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Review

Multiple regulatory effects of angiotensin II on the large-conductance Ca^{2+}- and voltage-activated potassium channel in vascular smooth muscle cells

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Abstract: Renin-angiotensin system (RAS) is involved in the regulation of vascular smooth muscle cell (VSMC) tension. Angiotensin II (Ang II) as the main effector molecule of RAS can increase the intracellular Ca^{2+} concentration and cause VSMCs contraction by activating angiotensin II type 1 receptor (AT1R). The large-conductance Ca^{2+}- and voltage-activated potassium (BK) channel is an essential potassium channel in VSMCs, playing an important role in maintaining membrane potential and intracellular potassium-calcium balance. The BK channel in VSMCs mainly consists of α and β1 subunits. Functional BKα subunits contain voltage-sensors and Ca^{2+} binding sites. Hence, increase in the membrane potential or intracellular Ca^{2+} concentration can trigger the opening of the BK channel by mediating transient K^+ outward current in a negative regulatory manner. However, increasing evidence has shown that although Ang II can raise the intracellular Ca^{2+} concentration, it also inhibits the expression and function of the BK channel by activating the PKC pathway, internalizing AT1R-BKα heterodimer, or dissociating α and β1 subunits. Under some specific conditions, Ang II can also activate the BK channel, but the underlying mechanism remains unknown. In this review, we summarize the potential mechanisms underlying the inhibitory or activating effect of Ang II on the BK channel, hoping that it could provide a theoretical basis for improving intracellular ion imbalance.

Key words: large-conductance Ca^{2+}- and voltage-activated potassium channel; angiotensin II; angiotensin II type 1 receptor; vascular smooth muscle

血管紧张素II对血管平滑肌细胞中大电导钙激活钾通道的多重调节作用

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摘 要：肾素-血管紧张素系统(renin-angiotensin system, RAS)是影响血管平滑肌细胞张力的重要因素。RAS主要活性物质血管紧张素II (angiotensin II, Ang II)可通过激活血管紧张素II-1型受体(angiotensin II type 1 receptor, AT1R)升高胞内Ca^{2+}浓度，收缩平滑肌细胞。大电导钙激活钾(large-conductance Ca^{2+}- and voltage-activated potassium, BK)通道是血管平滑肌细胞中分布最广、表达最多的钾离子通道，在维持细胞膜电位和胞内钾钙平衡中发挥重要作用。血管平滑肌细胞上的BK通道主要包含α与β1两种亚基。其中功能亚基BKα上分布有膜电位及Ca^{2+}感受器。因此当膜电位或细胞内Ca^{2+}浓度升高时会反馈性引起BK通道开放。然而，越来越多的研究显示，尽管Ang II可升高胞内Ca^{2+}浓度，但却通过激活PKC通路、促进AT1R与BKα通道形成

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的异源二聚体内吞、加快α与β1亚基解离等途径抑制BK通道的表达和功能。在一些情况下，Ang II对BK通道也可表现出激活作用，但机制尚不完全明确。该综述总结了Ang II对BK通道抑制或激活两方面效应的可能原因，为改善细胞内离子失衡提供理论依据。

关键词：大电导钙激活钾通道；血管紧张素II；血管紧张素II-1型受体；血管平滑肌
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1 Introduction

The big potassium (BK) ion channel, also known as the Maxi-K (maximum-potassium) channel, is characterized by large conductance ranging from 100 to 300 pS and sensitivity to Ca^{2+}. Hence, it is also called the large-conductance Ca^{2+}- and voltage-activated potassium channel. It was found that the diameter of the isolated rat renal afferent arteriole shrank dramatically after treatment with the BK channel blocker tetraethylammonium (TEA), and this effect could be reversed by the BK channel opener NS1619, suggesting that the BK channel is essential for maintaining vascular tone [1].

Tension of smooth muscle cells (SMCs) is a decisive factor of vascular constriction and relaxation via co-regulation of the intracellular K^+ and Ca^{2+}. Angiotensin II (Ang II), an octapeptide agonist in the renin-angiotensin system (RAS), plays a vital role in regulating cellular tension and vascular tone. It was found that Ang II activated angiotensin II type 1 receptor (AT1R) in SMCs and subsequently increased the intracellular Ca^{2+} concentration by mediating Ca^{2+} influx and Ca^{2+} release from the sarcoplasmic reticulum to induce vasoconstriction [2].

The voltage and Ca^{2+} sensors make the BK channel be activated during cell membrane depolarization and intracellular Ca^{2+} concentration increase, thus leading to outward K^+ currents [3]. Transient outward K^+ currents counteract Ca^{2+} influx to relax vessels and recover ion balance. However, increasing evidence has shown that Ang II has not only a promoting but also an inhibitory effect on the BK channel, implying that there may be some complex relationship between the BK channel and AT1R. In this review, we will discuss changes in the BK channel in vascular smooth muscle cells (VSMCs) after Ang II treatment and summarize the possible underlying mechanisms.

2 The structure and function of the BK channel

The BK channel is the most important Ca^{2+}-activated potassium channel in VSMCs. When the voltage-gated Ca^{2+} channel is open, Ca^{2+} influx and membrane potential depolarization stimulate the Ca^{2+} sensors and voltage sensors of the BK channel respectively. When the BK channel is activated, K^+ transient outward currents draw membrane hyperpolarization and voltage-gated Ca^{2+} channels close to avoid sustained Ca^{2+} influx and excessive vasoconstriction [4]. Many studies have demonstrated that the BK channel inhibitors TEA and cyclophosphamide (CTX) could depolarize membrane potential, resulting in vasoconstriction [5], suggesting that the BK channel plays an irreplaceable role in regulating relaxation of VSMCs and maintaining the balance of vascular tension.

