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Chapter

Potassium Channels as a Potential Target Spot for Drugs

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Abstract

Aberrant function or expression of potassium channels can be underlying in pathologies such as cardiac arrhythmia, diabetes mellitus, hypertension, preterm birth, and various types of cancer. The expression of potassium channels is altered in many types of diseases. Also, we have previously shown that natural polyphenols, such as resveratrol, and selective synthetic modulators of potassium channels, like pinacidil, can alter their function and lead to the desired outcome. Therefore, targeting potassium channels with substance, which has an influence on their function, is promising access to cancer, diabetes mellitus, preterm birth, or hypertension therapy. In this chapter, we could discuss strategies for targeting different types of potassium channels as potential targets for synthetic and natural molecules therapy.

Keywords: potassium channels, K channels, modulators of K channels, activators, inhibitors, natural polyphenols, resveratrol, K channels antibody

1. Introduction

Ion channels are protein molecules that form pores in the cell membrane and membranes of cellular organelles and allow passive flow of ions in the direction of their electrochemical gradient and result in electrical currents. Ion channels play key roles in membrane potential generation and many cellular activities such as signal transduction, neurotransmitter release, muscle contraction, hormone secretion, volume regulation, growth, motility, and apoptosis [1].

It is widely known that potassium channels (K channels) are transmembrane proteins that allow the flow of potassium across the membrane to regulate ion homeostasis, cell proliferation, migration, cell volume, and specific processes such as muscular contraction [2].

K channels are the most diverse ion channel type, and each subtype has a specific physiological role. K channels are highly attractive as targets for the development of novel therapeutics. However, the lack of detailed structural and functional insight of K channels and their diversity and ubiquity pose challenges for the development of selective drug candidates.

For many years the structure and types of K channels were unknown due to the lack of specific ligands for their activation or blocking. A progressive shift in the study of these structures has emerged since the discovery of animal toxins that are highly specific to individual types but also with the introduction of electrophysiological methods—voltage clamp and patch clamp, which have made it possible to test individual channel. In recent years, many genes detected participate in the encoding of these ion channels. Some subtypes are cloned and their biophysical properties determined,

but this has not led to a complete elucidation of their function [3]. Especially in recent years, studies on this membrane protein family in different tissue types dramatically increased. Parallel with this remarkable progress in our understanding of molecular diversity, structure, and function, a growing number of discoveries have linked K channel gene mutations with various diseases. Such diseases of the heart, kidney, pancreas, and central nervous system involve either mutation(s) in the K channel gene(s) and/or altered regulation of K channel function. The enhanced understanding of these diseases, facilitated by a combination of genomic and biophysical approaches, has helped our understanding of how various mutations affect channel function, contribute to disease etiology, and rationalize novel treatment strategies.

This review will survey the K channels crucial role in the physiologic and pathophysiological function and discuss the emerging understanding of their clinical influence. Once taken into account these strategies, K channels may represent suitable and easily accessible different disease biomarkers and targets for therapy.

2. Classification of K channels

Ion channels classified according to the type of ions they conduct, their structure, their expression pattern and mode of activation [4]. Potassium channels are composed of complexes of several protein subunits, each encoded by a different gene.

The general model of the K channel is a complex of four α subunits grouped in the form of a pore through the membrane. Two transmembrane helices and a short loop between them (called the P-loop) are trademarks of these channels. The P-loop contains the amino acid sequence of threonine-valine-glycine-tyrosine-glycine, which is the selective filter most responsible for the selective passage of K^+ ions through the channel. This architecture with two transmembrane helices and a loop is an essential and universal feature of the K channel, but further, different features characterize each channel subfamily. In addition to α subunits, a variety of accessory-regulatory subunits such as SUR, β, MinK, and KChiP and others enter the K channel composition [5].

Different types of K channels have been shown to comprise more than 100 different protein subunits that are tissue-specific and species-specific [6]. About 75 genes coding different types of K channels have detected in human genomes. Molecular studies of K channels have allowed their classification based on the primary amino acid sequence of the pore-containing subunit. This sequence motif, conserved across all K channels, was proposed to correspond to the selectivity filter of the pore-forming region of the channel protein. There are many (sub)types and isoforms of K channels divided into three groups based on transmembrane domains that make up the α subunit [3]. These channels are classified into three groups, based on the number of transmembrane domains (TMDs) (**Figure 1**). Within each family, ion channels with 65% identical amino acid sequences are further grouped into subfamilies [7]. The standard nomenclature for K channels is proposed by the *International Union of Basic and Clinical Pharmacology Committee on Receptor Nomenclature and Drug Classification* (NC-IUPHAR) [8], presented in **Figure 1** and **Tables 1–4**.

