Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Review

Potassium channels on smooth muscle as a molecular target for plant-derived Resveratrol

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Received April 7, 2020; **Accepted** May 3, 2020; **Published** June 25, 2020

Doi: http://dx.doi.org/10.14715/cmb/2020.66.4.18

Abstract: Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a phytoalexin present in a variety of plant species. Resveratrol has a wide spectrum of pharmacologic properties, and it exhibits versatile biological effects on different human and animal models. The studies have shown that potassium (K) channels can be potential targets in the mechanism of resveratrol action. K channels play a crucial role in maintaining membrane potential. Inhibition of K channels causes membrane depolarization and then contraction of smooth muscles, while the activation leads to membrane hyperpolarization and subsequently, relaxation. Five diverse types of K channels have been identified in smooth muscle cells in different tissue: ATP-sensitive K channels (K_{ATP}), voltage-dependent K channels (Kv), Ca^{2+} - and voltage-dependent K channels (BK_{Ca}), inward rectifier K channels (Kir), and tandem two-pore K channels (K_{2p}). The expression and activity of K channels altered in many types of diseases. Aberrant function or expression of K channels can be underlying in pathologies such as cardiac arrhythmia, diabetes mellitus, hypertension, preterm birth, preeclampsia, and various types of cancer. Modulation of K channel activity by molecular approaches and selective drug development may be a novel treatment modality for these dysfunctions in the future. The plant-derived non-toxic polyphenols, such as resveratrol, can alter K channel activity and lead to the desired outcome. This review presents the basic properties, physiological, pathophysiological functions of K channels, and pharmacological roles of resveratrol on the major types of K channels that have been determined in smooth muscle cells.

Key words: Resveratrol; Plant polyphenols; Potassium channels; Smooth muscle; Cardiovascular; Reproduction.

Introduction

Natural polyphenols are secondary metabolites of plants that have multiple activities in determining plant properties such as color, aroma, taste, solution, pathogen resistance, etc. One of the most studied, a natural polyphenol whose health benefit is well established on various models, is resveratrol (RSV).

RSV (3,5,4'-trihydroxy-trans-stilbene, Figure 1) is a phytoalexin present in a variety of plant species, including *Vitis vinifera* L. (grapes), *Arachis hypogaea* L. (peanuts), *Morus rubra* L. (mulberries) and *Reynoutria japonica* Houtt. The research carried out during the last two decades provided evidence that RSV have a wide spectrum of pharmacologic properties: anti-inflammatory, antioxidant, anticarcinogenic, antiaging, neuroprotective, and cardioprotective effects (1, 2).

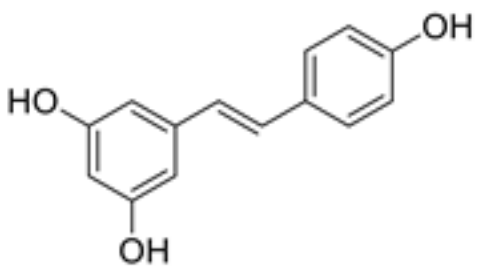

Figure 1. Chemical structure of resveratrol.

RSV exhibits versatile biological effects in preclinical studies on different human and animal models (2). Multiple effects happen due to the fact that RSV is a molecule with many targets in cells. These molecular targets include those that are modulated by direct physical interaction with RSV and others, which are modulated indirectly through changes at expression levels (3). Over 20 molecules have been identified that directly bind to RSV (1). Thus, RSV has been highlighted as "one molecule - many targets" (4). Different researches indicated many potential targets of RSV, such as cyclooxygenase, antioxidant enzymes, NAD^+ - dependent histone deacetylase sirtuin 1, estrogen receptor, inflammatory markers and NO produced by endothelial NO synthase (1, 4).

In addition, it has been shown that RSV promotes smooth muscle relaxation in human and animal models as blood vessels (5-9), human and rat uterus (10-12), gallbladder (13) as well and urinary bladder (14). Moreover, K channels have been implicated directly or indirectly in the actions of RSV (5, 6, 13). The mechanism of RSV on blood vessels mainly was explained

through its effects on endothelium. Endothelium-dependent mechanisms of relaxation by RSV include stimulation of endothelial NO production, inhibition of superoxide-mediated NO inactivation (1, 15) and stimulation of endothelium dependent hyperpolarization (EDH) (16). The endothelium-independent relaxation is partly mediated by different K channels in the membrane of vascular smooth muscle cells, including voltage-gated K (Kv) channels, big Ca-activated K (BK_{Ca}) channels, but not adenosine triphosphate-sensitive K (K_{ATP}) channels (5, 6).

While most of the effects of RSV were examined on vascular smooth muscle, the data of effects of RSV on other types of smooth muscle are limited on the uterus, gallbladder and urinary bladder. The mechanism of action of RSV on these types of smooth muscles partly included K channels (11-14).

It is very important that RSV can be found as nutritional supplement in the free sale and it has been proposed as a potential therapeutic to improve metabolic health. Besides all that, several potential therapeutic applications of RSV have come to light. Previous studies have evaluated safety, pharmacokinetics and metabolism of RSV and have reported RSV to be well tolerated in humans even at very high doses (17) and no evidence of toxicity associated with this compound found in rodents (10).

This review paper targets to summarize data obtained from the studies that have been investigated effects of RSV on smooth muscle and to clarify the role of K channels in observed effects.