With the development of electronic microscopy of cryogenically cooled samples (Cryo-EM) in recent years, the structure of the BK channel has been revealed gradually. The BK channel is reported to consist of functional and regulatory subunits. Four functional α subunits assemble as a tetrameric structure, each of which is composed of seven membrane-spanning regions (S0−S6) at N-terminus and four hydrophobic segments (S7−S10) at C-terminus. More precisely [6, 7], N-terminus located outside the cell membrane is connected to the S0 domain, which provides a binding site for regulatory subunits. The S1−S4 domains contain voltage sensors and can regulate the opening properties of the BK channel. Between S5 and S6 domain, a pore is formed (P-loop) as a gate and will transform into open conformation to allow K^+ passing through after voltage and Ca^{2+} sensor activation. There is a large cytosolic region at C-terminus, containing two regulators of conductance (RCK). RCK1 has Ca^{2+} and Mg^{2+} binding sites, and RCK2 forms a Ca^{2+} bowl with a high affinity to Ca^{2+}. Both are crucial for detecting the intracellular Ca^{2+} concentration [8].

So far, four regulatory β subunits (β1−β4) have been characterized to be involved in generating BK channel diversity. These β subunits modify BK channel activity and physiological functions, ranging from open properties and Ca^{2+} sensitivity to voltage-gating [9]. All β sub-

units contain two membrane-spanning regions (TM1 and TM2) which are connected by an extracellular loop. Their N- and C-termini locate inside the cells. VSMCs mainly express β1 subunit, which deeply affects the membrane potential and contraction ability of cells [10]. Although the low expressions of β2 and β4 at transcriptional level can also be found in VSMCs, their expressions at the protein level are rarely detectable. It was found that target deleting β1 subunit gene could decrease the voltage and Ca^{2+} sensitivity of the BK channel, thus disturbing the balance of membrane potential and finally resulting in high vascular tone or even hypertension [11]. In β1 subunit knockout mice, vessels showed a stronger contractile response to vasoconstrictors [12]. Additionally, increasing evidence indicates that the abnormal expression and function of β1 subunits are related to the development of other cardiovascular diseases, such as atherosclerosis and stroke [13].

In recent years, γ subunit is reported to be directly associated with BKα subunit in enhancing the BK channel activity through modifying the voltage and calcium sensitivity of α subunit. γ subunit is composed of short intracellular fragments, a transmembrane region and a long leucine-rich repeat (LRR) domain. So far, four types of auxiliary γ subunits have been identified in different tissues. Among them, γ1 subunit is expressed in arterial myocytes. After knocking down γ1 subunit expression, the systolic and diastolic functions of vessels induced by the BK channel blocker Iberiotoxin and the BK channel opener NS1619 were alleviated respectively [14].

3 The inhibitory effect of Ang II on the BK channel in VSMCs

Working as an active hormone in RAS, Ang II keeps the balance of blood pressure and electrolytes. By binding to AT1R, Ang II induces phosphoinositide 4, 5-bisphosphate (PIP_2) cleavage, resulting in the transmission of inositol trisphosphate (IP_3) and diacylglycerol (DAG) in VSMCs. Binding of IP_3 to IP_3 receptor (IP_3R) induces Ca^{2+} release from the sarcoplasmic reticulum into the cytoplasm for cell contraction. DAG regulates other ionic channels through activating protein kinase C (PKC) [15] (Fig. 1).

Toro *et al.* [16] tested whether Ang II affected the BK channel at the single-channel level by incorporating the BK channel from primary coronary SMCs into lipid bilayers, and found that Ang II inhibited K^+ currents in a dose-dependent manner. The same observation was reported by Minami *et al.* in porcine coronary artery SMCs [17]. Zhang *et al.* [18] confirmed that BK channel current reduction induced by Ang II was AT1R-dependent after transfection of both BKα and AT1R in HEK293T

