Remodeling of arterial tone regulation in postnatal development: focus on smooth muscle cell potassium channels

Anastasia A. Shvetsova, Dina K. Gaynullina, Olga S. Tarasova, Rudolf Schubert

Angaben zur Veröffentlichung / Publication details:

Shvetsova, Anastasia A., Dina K. Gaynullina, Olga S. Tarasova, and Rudolf Schubert. 2021. "Remodeling of arterial tone regulation in postnatal development: focus on smooth muscle cell potassium channels." *International Journal of Molecular Sciences* 22 (11): 5413. https://doi.org/10.3390/ijms22115413.

International Journal of
Molecular Sciences

MDPI

Review

Remodeling of Arterial Tone Regulation in Postnatal Development: Focus on Smooth Muscle Cell Potassium Channels

Anastasia A. Shvetsova [1,*], Dina K. Gaynullina [1,2], Olga S. Tarasova [1,3,†] and Rudolf Schubert [4,†]

1 Department of Human and Animal Physiology, Faculty of Biology, M.V. Lomonosov Moscow State University, 119234 Moscow, Russia; dina.gaynullina@gmail.com (D.K.G.); ost.msu@gmail.com (O.S.T.)
2 Department of Physiology, Russian National Research Medical University, 117997 Moscow, Russia
3 Laboratory of Exercise Physiology, State Research Center of the Russian Federation-Institute for Biomedical Problems, Russian Academy of Sciences, 123007 Moscow, Russia
4 Physiology, Institute of Theoretical Medicine, Medical Faculty, University of Augsburg, 86159 Augsburg, Germany; rudolf.schubert@med.uni-augsburg.de
* Correspondence: anastasiashvetsova92@gmail.com
† These authors contributed equally.

Abstract: Maturation of the cardiovascular system is associated with crucial structural and functional remodeling. Thickening of the arterial wall, maturation of the sympathetic innervation, and switching of the mechanisms of arterial contraction from calcium-independent to calcium-dependent occur during postnatal development. All these processes promote an almost doubling of blood pressure from the moment of birth to reaching adulthood. This review focuses on the developmental alterations of potassium channels functioning as key smooth muscle membrane potential determinants and, consequently, vascular tone regulators. We present evidence that the pattern of potassium channel contribution to vascular control changes from $K_{ir}2$, K_v1, K_v7 and TASK-1 channels to BK_{Ca} channels with maturation. The differences in the contribution of potassium channels to vasomotor tone at different stages of postnatal life should be considered in treatment strategies of cardiovascular diseases associated with potassium channel malfunction.

Keywords: potassium channels; postnatal development; vascular smooth muscle; systemic circulation; vascular remodeling

Citation: Shvetsova, A.A.; Gaynullina, D.K.; Tarasova, O.S.; Schubert, R. Remodeling of Arterial Tone Regulation in Postnatal Development: Focus on Smooth Muscle Cell Potassium Channels. *Int. J. Mol. Sci.* **2021**, *22*, 5413. https://doi.org/10.3390/ijms22115413

Academic Editor: Ana Belen Garcia-Redondo

Received: 28 April 2021
Accepted: 18 May 2021
Published: 21 May 2021

Potassium channels are transmembrane proteins which form potassium-selective pores. They are widely distributed among living organisms and are found in many cell types, including cells of the cardiovascular system. In cardiac and some vascular (mainly venous) myocytes, potassium channels mediate the repolarization phase of the action potential. In arterial smooth muscle cells, which commonly do not generate action potentials under physiological conditions, a change in potassium channel activity provides gradual shifts of the membrane potential [1,2]. This leads to alterations in the activity of voltage-gated calcium channels accompanied by changes in the calcium influx, as well as the intracellular calcium concentration and corresponding modifications of vascular tone. Of note, malfunctions of several potassium channel types are associated with arterial hypertension, diabetes mellitus and other metabolic disorders [3–6].

