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Potassium Channels and Uterine Vascular Adaptation to Pregnancy and Chronic Hypoxia

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Abstract

During a normal course of pregnancy, uterine vascular tone is significantly decreased resulting in a striking increase in uterine blood flow, which is essential for fetal development and fetal growth. Chronic hypoxia during gestation may adversely affect the normal adaptation of uterine vascular tone and increase the risk of preeclampsia and fetal intrauterine growth restriction. In this review, we present evidence that the regulation of K^+ channels is an important mechanism in the adaptation of uterine vascular tone to pregnancy and hypoxia. There are four types of K^+ channels identified in arterial smooth muscle cells: 1) voltage-dependent K^+ (K_v) channels, 2) Ca^{2+}-activated K^+ (K_{Ca}) channels, 3) inward rectifier K^+ (K_{IR}) channels, and 4) ATP-sensitive K^+ (K_{ATP}) channels. Pregnancy differentially augments the expression and activity of K^+ channels *via* downregulation of protein kinase C signaling in uterine and other vascular beds, leading to decreased uterine vascular tone and increased uterine blood flow. Sex steroid hormones play an important role in the pregnancy-mediated alteration of K^+ channels in the uterine vasculature. In addition, chronic hypoxia alters uterine vascular K^+ channels expression and activities *via* modulation of steroid hormones/receptors-mediated signaling, resulting in increased uterine vascular tone during pregnancy.

Keywords

Uterine artery; pregnancy; hypoxia; potassium channels; preeclampsia

1. INTRODUCTION

Pregnancy is associated with decreased uterine vascular tone and a significant increase in uterine blood flow that optimizes the delivery of nutrients and oxygen to the developing fetus. The adaptation of the uterine circulation to pregnancy is complex and is mediated, at least in part by enhanced vasodilation, decreased vascular tone and vascular remodeling. Although the mechanisms contributing to the profound decrease in uterine vascular tone and

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CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

significant rise in uterine blood flow during pregnancy are not completely understood, increasing evidence suggests that the regulation of K^+ channels may play a key role in the adaptations of uterine circulation to pregnancy [1–5]. The K^+ channels are the most important ion channels expressed in the plasma membrane of arterial smooth muscle cells and play a key role in the regulation of vascular tone and blood pressure [2, 3]. Stimulation of K^+ channels increases K^+ efflux in arterial smooth muscle cells, leading to membrane potential hyperpolarization and closure of voltage-dependent Ca^{2+} channels, which causes vasodilation and decreases in vascular tone. In contrast, inhibition of K^+ channels will cause membrane potential depolarization, decrease K^+ efflux and enhance voltage-dependent Ca^{2+} channels activities in arterial smooth muscle cells, resulting in vasoconstriction and increased vascular tone. Therefore, the K^+ channels activity is directly linked to contractile tone of vascular smooth muscle, and factors that regulate the activity of K^+ channels have major effects on vascular tone and blood flow [2, 6–9].

There are four types of K^+ channels that have been identified in arterial smooth muscle: 1) voltage-dependent K^+ (Kv) channels, 2) Ca^{2+}-activated K^+ (K_{Ca}) channels, 3) inward rectifier K^+ (K_{IR}) channels, and 4) ATP-sensitive K^+ (K_{ATP}) channels [2, 10]. In this review, we first present a brief summary of the fundamental physiological role and properties of these four K^+ channels in arterial smooth muscle, followed by the discussion of the role and properties of K^+ channels in uterine vascular smooth muscle and their adaptations to pregnancy. In addition, since hypoxia is a pathological condition in which the body as a whole or a region of the body is deprived of adequate oxygen supply and the arterial oxygen concentrations are under the normal physiologic range, short-term (acute) hypoxia or long-term (chronic) hypoxia exposure may result in cardiovascular dysfunction. Indeed, it has been demonstrated that chronic hypoxia during pregnancy is one of the most common insults to the maternal cardiovascular system and fetal development associated with increased uterine vascular tone and heightened risk of preeclampsia [1, 5, 6, 11–16]. Thus, we present the evidence that modulation of K^+ channels activity in uterine vasculature may be one of the important mechanisms underlying chronic hypoxia-mediated uterine vascular dysfunction during pregnancy.

2. K_{ATP} CHANNELS

2.1. Physiological Roles and Properties of K_{ATP} Channels in Vasculature

The ATP-sensitive potassium (K_{ATP}) channels were first identified in cardiac muscle [17, 18]. Up to now, they are found to be expressed in most excitable tissues including vasculature [19–21]. K_{ATP} channel is composed of at least two subunits: an inwardly rectifying K^+ channel six family (Kir6.x) that forms the ion conductive pore and a regulatory sulfonylurea receptor subunit (SUR) that accounts for several pharmacological properties [10, 22, 23]. Different combinations of Kir6.x and SUR.x isoforms/variants produce tissue-specific K_{ATP} channel subtypes with different features and distinct functional properties. Two types of K_{ATP} channels have been cloned and identified in smooth muscle cell, namely Kir6.2-SUR2B channels [24] and Kir6.1-SUR2B channels [25].