Orange is a Kv type with six transmembrane domains, with red main subtypes K_{Ca} channels; green is a Kir subtype with four transmembrane domains, and blue is a subtype with two transmembrane domains K_{2P}.

Understanding the role of K channels and detecting their subunits/proteins in different physiological and pathophysiological condition are essential, along with linking dysfunction of these channels to specific diseases and disorders. These facts speak to the importance of these channels, as a possible therapeutic site for the action of drugs that should prevent or stop unwanted conditions/states. Therefore, the study of their function and the expression of their proteins are of great importance.

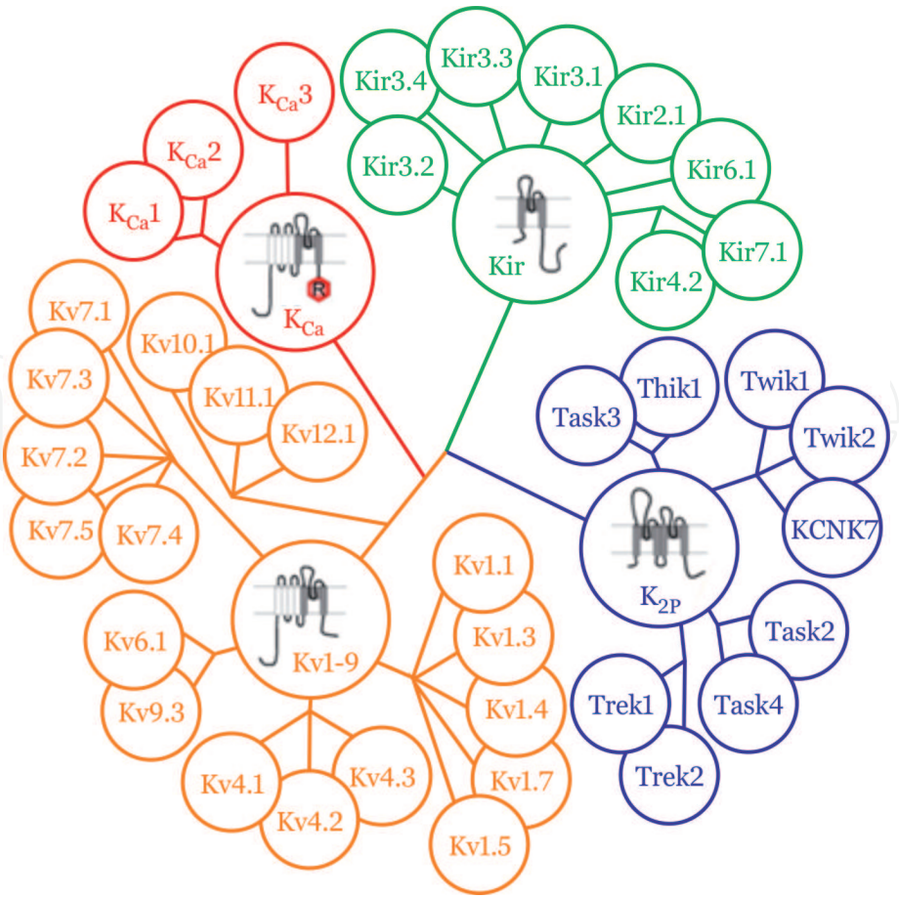

Figure 1.
Classification of main types and subtypes of K channels.

2.1 Voltage-dependent K channels (Kv) and their modulators

Kv channels are the largest superfamily of the K channel, coding with about 40 genes and containing 12 subfamilies, each with several representatives [9]. Representatives of Kv1–4, 7, and 10–12 subfamilies can form functional channels as homomers, while Kv5, 6, 8, and 9 must associate with Kv2 or three subunits to form a functional channel. The official nomenclature for Kv channels is Kva.b, where a and b denote the subfamily and ordinal number of channel discovery (**Figure 1**). There are six transmembrane domains in each subunit, designated as S1–S6. Four β-subunits are associated with α-subunits and located on the cytoplasmic side of the membrane [10]. There is a peptide loop between the S5 and S6 domains. Loops of α-subunits face the lumen of the pores and contribute to the formation of K^+ conductive pores [3]. Domain S4 is the central part of the voltage sensor necessary to activate the Kv channel. The opening/closing mechanism also contributes to the electrostatic interaction of negative charges on the S2 and S3 domains [11].