1. Potassium Channels Are Key Regulators of Arterial Tone

The membrane potential of arterial smooth muscle cells is a key determinant of vascular tone [7,8]. Indeed, a membrane potential shift by only a few millivolts towards hyperpolarization or depolarization leads to a considerable increase and decrease in arterial lumen, respectively [9]. Potassium channels of the cell membrane play a key role in the establishment of the resting membrane potential, as well as in the regulation of the membrane potential under the action of various vasoconstrictors and vasodilators [6,10].

Several functional types of potassium channels are described in arterial smooth muscle voltage-gated potassium channels (K_v), inward-rectifier potassium channels (K_{ir}), adenosine triphosphate-sensitive potassium channels (K_{ATP}), two-pore potassium channels (K_{2P}), as well as calcium-activated potassium channels of large conductance (BK_{Ca}) [8,11].

It has been shown that potassium channel blockade leads to the depolarization of smooth muscle cells and an increase in contractile responses of the vascular wall to stimuli of different nature. Activation of potassium channels, on the contrary, counteracts the development of contraction or causes the dilation of arterial smooth muscle [8,12]. Therefore, potassium channels reduce the depolarization of arterial smooth muscle and play anticontractile or vasorelaxation roles. Importantly, potassium channel activity can limit arterial responses to the contractile influence of sympathetic nerves [13,14], a principal determinant of systemic blood pressure.

2. Postnatal Development Is Associated with Structural and Functional Remodeling of the Systemic Circulation

The mammalian cardiovascular system undergoes crucial structural and functional changes after birth. The arterial smooth muscle layer thickens and the amount of contractile proteins rises [15–17]. This increases the ability of arteries to develop a contractile response. In addition, the density of sympathetic innervation of the arteries increases gradually with age [15,18,19]. Therefore, arteries become more susceptible to procontractile influences from the sympathetic nervous system at adult age. Moreover, considerable alterations in the mechanisms governing vascular smooth muscle contraction occur with development—the strong contribution of mechanisms that are weakly dependent on changes in the intracellular calcium concentration (calcium sensitization) in the newborn switches to more calcium-dependent mechanisms as the organism grows [15,18,20,21]. Finally, the anticontractile influence of the vascular endothelium decreases with age [22,23]. This structural and functional remodeling leads to a dramatic rise of systemic blood pressure, which almost doubles from the time of birth [18,23–25].

The impact of such important regulators of vascular tone as potassium channels also changes during postnatal life. The present review focuses on the developmental alterations of the vasomotor role of different potassium channel families in arteries of the peripheral circulation, which play a key role in the regulation of systemic blood pressure.

3. Developmental Alterations of Potassium Channel Functioning in Arteries of the Systemic Circulation

3.1. Voltage-Gated Potassium Channels (K_v Channels)

3.1.1. K_v Channels: Properties and Functions in Arteries

Voltage-gated potassium channels (K_v channels) are a large family of potassium channels which activate in response to membrane depolarization. A total of 12 subfamilies of K_v channels (K_v1–K_v12) exist, and the functionally most important subfamilies in arterial smooth muscle are K_v1, K_v2 and K_v7 [26,27]. In arterial smooth muscle, the main isoforms of K_v1 channels are $K_v1.2$, $K_v1.5$; of K_v2 channels is $K_v2.1$; and of K_v7 channels are $K_v7.4$ and $K_v7.5$ [8,28]. A unique feature of K_v7 channels is their relatively low activation threshold. The $V_{0.5}$ value (voltage that produces 50% activation) is +5 mV for K_v1 and K_v2, and only −34 mV for K_v7, as was shown in the rat mesenteric artery smooth muscle cells [29]. In other words, the activation threshold of K_v7 channels is close to the level of the resting membrane potential of arterial smooth muscle cells, which varies in the range from –40 to −65 mV [6,8,9]. A number of studies have demonstrated the important role of K_v1, K_v2 and, especially, K_v7 channels in maintaining basal tone and regulating contractile responses of arteries, since the blockade of these channels caused depolarization of arterial smooth muscle cells and the development of strong basal tone and enhanced vasoconstrictor responses [26,30–36].