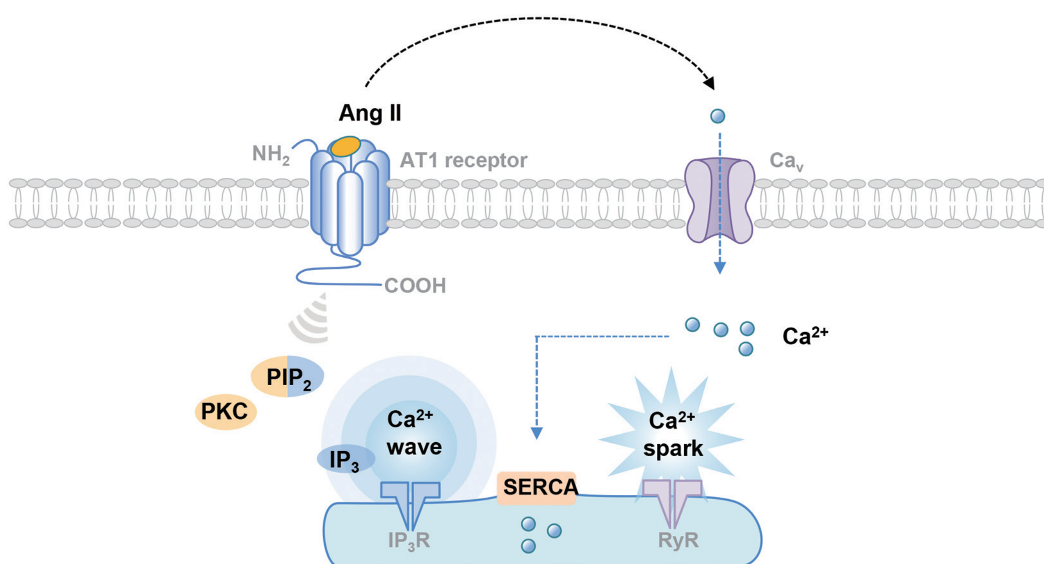

Fig. 1. The Ca^{2+} mobilizing effect of Ang II in VSMCs. After binding to AT1 receptor, Ang II mediates global Ca^{2+} increase through voltage-activated calcium channels (Ca_v) and calcium-induced calcium release mechanism of the sarcoplasmic reticulum. Ca^{2+} release from sarcoplasmic reticulum is dependent on inositol trisphosphate (IP_3) receptor (IP_3R) and ryanodine receptor (RyR) in the form of Ca^{2+} puff and Ca^{2+} spark, respectively. PIP_2: phosphoinositide 4, 5-bisphosphate; PKC: protein kinase C; SERCA: sarco/endoplasmic reticulum Ca^{2+}-ATPase.

cells. Additionally, Ang II downregulated not only the function of the BK channel but also α subunit protein expression in the membrane and whole cell lysate. However, this inhibitory effect was not attributed to the transcription level [19].

Several reasons are likely to explain these inhibitions.

3.1 The direct or indirect inhibitory effect of PKC

Variable phosphorylation sites in BKα subunit are modified by several protein kinases in divergent biophysical conditions for regulating BK channel diversity and activity. Generally, the BK channel can be activated by protein kinase A (PKA) and protein kinase G (PKG), and inhibited by PKC and c-Src kinase (c-Src) in VSMCs [20, 21]. Ang II accelerates the second message DAG transmission and PKC release. It was found that BK channel currents were weakened dramatically by the phosphorylation of S^{695} and S^{1151} in BKα subunit after adding a catalytic subunit of PKC [22, 23], suggesting that PKC suppresses the BK channel function directly by modifying some phosphorylation sites of BKα subunit. Ca^{2+} spark released from ryanodine receptor (RyR) in the sarcoplasmic reticulum is able to open the BK channel. Therefore, BK channel currents are alleviated markedly when Ca^{2+} spark is inhibited by the activation of phospholipase C (PLC), an upstream signal molecule of PKC. This effect could be eliminated after treating with the PKC inhibitor, due to enhancing the frequency of Ca^{2+} spark [24]. Meanwhile, the decreased BKα expression on the cell membrane induced by Ang II was also reversed after PKC inhibitor treatment [19], suggesting that Ang II suppresses both BK channel expression and function through PLC-PKC signaling pathway. Additionally, the inhibitory effect of Ang II on the BK channel also has PKC-independent pathway [56], because PKC inhibitor (staurosporine) pretreatment did not completely reverse BK channel inhibition by Ang II subsequent application (Fig. 2*A*).

3.2 Increased endocytosis and degradation of the BK channel

AT1R belongs to the G protein-coupled receptor (GPCR) family and contains seven transmembrane domains. In a normal physiological state, AT1R is mainly distributed on the cell membrane as monomers. Many recent studies have reported that AT1R could form dimers (homodimers or heterodimers) or higher order oligomers with themselves or other GPCRs, like AT1R-B_2R (bradykinin B_2 receptor) heterodimers, AT1R-C_1BR (Gαi-coupled type I cannabinoid receptor) heterodimers, AT1R-α_{2C}AR (α_{2C}-adrenergic receptor) heterodimers, and AT1R-AT2R (angiotensin II type 2 receptor) heterodimers [25–28]. Besides, AT1R was also found to co-locate with non-GPCRs such as AT1R-mineralocorticoid receptor heterodimers [29]. Zhang *et al*. [18] demonstrated that AT1R and BKα subunit could form a heterodimer after transfecting both AT1R and BKα plasmids into HEK293T cells. Fluorescence resonance

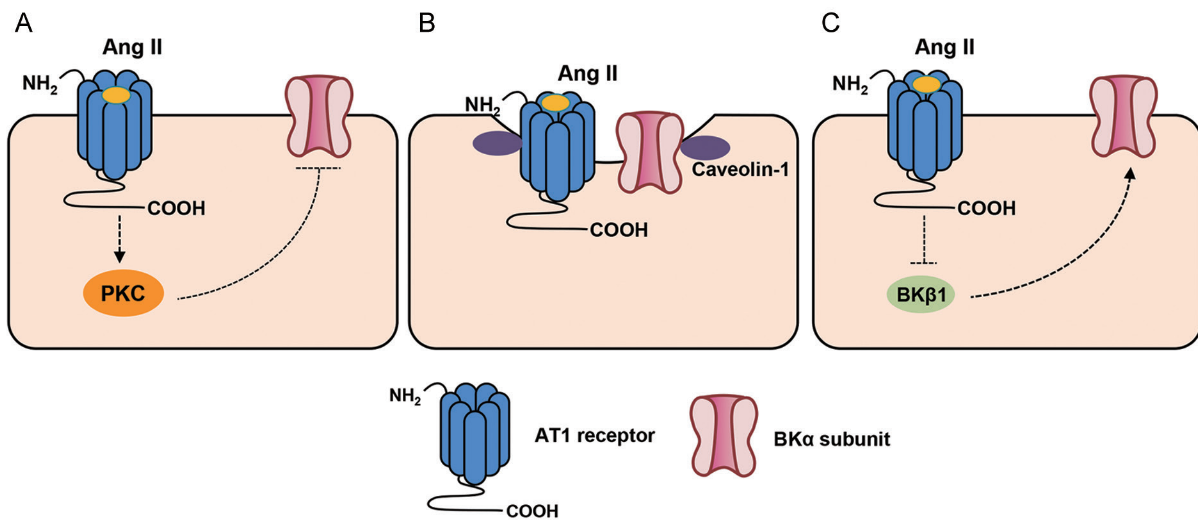

Fig. 2. Mechanisms of the inhibitory effect of Ang II on the BK channel in VSMCs. *A*: Ligand-induced AT1 receptor activation increases the combination and phosphorylation of protein kinase C (PKC), which inhibits the BK channel directly or indirectly. *B*: With the help of caveolin-1, AT1 receptor and BKα subunit assemble to form heterodimers and are internalized into the cytoplasm to avoid overactivation. *C*: AT1 receptor indirectly inhibits the voltage and Ca^{2+} sensitivity of the BK channel by impairing α and β1 subunits combination.