The biophysical properties, physiological regulation, and pharmacological properties of Kv channels are dependent on the combination of α subunits. The combination on four α subunits may be homo- or heteromultimers. Even more complex to these heteromultimers is their interaction with smaller accessory proteins including β subunits, KChIP, KchAP, and minK proteins, miRP peptide, and others [12, 13].

The isoforms of Kv channels dominant for smooth muscle are mainly Kv1, Kv2, Kv3, and Kv4. For example, in vascular smooth muscle cells, the most important subtypes of Kv channels are Kv1 (Kv1.1, Kv1.2, Kv1.3, Kv1.5, Kv1.6), Kv2 (Kv2.1), Kv3 (Kv3.1). Kv4 (Kv4 .2–3), and Kv7 (Kv7.1–5); in the smooth muscle of the uterus is Kv4 (Kv4.2, Kv4.3).

Activators	Inhibitors	Subtypes	Heteromultimers
-	α-dendrotoxin, margatoxin, tetraethylammonium (TEA)	Kv1.1	K_v1.2, K_v1.4, K_vβ1 i K_vβ2
-	margatoxin, α-dendrotoxin, noksiustoxin	Kv1.2	K_v1.1, K_v1.4, K_v β1 i K_v β2
-	margatoxin, noxiustoxin, TEA, maurotoxin, correolide	Kv1.3	K_v1.1, K_v1.2, K_v1.4, K_v1.6, K_v β1 i K_v β2
-	fampridine	Kv1.4	K_v1.1, K_v1.2, K_vβ1 i K_vβ2
-	fampridine	Kv1.5	K_vβ1 i K_vβ2
-	α-dendrotoxin, TEA	Kv1.6	K_vβ1 i K_vβ2
-	noxiustoxin, fampridine	Kv1.7	K_vβ1 i K_vβ2
-	fampridine	Kv1.8	K_vβ1 i K_vβ2
-	TEA	Kv2.1	K_v5.1, K_v6.1-6.4, K_v8.1-8.2, K_v9.1-9.3
-	fampridine, TEA	Kv2.2	K_v5.1, K_v6.1-6.4, K_v8.1-8.2, K_v9.1-9.3
-	fampridine, TEA	Kv3.1	-
-	fampridine, TEA	Kv3.2	-
-	TEA	Kv3.3	-
-	TEA	Kv3.4	MiRP2
-	fampridine	Kv4.1	KChIP 1-4, DP66, DPP10
-	-	Kv4.2	KChIP 1-4, DPP6, DPP10, K_vβ1, NCS-1, Navβ1
-	-	Kv4.3	KChIP 1-4, DPP6 and DPP10, MinK, MiRPs
-	-	Kv5.1	-
-	-	Kv6.1	-
-	-	Kv6.2	-

-	-	Kv6.3	-
-	-	Kv6.4	-
-	XE991, linopiridine	Kv7.1	-
retigabine	XE991, linopiridine, TEA	Kv7.2	-
gabapentin, retigabine	linopiridine	Kv7.3	-
retigabine	XE991, linopiridine, TEA	Kv7.4	-
retigabine, gabapentin	linopiridine, XE991	Kv7.5	-
-	-	Kv8.1	-
-	-	Kv8.2	-
-	-	Kv9.1	-
-	-	Kv9.2	-
-	-	Kv9.3	-
-	LY97241, terfenadine, dofetilide, kalmodulin, astemizole	Kv10.1	-
-	LY97241, hinidin	Kv10.2	-
RPR260243	astemizole, terfenadin, disopyramide, E4031, dofetilide, ibutilide	Kv11.1	minK, MiRP1
-	E4031	Kv11.2	minK
-	E4031	Kv11.3	minK
-	Ba^{2+}	Kv12.1	minK
-	Cs^{+}	Kv12.2	minK, MiRP1

Table 1.
Selective modulators of voltage-sensitive channels.