Intracellular ATP acts on Kir6.x to inhibit channel activity, while ADP stimulates channel activity through SUR. Changes in the cytosolic [ATP] to [ADP] ratio thus determine the

channel activity. Therefore, it is thought that K_{ATP} channels provide a link between cell metabolism and membrane excitability, and play an important role in metabolic regulation of blood flow. In addition, K_{ATP} channels may be also active in the resting state and play a role in the maintenance of basal tone in certain vascular beds [26]. Furthermore, K_{ATP} channels appear to be the target of a number of vasodilators and vasoconstrictors [27]. Several vasodilators, such as adenosine, prostacyclin, β-agonists enhance K_{ATP} channels activities *via* activating cAMP and protein kinase A (PKA) signaling, resulting in membrane hyperpolarization and vasodilation. In contrast, vasoconstrictors, such as angiotensin II, endothelin-1, serotonin, noradrenaline, α-agonists or neuropeptide decrease the activity of K_{ATP} channels *via* activating protein kinase C (PKC) pathways, causing vascular smooth muscle cell membrane depolarization and contraction [17, 28].

2.2. K_{ATP} Channels Blockers

The anti-diabetic sulfonylurea agents, such as glibenclamide, tolbutamide and tolazamide have been developed as K_{ATP} channels blockers. Sulfonylurea derivatives have been used since the 1950s for the treatment of noninsulin-dependent diabetes mellitus, in which they stimulate insulin secretion by inhibiting K_{ATP} channel activity in pancreatic β cells. Their potency to inhibit K_{ATP} channels in smooth muscle cells has been shown subsequently [29, 30]. Based on their property, suifonylureas, in particular the most potent representative agent glibenclamide, have been widely used in many experiments to show the role of K_{ATP} channels involved in vascular patho-physiologic functions [29].

2.3. K_{ATP} Channels Openers

K_{ATP} channels openers are a diverse group of pharmacologic agents that have the ability to increase cellular K^+ efflux and induce hyperpolarization of the smooth muscle cell membrane leading to smooth muscle relaxation. The most known representatives of this class of drugs are diazoxide, cromakalim, bimakalim, pinacidil, aprikalim, nicorandil, and minoxidil sulfate [17]. The ability of these compounds to open K_{ATP} channels is cell type dependent. However, these compounds have the greatest potency in smooth muscle. Cromakalim is the most widely used type of vasodilators in vascular smooth muscle [29, 30]. Studies in isolated arteries have demonstrated that these compounds directly activate K_{ATP} channels and induce vasodilation, which can be blocked by glibenclamide or other K_{ATP} channels inhibitors but not by other K^+ channels blockers [19, 31]. These studies suggest that K_{ATP} channels are the only target for these K_{ATP} channels openers. The exact mechanism of action of the K_{ATP} channels openers is not fully understood, however, evidence exists suggesting that they act on the K_{ATP} channels by decreasing the sensitivity of K_{ATP} channels to intracellular ATP [26, 32, 33].

2.4. Role of K_{ATP} Channels in Uterine Vascular Adaptation to Pregnancy

Adaptation of K_{ATP} channels in vascular smooth muscle may contribute to the hemodynamic changes associated with normal pregnancy. In a guinea pig animal model, it has been demonstrated that K_{ATP} channels play an important role in the regulation of vascular resistance and the activity of K_{ATP} channels is vascular beds- and pregnancy-dependent [5]. In this study, it has reported that systemic vascular resistance (SVR) is lower

and the SVR response to angiotensin II is diminished in the pregnant compared with the nonpregnant guinea pigs. After treatment with a K_{ATP} channels blocker, glibenclamide, the SVR response to angiotensin II was not difference between the pregnant and nonpregnant groups, suggesting that the lower SVR and response to angiotensin II is due to heightened K_{ATP} channels activity. Furthermore, pregnancy selectively increased the K_{ATP} channels activity in uterine, renal, coronary, and cerebral vascular beds and in the uteroplacental vasculature during angiotensin II infusion [5]. Thus, the pregnancy-induced stimulation of K_{ATP} channels activity is likely to be important for the regulation of vascular resistance and maintenance of blood flow in these vascular beds. However, other studies have demonstrated that glibenclamide has no significant effect on phenylphrine-induced contractions in ovine uterine arteries [1], which is in agreement with previous studies that glibenclamide did not affect the basal tone in renal, cerebral and pulmonary arteries [9, 35, 36]. This suggests that the role of K_{ATP} channel in regulating baseline vascular tone may be tissues and/or animal species-dependent. Although the baseline vascular tone is not affected by K_{ATP} channel, the findings that the K_{ATP} channels opener diazoxide caused a significant vasodilation and attenuated phenylphrine-induced contractions suggests that a functional role of K_{ATP} channels in the ovine uterine artery [1]. Similar studies have demonstrated that K_{ATP} channels are not involved in regulating basal tone in cerebral artery, but K_{ATP} channels play a role in vasodialtion caused by changes in metabolic state and by endogenous substances or synthetic K_{ATP} channels openers [2, 37]. In consistent with previous studies showing that pregnancy enhances K_{ATP} channels activity in guinea pig uterine artery [5], it has been shown that diazoxide-induced relaxations are significantly enhanced in pregnant as compared with that in nonpregnant uterine arteries [1]. These findings further suggest that pregnancy may up-regulate K_{ATP} channels activity, resulting in decreased uterine vascular resistance, which may contribute to the increased uterine blood flow during the course of pregnancy.