Regulation of potassium channels activity in smooth muscle

In smooth muscle cells, the resting membrane potential is primarily determined by the efflux of K^+ ions through several types of K channels in the plasma membrane, including Kv, K_{Ca}, Kir, K_{ATP} and two-pore K (K_{2P}) channels (Figure 2) (18). Since the equilibrium potential for K^+ ions is about -89 mV, opening of the K channel causes the membrane to hyperpolarize. Excitation of smooth muscle cells followed by depolarization of the membrane due to Na^+ or Ca^{2+} entry or Cl^- efflux leads to the opening of the voltage-dependent Ca^{2+} channels (VDCC), increased intracellular Ca^{2+} concentration, and activation of the cell contractile machinery. Depolarization also leads to the opening of Kv channels, and a corresponding increase in intracellular Ca^{2+} concentration in combination with depolarization causes the opening of BK_{Ca} channels. The opening of these channels produces compensatory hyperpolarizing currents that reduce the likelihood of VDCC opening and counteract contraction (19).

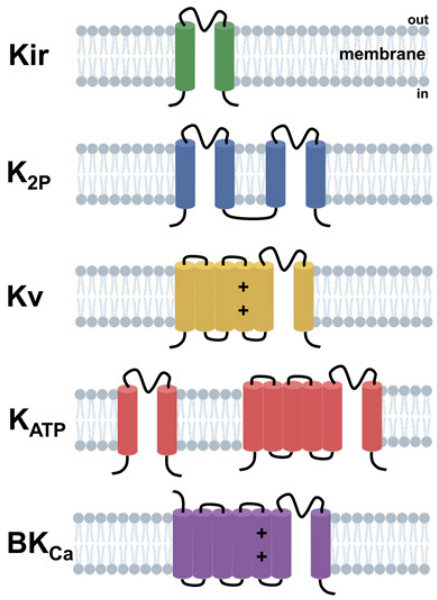

Figure 2. Diverse types of K channels identified in smooth muscle cells: inward rectifying K channels (Kir), two-pore K channels (K_{2P}), voltage-dependent K channels (Kv), adenosine triphosphate-sensitive K channels (K_{ATP}), and large conductance calcium-activated K channels (BK_{Ca}).

Subtypes of potassium channels in smooth muscle - Kir channels

The inward rectifying (Kir) channels are constructed from four α pore-forming subunits, each containing two transmembrane domains (M1 and M2) with a P-loop between them. Kir channel α subunit contains the cytoplasmic C- and N- terminus and the accessory subunits have not been identified (20).

The 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 outward K^+ current is limited and barely detectable (21). The explanation for the phenomenon of inward rectification lies in the fact that intracellular Mg^{2+} and polyamines (spermine and spermidine) block outward 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 the terminal C-terminus of the Kir channel, thereby inhibiting the passage of K^+ ions through the pore (22). Kir channels were identified on many excitable and non-excitable cells. Seven Kir channel subfamilies have been identified and they are further subdivided into four functional groups: 1) classical Kir channels (Kir2.x); 2) G-protein-modulated K channels (Kir3.x); 3) ATP-sensitive K channels (Kir6.x); 4) transport K channels (Kir1.x, Kir4.x, Kir5.x, and Kir7.x) (23).

Subtypes of potassium channels in smooth muscle - K_{ATP} channels

K_{ATP} channels were discovered by Noma on cardiomyocytes in 1983 (24). Shortly thereafter, these channels were identified on many other tissues including smooth muscle cells (20). Although named after their feature that an increase in intracellular ATP inhibits their activity, it has been shown that their activity can be modulated by a variety of signaling pathways unrelated to their sensitivity to ATP (25-27). The ATP/ADP ratio is the major factor that determines their activity. Increasing local metabolism leads to a decrease in ATP/ADP ratio, which increases the likelihood of K_{ATP} channel opening and leads to vascular smooth muscle cell relaxation. On the other hand, a decrease in local metabolism reverses the process and leads to an increase in vascular tone (28, 29). In addition to nucleotides, regulators and modulators of K_{ATP} channel activity include many mediators such as NO, vasoactive intestinal peptide, prostacyclin, acidosis, lactates, adenosine, protein

kinases, and others (25, 30).

Structurally, K_{ATP} channels are functional heterooctamers built of four pore-forming Kir6.x subunits and four regulatory subunits known as sulfonylurea receptors, SURx (22). So far, two Kir6.x genes (KCNJ8 for Kir6.1 and KCNJ11 for Kir6.2) and two SURx genes (ABCC8 for SUR1 and ABCC9 for SUR2A and SUR2B) have been identified. Kir6.x shares 40-50% homology in the amino acid sequence with other Kir channels. Structural studies suggest that Kir6.x has 2 transmembrane helices, a cytoplasmic N- and C- terminus, and a pore loop with a selective filter responsible for K^+ permeability (31). 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. They differ in the last 42 amino acids at the C-terminus. SUR2A is mainly present in the myocardium and skeletal muscle, while SUR2B is generally distributed in vascular smooth muscle cells (32). The SURx subunit has 3 transmembrane domains: TMD1 and TMD2 with 6 transmembrane segments each and TMD0, the N-terminal domain, with 5 transmembrane segments. There are two large intracellular loops that connect adjacent domains. Each intracellular loop contains nucleotide-binding domains: Walker's motif A and Walker's motif B. These domains catalyze the hydrolysis of ATP (31, 33).

Subtypes of potassium channels in smooth muscle - Kv channels

Kv channels are the largest superfamily of the K channels. They are encoded by about 40 genes in the human genome and contain 12 subfamilies, each with several representatives (34). Kv channels are heteromultimers built of four α subunits that form a pore and cytoplasmic β subunits. The α subunit of Kv channels contains six transmembrane domains (S1-S6), with a P loop between S5 and S6 domain, voltage sensor within the S4 domain and has cytoplasmic N- and C-terminus (35). The positive charge in S4 domain, caused by increased presence of lysine and arginine in its composition, determines voltage-dependent channel activation, while the N-terminus regulates Kv channel inactivation (36).

