when the auxiliary subunit is the predominant cause of a channelopathy, as in this case. There are several alternative names for this channelopathy, such as persistent hyperinsulinemic hypoglycemia of infancy, hyperinsulinemic hypoglycemia due to focal adenomatous hyperplasia, or congenital familial nesidioblastosis of pancreas with hyperinsulinism.

FHH is the most common cause of long-lasting hypoglycemia in neonates and infants. Persistent hypoglycemia lasting longer than two weeks and reiterative severe hypoglycemic episodes during the first month of life are prominent clinical characteristics [229]. FHH is caused by an impaired negative feedback regulation of insulin secretion when low glucose levels rise. Brain damage from recurrent episodes of hypoglycemia may occur, so treatment requires early aggressive intervention [230]. To date, seven different molecular variants of the disease have been described. In this review, we will consider only the critical variants of the KATP channel that are related to a SUR1 receptor gene (encoded by the *ABCC8 gene* located in chromosome 11p15, FHH1) [231], and to a

Table II
KCNJ mutations not related to KATP channels associated with nutrition-related syndromes. Description of mutations in the different KCNJ genes, which present as syndromes with deleterious effects on nutrition. Other mutations in these genes can cause arrhythmias, seizures, deafness, amaurosis, and kidney disorders. Most of these channels are expressed in kidneys and their mutations will cause dietary electrolyte imbalances.

Gene	Chromosome	OMIM access #	Channel	Mutations	Syndrome	Suggested Nutrients
KCNJ1	***11q24.3***	600359	K_{ir} 1.1	0.0001: TYR60-to-TER (N- terminal region, truncates protein at first transmembrane domain)0 .0002: 1-BP insertion in Codon 15, frameshift mutation, premature termination at codon 54 (N- terminal region)0 .0003: SER200-to-ARG (Truncates protein at first transmembrane domain)0 .0004: TRP58-to-TER (N-terminus)0 .0005: ALA195-to-VAL (C-terminal region)0 .0006: MET338-to-THR (C- terminal region)0 .0007: ALA198-to-THR (C- terminal region)0 .0008: GLY167-to-GLU (Pore)0 .0009: ASP108-to-HIS (P-loop)0 .0010: LYS124-to-ASN (P-loop)	Bartter syndrome, type 2	Salty foods, foods high in K^+
KCNJ2	**17q24.3**	600681	K_{ir} 2.1	0.0001: ASP71-to-VAL (N- terminal region)0 .0002: ARG218-to-TRP (C- terminal region)0 .0003: GLY300-to-VAL (C- terminal region)0 .0004: 12 BP deletion, resulting in the deletion of amino acid 95 to 98 (first transmembrane domain)0 .0005: 6 BP deletion, resulting in the deletion of amino acid 314 to 315 (C-terminal region)0 .0006: ARG67-to-TRP (N- terminal region)0 .0007: PRO186-to-LEV (C- terminal region, associated to PIP2 interaction)0 .0008: VAL302-to-MET (C- terminal region)0 .0009: ASN216-to-HIS (C- terminal region)0 .0010: ASP172-to-ASN (C- terminal region)0 .0011: THR75-to-ARG (N- terminal region)0 .0012: CYS54-to-PHE (N- terminal region)0 .0013: THR305-to-PRO (C- terminal region)0 .0014: VAL93-to-ILE (first transmembrane domain)	Andersen syndrome	Diet low in carbohydrates and Na^+ are recommended in some cases.
KCNJ5	**11q24.3**	600734	K_{ir}3.4	(Most of them near the selectivity filter or affecting the rectification or conductance) G151R, G151E, I157S,T158A, L168R, E246 K,G247R	Familial Hyperaldosteronism Type II	Antihypertensive diet. DASH diet
KCNJ10	**1q23.2**	602208	K_{ir} 4.1	0.0001: ARG65-to-PRO (eliminated a PDZ-binding domain, that is related to interaction with PIP2 and is required for expression of the protein at the cell surface)0 .0002: ARG199-to-TER (C- terminal region)0 .0003: CYS140-to-ARG (P-loop)0 .0004: THR164-to-ILE (C- terminal region)0 .0005: ALA167-TO-VAL (C- terminal region)0 .0006: ARG297-to-CYS (C- terminal region)0 .0007: GLY77-to-ARG (first transmembrane domain)0 .0008: PRO194-to-HIS (C- terminal region)0	SESAME Syndrome/EAST syndrome	Diet low in carbohydrates and Na^+ are recommended