3.1.2. The Vasomotor Role of K_v Channels Decreases with Maturation

In earlier studies, 4-aminopyridine (4-AP) was used as a blocker of K_v channels [37]. It was demonstrated that the cumulative addition of 4-AP caused contraction of isolated aorta segments from newborn rats, while its effects on adult aorta were considerably less pronounced [38]. In accordance with this, 4-AP inhibited [38] or completely blocked [39] the outward potassium current in isolated smooth muscle cells from newborn, but not adult, aorta. In contrast, the effects of 4-AP on resting tone and 5-HT (5-hydroxytryptamine or serotonin)-induced contractions were more pronounced in cerebral arteries of adult sheep than in fetuses [40], suggesting an increase in K_v-functional contribution with maturation. However, in recent studies, 4-AP was shown to activate $K_v7.4$ channels [41] and increase the intracellular pH affecting BK_{Ca} currents [42], which complicates the interpretation of the results obtained using this inhibitor.

Recently, selective blockers for K_v1, K_v2 and K_v7 channels have become available: DPO-1, stromatoxin and XE991, respectively [33,43,44], which made it possible to evaluate the contribution of these K_v channel subfamilies to the regulation of arterial tone separately.

With the use of DPO-1 (1 μM), it was shown that the contribution of the K_v1 subfamily decreases with maturation [45]. DPO-1 caused the development of basal tone, increased contractile responses and sensitivity to the α_1-adrenoceptor agonist methoxamine in saphenous arteries of young rats (10 to 15 days old), while no effect was observed in arteries of adult animals (2 to 3 months old) [45]. The decrease in the functional impact of K_v1 channels during development may be associated with a decrease in their expression. This assumption is supported by data showing a decrease in $K_v1.2$ channel protein expression in rat aorta in the period between birth and adulthood [39].

Stromatoxin, a blocker of the K_v2 subfamily, did not affect the contractile responses of saphenous arteries, either in young or in adult rats [45], although an increase in $K_v2.1$ channel protein expression with maturation was previously demonstrated in rat aorta [39]. Perhaps the levels of expression and, consequently, functional contribution of K_v2 channels may differ between the aorta and saphenous arteries.

The functional role of K_v7 channels strongly declines with maturation. Blockade of these channels with XE991 and linopirdine led to the development of basal tone, increased contractile responses and sensitivity to the α_1-adrenoreceptor agonist methoxamine and the thromboxane A2 receptor agonist U46619 in saphenous arteries of young rats [45,46]. These effects were considerably less pronounced in arteries of adult rats. The differences found were associated with a smaller effect of K_v7 channel blockade on the membrane potential of smooth muscle in adult rats [45]. These effects are probably associated with a decrease in channel expression in arterial smooth muscle with development. Indeed, a decrease in $K_v7.4$ channel protein expression was demonstrated with maturation. Importantly, the protein expression of the accessory KCNE4 subunit, which was shown to strongly augment $K_v7.4$ channel protein expression and $K_v7.4$ channel activity [47], also declined with age [45]. In addition to different expression levels, the functional impact of K_v7 channels depends on the activity of other potassium channels. A recent study demonstrated that BK_{Ca} channel activity (which increases with age, see further in detail) suppresses K_v7 channel functional availability in saphenous arteries of adult, but not young, rats [46].

Thus, the results with the use of selective K_v channel subfamily blockers allow the suggestion that the vasomotor role of K_v1 and, especially, K_v7 channels in systemic arteries decreases from the early postnatal period to adulthood. Moreover, their functional availability can be suppressed by the increasing contribution of other potassium channels, for example BK_{Ca} channels, with age.