2.5. Role of K_{ATP} Channels in Uterine Vascular Adaptation to Hypoxia

Not only do K_{ATP} channels play an important role in regulating vascular contractility in physiologic condition but they also play a key role in vascular dysfunction in various pathophysiological conditions including hypertension, diabetes, ischemia and hypoxia. It is well known that oxygen is a vasoactive substance in the peripheral circulation. Higher oxygen may cause vasoconstriction, whereas hypoxia induces vasodilation. Although the exact mechanisms underlying oxygen-mediated vasoreactivity are not fully understood, increasing evidence suggests that K_{ATP} channels may be involved in hypoxia-induced vasodilation [2, 38–40]. Acute hypoxia activates K_{ATP} channels either by acting directly on arterial smooth muscle cells or by inducing release of vasodilator metabolites, which in turn activate K_{ATP} channels *via* receptor-coupled signaling [41–43]. K_{ATP} channels activities are mainly regulated by intracellular ATP and ADP levels. Thus, hypoxia-mediated vasoreactivity may occur as a consequence of hypoxia-mediated changes of intracellular nucleotide levels in vasculature. Hypoxia can cause a reduction in intracellular ATP or elevation in intracellular ADP leading to vasodilation, which was inhibited by K_{ATP} channels blocker glibenclamide in cerebral arteries, coronary, renal and skeletal muscle circulations [2, 38–40]. These observations suggest a key role of K_{ATP} channels in hypoxia-mediate vasodilation.

Although the role of K_{ATP} channels in hypoxia-mediated vasodilation is well established in many vasculatures including coronary, cerebral, renal, and skeletal muscle circulation, a lack of effect of hypoxia on K_{ATP} channels activities has also been reported in rat cremaster arteries [44]. Furthermore, a study has demonstrated that K_{ATP} channels are not activated during hypoxia *via* changes in cell metabolism in rat femoral artery, but that hypoxia-mediated vasodilation is regulated by changes in intracellular Ca^{2+} concentration $[Ca^{2+}]_i$ through modulation of calcium channel activity [45]. The different roles of K_{ATP} channels in hypoxia-mediated vasoreactivity may be due to differences in the species, vascular beds, or experimental conditions. In addition, the role of K_{ATP} channels is also dependent on the extent and duration of hypoxia. For example, in pulmonary arteries K_{ATP} channels are not involved in regulating vascular tone in either normoxia or moderate hypoxia. However, K_{ATP} channels play an important role in pulmonary vasoreactivity in sustained and severe pulmonary hypoxia [36]. Furthermore, not only does hypoxia induce vasodilation in many vascular beds, but it also can cause vasoconstriction [46], and K_{ATP} channels may also play an important role in hypoxia-mediated vasoconstriction. Indeed, recent studies in high-altitude sheep model have demonstrated that chronic hypoxia selectively enhances uterine vascular tone in pregnant but not nonpregnant sheep [47–49]. Further studies indicated that chronic hypoxia decreased K_{ATP} channels opener diazoxide-induced relaxation in pregnant uterine arteries and eliminated pregnancy-mediated response [1]. These observations suggest that chronic hypoxia-mediated enhanced uterine vascular tone may be attributed, in part, to a decrease in K_{ATP} channels activities.

2.6. Regulation of K_{ATP} Channels by PKC

There is growing body of studies suggest that PKC may play an important role in regulating K_{ATP} channels. Inhibition of K_{ATP} channels following exposure to vasoconstrictor agonists has been reported in many vascular beds [2, 17]. A modulation of vascular K_{ATP} channels by vasoconstrictors is through the activation of PKC signaling [2, 17]. Studies in guinea pig urinary bladder smooth muscle demonstrated a role of PKC in the inhibition of K_{ATP} channels by muscarinic receptor agonists [50]. Similar findings have shown that phorbol ester, a PKC activator, inhibits K_{ATP} channels currents in mesenteric arteries [51] and insulin secreting cells [52]. Furthermore, many studies suggest that vasoconstrictor hormones and neurotransmitters may inhibit K_{ATP} channels function *via* the activation PKC in vascular smooth muscle [27, 53, 54]. In the recent studies, it has been demonstrated that pregnancy down-regulates the PKC activity associated with an increased K_{ATP} channels activity in uterine arteries, whereas chronic hypoxia selectively enhances the PKC activity associated with a decreased K_{ATP} channels activity in pregnant but not nonpregnant uterine arteries [1, 47–49]. These observations suggest that pregnancy and chronic hypoxia-mediated changes of K_{ATP} channels activities are regulated through PKC-mediated signaling pathway in uterine arteries.

Although the molecular basis for PKC to regulate K_{ATP} channels in vasculature is not well established, a number of studies have shown that the K_{ATP} channel composed of Kir6.1/SUR2B is inhibited by PKC [28, 54, 55]. In addition, trafficking studies have revealed that PKC initiates internalization of the channel complex leading to the decreased channel activity [56]. Furthermore, PKC-mediated phosphorylation of the channels is also an

important mechanism by which the activity of K_{ATP} channels can be modulated, which leads to an alteration in channel properties by modifying kinetics and/or the number of channels at the cell membrane [57, 58].