The expression pattern depends on the compartment and/or conditions like gravid or not in the uterus and part of lent blood vessels. This heteromultimerization seems to modulate Kv current expression, sensitivity to various substances, as well as biophysical properties of channels such as inactivation [14–18]. Further, research shows that the most important isoforms for the proliferation, activation, migration, and apoptosis of tumor cells are Kv1.3, Kv1.5, Kv2.1, Kv41, Kv9.3, Kv10.1, and Kv11.1 [19].

A recognizable feature of Kv channels is their sensitivity to pharmacological modulators. The compounds most commonly used to inhibit Kv channels are 4-aminopyridine (4-AP) and tetraethylammonium (TEA). In general, Kv channels of vascular

smooth muscle cells exhibit higher sensitivity to 4-AP, which nonspecifically inhibits members of the Kv1–4 subfamilies of these channels [20]. Electrophysiological imaging showed that the channels encoded by Kv1.2 and Kv1.5 genes were relatively sensitive to 4-AP, while Kv2 channels inhibited TEA more effectively. The 4-AP concentrations required for the half-maximal inhibition of Kv channel function varied between 0.3 mM and 1.1 mM. These differences in channel sensitivity attribute to the different expressions of Kv channel subtypes, the use of different animal species in studies, differences in sex, cell isolation techniques, and imaging conditions [12, 20].

2.1.1 Ca^{2+}- and voltage-dependent K channels (KCa) channels and their modulators

Ca^{2+}-sensitive Kv channels other than voltage-dependent depolarizations, for opening, also require an increased concentration of Ca^{2+} ions in the cytoplasm [21]. They are divided into channels with high ($K_{Ca}1$-BK_{Ca}, maxi K, 100–300 pS), intermediate ($K_{Ca}3$-$IK_{Ca,}$ 25–100 pS), and low conductivity ($K_{Ca}2$-SK_{Ca}, 2–25 pS) [22]. $K_{Ca}1$ channels are activated by membrane depolarization and/or Ca^{2+} binding to the channel; $K_{Ca}2$ and $K_{Ca}3$ channels are voltage-independent and activated by Ca^{2+} binding to calmodulin that constitutively binds to the channels [23].

$K_{Ca}1.1$ channels form of α pore-forming subunits and auxiliary β or γ subunits. The four α subunits can build a functional channel on their own. Associated accessory subunits act as potent regulators of most channel characteristics, including voltage and Ca^{2+} sensitivity, as well as sensitivity to pharmacological modulators.

The differences in $K_{Ca}1.1$ channels and Kv channels are the presence of an additional transmembrane (S0) segment with the extracellular N-terminus, as well as the presence of a long intracellular C-terminus, forming the so-called "channel tail." Furthermore, unlike Kv channels, where the voltage sensor is localizing in the S4 domain, the positively charged residues responsible for the voltage dependence of the $K_{Ca}1.1$ channels are less centralized and present in the S2, S3, and S4 domains [21]. There are different intracellular partners of these channels. Also, $K_{Ca}1.1$ channels can be the targets of a number of posttranslational modifications such as oxidation, glycosylation, and phosphorylation reactions. Finally, the association of α subunits with different regulatory subunits further contributes to increasing the diversity of these channels [23, 24].

Furthermore, four types of β subunits (β1–4) and four types of γ subunits (γ1–4) modulate almost all the physiological and pharmacological properties of

Activators	Inhibitors	Subtypes
NS004, NS1619	paxilline, caribdotoxin , iberiotoxin, TEA	$K_{Ca}1.1$
EBIO, NS309	apamin, UCL1684, TEA	$K_{Ca}2.1$
NS309, EBIO	UCL1684, apamin, TEA	$K_{Ca}2.2$
EBIO, NS309	apamin, UCL1684, TEA	$K_{Ca}2.3$
NS309, EBIO SKA-121	caribdotoxin, TRAM-34, senikapok	$K_{Ca}3.1$

Table 2.
Selective modulators of Ca^{2+}- and voltage-sensitive channels (K_{Ca}).