Four α subunits which enter into the structure of functional Kv channels can be the same or different; hence, physiological regulation, biophysical and pharmacological properties of these channels show great variations. Furthermore, interaction with smaller accessory proteins including β subunits, KChIP, KchAP and minK proteins, miRP peptide and others, makes Kv channels even more complexed (37, 38).

Kv channels exhibit strong voltage dependence. Depolarization of the cell membrane leads to their activation and to an increase in hyperpolarizing outward currents. The resulting hyperpolarization of smooth muscle cells inactivates VDCC channels and consequently reduces smooth muscle tone (27).

Subtypes of potassium channels in smooth muscle - K_{Ca} channels

K_{Ca} channels play an important role in cell excitability by registering and responding to changes in intracellular Ca^{2+} concentration. Based on their conductivity, the K_{Ca} channel family is divided into channels with large (BK_{Ca}, ~ 100-300 pS), intermediate (IK_{Ca}, ~ 25-100 pS) and small conductance (SK_{Ca}, ~ 2-25 pS) (39). While BK_{Ca} channels are activated by membrane depolarization and/or Ca^{2+} binding to the channel, SK_{Ca} and IK_{Ca} channels are voltage-independent and activated by Ca^{2+} binding to calmodulin that constitutively binds to the channels (40). The remaining three members of this group are included in the nomenclature of Ca-dependent K channels, given the structural similarity to them and the association with the genes encoding them. However, better understanding of the functional features of these channels in recent years have contributed to their separation into new categories. Specifically, these three channels have been shown to be almost completely insensitive to Ca^{2+}. Na-sensitive K channels ($K_{Na}1.x$), formerly referred to as $K_{Ca}4.1$ and $K_{Ca}4.2$, are activated in response to changes in intracellular Na^+ and/or Cl^- concentrations, whereas the $K_{Ca}5.1$ channel triggers an increase in intracellular pH. For these reasons, this subfamily of K channels with six transmembrane domains is now called "Ca and Na-dependent K channels" (41).

BK_{Ca} channels

BK_{Ca} ($K_{Ca}1.1$, Slo or MaxiK) channels are constructed of α pore-forming subunits and auxiliary β or γ subunits. The four α subunits can form a functional channel on their own. Associated accessory subunits represent potent regulators of most channel characteristics, including voltage and Ca^{2+}-sensitivity, as well as sensitivity to pharmacological modulators (25). Each α subunit consists of seven transmembrane domains (S0-S6) with a P-loop and a selective filter for K^+ between the S5 and S6 domains. What distinguishes BK_{Ca} channels from Kv channels is 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 precisely localized in the S4 domain, the positively charged residues responsible for the voltage-dependence of the BK_{Ca} channels are less centralized and present in the S2, S3, and S4 domains (42). The large C-terminus of the BK_{Ca} channel contains two homologous structural units called "regulators of conductance for K^+" (RCKs): the proximal RCK domain (RCK1) and the distal RCK domain (RCK2). These two domains are responsible for the sensitivity of the BK_{Ca} channels for Ca^{2+} and Mg^{2+}. While the RCK1 domain plays a role in the formation of the Ca^{2+}-binding site, RCK2 contains an additional domain that binds Ca^{2+} ions with very high affinity - Ca^{2+}-bowl (43). Four pairs of RCK1 and RCK2 domains form the Ca^{2+}-sensitive apparatus responsible for allosteric modification and activation of BK_{Ca} channels upon Ca^{2+} binding. The N-terminus of the RCK1 domain was shown to be linked to the C-terminus of the S6 transmembrane domain of the BK_{Ca} channel via the S6-RCK1 linker; therefore, the S6 transmembrane domain plays a very important role in the formation of conformational changes of BK_{Ca} channels that promote Ca^{2+} binding to RCK1 (44).

Four types of β subunits (β1-4) and four types of γ

subunits (γ1-4) modulate almost all the physiological and pharmacological properties of BK_{Ca} channels. β subunits contain two, while γ subunits are constructed from a single transmembrane domain. The mechanism by which regulatory subunits interact with α subunits and regulate BK_{Ca} channel activity is extremely complicated, but it is critical for the study and understanding of vascular disease (43, 45). Theoretically, α subunits and regulatory β or γ subunits of BK_{Ca} channels are found in a stoichiometric ratio of 1:1. However, research indicates that the population of these channels is not homogeneous and that there are groupings of BK_{Ca} channels with fewer than four regulatory subunits. Numerous evidence suggests that the stoichiometry of the subunits of these ion channels is dynamic. Thus, for example, expression of β1 subunits may be selectively upregulated or downregulated in vascular smooth muscle cells, without reflecting the expression of α subunits. This occurs under the influence of various physiological and pathophysiological states as well as during hormonal stimulation and leads to increased or decreased channel activity (46).

Under experimental conditions, BK_{Ca} channels can be activated by changing the voltage in the presence or absence of Ca^{2+}. It has long been known that voltage and Ca^{2+} channel dependencies are independent of each other, which means that both can increase the probability of channel opening (47). Activation of the BK_{Ca} channel by changing membrane potential has no fixed value and is more dependent on Ca^{2+} concentration. Under conditions of low Ca^{2+} concentration, BK_{Ca} channels act as pure voltage-dependent channels. Although, as noted, the mechanism of voltage dependence is independent of its binding, Ca^{2+} shifts many parameters of voltage dependence toward more negative potentials and permits channel activity at the basal range of membrane potentials (−60 to −30 mV) in relaxed cells (48).