3. BK_{CA} CHANNELS

3.1. Physiological Roles and Properties of BK_{Ca} Channels in Vasculature

Large-conductance (200~250 pS), Ca^{2+}-activated K^+ channels are activated both by changes in intracellular Ca^{2+} concentration and membrane depolarization. The channels have a high single-channel conductance, thus it is also called as "big" K_{Ca} channels (BK_{Ca} channels) [20]. BK_{Ca} channels are comprised of a pore formed by four α-subunits and four regulatory β-subunits. The α-subunit has seven transmembrane domains (S0-S6) [20, 21, 59]. In addition, the BK_{Ca} channels have four β-subunit isoforms (β1, β2, β3, β4), each with two transmembrane domains. It has been shown that the β1-subunit predominates in vascular smooth muscle [60, 61]. The major role of β1-subunit is to enhance the apparent Ca^{2+} sensitivity of the channel [62–65]. BK_{Ca} channels, a tetramer of α-subunits, associate with auxiliary β-subunits in a tissue-specific manner, modifying the channel's gating properties.

BK_{Ca} channels play an important physiologic role in regulating vascular smooth muscle contractility and blood pressure [60, 61, 66]. Studies in BK β1-subunit knockout mice have demonstrated that Ca^{2+} spark-induced BK current is significantly reduced and the mean arterial blood pressure is elevated in the β1-subunit-null mice, leading to left ventricular hypertrophy [67]. In addition, BK_{Ca} channels also play a key role in the regulation of myogenic tone. Increased blood pressure induces membrane depolarization and increases $[Ca^{2+}]_i$ leading to the activation of BK_{Ca} channels [2]. Activation of BK_{Ca} channels in turn enhances K^+ efflux and counteracts depolarization and constriction-induced by pressure or vasoconstrictors.

3.2. BK_{Ca} Channels Blockers and Openers

BK_{Ca} channels are very effectively blocked by the scorpion peptide toxin charybdotoxin (ChTX), the related peptide iberiotoxin (IbTX) and slotoxin [68, 69]. These blockers bind to the outer vestibule of the channel to physically occlude the pore and prevent ion conduction. Several tremorgenic indole alkaloids molecules such as paxilline, penitrem A and verruculogen are also potent blockers of BK_{Ca} channels. In addition, tetraethylammonium (TEA) is a broad-spectrum K^+ channel blocker. However, low concentrations of TEA (≤ 1 mM) can selectively block the BK_{Ca} channels.

BK_{Ca} channels openers comprise a large series of synthetic benzimidazolone derivatives such as NS004 and NS1619, biaryl amines, biarylureas, pyridyl amines, 3-aryloxindoles, benzopyrans, dihydropyridines, and natural modulators such as dihydrosoyasaponin-1 (DHS-1) and flavonoids. Both NS004 and NS1619 are known as α-subunit-selective BK openers. NS1619 is the only compound without any effects on other ion channels. Other than benzimidazolone derivatives, a wide structural diversity of drugs such as carbonic anhydrase inhibitors has also been shown BK activation properties. In addition, various drugs such as niflumic, flufenamic, and mefenamic acids, as well as 17-β estradiol, can activate BK channels in a nonselective manner [2, 70–74].

3.3. Role of BK_{Ca} Channels in Uterine Vascular Adaptation to Pregnancy

Both α and β1-subunits of BK_{Ca} channels are expressed exclusively in ovine uterine arterial smooth muscle cells with no evidence of their existence in the endothelium [4, 7, 75]. Recent studies have shown a pregnancy-related modification of BK_{Ca} channels gene expression patterns in uterine vasculature [4, 13, 76, 77]. Three α-subunit species were found in uterine arterial smooth muscle of nonpregnant sheep with 83, 100, and 105 kDa. During pregnancy, there was an absence of the 83-kda protein and a marked decrease in the 105-kDa protein, both reappearing ≥30 days after delivery. The 100-kDa α-subunit rises during pregnancy, but it does not appear to equal the fall in the other two species, suggesting that total channel density may actually fall in pregnancy [4]. Other studies showed that the α-subunit of 100 kDa was not significantly different in uterine arteries between nonpregnant and pregnant sheep [6]. One possible reason for this apparent difference may be because of the different sizes of the vessels used [4, 6]. The BK_{Ca} β2-subunits are present in ovine uterine arterial smooth muscle cells, but the levels are low and unchanged throughout the reproductive cycle. However, the β1-subunit expression is increased in pregnant uterine arteries as compared with nonpregnant vessels [4, 6]. The increased β1-subunit expression during pregnancy parallels the rise in uterine blood flow [4, 76, 77]. Electrophysiological studies demonstrated a greater whole-cell K^+ current density in pregnant, as compared with nonpregnant, uterine arteries. Both of the tetraethylammonium (TEA) and iberiotoxin inhibit K^+ currents to the same extent in uterine arterial myocytes. This suggests that the BK_{Ca} channel current density is significantly increased in uterine arteries of pregnant animals [6]. Upregulation of β1-subunit expression during pregnancy is likely to enhance the Ca^{2+} sensitivity of the BK_{Ca} channels and facilitate the activation of the channel and the consequent reduction in uterine vascular tone in pregnancy. Indeed, previous studies have demonstrated that intra-arterial infusion of TEA into the uterine artery circulation of late-gestation sheep causes a decrease of basal uterine blood flow from 50% to 80% in the absence of systemic effects [13, 77]. This is consistent with the recent findings that TEA inhibited K^+ currents by 53% in pregnant uterine arteries, and TEA significantly increased pressure-dependent vascular tone in ovine pregnant uterine arteries and eliminated the difference of the myogenic response between nonpregnant and pregnant uterine arteries [6]. These observations suggest that the heightened BK_{Ca} channels activity is one of important mechanisms in regulating uterine vascular tone and maintaining uteroplacental blood flow in pregnancy.