(*continued on next page*)

Table II (*continued*)

Gene	Chromosome	OMIM access #	Channel	Mutations	Syndrome	Suggested Nutrients
				.0009: ARG348-to-CYS (C- terminal region)0 .0010: ARG65-to-CYS (N- terminal region)0 .0011: PHE75-to-CYS (first transmembrane domain)0 .0012: 1 BP deletion, 775G (frameshift and premature termination)0 .0013: ARG175-to-GLN (C- terminal region)		
KCNJ15	**21q22.13-q22.2**	602106	K_{ir} 4.2	Single nucleotide polymorphism in exon 4	Significant association with an increased risk of type 2 diabetes mellitus	Low carb diet
KCNJ16	**17q24.3**	605722	K_{ir} 5.1 (heteromeric channels with KCNJ10 or KCNJ15)	0.0001: ARG137-to-CYS (pore region)0 .0002: ARG176-to-TER (C- terminal region)0 .0003: ILE132-to-ARG (pore region)0 .0004: PRO250-to-LEU (C- terminal region)0 .0005: GLY135-TO-ALA (pore region)0 .0006: THR64-to-ILE (N- terminal region)	Hypokalemic tubulopathy and deafness.	Include plenty of high potassium foods which are low in carbohydrate. Avoid alcohol
KCNJ18 (and KCNJ12)	**17p11.2 (and 17p11.2/21 38)**	613236 (and 602323)	Kir 2.6 (and Kir 2.2)	R399X, Q407X and others that alter rectification in Kir 2.6.	Hypokalemic periodic paralysis (with thyrotoxicosis for Kir 2.6)	Include plenty of high potassium foods which are low in carbohydrate. Avoid alcohol