3.2. Two-Pore Potassium Channels (K_{2P})

3.2.1. K_{2P} Channels: Properties and Functions in Arteries

These channels were discovered in the vasculature relatively recently [48,49]. The channel is formed by two subunits, each has two pore-forming loops (P-loop, hence the name of the channel, K_{2P}). Originally, K_{2P} channels were described as leakage channels,

since at resting conditions they carry an outward potassium current, and the probability of channel opening does not depend on the membrane potential [11,50,51]. Research over the last few years has changed the image of these channels from being simply leak channels to regulatory channels having important roles in the control of cell excitability [52]. These facts indicate the involvement of K_{2P} channels in the maintenance of the resting potential, denoting their importance for the regulation of arterial tone.

There are six functional classes of K_{2P} channels. One of them, the acid-sensitive TASK-1 channel, is of particular interest. Recently, it was shown that a mutation in the *KCNK3* gene encoding the TASK-1 channel is associated with familial and idiopathic forms of pulmonary hypertension [53].

3.2.2. The Impact of TASK-1 Channels on the Regulation of Vascular Tone and Blood Pressure Dramatically Decreases with Maturation

The functional role of these channels is important in pulmonary circulation [53–55], but very little is known about their function in systemic arteries. The ontogenetic aspect of TASK-1 channel function in systemic arteries has been studied very little. The only work devoted to this issue indicated a decrease in their vasomotor role in early postnatal ontogenesis [24].

Blockade of TASK-1 channels was shown to increase basal tone and contractile responses to methoxamine in the saphenous artery of young, but not adult, rats [24]. In arteries of adult rats, TASK-1 channel blockade did not lead to such a pronounced depolarization of the smooth muscle cells as was observed in young animals. Intravenous administration of AVE1231, a TASK-1 channel blocker [56], led to a considerable increase in mean blood pressure at young age, but not in adulthood, which indicates a decrease in the role of TASK-1 channels in blood pressure control with maturation. Finally, both TASK-1 mRNA and protein content in arterial tissue decreased as the rats grew older [24].

Therefore, the anticontractile role of TASK-1 channels in the arteries of systemic circulation and their impact to the lowering of blood pressure most likely declines with maturation.

3.3. Inward-Rectifier Potassium Channels (K_{ir} Channels)

3.3.1. K_{ir} Channels: Properties and Functions in Arteries

Inward-rectifier potassium channels mediate an inward potassium current at membrane potentials more negative than the equilibrium potassium potential ($E_M > E_K$) and a less pronounced outward potassium current at membrane potentials more positive than the equilibrium potassium potential ($E_M < E_K$) [57]. The property of inward rectification is determined by the influence of intracellular substances—magnesium ions and polyamines, which block the outward potassium current at $E_M < E_K$ [58,59]. There are seven subfamilies of K_{ir} channels, the second ($K_{ir}2$) and sixth subfamilies ($K_{ir}6$) are expressed in arterial smooth muscle [8]. The sixth subfamily of K_{ir} channels has distinct functional and regulatory features and therefore is classified into a class of ATP-dependent potassium channels (K_{ATP} channels) which will be discussed separately (see Section 3.4 below).

Arterial smooth muscle cells express $K_{ir}2.1$, $K_{ir}2.2$ and $K_{ir}2.4$ isoforms. Using $K_{ir}2.1$ gene knockout mice, it was demonstrated that this isoform is primarily functionally important in cerebral arteries at least in the early postnatal period, since the data were obtained on young animals [60]. When the level of the membrane potential of arterial smooth muscle is more positive than E_K (at physiological resting membrane potentials), K_{ir} channels mediate an outward hyperpolarizing current which counteracts the contraction of arteries. Indeed, a number of studies have demonstrated that K_{ir} channels are involved in maintaining the resting potential since their blocker barium chloride caused a depolarization of arterial smooth muscle [61–63]. Moreover, pretreatment of the rat coronary, cerebral and tail small arteries with barium chloride inhibited KCl-induced vasodilation, indicating that $K_{ir}2$ channels mediate this reaction [61,63].