energy transfer (FRET) showed that their combining region was close to N-terminus of BKα subunit [18].

For preventing receptor over-activation, receptors will be internalized from the membrane into the cytoplasm, where they isolate from their ligands to terminate the reaction. Oligomers on the cell membrane will be internalized into the cytoplasm after whichever has been activated by their specific ligands. In mammals, several endocytic pathways are involved in receptor internalization. Among them, the clathrin-independent endocytic pathway has been known gradually [30]. AT1R internalization mediating by caveolae is related to the clathrin-independent endocytic pathway. Caveolae are small flask-shaped nonclathrin-coated plasma membrane invaginations, abundant with cholesterol and glycosphingolipids. Caveolae accumulate in cells in a single form or clusters. By forming 50–100 nm endocytic vesicles, they participate in membrane receptor endocytosis [31]. Caveolin is defined as the component of caveolae located on the cell membrane, the N-terminal membrane attachment domain of that contains 20 hydrophobic amino acids, which are relevant to form caveolin oligomers or interact with other proteins [32].

Data analysis shows that similar caveolin binding motifs are present in both human BKα (1102-YNML-CFGIY-1110) and human AT1R (304-FLGKK-FKRY-312) [21]. Stimulation by agonists like Ang II promotes AT1R to interact with caveolin-1 and then gather around caveolin-enriched regions [33]. It was reported that BKα subunit had lower channel currents after activation, for it combined with caveolin-1 [34]. Lu *et al.* [21] confirmed that AT1R and BKα subunit could form heterodimers and co-internalize through the caveolae-mediated clathrin-independent endocytic pathway. After mutating the binding motifs between AT1R and caveolin, the inhibitory effect of Ang II on the BK channel was completely blocked. The inhibition of BK channel currents could also be recovered after incubating cells with dynasore, an endocytosis inhibitor [19]. Therefore, we infer that reducing the number of BKα subunits on the cell membrane through promoting AT1R-BKα heterodimer endocytosis may be one of the underlying mechanisms of the inhibitory effect of Ang II on BK channel.

Endocytic receptors mainly have two endings: (1) recycled to surface again; (2) degraded through proteasome or lysosome pathways. Biotinylation experiments demonstrated that long exposure (8 h) to Ang II down-regulated the protein level of BK channel both on the whole cell and surface to 66% and 63% respectively, and this could be alleviated by proteasome inhibitor MG132 and lysosome inhibitor bafilomycin A [19]. Thus, most AT1R-BKα heterodimers are endocytosed and degraded through proteasome and lysosome pathways after Ang II stimulation instead of recycling to the cell surface again (Fig. 2*B*).

3.3 Down-regulation of BKβ1 subunit

VSMCs mainly express BKβ1 subunit. Ample evidence has demonstrated that β1 subunit can help voltage sensors of BKα keep active conformation, thus enhancing the open dwell time of the BK channel. Ang II infusion *in vivo*, especially when β1 subunit expression is decreased, is likely to induce hypertensive symptoms [36], suggesting that β1 subunit could alleviate the vasopressor activity of Ang II via increasing the BK channel opening probability. With the help of overlap extension technique, Castillo *et al.* [37] discovered that the cytoplasmic N-terminus region of β1 subunit was mainly responsible for modifying BKα voltage sensors. After deleting the N-terminus fragment of β1 subunit, the active conformation of the BK channel returned to the non-activated state within a very short period of time. They further successfully narrowed down the structural determinants in N-terminus of β1 subunit and found two lysine residues (K3 and K4), which were recognized as the bridge to connect β1 subunit and BKα voltage sensors. Ang II enhances AT1R-BKα heterodimers gathering in the caveolae-enriched region. However, no β1 subunit expression was detected in this place [35], suggesting that Ang II led to dissociation of BKα and β1 subunits, thus abolishing the sensitization effect of β1 subunit to BKα subunit and further reduced Ca^{2+} sensitivity and function of the BK channel (Fig. 2*C*).

4 The activating effect of Ang II on the BK channel in VSMCs

Contrary to the inhibitory function of Ang II on the BK channel, many other studies showed that Ang II had an activating effect on the BK channel [38]. By using fresh intestinal myocytes of the guinea pig ileum, Romero *et al.* found that Ang II or its synthetic analog can raise BK channel activity, because their stimulation provoked a Ca^{2+}- and dose-dependent activation of the BK channel bathed in high-K^+ solution. Meanwhile, this

effect could be abolished by specific AT1R blocker losartan [39], indicating that the high intracellular Ca^{2+} concentration increased by Ang II was an intermediate step to enhance the open probability of the BK channel.

Several reasons are likely to explain this phenomenon.