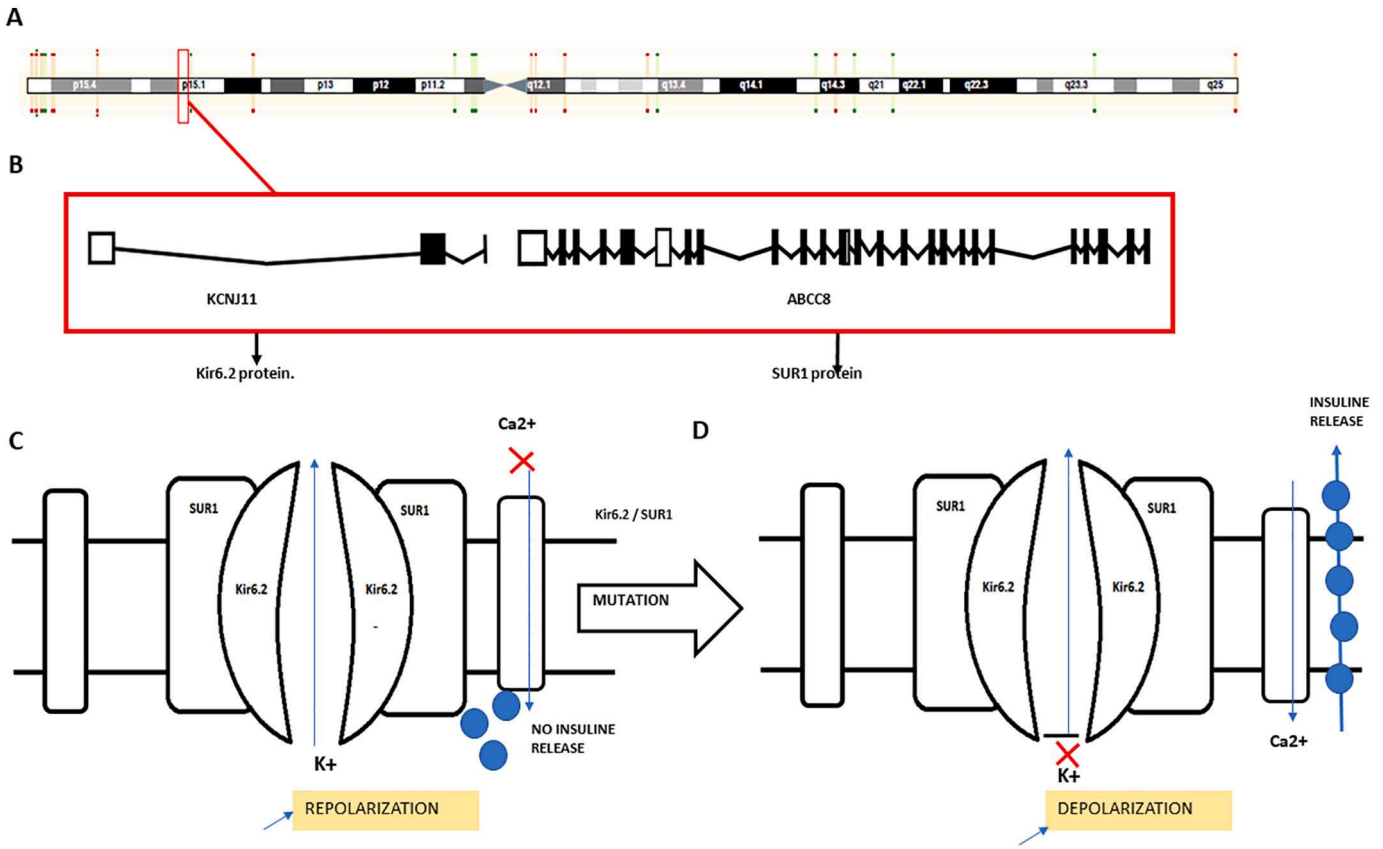


Fig. 8. molecular basis of KATP channel mutations. Phenotypical consequence: congenital hyperinsulinism. In (A) Chromosome 11 is shown. The red rectangle shows the region where KCNJ11 and ABCC8 are located within the chromosome. (B) Zoom in to show the *KCNJ11* and *ABCC8* genes and the correspondening proteins that they encode for. (C) Normal functioning of the KATP channel in β- cells from pancreatic islets. In low ATP/ADP concentration ratios, the channel is open, the cell is hyperpolarized and no insulin is required. This channel allows for outward potassium current that brings the cell membrane potential towards the potassium equilibrium potential when is open. As a result, Ca^{2+} channels in this situation remain closed and there is no signal for insulin vesicles to fuse with the cell membrane to release the hormone. The channel is inhibited by high ATP/ADP ratios and hence insulin release in promoted in these situations. (D) Pathogenesis mechanism of a KATP mutated channel (Kir6.2/SUR1). The channel has a loss- of-mutation and it remains open. This leads to a depolarized membrane potential with open calcium channels near their window current. An inward calcium current and release from intracellular stores rises intracellular calcium levels, triggering insulin release from the pancreatic beta cells leading to hyperinsulinism.

Kir6.2 gene (the *KCNJ11 gene* located in chromosome 11p15.1, FHH2) [232–234]. These genetic changes are the most frequent findings with an incidence of about 1 in every 40,000–50,000 newborns [235], though it can increase s up to 1 in every 3000–10,000 newborns in Arabic and Jewish populations [236,237]. A summary of the genomic changes related to FHH are shown in Fig. 8. One of the treatments indicated for patients with KATP malfunction is diazoxide, (a KATP channel opener) [229,238], which is effective in 50 % of the children with this condition. The other 50 % are usually treated with pancreatectomy [239]. The prognosis is good with these approaches in most children, and surgery can be especially useful in some cases [229,239]. These KATP malfunction children also have feeding problems. They usually require either higher feeding rates (every 3–4 h). If frequent feeding is not enough to prevent hypoglycemic crisis, hypertonic glucose infusion or the administration of continuous intragastric dextrose may be required [240,241]. In those children that grew to adolescence, ketogenic diets (low carbohydrate, high fat), have shown to be useful, if applied for 2 years or more [242].

Transient neonatal diabetes mellitus (TNDB) is a form of diabetes that presents in neonates during the first few weeks of life. After a few months infants go into remission. They can relapse, and it is important to prevent permanent diabetes in adolescence or adulthood. These patients show slow growth rates before birth, followed by hyperglycemia, dehydration and failure to blossom during infancy [243]. The genes implicated in 70 % of the cases are located in a region of the long (q) arm of chromosome 6 (6q24). These cases are referred to as 6q24-related TNDB, and most of these cases are not inherited. Other genetic causes include genetic changes in the *KCNJ11* and *ABCC8* genes, though this will usually cause permanent neonatal diabetes type 2 (NT2DM) [244].