3.4. Role of BK_{Ca} Channels in Uterine Vascular Adaptation to Hypoxia

In many vascular beds, hypoxia causes local vasodilation. This response increases blood flow to the affected organ and thus promotes restoration of tissue oxygenation. Numerous studies suggest that the hypoxia-induced vasodilation and blunted vasoconstriction are associated with an increased BK_{Ca} channels expression and/or their activities in the vasculatures [9, 78–81]. In the lung, hypoxia causes local vasoconstriction. Paradoxically, the hypoxia-induced pulmonary hypertension is also associated with an increased expression of BK_{Ca} channels [82, 83], which might suggest an adaptive mechanism counteracting pulmonary hypertension since BK_{Ca} channels activation serves as a feedback modulator of vascular tone when cytoplasmic calcium becomes elevated [2]. In the uteroplacental circulation, hypoxia-induced fetoplacental vascular constriction has been well demonstrated

[84]. The hypoxia-induced fetoplacental vascular constriction is largely mediated by hypoxic inhibition of Kv channels rather than its effect on BK_{Ca} channels in smooth muscle of small fetoplacental arteries [85]. In pregnant sheep, chronic hypoxia enhances uterine vascular tone [47]. Although the mechanisms underlying chronic hypoxia-mediated elevation of uterine vascular tone in pregnant animals are not completely understood, the reduction of uterine vascular BK_{Ca} channels activities is a possible mechanism, given a key role of BK_{Ca} channels in the regulation of uterine vascular tone during normal course of pregnancy [6].

3.5. Regulation of BK_{Ca} Channels by Sex Steroid Hormones

Pregnancy is a state with substantially higher levels of estrogen and progesterone as compared with the nonpregnant state. Growing evidence suggests that the increased levels of sex steroid hormones may regulate uterine vascular tone and uterine blood flow *via* alteration of BK_{Ca} channels-mediated signaling [4, 6, 76, 77, 86–88]. In ovariectomized sheep or mice, the estrogen treatment enhanced β1-subunit mRNA and protein expression in uterine arteries and myometrial smooth muscle, which suggests a possible role of the steroid hormone in modulating BK_{Ca} channels expression [7, 89]. Indeed, the direct treatment of uterine arteries from nonpregnant animals with estrogen and progesterone for 48 hours *ex vivo* significantly enhanced β1-subunit protein expression in uterine arterial smooth muscle [6]. The expression of β1 subunit was also found higher in the follicular phase as compared with the luteal phase of the ovarian cycle in nonpregnant sheep, probably because of relatively high estrogen levels that were produced endogenously by the ovaries [75, 90]. Furthermore, TEA had no significant effects on basal uterine vascular resistance and blood flow, but produced a dose-dependent inhibition of the estradiol-17β ($E_2β$)-induced rise in uterine blood flow when infused into the uterine arterial circulation of ovariectomized nonpregnant ewes [91]. In addition, $E_2β$-mediated uterine vasodilation is also associated with BK_{Ca} channels activation [4, 76, 77, 88, 91–95]. These observations suggest that the regulation of uterine vascular tone by BK_{Ca} channels is modulated by sex steroids.

As compared with estrogen, the effect of progesterone in the regulation of BK_{Ca} channels is less well established. In contrast to estrogen, progesterone inhibits the BK_{Ca} channel current in Xenopus oocytes [96]. The inhibitory effect of progesterone on BK_{Ca} channels may partly explain its antagonism against estrogen-mediated vasorelaxation as shown *in vitro* in porcine coronary arteries [97]. Given the fact that progesterone plays an important role in regulating uterine blood flow during pregnancy [92, 98], whether progesterone-mediated uterine vascular tone is regulated through modulation of BK_{Ca} channels needs to be further investigated.

3.6. Regulation of BK_{Ca} by PKC

The activation of PKC has been shown an inhibition of BK_{Ca} channels in various vascular beds [99, 100]. Studies in porcine coronary artery have demonstrated that PKC activators inhibit the BK_{Ca} channels activation by increasing in cytosolic free Ca^{2+} and phosphorylation of the channel protein [99, 101]. In addition, PKC-induced phsophorylation of the channel protein inhibits BK_{Ca} channels activities in smooth muscle, and decreases its sensitivity to be activated by cGMP-dependent protein kinas I or PKA [60, 101]. Recent

studies have shown that the activation of PKC by PDBu significantly inhibits the whole-cell K^+ current in uterine arterial myocytes. The inhibition of K^+ currents by PDBu is significantly greater in the myocytes of pregnanat sheep than that in nonpregnant animals [6]. It has been further demonstrated that the PDBu-induced reduction of K^+ currents is predominately mediated by inhibiting the BK_{Ca} channels. PKC plays an important role in the regulation of vascular smooth muscle contractility [102, 103]. The finding that the activation of PKC inhibited BK_{Ca} channels activity and increased pressure-dependent myogenic tone in pregnant uterine arteries provides a functional link between BK_{Ca} channels and PKC-mediated attenuation of myogenic tone of uterine arteries in pregnancy.