4.1 The alternative splices of BKα subunit

BKα cDNA is encoded by 27 constitutive exons. More precisely, the transmembrane regions S0–S6 are encoded by exons 1–9, which contain voltage sensors and pore domains. Exons 9–27 encode S7–S10 in long C-terminus, including RCK1, RCK2 and Ca^{2+} bowl domains. Highly alternative splice regions are distributed in these exons, and they are located in N-terminus (before exon 1), before RCK1 domain (between exons 9–11), between exons 17 and 19, next to RCK2 domain (between exons 20 and 21), before Ca^{2+} bowl (between exons 23 and 24), and C-terminus (after exon 27) [9]. These variable alternative splice regions make BKα subunit form different splicing variants, and therefore are suitable for diverse physiological activities.

The ZERO variant of the BK channel constitutes large part of BKα mRNA in VSMCs. Another variant that has been most studied is BK e21 exon, which is also known as BK STREX (stress-axis regulated exon) [40]. This variant is characterized by an insert of 58 conserved amino acids in the splice site C2 between RCK1 and RCK2. Compared with the ZERO phenotype, STREX has stronger calcium sensitivity that represents a sharper shift of the conductance-voltage curve [41]. ZERO has a specific phosphorylated serine residue at C-terminus (S^{869}), which can be phosphorylated and activated by PKA. However, in STREX, PKA has another phosphorylation site within the STREX region, which makes the activating effect of PKA on the BK channel be neutralized [42]. PKC inhibits the BK channel via the Ser^{695} phosphorylation site located between RCK1 and RCK2. In STREX, PKC additionally activates a palmitoylated site within the STREX region, resulting in disappearance of the inhibitory effect [40]. Therefore, unlike ZERO, Ang II could not inhibit the open probability of BK-STREX through the PKC pathway (Fig. 3*A*).

4.2 The involvement of AT2 receptor (AT2R)

In RAS, Ang II is known to bind with two angiotensin receptors: AT1R and AT2R. AT1R is involved in various physiological functions ranging from cardiac contractility and vasoconstriction to aldosterone secretion, renal tubule sodium reabsorption and sympathetic nervous system activation [43]. Compared with AT1R, it is more difficult to observe the beneficial effect of AT2R unless AT1R is blocked [44]. AT2R attenuated AT1R signaling cascades, thus counteracting its vasoconstrictive effect [45]. Overexpression of AT2R in cardiomyocytes alleviated the pressor and chronotropic effects mediated by AT1R [46]. The function of BK channel in the mesenteric artery increased dramatically after exposure to

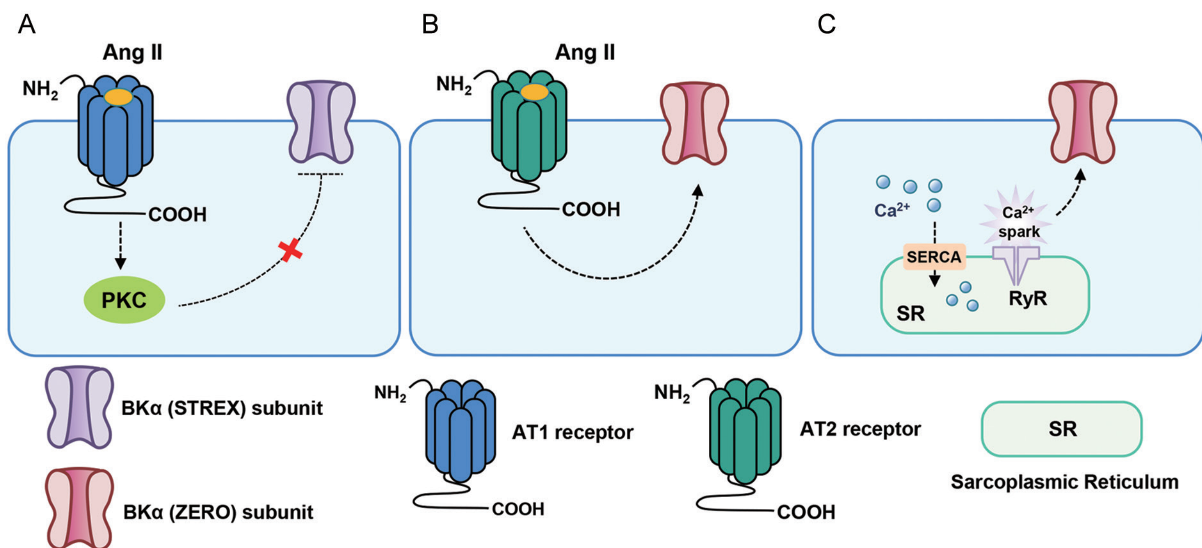

Fig. 3. Mechanisms of the activating effect of Ang II on the BK channel in VSMCs. *A*: A special palmitoylated site within BKα (STREX) can also be activated by PKC, which eliminates the inhibitory effect on BK channel. *B*: Angiotensin II type 2 receptor (AT2 receptor) enhances BK channel activity. *C*: Ca^{2+} spark released from the ryanodine receptor (RyR) is closely related to BK channel activation.

Ang II, and this stimulatory effect could be completely prevented by blocking AT2R with PD123319 but not the AT1R blocker losartan [47] (Fig. 3*B*), indicating that the function of the BK channel could be enhanced by Ang II binding with AT2R.

4.3 The term of Ca^{2+} in activating the BK channel

Ca^{2+} is a particularly important biological messenger in SMCs. Thousands of proteins contain Ca^{2+}-binding motifs, which combine with Ca^{2+} to exert distinctly different roles in specific situations [48].