Permanent NT2DM is an autosome dominant inherited disorder characterized by the onset of hyperglycemia within the first six months of life. NT2DM is associated with partial or complete insulin shortage [245]. Mutations can be found in the *ABCC8* gene encoding the SUR1 channel subunit (less than 20 %), or in the Kir 6.2 channel itself (the *KCNJ11* gene) in most of the cases, at MIM 618856 [245]. These patients should be rapidly rehydrated and treated with insulin. Usually a high caloric intake is necessary for an appropriate weight gain during growth [245]. When mutations are located in the main Kir 6.2 channel subunit in the N-terminus or C-terminus regions, these mutations usually activate the channel [246].

Maturity-onset diabetes of the young (MODY) is a clinically heterogeneous group of patients with a different monogenic basis and mendelian inheritance in which there is always a β-cell malfunction [247]. About fourteen different genes have been identified as a cause for MODY, and one of them is the *KCNJ11* gene, which accounts for the most common MODY13 variant [248]. These patients usually are not obese, nor are they insulin-resistant [249]. A low to mild carbohydrate intake diet should be recommended for these patients. Globally these patients could represent up to 5 % of the diabetic population, and it is sometimes difficult to differentiate these patients from T2DM or Type 1 diabetes [250,251]. The E23K is a common polymorphism in the KCBJ11 gene associated with greater susceptibility to T2DM [252,253]. This will be discussed with polymorphisms of the Kir6.2 channel below. Table III summarizes the mutations observed in the *KCNJ 11* gene and the resulting phenotypes.

2.3.2.2. KATP polymorphisms and type 2 diabetes mellitus. Most of Diabetes mellitus (DM) cases around the world (90–95 %) have been identified as T2DM, and this disease has a clear association with other conditions, such as metabolic syndrome and obesity [254]. T2DM is considered a multifactorial disease that involves genetic and environmental factors. If not controlled, T2DM causes early and late-term complications from high glucose blood levels that can cause Hyperosmolar hyperglycemic syndrome (HHS), ketoacidosis and vascular damage (macro and microangiopathy), respectively [255]. The pathophysiology of T2DM involves insulin resistance in peripheral tissues with an increment of plasmatic glycemia, leading to islet β-cell s stimulation to produce and release more insulin, which results in overproduction and functional claudication of beta cells, together with glucotoxicity and lipotoxicity [256,257].

KATP channels in islet β-cells, skeletal muscle and liver play a fundamental key role in glucose metabolism, functioning as a metabolic

Table III
KCNJ11 mutations associated to nutrition-related syndromes. Exhaustive description of the KCNJ11 mutations, and their resulting phenotypes. Not only there are disease-related mutations, such as those found in familial hyperinsulinemic hypoglycemia-2, but also mutations related to specific disease susceptibility (type 2 diabetes mellitus)

Gene	Chromosome	OMIM access #	Channel	Mutations	Phenotype (MIM #)	Inheritance
KCNJ11	11p15.1	600937	$K_{ir}6.2$	0.0001: LEU147-to-PRO0 .0009: TYR12-to-TER0 .0010: 88G-T, PROMOTER REGION.0 .0011: PRO254-to-LEU0 .0013: HIS259-to-ARG0 .0019: ARG301-to-HIS0 .0020: GLY156-to-ARG0 .0022: GLU282-to-LYS0 .0025: THR298DEL	Hyperinsulinemic hypoglycemia, familial 2. (601820)	AD, AR
				0.0012: CYS42-to-ARG0 .0017: GLY53-to-SER0 .0018: GLY53-to-ARG 0.0002: ARG201-to-HIS0 .0003: VAL59-to-MET0 .0004: ARG201-to-CYS0 .0005: VAL59-to-GLY0 .0006: ARG50-to-PRO0	Diabetes mellitus, transient neonatal 3. (610582)	AD
				.0007: LYS170-to-ARG0 .0008: LYS170-to-ASN0 .0015: CYS166-to-PHE0 .0016: ILE167-to-LEU0 .0021: GLY53-to-ASP0 .0023: PHE60-to-TYR	Diabetes, permanent neonatal 2. (618856)	AD
				0.0024: GLU227-to-LYS	Maturity-onset diabetes of the Young, type 13. (616329)	AD