Subtypes of potassium channels in smooth muscle - K_{2P} channels

K_{2P} channels were first described on yeast in 1995, and then their human homologues were discovered. Each K_{2P} channel subunit consists of two regions that participate in pore formation (P1 and P2, hence their name) and 4 transmembrane domains (M1-M4). Functional channels are built as dimers of these subunits that form a single pore selectively permeable to potassium (49). There are 15 members of the K_{2P} channel family. Leak K^+ currents regulate the resting membrane potential and excitability of many mammalian cells. K_{2P} channels are open at physiological, resting potential and play a key role in controlling and stabilizing the resting membrane potential and cell volume. These are voltage-independent channels that, under physiological conditions (high K^+ concentration in the cytoplasm and low extracellular), conduct K^+ ions from the cell into the extracellular space (50).

Effects of Resveratrol on the different smooth muscle K channels

Effects of Resveratrol on the smooth muscle K_{ATP} channels

K_{ATP} channels are voltage-gated independent channels. These channels are designated as a "metabolic sensor" that converts metabolic status into electrical activity (51). These channels are found both in the plasma membrane of cells and in the intracellular membranes of the mitochondria, the sarcoplasmic reticulum (52), zymogenic granules and nuclear membranes (53). K_{ATP} channels are generally closed under normal physiological conditions and open in response to changes in altered cellular metabolic states, such as ischemia and hypoxia. They play a significant role in ischemia, where they exert a protective effect on the myocardium. Smooth muscle K_{ATP} channels are involved in the process of vasodilation and play an important role in control of vascular tone (54).

The most benefits of RSV application have been attributed to its effects on blood vessels, through endothelium-dependent and endothelium-independent pathways (55). The K_{ATP} channel on vascular smooth muscle contains four Kir6.1 subunits and four SUR2B subunits and can be functional only if expressed as complex on the sarcolemma in 1:1 ratio (56). The SUR subunit determines the specificity and selectivity of K_{ATP} channel for agonists and antagonists (57). Although, the most of the RSV benefits have been attributed to its cardiovascular effects, it could be noticed that K_{ATP} channels are not involved in this mechanism of action. The study on the rat aorta without endothelium on contractions elicited by phenylephrine showed that K_{ATP} channels are not involved in vasorelaxation effects of RSV (58). Also, results obtained on contractions provoked by electrical field stimulation of endothelium-denuded rat portal vein confirmed that K_{ATP} channels do not contribute to the RSV effect (6). In accordance with previous, the contribution of K_{ATP} channels in RSV-induced dilatation was not involved in dilatation of porcine retinal arterioles (7). The results obtained on the human blood vessels, on endothelium-denuded segments of internal mammary artery are in line with results obtained on animal blood vessels (59).

On the contrary, some papers indicated that K_{ATP} channels may be included in RSV benefit effects of non-vascular smooth muscle. It has been shown that RSV has potent and dose-dependent relaxant effects on the guinea pig fundic muscle (60). The proposed mechanism in this study included K_{ATP} channels as target site for RSV. Additionally, another study conducted on gastrointestinal smooth muscle from rats, also confirms that RSV and genistein relax those muscle and confirm that K_{ATP} channels are included in the reduction of the mean contractile amplitude (61). Furthermore, it has been shown that in RSV-induced relaxation of human gallbladder smooth muscle K_{ATP} channels are involved (62).

The enrollment of K_{ATP} channels in protective effects of RSV was indicated on smooth muscle cells of uterus. It is well-known that K_{ATP} channels have an important role in relaxation of this type of tissue (63, 64). The two combination of K_{ATP} channels, Kir6.1/SUR2B and Kir6.2/SUR1, were detected on the transcription level in the smooth muscle of rat and human uterus (65, 66). Kir6.1/SUR2B combination of K_{ATP} channel is higher expressed on non-pregnant myometrium compared to late gestation (66). Further research has pointed that benefits of RSV are dependent on the types of the contractions (11). In rat non-pregnant myo-

metrium application of glibenclamide, specific inhibitor of K_{ATP} channels, antagonized the effect of RSV on the spontaneous rhythmic contractions and of phasic oxytocin-induced contractions, but this inhibition was not observed on the tonic oxytocin-induced contractions (11). It is very interesting that expression of K_{ATP} channels depends on the gestational stage and the presence of labor contractions (67), which indicates that benefits of RSV through K_{ATP} channels could be different based on the stage of pregnancy. The study of the effects of RSV on human term pregnant myometrium confirmed the role of K_{ATP} channels in RSV mechanism of action. The observation that K_{ATP} channels are involved in RSV effects on the phasic oxytocin-induced contractions is in agreement with the study conducted on rat non-pregnant myometrium. In the study performed by Du et al. (68), it was discovered that there are more K_{ATP} channels in myometrium of parturient women over 35 years then in younger. This could indicate that RSV may have more benefits for pregnant women that belong to the risk group and can suffer from complications.

Effects of Resveratrol on the smooth muscle Kv channels

Understanding the role of K channels and detecting their subunits/proteins in different physiological and pathophysiological condition is essential, along with making a connection between dysfunction of these channels and specific diseases and disorders. Investigations performed so far point out the importance of K channels as potential therapeutic targets in the mechanism of action of drugs that could be used in the treatment or prevention of mentioned disorders. In smooth muscle cells membrane hyperpolarization occurs in response to RSV leading to vasodilation, making RSV a candidate for the treatment of a wide variety of disorders including hypertension, ventricular arrhythmia, preterm delivery, dysmenorrhea, urinary bladder dysfunction (9, 11, 12, 14).

Many studies suggested that Kv channels could be the targets of RSV, directly and/or indirectly (69). Polyphenols, including RSV, seem to act through several different mechanisms, including regulation of membrane potential, DNA transcription, enzyme activity, secretion, apoptosis, mitochondrial activity, and intracellular ion homeostasis, including the modulation of the intracellular potassium-calcium ion concentration (70).