It was reported that Ang II could mediate Ca^{2+} influx and enhance the sensitivity of sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA). This Ca^{2+} influx is also a signal for ER/SR store to release Ca^{2+}. Ca^{2+} release from the ER/SR is mediated by two families of Ca^{2+} channels, the IP_3R and the RyR [48]. Scientists give Ca^{2+} currents different definitions according to their magnitude, duration and range. Ca^{2+} released from IP_3R is defined as Ca^{2+} puff. Relatively, a high concentration, high speed and limited range of Ca^{2+} flow released from RyR is classified as Ca^{2+} sparks. Most Ca^{2+} sparks generate near the BK channel, where they activate spontaneous transient outward K^+ channel [24]. Therefore, it is widely accepted that Ca^{2+} sparks are essential in triggering the BK channel [49]. Unfortunately, the form of Ca^{2+} release from ER/SR store induced by Ang II remains poorly defined (Fig. 3*C*).

5 Conclusion and prospect

Ion balance in SMCs is essential for maintaining vascular tone. Under physiological conditions, the inhibitory effect of Ang II on the BK channel ensures vessel contraction within the normal range and this effect usually lasts for 2–3 min. Clinical studies have demonstrated the prevalence of BK channel inhibition in hypertensive patients [50]. Specifically, the BK channel in superior mesenteric artery SMCs of hypertensive patients presents a significant lower frequency and amplitude of outward currents as compared with normotensive subjects, suggesting that there may be some pathological factors involved in long-term BK channel inhibition in hypertensive diseases.

Some recent studies discovered distribution of an autoantibody in a wide range of hypertensive diseases [51, 52], and this autoantibody known as angiotensin II type 1 receptor autoantibody (AT1-AA) could specifically bind with the second extracellular loop of AT1R, acting as a receptor agonist like Ang II [53]. Our previous study [54] demonstrated that AT1-AA had a longer activating effect on AT1R than Ang II, causing sustained vasoconstriction and increasing blood pressure by activating Ca^{2+} and PKC signaling pathways. AT1-AA stimulation reduced the open probability of the BK channel in SMCs as least for 30 min, indicating that long-term RAS hyperactivity, induced by AT1-AA, attenuated BK channel currents, which may be a contributing factor for sustained vasoconstriction.

It is necessary to correct BK channel dysfunction for the sake of improving abnormal blood pressure. The percentage of STREX phenotype was found to be increased in a rat model of hypertension [55], which may be a negative feedback response to the inhibitory effect on the BK channel. In addition, RyR agonists could relax vessels by activating the BK channel via Ca^{2+} spark release [24]. Therefore, we will further focus on how to alleviate the inhibition of the BK channel when abnormal activity of the RAS occurs.

REFERENCES

1 Fallet RW, Bast JP, Fujiwara K, Ishii N, Sansom SC, Carmines PK. Influence of Ca^{2+}-activated K^+ channels on rat renal arteriolar responses to depolarizing agonists. Am J Physiol Renal Physiol 2001; 280: F583–F591.

2 Mehta PK, Griendling KK. Angiotensin II cell signaling: physiological and pathological effects in the cardiovascular system. Am J Physiol Cell Physiol 2007; 292: C82–C97.

3 Ge L, Hoa NT, Wilson Z, Arismendi-Morillo G, Kong XT, Tajhya RB, Beeton C, Jadus MR. Big Potassium (BK) ion channels in biology, disease and possible targets for cancer immunotherapy. Int Immunopharmacol 2014; 22: 427–443.

4 Hu XQ, Zhang L. Function and regulation of large conductance Ca^{2+}-activated K^+ channel in vascular smooth muscle cells. Drug Discov Today 2012; 17: 974–987.

5 Brayden JE, Nelson MT. Regulation of arterial tone by activation of calcium-dependent potassium channels. Science 1992; 256: 532–535.

6 Wang L, Sigworth FJ. Structure of the BK potassium channel in a lipid membrane from electron cryomicroscopy. Nature 2009; 461: 292–295.

7 Toro L, Li M, Zhang Z, Singh H, Wu Y, Stefani E. MaxiK channel and cell signalling. Pflugers Arch 2014; 466: 875–886.

8 Lee US, Cui J. BK channel activation: structural and functional insights. Trends Neurosci 2010; 33: 415–423.

9 Latorre R, Castillo K, Carrasquel-Ursulaez W, Sepulveda RV, Gonzalez-Nilo F, Gonzalez C, Alvarez O. Molecular determinants of BK channel functional diversity and functioning. Physiol Rev 2017; 97: 39–87.

10 Wu RS, Marx SO. The BK potassium channel in the vascular smooth muscle and kidney: alpha- and beta-subunits. Kidney Int 2010;78: 963–974.

11 Brenner R, Perez GJ, Bonev AD, Eckman DM, Kosek JC, Wiler SW, Patterson AJ, Nelson MT, Aldrich RW. Vasoregulation by the beta1 subunit of the calcium-activated potassium channel. Nature 2000; 407: 870–876.

12 Pluger S, Faulhaber J, Furstenau M, Lohn M, Waldschutz R, Gollasch M, Haller H, Luft FC, Ehmke H, Pongs O. Mice with disrupted BK channel beta1 subunit gene feature abnormal Ca^{2+} spark/STOC coupling and elevated blood pressure. Circ Res 2000; 87: E53–E60.

13 Leo MD, Bannister JP, Narayanan D, Nair A, Grubbs JE, Gabrick KS, Boop FA, Jaggar JH. Dynamic regulation of beta1 subunit trafficking controls vascular contractility. Proc Natl Acad Sci U S A 2014; 111: 2361–2366.

14 Evanson KW, Bannister JP, Leo MD, Jaggar JH. LRRC26 is a functional BK channel auxiliary gamma subunit in arterial smooth muscle cells. Circ Res 2014; 115: 423–431.