4. K_V CHANNELS

4.1. Physiological Roles and Properties of K_v Channels in Vasculature

Voltage-dependent K^+ (K_v) channels including K_v 1.5 and K_v 1.6 families have been identified in smooth muscle of most vascular beds [2, 104–109]. They have been sub-classified on the basis of their voltage dependence and pharmacology. The basic structure of K_v channels is conserved among different families. Each channel is composed of four α-subunits, themselves composed of six regions of trans-membrane hydrophobic amino acids (S1–S6). The S4 region is considered as the voltage sensor. In addition to these α-subunits, there are β-subunits that may play an important role in modulating the gating properties of the α-subunits [65, 110–112]. K_v channels are voltage dependent. K_v channels are activated in response to membrane depolarization and they are involved in action potential repolarization in electrically excitable muscle such as cardiomyocytes. In addition, the activity of K_v channels contributes to the regulation of resting membrane potential and basal vascular tone [2].

4.2. Pharmacological Blockers and Openers

Because of the ubiquitous expression of multiple classes of K_v channels in vasculatures, there is lack of selective blockers/openers. 4-Aminopyridine (4-AP) is the most selective known blockers of K_v channels in vasculatures [105, 113, 114]. The half-block concentration of 4-AP for K_v channels is in the range of 0.2 ~1.1 mM, which does not inhibit BK_{Ca} channels. Thus it has been used to separate K_v currents from BK_{Ca} currents that are also activated by membrane depolarization [2, 115–118]. In addition to 4-AP, there are some other agents that may inhibit K_v channels such as agitotoxin-2, phencyclidine, tedisamil and quinidine [2, 105, 113, 114]. At higher concentrations, TEA and glibenclamide may also inhibit K_v channels in vasculatures [2].

K_v channels are opened by membrane depolarization. In addition, these channels can be activated by cAMP-protein kinase A signaling pathway and some other vasodilators such as adenosine, PGI_2 and CGRP [119, 120]. On the other hand, vasoconstrictors, including endothelin and angiotensin II, appear to close K_v channels through PKC-mediated signaling [121–123]. Recent studies have demonstrated that Rho kinase-mediated signaling pathway may close K_v channels [122]. Thus, the inhibition of K_v channels activation may contribute to vasoconstrictor-induced depolarization of arteriolar smooth muscle cells.

4.3. Role of K_V Channels in Uterine Vascular Adaptation to Pregnancy

Pressure-induced membrane depolarization is one of the important mechanisms in the development of myogenic tone in pressurized arterial beds and the extent of pressure-induced depolarization is regulated by K_v channels [2, 124, 125]. In rats, it has been demonstrated that pregnancy enhances pressure-induced myogenic tone in small uteroplacental arteries associated with an increased Ca^{2+} influx and enhanced smooth muscle cell depolarization [126]. Pretreatment with 4-AP in the uterine arteries from nonpregnant rats inhibited the activity of K_v channels and mimicked the effects of pregnancy by increasing pressure-induced depolarization, elevation of $[Ca^{2+}]_i$, and development of myogenic tone. Furthermore, K_v channels currents were also decreased in the uterine arterial myocytes isolated from pregnant rats compared with those of nonpregnant control. These observations suggest that a decrease in K_v channels activity may be a mechanism mediating the pregnancy-induced augmentation of myogenic tone in rat uetroplacental arteries.

4.4. Role of K_V Channels in Vascular Adaptation to Hypoxia

K_v channels may play an important role in hypoxia-mediated pulmonary vasoconstriction [127–129]. Since K_v channels contribute to the membrane potential in pulmonary vascular smooth muscle cells as they do in the systemic arteries, hypoxia induced pulmonary arterial depolarization may be regulated *via* inhibiting K_v channels. Indeed, acute hypoxia inhibits K_v channels activity in pulmonary artery smooth muscle cells and induces membrane depolarization and a rise in intracellular Ca^{2+} that triggers vasoconstriction. Prolonged hypoxia decreases the expression of K_v channels and reduces K_v channels currents in the vessel [10, 129]. These observations suggest that the reduction of K_v channels activity in response to acute or chronic hypoxia may contribute to the hypoxia-mediated pulmonary hypertension.

Similar to pulmonary arteries, human fetoplacental vessels also produce vasoconstriction in response to hypoxia. In human fetoplacental artery perfused at a constant flow rate [85], both hypoxia and 4-AP reversibly increased perfusion pressure in non-additive manner, suggesting they act *via* a common mechanism. Western blotting and RT-PCR analyses showed the expression of K_v channels in the fetoplacental vessels. In addition, patch-clamp experiments demonstrated that hypoxia reversibly inhibited K_v, but not BK_{Ca} or ATP-dependent currents, in the fetoplacental arteries smooth muscle cells. These observations suggest that human fetaplcental vessels produce vasoconstriction in response to hypoxia and this response is mainly mediated by hypoxic inhibition of K_v channels in the smooth muscle of small fetoplacental arteries [85].

5. K_{IR} CHANNELS

5.1. Physiological Roles and Properties of K_{IR} Channels in Vasculature

Inward rectifier K^+ (K_{IR}) channels have been found in smooth muscle of small-diameter resistance vessels such as small coronary and cerebral arteries [111, 130, 131]. K_{IR} channels conduct K^+ ions into cells from negative potentials to more positive potentials, which cause strong inward K^+ currents [17]. The inward current is much larger than the outward current.