The recent findings on effect of RSV on blood vessels are consistent with *in vivo* (71) and *in vitro* (9) data, suggesting that RSV has endothelium-dependent and independent mechanism of action. It is assumed that increased NO production and/or NO availability might be the mechanism by which RSV induce vascular vasodilatation. A numerous published study have suggested that Kv channels may play a role in endothelium-independent relaxant RSV mechanism of action (5-9). In addition to variation of the expression of Kv channels between various vascular beds, differences have been observed in pathological conditions. Thus, in the experimental model of rat hypertension, the smooth muscle cells of the renal vasculature manifested diminished Kv currents (37). Su et al. (72) have shown that the incubation of vascular smooth muscle cells in high glucose reduced Kv current and decreased expression of Kv1.x channels. That has strong impact on effects of K channel modulators including RSV. As confirmation, we have been shown that diabetes mellitus has influence on expression of Kv channels, especially on Kv1.3, and that target molecules for RSV relaxation action are changed (9). The immunohistochemical (IHH) staining results have shown that Kv1.3 channels were present on the endothelium of the renal artery from diabetic rats, while Kv1.1, Kv1.2, Kv1.6, Kv4.2 channels were detected only in the media. On the other hand, in renal arterial vessels from healthy rats, all mentioned Kv channels were present in the endothelium as well as in the media (9). These results suggest that Kv1.3 channels are an important factor of mediating K^+ currents in the renal artery indicating the potentially critical role of these channels in blood pressure regulation in diabetes mellitus. Also, Kv1.3 is a convenient target for RSV action in vasodilatation. The endothelial dysfunction developed during prolonged hyperglycemia leads to down-regulation of K_{Ca} 1.1, Kv1.1, Kv1.2, Kv1.6 and Kv4.2 channels, while up-regulation of Kv1.3 channel expression has been observed (9). The expression of K_{ATP} channels is almost unchanged.

The studies mostly focus on two interlinked mechanisms of vasorelaxant action, the direct effect on the intracellular calcium concentration and the downstream indirect effects on cellular potassium regulation (70).

Previous studies performed on smooth muscles of uterus have confirmed that Kv channels participate in the RSV relaxant effects on the contractions of non-pregnant and pregnant animal and human myometrium. The main subtype witch confirmed participation in RSV action were Kv4.2 and Kv4.3 (11, 12). Furthermore, results of studies on rat urinary bladders suggest that RSV prevents bradykinin-induced contractions by actions due to inhibition of Ca^{2+} influx and indirect involvement of K channels (14).

Effects of Resveratrol on the smooth muscle K_{Ca} channels

The opening of BK_{Ca} channels lead to the hyperpolarization of membrane caused by the tuning between Ca^{2+} and voltage sensors (73), and the activation of BK_{Ca} channels relaxed the smooth muscle (64). Additionally, BK_{Ca} are the major type of K-channels expressed on blood vessels. The extensive analysis of K channels proteins and IHH staining with specific antibodies indicates that BK_{Ca} channels are present in both, the endothelium and the vascular smooth muscle (19, 38, 74-76). It has been noted that RSV has endothelium –independent and dependent mechanism of action (77). Calderone et al. (78) recognized RSV like opener of BK_{Ca} channels in endothelium and smooth muscles of thoracic aorta of male Wistar rats.

They suggested that release of endothelial NO seems to be a main, very important factor of the vasodilator profile of RSV. In addition, the functional effects caused by RSV activation of endothelial BK_{Ca} channels were more pronounced then the effects caused by the activation of BK_{Ca} channels expressed in the smooth muscle-cells of rat aorta. Very similar results have been obtained regarding high selective opener of BK_{Ca} channels NS1619. The findings are consistent with the data obtained on different blood vessels (rat portal vein, porcine

retinal arterioles and human umbilical vein). It has been shown that, without endothelium, the BK_{Ca} channels partly mediate the relaxant effect of RSV (6, 7, 79). Nevertheless, the results of previous studies show that BK_{Ca} channels were not involved in the relaxant effect of RSV in blood vessels without endothelium- rat aorta, mesenteric artery and in human mammary artery (5, 59, 77, 80, 81).

When it comes to other types of smooth muscle tissues, the abundant presence of BK_{Ca} channels had been shown in the smooth muscle cells of the rat and human uterus (11, 12). Based on the antagonism noted between highly specific blocker of BK_{Ca} channels iberiotoxin and RSV, it is reasonable to conclude that BK_{Ca} channels are involved in the RSV mechanism of action on human pregnant myometrium and rat non-pregnant uterus (10-12). However, there is discrepancy too. The RSV relaxant effect on tonic contraction did not include BK_{Ca} channels. Conversely on spontaneous and oxytocin-elicited phasic type of contractions iberiotoxin antagonized RSV effects, suggesting involvement of BK_{Ca} channels (11). These findings support the notion that RSV has multiple target of action in the cell and that its action dependent on the cell condition.

There are data that demonstrate that VDCC are potential targets of RSV having in mind their direct inhibition by RSV, and their indirect activation by BK_{Ca} channels (70).

Excluding smooth muscle cells, in the β cells, Chen et al. have suggested that RSV could activate BK_{Ca} channels through an increase of intracellular Ca^{2+} (82). This discrepancy in the results obtained in the various experimental models strongly suggests tissue and species selectivity of RSV.

Effects of Resveratrol on the smooth muscle potassium channels in different body systems

Effects of Resveratrol on the smooth muscle potassium channels in cardiovascular system

Cardiovascular diseases (CVD) still represent group of the diseases with the highest morbidity and mortality, worldwide. WHO warns that, by 2030, the global prevalence of the CVD-related deaths could easily climb to the point of 23.3 million people. In the spectrum of the CVD, most fatalities originate as the consequence of hypertension and coronary artery disease (CAD) (83, 84). Some of them, if left untreated, will finally progress to the heart failure, condition with the repercussion on the entire organism and the quality of life.