ALA: alanine ARG: arginina ASN: asparagine ASP: aspartic acid CYS: cysteine GLU: glutamic acid GLY: glycine HIS: histidine ILE: isoleucine LEU: leucine LYS: lysine MET: methionine PHE: phenylalanine PRO: proline SER: serine THR: threonine TRP: tryptophan TYR: tryptophan VAL: valine.
DEL: deletion. AD: autosomal dominant. AR: autosomal recessive.

sensor when ATP intracellular levels change due to cell metabolism [31]. In islet β-cells, higher glucose plasma levels lead to higher ATP generation due to glucose metabolism, and this, in turn, closes the KATP channels and depolarizes the membrane. The membrane depolarization opens voltage gated Ca^{2+} channels in the plasma membrane, promoting a Ca^{2+} influx that triggers a Ca^{2+} release from intracellular stores. As a consequence, this results in an incremental increase in intracellular Ca^{2+} levels and the release of vesicles containing insulin (insulin secretion) [31,258]. Therefore, the malfunction of KATP channels has an important role in the dysregulation of glucose metabolism. There is clear evidence from loss-of-function and gain-of-function mutations in the *ABCC8* and *KCNJ11* genes (codifying genes of KATP channel proteins SUR1 and Kir6.2 respectively) [259,260] that explaining the development of metabolic diseases related to glucose metabolism. as mentioned before. Nevertheless, not every genetic variation in these genes is deleterious. Single nucleotide polymorphisms (SNPs) occur normally in essentially all individuals and are the most common type of genetic variation found in the human genome [261]. However, they might modify the risk of occurrence of this and related diseases [261]. They are highly frequent and occur approximately once every 1000 nucleotides [261]. It has been estimated that about 54 % of SNPs are not deleterious, with a frequency of less than 1 % in the genome that cause genetic problems [262]. [Is that wording correct?] In T2DM, several studies have demonstrated that certain SNPs, for example in the *KCNJ11* and *ABCC8* genes, are associated with a higher risk of susceptibility to T2DM in the global population [263]. A considerable number of *KCNJ11* SNPs have now been identified [261].

The E23K variant (rs5219) is the most described KATP channel polymorphism, and it shows the clearest association with T2DM, significantly increasing the risk of contracting this disease [264]. This locus is located at codon 23 of the *KCNJ11* gene, consisting of a G-to-A change in nucleotides, which results in a glutamic acid (E) to lysine (K) substitution, located in the N-terminal portion of the main subunit of the Kir6.2 channel [258]. This amino acid substitution results in a conformational alteration due to the fact that lysine has a positive charge, unlike glutamic acid [265]. Because of this substitution, the probability for the KATP channel opening is increased, whereas the inhibition by ATP is reduced due to a reduction in affinity in the ATP-binding region of the channel [258,261,265]. Collectively, this results in impaired insulin secretion [266]. This effect in insulin secretion appears to be more significant in carriers of both A alleles (genotype AA) compared to heterozygotes GA, [267]. In spite of the findings discussed above, some have suggested a less clear correlation between E23K SNPs and functional alterations in KAPT channels [258]. Some polymorphisms, such as the E23K polymorphism, have been related to other characteristics associated with some of the T2DM, such as hypertension and increased HbA1c levels [268].

Various channel-related treatments have been used to reduce the effects of T2DM. For example, KATP channel blockers have been used to induce insulin secretion in T2DM [31,258]. However, treatment response to sulfonylureas in E23K carriers seems to be different than in normal allele homozygotes carriers, according to certain case-control studies in particular populations. A pharmacogenetic study compared patients with T2DM homozygote and heterozygotes to E23K polymorphism (AA and GA genotypes respectively) to normal homozygotes (GG genotype) patients, and found that carriers of A alleles (lysine-K alleles) had better therapeutic responses to sulfonylureas, compared to lower-risk homozygotes. Reductions in HbA1c levels in A allele carrier group (AA + GA genotypes) patients treated with gliclazide, glibenclamide and glimepiride were higher than in normal heterozygotes [269].