$K_{Ca}1.1$ channels. β subunits contain two, while γ subunits are constructed from a single transmembrane domain. The mechanism by which helper subunits interact with α subunits and regulate $K_{Ca}1.1$ channel activity is extremely complicated, but it is critical for the study and understanding of the vascular disease. In vascular smooth muscle cells, the β1 subunit is the predominant isoform, and its dysfunction is associated with diabetes, hypertension, and other vascular diseases. Deletion of the gene for the β1 subunit causes a significant decrease in Ca^{2+}-sensitivity of the channel. As auxiliary subunits of $K_{Ca}1.1$ channels, γ subunits also affect their activity by modulating voltage and Ca^{2+}-dependence. They play a role in the regulation of smooth muscle tone, and change in the gene encoding them leads to a decrease in the activity of functional $K_{Ca}1.1$ channels lead to constrictions [25–27]. Expression of β1 subunit can be selectively upstream or downstream-regulated in smooth muscle cells, without reflecting to α subunit expression. Occurs under the influence of various physiological and pathophysiological conditions, as well as during hormonal stimulation and that increase or decrease the channel activity [26, 28].

$K_{Ca}1.1$ channels also represent important targets in the mechanism of action of various activators or inhibitors. Adenosine and β-adrenergic agonists activate $K_{Ca}1.1$ channels via cAMP-dependent and cGMP-dependent pathways. Especially in vascular smooth muscle cells, elevated levels of cGMP and activation of PKG with NO result in the phosphorylation of BKCa and their subsequent activation. On the other hand, angiotensin II and endothelin-1 inhibit $K_{Ca}1.1$ channels in coronary arteries by PKC-independent mechanisms [29].

The pharmacology of $K_{Ca}1.1$ channels spread from nonspecific blockade with TEA and alkaloids, like paxillin, to more effective specific inhibitors scorpion toxins, such as iberiotoxin and charybdotoxin. Although these compounds do not have pure therapeutic potential, they are very useful tools for studying the function of these channels. Several small-molecule $K_{Ca}1.1$ channel openers have been detected for both native and cloned channels. For example, benzimidazole NS-1619 activates $K_{Ca}1.1$ channels, but its functional effects also include inhibition of Ca^{2+} currents and Kv channels. And many other substances can modulate the activity of $K_{Ca}1.1$ channels, such as estrogen, reactive oxygen species and ethanol [22, 30, 31].

$K_{Ca}2.1$, $K_{Ca}2.2$, and $K_{Ca}3.1$ channels are mostly present in neurons, endothelium of the blood vessels, epithelium, and in several types of smooth muscle, e.g., in the urinary tract. Thus, the opening of these channels is independent of the membrane potential but strictly dependent on Ca^{2+}. Complex Ca^{2+} calmodulin induces a conformational change leading to the opening of the pore [32].

Pharmacologically, $K_{Ca}2$ channels are highly sensitive to bee venom and apamin with different affinity for all channel isoforms: $K_{Ca}2$ channels are the most sensitive and $K_{Ca}1$ the least. Scilatoxin, biculculin, dequalinium, and its more potent derivative UCL1684 are also potent inhibitors of these channels group. The compounds, such as clotrimazole and TRAM-34, are more specific inhibitors of $K_{Ca}3.1$ channel. $K_{Ca}3.1$ current can be reduced by the scorpion toxin charybdotoxin, like $K_{Ca}1.1$ channels. Both types of channels are activated by chlorzoxazone, zoxazolamine, riluzole, 1-EBIO, its more potent DC-EBIO derivative, and NS-309. However, these compounds are not successful, such as Ca^{2+} for channel activation. Moreover, an increase in channel sensitivity for Ca^{2+} is an assumed mechanism of their action [31].

2.2 Inwardly rectifying K channels (Kir) and their modulators

The inwardly rectifying (Kir) channels conduct K^+ ions into the cell at a membrane potential more negative than the equilibrium potential for K^+, while at more positive potentials, the output K^+ current is limited and barely detectable [33]. The explanation for the phenomenon of inward rectification is in the fact that intracellular Mg^{2+} and polyamines (spermine and spermidine) block output K^+ currents.

As carriers of positive charge, polyamines and Mg^{2+} interact with the negatively charged amino acids present in the transmembrane M1 domain and terminal C-terminus of the Kir channel, thereby inhibiting the passage of K^+ ions through the pore [34]. Kir channels have been identified in many types of cells. Seven subfamilies are identified so far (**Figure 1** and **Table 3**).