It is well known that RSV has demonstrated to have many protective effects on the cardiovascular system and even after decades of being researched, it is still one of the most fascinating natural-source originating substance with proven and immeasurable efficacy on the cardiovascular system (CVS). Considering its multiple molecular targets involved in the function of the entire CVS, RSV is characterized as an important cardioprotective agents.

The story about French paradox is usually mention when the benefits of RSV needs to be highlighted. The French paradox concept, which as built during 80s, stated that, despite consuming food with high intake of dietary cholesterol and saturated fat, the Mediterranean

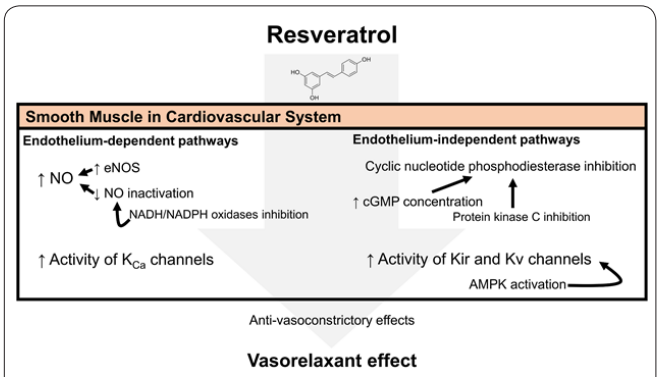

Figure 3. Vasorelaxant effect of resveratrol on the smooth muscle in cardiovascular system.

countries have continuously been reporting low coronary heart disease (CHD) death rates (85). It is believed that it is connected with the custom of using the glass of red wine during the meals. The benefits originate from the proven impact of RSV in consumed wine on cardiovascular system. Although, there is a lot of evidence of the protective effects of RSV and other polyphenols on the heart, we will here focus only on vascular smooth muscle in the CVS. The most important benefit from RSV on blood vessels is its vasorelaxant effect (Figure 3). However, the mechanism of this effect is still unknown, and based on available studies endothelium-dependent and –independent pathways are included (86). There are evidence that RSV has anti-vasoconstrictory effects, also. The endothelium-dependent relaxation of blood vessels by RSV is in line with its effect to increase synthesis/releases of NO and/or decreasing of NO inactivation (87). The same group of authors indicated that RSV at the same time inhibits vascular NADH/NADPH oxidases and thus prevent NO from inactivation caused by oxygen radicals. Additionally, it has been shown that RSV increases expression and activity of endothelium nitric oxide synthase eNOS (88). RSV can increase the activity of K_{Ca} channels in the endothelial cells obtained from human umbilical vein (89). All those vasodilatory endothelium-dependent effects of RSV are observed in experiments with low concentration of RSV (10-30 μmol/L). However, high concentrations (> 60 μmol/L) of RSV are required for endothelium-independent effects on relaxation (90) and those effects are correlated to the different NO-independent effect (86). Endothelium-independent effects of RSV may include inhibition of cyclic nucleotide phosphodiesterase (for which is shown that is inhibit by quercetin, flavonoid) (91), increasing concentration of cGMP (92) or by inhibition of protein kinase C (93). Also, possible role of potassium channels in those effects has been discussed in some studies knowing that those channels have the important role in the regulation of basal tone.

Vasorelaxation is the most extensively studied effect of RSV on vascular vessels, and it had been mentioned that RSV can act through endothelium-dependent and endothelium-independent paths. The ability of RSV to induce endothelium-dependent hyperpolarization of smooth muscle cells may compensate for pathologic absence or dysfunction of eNOS and cyclooxygenase-1 (94).

Large proportion of all K-channels expressed on vascular smooth muscle cells belongs to BK_{Ca} chan-

nels (95), that have important role on the modulation of the tone of vascular smooth muscle (96, 97). They are involved in regulation of the muscular response on different vasoconstrictors (27, 98). RSV has been recognized as opener of BK_{Ca} channels, acting on the α-subunit of the channels (78, 99). It seems that activation of the endothelial BK_{Ca} channels by RSV is more pronounced and relevant compared to activation of the BK_{Ca} channels expressed in the vascular smooth muscle cell (78). However, numerous studies indicated increasing expression of BK_{Ca} channels on vascular smooth muscle cellsin hypertension animal models (100-102). Thus, RSV may be promising agents in the treatment of hypertension, and its endothelium-independent effect on blood vessels may be additional benefit. It is reported that endothelium of blood vessels could be impaired due to hypertension (103, 104), diabetes (105, 106), and vasorelaxant agent able to act independently of endothelium presents powerful tool.

The relaxant effects of RSV were observed on human bypass grafts as well. Among bypass grafts the most used are graft of human saphenous vein and internal mammary artery and on the both of them peri- and postoperative spasm of the grafts presents main problem in cardiovascular surgery and finding the adequate treatment for those grafts is still problem (107). Additionally, it is observed that endothelium of bypass grafts can be damaged due to acute pressure distension during intraoperative preparation graft, prolonged *ex vivo* preservation, and storage conditions (108, 109). Thus, relaxant agent with mechanism of action independent of endothelium is needed. And it has been shown that RSV potently relax human internal mammary artery, without endothelium (59). In those effects' contribution of Kvx and Kv1.3 channels located in vascular smooth muscle were observed (59). The same channels were included in RSV effects on vascular smooth muscle of rat aorta (77). On the other hand, Shen et al. (94) reported that K_{ATP} and BK_{Ca} channels are involved in RSV mechanism independent of endothelium on abdominal rat aorta.

One of the first article that reported involvement of K-channels on vascular smooth muscle cells in RSV effects was published by Gojkovic-Bukarica et al. (5) 12 years ago. In that research the involvement of Kv channels in the relaxant effect of RSV through endothelium-independent pathway has been identified on rat mesenteric artery.