Another SNP located in the *KCNJ11* gene is the I337V polymorphism, which is frequently associated with the E23K variant in more than 75 % of E23K carriers. It consists of an A-to-G substitution, resulting in a change from isoleucine to valine at the codon 337 [270]. Both SNPs, E23K and I337V are associated, because they are genetically in linkage disequilibrium (LD), which suggests that the frequency of association of both alleles to a given condition is higher than expected if the loci are independent and associated randomly.

Several other SNPs with a possible association with T2DM have been described in the *KCNJ11* gene, such as rs5210 and rs5218. Both of these SNPs are located in the highly conserved 3′ untranslated region (UTR) of the *KCNJ11* gene [261]. Data are less clear than for the E23K polymorphism, where there is some contradictory and yet insufficient results [271,272]. The E23K polymorphism has a strong linkage with another polymorphism variant located in the adjacent SUR1 gene called S1369A. This variant consists of a T-to-G substitution, resulting in a serine-to-alanine amino acid change at codon 1369 in the *ABCC8* gene for the SUR1 protein [258]. Both SNPs are tightly associated, and in fact form a haplotype, and as a result 95 % of two copy carriers of the E23K variant also possess two copies of the S1369A variant [273]. This suggests that either variant could be responsible for an increase in the risk of acquiring the disease. Both genetic al and populational studies have analyzed the statistical risk of contracting T2DM and having these SNPs present alone or together [274,275]. The functional implications of these two SNPs and their involvement in the synthesis of KATP channels remain controversial, but some evidence suggests that the presence of the S1369A variant in the *ABCC8* gene decreases the ATP inhibition in the channel by increasing the ATPase s activities [276]. Finally, other research is also consistent with this hypothesis and provides additional evidence that the co-expression of both variants (E23K/S1369A) decreases the ATP sensitivity of the KATP channel. This is reflected as a reduction in ATP half-maximal inhibitory concentration (IC50) [277]. In summary, due to their genetic linkage, it is difficult to distinguish e separately the statistical evidence for the responsibility of each SNP alone and in combination in contracting T2DM. Thus the exact influence of each of these SNPs, alone or in combination, remains unclear. Fig. 9 summarizes the various SNPs linked with T2DM in the KATP main subunit (Kir6.2, *KCNJ11* gene) and auxiliary subunit (SUR1, *ABCC8* gene).

Finally, there is now abundant information on how nutrition and diet should be undertaken for T2DM. For this, we will only refer here to the recommendations of the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK), National Institutes of Health, USA (see https://www.niddk.nih.gov/health-information/diabetes/overview/diet-eating-physical-activity).

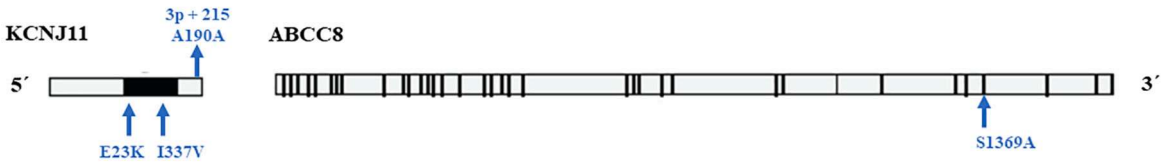
3. Final comments

On a more general and philosophical view, life is a quality that can be distinguished from inert matter due to the presence of biological processes, such as signaling and self-sustaining and replicating mechanisms, Thus life has been described by its capacity for growth, reaction to stimuli, metabolism, energy transformation, and reproduction. It is the result of complex and intricate networks operating in different time and space that yield homeostatic results in spite of changes in the environment. Inside cells the controls over the concentrations of various chemicals and nutrients and the organization and interrelationship between certain levels of information are necessary in order to sustain life. In higher, more complex organisms additional layers of information are needed and communication between different cell types in different arrays or tissues are essential, resulting in the evolution of systems like the nervous system or endocrine system to perform certain higher level tasks. To receive and process information, energy is required, and to generate chemical energy, nutrients are needed. Thus, nutrients are critical as an energy source, but nutrients can also impact cells in indirect ways, such as modulating allosterically enzymatic pathways or modulating the genomic expression of certain proteins. The latter concept forms the basis of nutrigenomics

In cells, energy is coupled to electrochemical gradients that are used to generate and store in high energy molecules like ATP. The formation of cellular energy and its storage in electrochemical gradients takes place via ion channels and depends on many additional proteins and the

A

a1.



a2.