K_{IR} channels are composed of two trans-membrane regions M1 and M2 and a H5 region dipping into the membrane to line the outer part of the pore [10]. There are several K_{IR} gene subfamilies such as K_{IR} 2.0, K_{IR} 2.1–4 and K_{IR} 6.0-2. K_{IR} 2.1 is predominately expressed in smooth muscle of small-diameter resistance vessels, rather than in larger arteries. The activity of K_{IR} channels depends on the membrane potential and the extracellular K^+ concentrations ($[K^+]_o$) [117, 132]. With a small increase in $[K^+]_o$, the channel conducts inward current at membrane potentials negative to the new E_k, but the outward current maintains the same situation [117, 132]. In contrast to K_v and BK_{Ca} channels that are activated by membrane depolarization, K_{IR} channels are activated by membrane hyperpolarization and induce vasodilation [2]. K_{IR} channels provide the dominant K^+ conductance near the resting membrane potential and may modulate basal vascular tone.

5.2. Pharmacological Blockers and Openers

Ba^{2+} is a relatively selective inhibitor of K_{IR} channels in vascular smooth muscle cells, with a dissociation constant (K_d) in the micromolar ranges (~2 μM) [117, 133]. This blockade is voltage dependent and the extent of inhibition is greater at more negative membrane potentials. Although Ba^{2+} can block other K^+ channels, it is much less effective at blocking the function of other K^+ channels expressed in vasculature. For example, the K_d for the K_{ATP} channel at −60 mV is 200 μM, and the K_d values for the BK_{Ca} and K_v channels are in the millimolar range. Thus Ba^{2+} is a useful tool to distinguish the K_{IR} channels from other K^+ channels [2, 133]. Both Ca^{2+} and Mg^{2+} also block K_{IR} channels activity in vasculature at physiological concentrations. External Ca^{2+} and Mg^{2+} (5 mM) reduce the K_{IR} channels currents by 47% and 41%, respectively, at −60 mV, in a largely voltage-independent manner. In addition, external Cs^+ also blocks K_{IR} channels in vascular smooth muscle cells with a K_d of 2.9 mM at -60 mV. The inhibition of K_{IR} channels currents in vascular smooth muscle cells is highly voltage dependent with rapid kinetics [17, 133]. Taken together, it suggests that multiple ions can modulate the K_{IR} channels activity. In addition, there are several agents that can activate K_{IR} channels. For example, C-type natriuretic peptide, EDHF, adenosine, and bradykinin, which activate PKA and protein kinase G, may open vascular K_{IR} channels [134–135].

5.3. Regulation of Vascular K_{IR} Channels by PKC and PKA

Vascular K_{IR} channels can be down-regulated by vasoconstrictors [53, 136]. Among other K^+ channels, the regulation of K_{IR} channels by vasoconstrictors such as ET-1 and Angiotensin II is closely related to PKC activation. Several PKC isoforms have been identified in vascular smooth muscle cells. Previous studies have shown that ET-1 and angiotensin II activate Ca^+-independent PKC_ε to inhibit K_{ATP} and K_v currents. However, the inhibitory effects of ET-1 and angiotensin II on K_{IR} channels activity are mediated by the PKC_α activation. These observations suggest that PKC isoforms may contribute differentially to the vasoconstrictors-mediated regulations of different K^+ channels activities [53, 136]. In contrast to PKC, PKA may play an important role in the activation of K_{IR} channels in the vasculature. PKA-coupled vasodilators such as adenosine and bradykinin induce vasodilation through the activation of K_{IR} channels in vascular smooth muscle *via* cAMP-PKA signaling pathway [27].

5.4. Role of K_{IR} Channels in Vascular Adaptation to Pregnancy and Hypoxia

The K_{IR} 6.1 channel mRNA has been readily detected by RT-PCR in human fetoplacental arteries and veins, and a protein expression band at ~ 55 kDa in the vessels has been detected by Western blot analysis [137]. This finding opens a door to further study of the functional role of K_{IR} channels in the regulation of uteroplacental vascular tone in pregnancy. In addition, recent studies have demonstrated that functional K_{IR} 6.1 and K_{IR} 6.2 channels are expressed in human pregnant myometrium smooth muscle cells and the downregulation of K_{IR} 6.1 and K_{IR} 6.2 channels expression in the myometrium may contribute to the enhanced uterine contractility associated with the onset of labor [138–140].

Vasodilations in response to hypoxia in certain peripheral vasculatures such as cerebral and small coronary arteries are likely a protective response to increase local blood flow. One of the mechanisms underlying hypoxia-induced vasodilation is *via* the activation of K_{IR} channels by hypoxia. Park *et al.* [53] have examined the effects of acute hypoxia on Ba^{2+}-sensitive inward rectifier K^+ (K_{IR}) current in rabbit coronary arterial smooth muscle cells. They have demonstrated that the density of K_{IR} current is greater in cells isolated from small-diameter coronary arteries than in cells from larger arteries. Hypoxia induces an increase in K_{IR} current in small coronary artery smooth muscle cells. The hypoxia-induced increased in K_{IR} currents is attenuated by the inhibition of adenylyl cyclase and PKA. In Langendorff-perfused rabbit hearts, hypoxia-induced increase in coronary blood flow is inhibited by Ba^{2+}. These findings suggest that the hypoxia-induced coronary vasodilation, at least partly, regulated by the activation of K_{IR} channels *via* cAMP- and PKA-dependent signaling pathways. In contrast to hypoxic vasodilation, hypoxia may induce vasoconstriction in certain vessels including pulmonary and fetoplacental arteries. However, there is no evidence at present to suggest a role of K_{IR} channels in hypoxia-induced vasoconstriction. Given the finding that chronic hypoxia enhanced uterine vascular tone in pregnant sheep associated with an increase in PKC activity in uterine arteries [47], it is plausible to propose that hypoxia may inhibit K_{IR} channels activation *via* PKC-dependent mechanism and the attenuation of K_{IR} channel activation may play a role in hypoxia-mediated enhanced uterine vascular tone during pregnancy.