Structure of Kir channel is consisting of four α subunit-forming subunits, each containing two transmembrane domains (M1 and M2) and a P-loop between them. The properties and functions of Kir channels vary between different tissues and species. For example, Kir channel expression is most pronounced in the smooth muscle of the autoregulatory vascular compartments, such as the coronary and cerebral circulation. Kir duct expression increases with decreased blood vessel diameter. The difference in expressive Kir channels can be explained by the fact that the conduction artery shows a very small response to a smaller version of extracellular K, whereas resistant arteries show a positive response [35].

Activators	Inhibitors	Subtypes	Associated subunits
-	tertiapin-Q , Ba^{2+}, Cs^+	Kir1.1	-
PIP_2	spermine, spermidine, putrescine, Mg^{2+}, Ba^{2+}, Cs^+	Kir2.1	-
-	Mg^{2+}, Ba^{2+}, Cs^+	Kir2.2	-
-	Mg^{2+}, spermine, spermidine, putrescine, Ba^{2+}, Cs^+	Kir2.3	-
Mg^{2+}	Cs^+, Ba^{2+}	Kir2.4	-
PIP_2	tertiapin-Q , Ba^{2+}	Kir3.1	-
PIP_2	pimozide, desipramine	Kir3.2	-
PIP_2	-	Kir3.3	-
PIP_2	tertiapin-Q	Kir3.4	-
-	Ba^{2+}, Cs^+	Kir4.1	-
-	Ba^{2+}, Cs^+	Kir4.2	-
-	Ba^{2+}	Kir5.1	-
diazoxide,minoxidil nicorandil,cromakalim, pinacidil, resveratrol,	glibenclamide, tolbutamide	Kir6.1	SUR1, SUR2A, SUR2B
diazoxide,minoxidil nicorandil,cromakalim, pinacidil, resveratrol,	glibenclamide, tolbutamide	Kir6.2	SUR1, SUR2A, SUR2B
-	Ba^{2+}, Cs^+	Kir7.1	-

Table 3.
Selective modulators of inwardly rectifying K channels (Kir).

ATP-sensitive Kir channels (K_{ATP}) are the exceptions, which have a more complex heterooctamer structure with multiple types of accessory subunits [3, 5]. Structurally, K_{ATP} channels form of four pore-forming Kir6.x subunits and four regulatory subunits known as sulfonylurea receptors, SURx. Kir6.x subunits are responsible for ATP inhibition and SURx for nucleoside-diphosphate activation.

Functional expression of the K_{ATP} channel requires coexpression of Kir6.x and SURx subunits in a 1:1 ratio. SUR1 is predominantly present in pancreatic β cells. SUR2 has two variants, SUR2A and SUR2B, which are generated by alternative excision of exon 38 in the ABCC9 gene. SUR2A is mainly present in the myocardium and skeletal muscle, while SUR2B generally is distributed in the vascular and myometrial smooth muscle cells [17, 25, 35, 36].

Numerous studies have highlighted that K_{ATP} channels in vascular smooth muscle cells play an important role in achieving systemic vasodilation during hypoxia, increasing blood flow to the heart, kidney, and muscle. This vasodilation is attributed to the release of NO or adenosine due to hypoxia but also to the direct effect of hypoxia itself. During hypoxia, K_{ATP} channels may be activated by a decrease in ATP, a decrease in pH and partial pressure of oxygen, or an increase in intracellular lactates and ADP. These factors can activate K_{ATP} channels directly and/or potentiate NO activation [37].

K_{ATP} channels play their roles in the mechanism of the action of relaxation and contraction by interacting with various protein kinases. Thus, K_{ATP} channels activated by protein kinase A (PKA) and cGMP-dependent protein kinase participate in the mechanism of action of endogenous vasodilators such as adenosine and prostacyclin. On the other hand, activation of protein kinase C (PKC) and vasoconstrictor induced increases in intracellular Ca^{2+} caused by noradrenaline, vasopressin, endothelin, and angiotensin II were accompanied by inhibition of the K_{ATP} channel [38–40].

K_{ATP} channels in the smooth muscle are inhibited by antidiabetics from a group of sulfonylurea derivatives, such as glibenclamide and tolbutamide. Glibenclamide is the most commonly used K_{ATP} channel inhibitor in vascular smooth muscle studies, whereas tolbutamide shows much lower potency [13, 41].

In the study of potential drugs, the core interest is directed towards K_{ATP} channels, since they exhibit activity under basic conditions and significantly contribute to the control of the resting membrane potential [42].