15 Wynne BM, Chiao C, Webb RC. Vascular smooth muscle cell signaling mechanisms for contraction to angiotensin II and endothelin-1. J Am Soc Hypertens 2009; 3: 84–95.

16 Toro L, Amador M, Stefani E. ANG II inhibits calcium-activated potassium channels from coronary smooth muscle in lipid bilayers. Am J Physiol 1990; 258: H912–H915.

17 Minami K, Fukuzawa K, Nakaya Y. Protein kinase C inhibits the Ca^{2+}-activated K^+ channel of cultured porcine coronary artery smooth muscle cells. Biochem Biophys Res Commun 1993; 190: 263–269.

18 Zhang Z, Li M, Lu R, Alioua A, Stefani E, Toro L. The angiotensin II type 1 receptor (AT1R) closely interacts with large conductance voltage- and Ca^{2+}-activated K^+ (BK) channels and inhibits their activity independent of G-protein activation. J Biol Chem 2014; 289: 25678–25689.

19 Leo MD, Bulley S, Bannister JP, Kuruvilla KP, Narayanan D, Jaggar JH. Angiotensin II stimulates internalization and degradation of arterial myocyte plasma membrane BK channels to induce vasoconstriction. Am J Physiol Cell Physiol 2015; 309: C392–C402.

20 Hill MA, Yang Y, Ella SR, Davis MJ, Braun AP. Large conductance, Ca^{2+}-activated K^+ channels (BKCa) and arteriolar myogenic signaling. FEBS Lett 2010; 584: 2033–2042.

21 Lu T, Zhang DM, Wang XL, He T, Wang RX, Chai Q, Katusic ZS, Lee HC. Regulation of coronary arterial BK channels by caveolae-mediated angiotensin ii signaling in diabetes mellitus. Circ Res 2010; 106: 1164–1173.

22 Schubert R, Noack T, Serebryakov VN. Protein kinase C reduces the KCa current of rat tail artery smooth muscle cells. Am J Physiol 1999; 276: C648–C658.

23 Zhou X, Wulfsen I, Utku E, Sausbier U, Sausbier M, Wieland T, Ruth P, Korth M. Dual role of protein kinase C on BK channel regulation. Proc Natl Acad Sci U S A 2010; 107: 8005–8010.

24 Jaggar JH, Nelson MT. Differential regulation of Ca^{2+} sparks and Ca^{2+} waves by UTP in rat cerebral artery smooth muscle cells. Am J Physiol Cell Physiol 2000; 279: C1528–C1539.

25 AbdAlla S, Lother H, El MA, Quitterer U. Increased AT(1) receptor heterodimers in preeclampsia mediate enhanced angiotensin II responsiveness. Nat Med 2001; 7: 1003–1009.

26 Rozenfeld R, Gupta A, Gagnidze K, Lim MP, Gomes I, Lee-Ramos D, Nieto N, Devi LA. AT1R-CB1R heteromerization reveals a new mechanism for the pathogenic properties of angiotensin II. EMBO J 2011; 30: 2350–2363.

27 Bellot M, Galandrin S, Boularan C, Matthies HJ, Despas F, Denis C, Javitch J, Mazeres S, Sanni SJ, Pons V, Seguelas MH, Hansen JL, Pathak A, Galli A, Senard JM, Gales C. Dual agonist occupancy of AT1-R-alpha2C-AR heterodimers results in atypical Gs-PKA signaling. Nat Chem Biol 2015; 11: 271–279.

28 Yu L, Zheng M, Wang W, Rozanski GJ, Zucker IH, Gao L. Developmental changes in AT1 and AT2 receptor-protein expression in rats. J Renin Angiotensin Aldosterone Syst 2010; 11: 214–221.

29 Tsai CF, Yang SF, Chu HJ, Ueng KC. Cross-talk between mineralocorticoid receptor/angiotensin II type 1 receptor and mitogen-activated protein kinase pathways underlies aldosterone-induced atrial fibrotic responses in HL-1 cardiomyocytes. Int J Cardiol 2013; 169: 17–28.

30 Chaudhary N, Gomez GA, Howes MT, Lo HP, McMahon KA, Rae JA, Schieber NL, Hill MM, Gaus K, Yap AS, Parton RG. Endocytic crosstalk: cavins, caveolins, and caveolae regulate clathrin-independent endocytosis. PLoS Biol 2014; 12: e1001832.

31 Cheng JPX, Nichols BJ. Caveolae: one function or many? Trends Cell Biol 2016; 26: 177–189.

32 Krajewska WM, Maslowska I. Caveolins: structure and function in signal transduction. Cell Mol Biol Lett 2004; 9: 195–220.

33 Ishizaka N, Griendling KK, Lassegue B, Alexander RW. Angiotensin II type 1 receptor: relationship with caveolae and caveolin after initial agonist stimulation. Hypertension 1998; 32: 459–466.

34 Riddle MA, Hughes JM, Walker BR. Role of caveolin-1 in endothelial BKCa channel regulation of vasoreactivity. Am J Physiol Cell Physiol 2011; 301: C1404–C1414.

35 Lu T, Jiang B, Wang XL, Lee HC. Coronary arterial BK channel dysfunction exacerbates ischemia/reperfusion-induced myocardial injury in diabetic mice. Appl Physiol Nutr Metab 2016; 41: 992–1001.

36 Howitt L, Morris MJ, Sandow SL, Murphy TV. Effect of

diet-induced obesity on BKCa function in contraction and dilation of rat isolated middle cerebral artery. Vasc Pharmacol 2014; 61: 10–15.