6. CONCLUDING REMARKS

It is evident that K^+ channels play an important role in the regulation of vascular tone. In general, the activation of K^+ in arterial smooth muscle causes a decrease in vascular tone and an increase in blood flow *via* vasodilation. In contrast, the inhibition of K^+ channels results in vasoconstriction. Pregnancy is associated with increased sex steroids hormones/receptors levels in uterine vasculature (Fig. 1). The increased steroid hormones/receptors differentially attenuate PKC-mediated signaling in uterine arterial smooth muscle cells [15, 142], leading to differential upregulation of K^+ channels expression and/or their activities, which are likely to contribute to the decreased uterine vascular tone and increased uterine blood flow in pregnancy. Exposed to hypoxia during pregnancy attenuates the effects of sex steroid hormones/receptors, leading to enhanced PKC activation in pregnant uterine arteries. The selective inhibition of K^+ channels activities by the increased PKC activation is likely to contribute significantly to the maladaptation of uterine vascular hemodynamics in pregnancy

complicated by preeclampsia and fetal intrauterine growth restriction in response to hypoxia. As the knowledge of structures and properties of each K^+ channels and their physiological and pathological roles in uterine vasculature continues to grow, it should become possible to develop pharmacologic therapeutic strategies targeting on K^+ channels to prevent or treat uterine vascular dysfunction in pregnancy complications such as diabetes and hypertension in gestation, preeclampsia and fetal intrauterine growth restriction.

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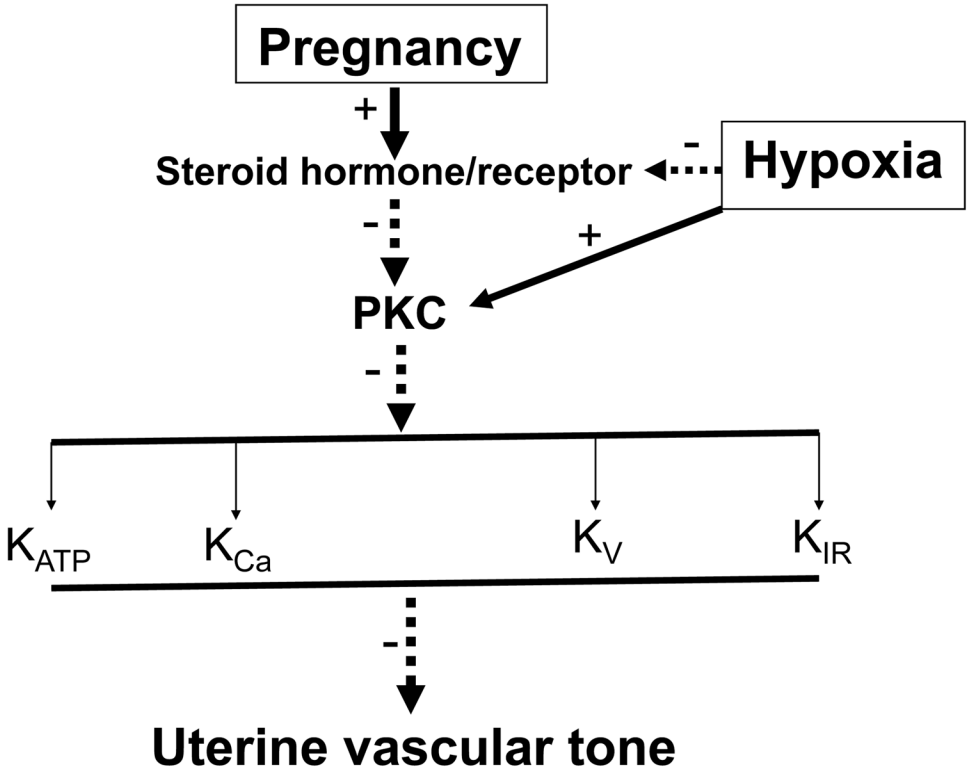

Fig. 1. The potential role of pregnancy and hypoxia in regulation of K^+ channels in uterine vasculatures

Activation of protein kinase C (PKC) results in inhibition of K^+ channels activity. The increased sex steroid hormones/their receptors during pregnancy down-regulate PKC gene expression and/or activity in uterine artery smooth muscle cells, which leads to a selectively increased K^+ channels expressions and activities in uterine vasculatures during pregnancy. However, chronic hypoxia during pregnancy enhances PKC activity via down-regulation of steroid hormone-mediated signaling, resulting in decreased K^+ channels activities and increased uterine vascular tone.