Also, it is very important to notice that RSV can activates AMPK, and after that AMPK in vascular smooth muscle cells appears to favor vasodilatations/opposing vasoconstriction (110, 111). Action of AMPK depends on the type of the K channels, and localization/type of the blood vessels. In case of BK_{Ca} channels in rat and mouse mesenteric and hamster femoral arteries, AMPK opens those channels that leading to the hyperpolarization of smooth muscle and thus relaxation (112). Moreover, it is interesting that AMPK is potent regulator of Kir and Kv channels. It is observed that AMPK downregulates Kir and Kv1.5/7.1 channels partly by activating ubiquitin ligase (113-116). This is important as Kir and Kv is abundantly expressed in brain parenchymal arteriolar smooth muscle cells (117). Particularly, Kv channels play role in determining arterial diameter and blood flow in brain arteries, especially in capillaries where K_{Ca} is not present (118).

There is limited data available for cardioprotective benefits of RSV investigated on veins. Although, the anti-vasoconstrictory effects of RSV on norepinephrine- and electrical field stimulation- evoked contractions were observed on rat portal vein (6). However, only BK_{Ca} smooth muscle channels were partly involved in the RSV-induced inhibition of neurogenic contractions. Another investigation of the effects of RSV on vein was on human umbilical vein (79). *In vitro* studies of this endothelium-denuded vein reveal that Kv, K_{Ca}, and Kir channels play important role in the RSV-induced vasodilatation.

Effects of Resveratrol on the smooth muscle potassium channels in respiratory system

Overall, functional capacity and structural integrity of the lungs predominantly rely on the cell population known as alveolar epithelial cells type 2 (AEC2), which represent major distal lung stem cells and a source of surfactant, substance that preserve collapsing of the lungs. However, population of those cells starts to diminish throughout the time, structural support and the architecture of the lungs starts to gradually breaking down leading to an irreversible declination in a lung function. Additionally, aged lungs show incapability of reparative mechanisms to stand upon accumulated DNA damage, disharmony in immune, endothelial and mesenchymal stromal cells proliferation and deficient response to injuries due to trauma (119). Through interrupting major signal pathways in the compartments of the entire lungs, from the inflamed trachea to the enlargement and dissolution of the alveoli sacks, inflammation or disrupted antioxidative capacity finally leads to a chronic lung disease (CLD), specter of diseases with global burden, including chronic obstructive pulmonary disease (COPD), emphysema and chronic bronchitis. Also, contributive factor in the deterioration of lung function represents telomerase shortening, important hallmark linked with the development of lung fibrosis and emphysema (119, 120).

RSV, an agonist of sirtuin deacetylase SIRT1 molecule, exerts prophylactic properties in many rate-limiting steps with unfavour consequences in the respiratory system. In aged lungs, disruption in the survival pathways in AEC2 can be prevented by RSV-induced modulation of the SIRT1 activity that causes diminished apoptosis and increased cellular survival and hence slows the ageing phenotype. Although aging of the lungs represents natural process which is expected to occur over decades, RSV tends to preserve the number of healthy AEC2 over time, gradually slowing the rate of its dysfunction and protecting from acute respiratory failure. The protective mechanisms of RSV in the respiratory diseases with the most significant clinical correlation are mainly due to its K-independent properties (120). However, considering wide distribution of K-channels through the entire respiratory tract, effects of RSV predominantly exerted through K_{ATP}, Kv and K_{Ca} channels will be further noted (Figure 4).

K_{ATP} channels presented in the pulmonary vasculature regulate pulmonary blood flow with very stabile expression in the smooth muscle cells during physiological conditions. However, during the sepsis or ARDS,

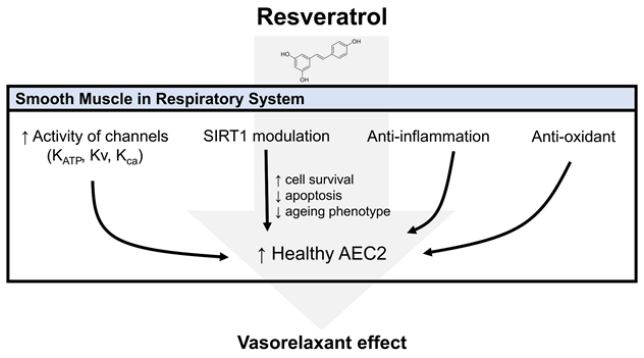

Figure 4. Vasorelaxant effect of resveratrol on the smooth muscle in respiratory system.

induced hypoxic pulmonary vasoconstriction (HPV) results in the disorder of the ratio in the ventilation and perfusion of the alveolus units. Also, variety of the inflammatory mediators released in the endotoxemic diseases can additionally enhance HPV severity and increase pulmonary artery resistance (121). Upregulation of the expression in K_{ATP} channels seen in pathophysiological conditions that worsen lung function represents mechanism by which lung tissue can resist severe disorders of the oxygen and carbon-oxide volumes with following pulmonary insufficiency. By enhancing the number and function of those channels, lung tissue enhances the capacity to respond on circulating vasoactive compounds in the reduced pulmonary blood flow due to HPV. Expression of the integrative part of the K_{ATP} molecule, Kir6.1 subunit, is known to be increased in endotoxemia mechanisms that include NFkB signal pathways and represent possible pathway to reduce HPV via increased efflux of K^+ and decreased intracellular Ca^{2+}, causing pulmonary arterial smooth muscle cell (PASMC) relaxation (121, 122). If prolonged, essential response of PASMC during global alveolar hypoxia in HPV leads to pulmonary hypertension (PH), right ventricular hypertrophy, heart failure and consecutively death. Specific K channels presented in PASCM, particularly the Kv Kv2.1, Kv1.5 and Kv9.3 channels were involved in the hypoxic response, with deficiency of Kv1.5 showing partial inhibition of HPV. It is shown that RSV exerts protective effects in PH, through modulation of its additional activity: anti-inflammatory, antioxidant, SIRT1-modulating response (122).