2.3 K channels with two pores (K_{2P}) and their modulators

K_{2P} channel subunit consists of two regions that participate in pore formation (P1 and P2, hence their name) and four transmembrane domains (M1–M4). Functional channels form as dimers of these subunits that form a single pore selectively permeable to potassium [43]. Activity of these channels is voltage-independent, and they under physiological conditions (high concentration of K^+ in the cytoplasm and low extracellular) conduct K^+ ions from the cell into the extracellular space [44], leading to stability of the resting membrane potential. K_{2P} channel activity is regulated by a wide variety of factors such as pH, stretching of membrane, temperature, and endogenic compounds like arachidonic acid. K_{2P} channels play important roles in many physiological processes: neuroprotection, cerebrovascular vasodilation, regulation of aldosterone production and secretion, depression, chemoreception, and pulmonary vasoconstriction [45].

The neuroprotective agent riluzole, currently in use for the treatment of amyotrophic lateral sclerosis, has been shown to be an activator of TREK-1 and TRAAK channels. Volatile general anesthetics such as chloroform and isoflurane have also been shown to target TREK-1 channels [3].

Activators	Inhibitors	Subtypes
-	-	$K_{2P}1.1$/TWIK1
arachidonic acid, halothane, chloroform, isoflurane, membrane elongation, heat, acidic pH	norfluoxetine	$K_{2P}2.1$/TREK1
halothane	methanandamide, anandamide, acidic pH	$K_{2P}3.1$/TASK1
arachidonic acid, riluzole, membrane elongation, heat	-	$K_{2P}4.1$/TRAAK
-	-	$K_{2P}5.1$/TASK2
-	-	$K_{2P}6.1$/TWIK2
-	-	$K_{2P}7.1$
halothane	methanandamide, anandamide	$K_{2P}9.1$/TASK3
arachidonic acid, halothane, membrane elongation	-	$K_{2P}10.1$/TREK2
-	-	$K_{2P}12.1$/THIK2
-	halothane	$K_{2P}13.1$/THIK1
-	-	$K_{2P}15.1$/TASK5
acidic pH	-	$K_{2P}16.1$/TALK1
acidic pH	-	$K_{2P}17.1$/TALK2
-	arachidonic acid	$K_{2P}18.1$/TRESK

Table 4.
Selective modulators of K channels with two pores K_{2P}

3. Natural polyphenols and antibody for K channels a promise for future cancer treatment

3.1 Natural polyphenols

Natural polyphenols are secondary metabolism of plants that have multiple activities in determining plant properties such as color, aroma, taste, solution, pathogen resistance, etc. Natural polyphenols have been expanding in the interest of

both the scientific community and the public over the past decade when they have shown to have a significant function in the prevention of cancer, cardiovascular disease, diabetes and neurodegenerative disorders, etc. [46–49]. Polyphenols are the most common antioxidant constituents, and their source is various foods of plant origin: fruits, vegetables, seeds, especially nuts, chocolate, wine, tea, and coffee.

Research carried out during the last decade provided evidence that natural, biologically active polyphenols, such as resveratrol, genistein, quercetin, and catechin-gallate, and curcumin have a wide spectrum of pharmacologic properties such as anti-inflammatory, antioxidant, anticarcinogenic, antiaging, neuroprotective, and cardioprotective effect. Resveratrol, stilbene from grape and red wine, genistein, isoflavone from soy-based food, and catechin-gallate from tea influence cancer initiation, promotion, and progression through diverse signal-transduction pathways that control cell growth and division, inflammation, apoptosis, metastasis, and angiogenesis [50].

Many studies suggested that Kv channels could be the targets of polyphenols, directly and indirectly [17, 47, 51]. Furthermore, there is evidence that modulation of Kv channels via the PI_3K/Akt/mTOR pathway may be a possible indirect mode of action of polyphenols [52, 53]. The PI_3K/Akt/mTOR pathway is known to play an important role in cell survival (inhibition of apoptosis), proliferation, and cell metabolism, and PI_3K activity has been linked to a variety of human cancers [54]. As described above, the effect on the kinase pathway would result in the modulation of K channel function.