Gene	Polymorphism	Position
KCNJ11	E23K	Exon 1 – codon 23 (G to A change)
	I337V	Exon 1 – codon 337 (A to G change)
	3p + 215 (rs5210)	3´ UTR
	A190A (rs5218)	3´ UTR
ABCC8	S1369A	Exon 33 – codon 1369 (T to G change)

B

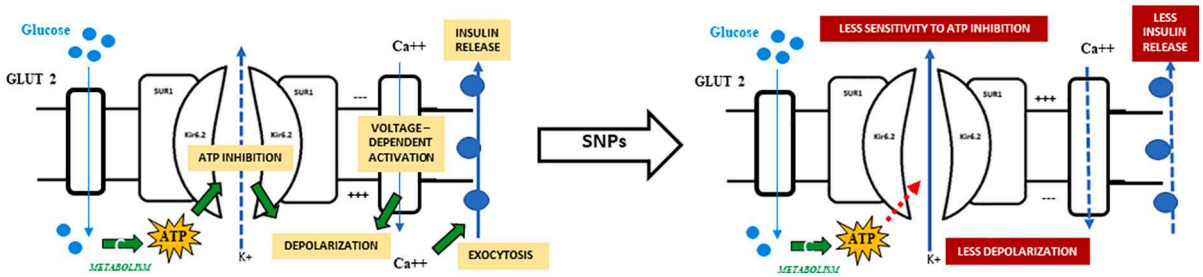


Fig. 9. Molecular basis of KATP single nucleotide polymorphisms (SNP) related to type 2 Diabetes mellitus (T2DM). (A) Most relevant SNPs related with T2DM in the *KCNJ11* and *ABCC8* genes. (a1) shows both genes located in chromosome 11, with some of the most important SNPs related to T2DM risk. *KCNJ11* encodes Kir6.2 main subunit for the channel protein, and has a single exon. The *ABCC8* gene is composed by 35 exons, and encodes for the SUR1 protein. Both proteins form the ATP sensitive potassium channel (KATP). Exons are represented as black boxes. (a2) represents a synthesis of the SNPs information, showing the position in the genome of the involved genes (*KCNJ11* and *ABCC8*)- It also shows the type of nucleotide substitution. (B) KATP channel in pancreatic β cells. In the *left panel* is shown the normal physiology of insulin secretion in islet β cells, involving ATP inhibition of K^+ current through KATP channel as mentioned before. The presence of these variants in the KATP channel encoding genes (*right panel*) has been related with less ATP affinity and higher aperture probability of the KATP channel, and as a consequence with less depolarization and impaired insulin secretion by exocytosis being of the multifactorial causes leading to T2DM.

presence of membrane barriers to free ion flow. Ion channels are critical for the maintenance of membrane transmembrane potentials and their abilities to generate high energy molecules from channels in specialized cellular organelles (mitochondria). In animal cells the 2TM inward rectifier potassium channels are an example of membrane channels were nutrigenomics plays an essential role. We know that these channels can be modulated by many nutrients from different diets as well as electrolytes. There are genomic changes in the main subunits or auxiliary subunits of these channels that can produce gain (or loss) of function, and this is important in yielding different pathological phenotypes where the nutrition or diet and electrolyte balance could be compromised. Some of these membrane channels have the additional peculiarity of being expressed in multiple tissues, such as the kidney and also in the pancreas. For example, as KATP channels in pancreatic β-cells, where their function is modulated by high levels of intracellular ATP or ATP/ADP ratios that control insulin release. The dysfunction of these channels has profound effects on electrolyte balance in the case of Kir channels or in insulin release in the case of KATP channels (main subunit or auxiliary subunit SUR1), and this eventually results in pathological consequences.

We feel strongly that it is important gather more information on how nutrients and their metabolites can be modulators of ion channel function and expression. Such information could be critical for preventing or controlling the development of certain diseases.

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Declaration of competing interest

The authors confirm that there is no conflict of interest.

Data availability

No data was used for the research described in the article.

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