37 Castillo K, Contreras GF, Pupo A, Torres YP, Neely A, Gonz Lez C, Latorre R. Molecular mechanism underlying β1 regulation in voltage- and calcium-activated potassium (BK) channels. Proc Natl Acad Sci U S A 2015; 112: 4809–4814.

38 Zhang Z, Qian L, Wang R. Molecular mechanisms underlying renin-angiotensin-aldosterone system mediated regulation of BK channels. Front Physiol 2017; 8: 698

39 Romero F, Silva BA, Nouailhetas VL, Aboulafia J. Activation of Ca^{2+}-activated K^+ (maxi-K^+) channel by angiotensin II in myocytes of the guinea pig ileum. Am J Physiol 1998; 274: C983–C991.

40 Zhou X, Wulfsen I, Korth M, McClafferty H, Lukowski R, Shipston MJ, Ruth P, Dobrev D, Wieland T. Palmitoylation and membrane association of the stress axis regulated insert (STREX) controls BK channel regulation by protein kinase C. J Biol Chem 2012; 287: 32161–32171.

41 Chen L, Tian L, MacDonald SH, McClafferty H, Hammond MS, Huibant JM, Ruth P, Knaus HG, Shipston MJ. Functionally diverse complement of large conductance calcium- and voltage-activated potassium channel (BK) alpha-subunits generated from a single site of splicing. J Biol Chem 2005; 280: 33599–33609.

42 Tian L, Duncan RR, Hammond MS, Coghill LS, Wen H, Rusinova R, Clark AG, Levitan IB, Shipston MJ. Alternative splicing switches potassium channel sensitivity to protein phosphorylation. J Biol Chem 2001; 276: 7717–7720.

43 Padia SH, Carey RM. AT2 receptors: beneficial counter-regulatory role in cardiovascular and renal function. Pflugers Archiv 2013; 465: 99–110.

44 Carey RM. Update on angiotensin AT2 receptors. Curr Opin Nephrol Hypertens 2017; 26(2): 91–96.

45 Inuzuka T, Fujioka Y, Tsuda M, Fujioka M, Satoh AO, Horiuchi K, Nishide S, Nanbo A, Tanaka S, Ohba Y. Attenuation of ligand-induced activation of angiotensin II type 1 receptor signaling by the type 2 receptor via protein kinase C. Sci Rep 2016; 6: 21613

46 Masaki H, Kurihara T, Yamaki A, Inomata N, Nozawa Y, Mori Y, Murasawa S, Kizima K, Maruyama K, Horiuchi M, Dzau VJ, Takahashi H, Iwasaka T, Inada M, Matsubara H. Cardiac-specific overexpression of angiotensin II AT2 receptor causes attenuated response to AT1 receptor-mediated pressor and chronotropic effects. J Clin invest 1998; 101: 527–535.

47 Dimitropoulou C, White RE, Fuchs L, Zhang H, Catravas JD, Carrier GO. Angiotensin II relaxes microvessels via the AT(2) receptor and Ca^{2+}-activated K^+ (BKCa) channels. Hypertension 2001; 37: 301–307.

48 Cheng H, Lederer WJ. Calcium sparks. Physiol Rev 2008; 88: 1491–1545.

49 Nelson MT, Cheng H, Rubart M, Santana LF, Bonev AD, Knot HJ, Lederer WJ. Relaxation of arterial smooth muscle by calcium sparks. Science 1995; 270: 633–637.

50 Cheng J, Mao L, Wen J, Li PY, Wang N, Tan XQ, Zhang XD, Zeng XR, Xu L, Xia XM, Xia D, He K, Su S, Yao H, Yang Y. Different effects of hypertension and age on the function of large conductance calcium- and voltage-activated potassium channels in human mesentery artery smooth muscle cells. J Am Heart Assoc 2016; 5: e3913.

51 Fu ML, Herlitz H, Schulze W, Wallukat G, Micke P, Eftekhari P, Sjogren KG, Hjalmarson A, Muller-Esterl W, Hoebeke J. Autoantibodies against the angiotensin receptor (AT1) in patients with hypertension. J Hypertens 2000; 18: 945–953.

52 Zhu F, Sun Y, Wang M, Ma S, Chen X, Cao A, Chen F, Qiu Y, Liao Y. Correlation between HLA-DRB1, HLA-DQB1 polymorphism and autoantibodies against angiotensin AT1 receptors in Chinese patients with essential hypertension. Clin Cardiol 2011; 34: 302–308.

53 Wallukat G, Homuth V, Fischer T, Lindschau C, Horstkamp B, Jupner A, Baur E, Nissen E, Vetter K, Neichel D, Dudenhausen JW, Haller H, Luft FC. Patients with preeclampsia develop agonistic autoantibodies against the angiotensin AT1 receptor. J Clin invest 1999; 103: 945–952.

54 Zhang S, Zheng R, Yang L, Zhang X, Zuo L, Yang X, Bai K, Song L, Tian J, Yang J, Liu H. Angiotensin type 1 receptor autoantibody from preeclamptic patients induces human fetoplacental vasoconstriction. J Cell Physiol 2013; 228(1): 142–148.

55 Wan XJ, Zhao HC, Zhang P, Huo B, Shen BR, Yan ZQ, Qi YX, Jiang ZL. Involvement of BK channel in differentiation of vascular smooth muscle cells induced by mechanical stretch. Int J Biochem Cell Biol 2015; 59: 21–29.

56 Minami K, Hirata Y, Tokumura A, Nakaya Y, Fukuzawa K. Protein kinase C-independent inhibition of the Ca^{2+}-activated K^+ channel by angiotensin II and endothelin-1. Biochem Pharmacol 1995; 49(8): 1051–1056.