Polyphenols are thought to have several different mechanisms that prevent cardiovascular disease. The following effects are reported in the literature: antioxidant, anti-aggregation, beneficial effects on plasma HDL-cholesterol levels (raising HDL-cholesterol levels), inhibition of LDL-cholesterol oxidation, improvement of endothelial function, and stabilization of atherosclerotic plaque [55]. The mechanism of the vasodilatory action of polyphenols is not fully understood. Still, there are many results that polyphenols included K channels in their mechanism of action [46–48]. It is shown that these molecules can cause endothelium-dependent and endothelium-independent relaxation of the blood vessel. Polyphenols are known to modulate many intracellular signaling pathways as well as the expression of individual genes. Thus, plant polyphenols have been described to activate endothelial NO synthase (eNOS), increase nitric oxide production, and thus induce endothelium-dependent vasodilation. Activation of eNOS occurs due to an increase in the intracellular level of Ca^{2+} ions and phosphorylation of PI_3 kinase.

Previous reports indicated that resveratrol inhibits vasocontractile response and relaxes different arteries and vein by the activation of smooth muscle Kv and $K_{Ca}1.1$ channels [47, 48]. But, data from electrophysiological studies suggest that resveratrol inhibits L-type Ca^{2+} channels and enhances activity of the K_{ATP} channels in rat hearts [51].

Additionally, it has been shown that the K channel family affects cell function and plays a significant role in regulating myometrium contractility [5, 19]. Changes in the expression or activity of K channels can translate into inadequate repolarization leading to aberrant uterine activity. Thus, K channel alterations may contribute to certain pathophysiological conditions such as preterm labor. Many studies have shown that opening of different types of K channels leads to the relaxation of nonpregnant as well as pregnant myometrium [5, 17, 19, 26, 56]. It seems that function and molecular expression of K channels are dependent of stages of pregnancy, the age, and of hormones influences [17, 57]. K channels, as a novel target to prevent preterm delivery with nontoxic natural polyphenols, are the important work in addressing the need for innovative tocolytic therapeutics.

In such a scenario, combination treatment with K channel modulators and natural polyphenols could be beneficial for cardiovascular, renal, or gynecologic disorders.

3.2 Antibodies

The increasing knowledge on the expression of K channels in tumors, together with the information on the structure and function of these molecules and the possibility of detailed in vitro and in vivo studies, makes this family of channels an attractive candidate for the design of personalized therapies for oncological diseases.

As already stated, in addition to regulating many physiological functions, K channels are aberrantly expressed in different types of tumors. In cancer cells, K channel activity regulates cell proliferation, resistance to apoptotic cell death, tumor angiogenesis, invasiveness, and metastatic spread. Moreover, being expressed in cells of the tumor microenvironment, K channels can also modulate the immune/inflammatory response, which contributes to the drive of cancer establishment and progression [18, 58]. After many years of studies, some K channels are emerging as novel cancer biomarkers, to be employed to stratify patients for either prognostic or predictive purposes [59].

Although the attempts to generate blocking monoclonal antibodies using conventional approaches have shown limited success, the insight that structural studies have provided in the last few years makes it possible to design alternative strategies with higher chances of success. This opens doors for a new approach to combine the advantageous features of K channels-specific antibodies and their modulators and will undoubtedly result in improved therapy alternatives in the near future.

It anticipates that a detailed understanding of structural aspects would revolutionize and refine approaches targeting K channels for therapeutic purposes.

4. Conclusion

K channels are crucial for all aspects of life by regulating the excitability of neurons and the heart, contracting muscles, secreting hormones, moving fluid, and activating the immune cell. K channel modulation accordingly offers tremendous opportunities for drug development. However, with 7% of clinically used drugs targeting ligand-ion channels and only 5% of voltage-gated channels targeted, ion channels are currently "underrepresented" drugs in clinical practice [60]. The reason for this discrepancy is the fact that K channels belonging to a single subtype can be found in the different tissues, e.g., the heart and brain, where they play different roles in the nervous excitability and contractility of the heart muscle. It was mentioned above that even within the same tissue there are subtypes of channels that potentially play different roles in disease and physiology, thus making sub-selective modulators of each subtype of K channels desirable as candidates for drug development. The ubiquity of K channels makes it important to develop highly selective agents. Furthermore, numerous studies have shown that different diseases as diabetes mellitus and hypertension cause changes in K channel expression and function that further complicate solution innovative sub-selective therapeutics or antibodies. However, it is not remote the time in which it will be possible to target specific K channels for therapeutic purposes.

Conflict of interest

The author declares no conflict of interest.

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