Effects of Resveratrol on the smooth muscle potassium channels in the gastrointestinal system

As a result of powerful interplay with complex signaling cascade caused by activation of different membrane receptors, every vital function of the gastrointestinal system requires presence of the K channels.

Kv channels in the excitable cells in the gastrointestinal (GI) tract respond to the action potential with rapid depolarization of the plasma membrane, managing muscle contractility and neuronal sensitivity of the mucosal plexus. However, in the nonexcitable cells such as epithelia of the GI tract, they are involved in a variety of function within cells: regulation of a cell volume, cell migration and proliferation, apoptosis, electrolyte and substrate transport (123).

One of the major factor causing biliary colic represents obstruction of the cystic duct/common bile duct with the preformed gallstones. If prolonged, biliary duct obstruction can cause inflammation of the gallbladder leading to a complication. First-line treatment of biliary colic includes non-steroidal anti-inflammatory agents (NSAIDs, ketorolac, diclofenac) and anti-cholinergic drugs (scopolamine). However, growing number of studies tends to evaluate more efficacy approaches in the treatment of such diseases and the natural products with anti-inflammatory properties have very promising potential. In studies evaluating potential use of RSV for the treatment of biliary colic and other gastrointestinal colic-like pain (61), it was shown that K_{ATP} and BK_{Ca} channels are directly involved in the RSV-mediated relaxation pathways. Certain proportion in this response plays K-independent mechanisms which include NO, cAMP and cGMP signal pathways (62).

Effects of Resveratrol on the smooth muscle potassium channels in reproductive system

Throughout their different reproductive stages, a large proportion of women (>50%) worldwide is facing (almost daily) with intermittent or permanent discomforts in the pelvic region, commonly known as dysmenorrhea (124). The ground of its pathophysiology lies in the uterine smooth muscle cells activity, which, if overly activated, through abnormal high-amplitude/frequency can overstimulate normal contraction production. Detailed underlying mechanisms involved in the uterine contraction served as a good starting point for numerous researchers evaluating the RSV-elicited relaxation in the smooth muscle cells of uterus (11). Now we know that RSV can strongly inhibit not only the spontaneous rhythmic contractions, but also those induced by oxytocin, prostaglandins, acetylcholine.

The abnormal contractility can trigger another series of unwanted events, such as infertility, endometriosis, spontaneous miscarriage or preterm birth (11, 124). All those clinically relevant issues can be thought as potential sites for the RSV enhancement, since there is no adequate drug to be applied in that conditions yet. The fact that K_{ATP} channels play important modulatory role on the spontaneous and oxytocin-induced uterine contraction and that connect uterine cellular metabolism with the electrical activity, is used to evaluate potential role of RSV in the uterine contraction suppression. Similarly, to K_{ATP}, other types of K channels are involved in the relaxant effects of the uterus, particularly BK_{Ca} and Kv channels (125). However, one subtype of channels is specially interesting for the linkage of uterine dysfunctionality and proven RSV effects, a Kir that hyperpolarize smooth muscle in the uterine tissue and promote their stability. RSV acts differently depending on the type of contraction uterine muscle achieved (105). According to studies, RSV may produce relaxation of the spontaneous rhythmic and oxytocin-induced contractions by activating different myometrial K channels, but the tonic contractions seems to be more resistant to the same amount of RSV. However, it is known that myometrial Kir6.1, Kir6.2, $K_{Ca}1.1$, Kv2.1, Kv4.2 channels represent potential targets that mediate majority of RSV benefits (105).

The increasing prevalence of disorders and diseases during pregnancy, such as maternal obesity, gestational diabetes mellitus and preeclampsia yield the need

to find a safe and specific therapeutic solution. Preeclampsia is a complication affecting pregnant women worldwide, which usually manifests as severe maternal hypertension (126). RSV has potential as a treatment for preeclampsia. Hannan et al. (127), envisage that to treat preeclampsia, RSV would only need to be given for a few weeks in the second half of pregnancy.

RSV, as a natural nontoxic compound, has a wide-range of beneficial properties, including potent relaxation of smooth muscle of fetoplacental blood vessels and myometrium, and antidiabetic effects.

Conclusion

Changes in the activity of K channels occur under the influence of various physiological and pathophysiological conditions. Decrease or increase in their activity is predominantly the consequence of either direct pathological damage to the tissue expressing it or changes in the tissue metabolic demands, their aberrant, genetic dysmorphia or disruption in the proper signal pathways. Those changes in the expression can cause inadequate cell repolarization, which, as a result, have aberrant smooth muscle activity, decreased cellular/tissue integrity and lack of their specific functional properties. The circle of events can be broadened by different hemodynamic, oxidative, inflammatory and other cellular mediators contributing progression of the disease. Still, it certainly contains K channels as central targets, slow the progression or even prevent such diseases.

Taking all of this into consideration, the idea of having the plant derivated substance able to relax human blood vessel with endothelial dysfunction tends to be particularly promising. Additionally, identifying resveratrol as K channels activator, targeting them as a potential therapeutic target in disorders with aberrant contractility of smooth muscles, has a promising future. In such a scenario, combination treatment with K channel modulators and/or natural polyphenols could be beneficial for cardiovascular, renal, or gynecologic disorders like dysmenorrhea or preterm delivery. Result of the potential implementation of natural polyphenols into therapeutic protocols could be an improvement in the efficacy and safety in the treatment.

Funding

This work was supported by the Research Grant No. TR31020 of Ministry of Education, Science and Technological Development of Republic of Serbia.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

This work was supported by CONICYT PIA/APOYO CCTE AFB170007.

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