3.3.2. The Vasomotor Role of $K_{ir}2$ Channels Decreases with Maturation

The contribution of $K_{ir}2$ channels on the regulation of vascular tone, as well as its expression pattern during ontogenesis, is not fully understood. It was shown that $K_{ir}2.1$ and $K_{ir}2.4$ mRNA expression decreased with age, while the expression of $K_{ir}2.2$ increased during postnatal maturation in smooth muscle cells of the rat saphenous artery [45]. In functional experiments on the sheep middle cerebral artery, blockade of $K_{ir}2$ channels with barium chloride did not affect basal tone and contractile responses to 5-HT in either adult sheep or sheep fetuses [40]. However, another agonist, noradrenaline, enhanced the contractile responses of middle cerebral arteries of sheep fetuses in the presence of barium chloride, which was not observed in arteries of adult animals [64]. In addition, barium chloride increased the contractile responses to the α_1-adrenoceptor agonist methoxamine in rat saphenous arteries at different stages of development and the extent of this effect declined with age [45]. A greater contraction during the blockade of K_{ir} channels in young rats was accompanied by a greater depolarization of the smooth muscle membrane potential compared to adults [45].

Therefore, results of a few studies suggest a decrease in the functional role of $K_{ir}2$ channels with age [45,64]. The decline of $K_{ir}2.1$ and $K_{ir}2.4$ expression may result in the decline of their vasomotor role. However, more studies on this issue should be conducted.

3.4. ATP-Sensitive Potassium Channels (K_{ATP} Channels)

3.4.1. K_{ATP} Channels: Properties and Functions in Arteries

K_{ATP} channels are sensitive to the concentration of ATP in cell cytoplasm. The intracellular ATP concentration is quite high at physiological resting conditions and K_{ATP} channels are closed. However, under conditions of limited oxygen and substrates, ADP accumulates, which activates the K_{ATP} channel and leads to an efflux of potassium from the cell, hyperpolarizing the membrane potential. Thus, the ADP/ATP ratio is a key physiological regulator of K_{ATP} channel activity [65,66]. Relaxation of arteries under functional and reactive hyperemia occurs largely due to the activation of K_{ATP} channels [67,68]. It is important to note that under such pathological conditions as hypoxia, ischemia, and sepsis, the role of K_{ATP} channels in the regulation of arterial tone is extremely large [69,70].

3.4.2. The Vasomotor Role of K_{ATP} Channels under Normal Physiological Conditions Does Not Change during Postnatal Development

The functional role of K_{ATP} channels during ontogenesis has been poorly studied. Of note, the results of these studies qualitatively depend on the method employed to assess the vasomotor role of K_{ATP} channels—using an activator or a blocker.

In one of the early studies, lemakalim, an activator of K_{ATP} channels, relaxed the middle cerebral artery in both adult sheep and fetuses [71]. At the same time, the sensitivity to lemakalim was considerably higher in adult sheep, which suggests an increase in the functional impact of K_{ATP} channels in the regulation of vascular tone with age. Later on, this group demonstrated a qualitatively similar result using another K_{ATP} channel activator—pinacidil. The incubation of segments of the middle cerebral artery with pinacidil resulted in a weakening of contractile responses to noradrenaline in adult sheep, but not in fetuses [64].

The K_{ATP} channel blocker, glibenclamide, did not increase the basal tone and contractile responses to noradrenaline of the middle cerebral artery in either adult sheep or fetuses [64]. Similarly, no effect of glibenclamide on basal tone and contractile responses to the α_1-adrenoceptor agonist methoxamine was found in the rat saphenous artery at different stages of postnatal development [45].

Apparently, under normal physiological conditions, K_{ATP} channels are not active in the vasculature of either young or adult animals, and, therefore, the effect of their blockade on vascular tone cannot be observed. At the same time, results obtained with the use of activators suggest that the functional contribution of these channels grows as the organism

ages. It is possible that the number of these channels increases with age, as it has been shown for other tissues, for example the rat myocardium [71].

3.5. Calcium-Activated Potassium Channels of Large Conductance (BK_{Ca} Channels)

3.5.1. BK_{Ca} Channels: Properties and Functions in Arteries

Calcium-activated potassium channels of large conductance (BK_{Ca} channels) are regulated by both the membrane potential and the intracellular calcium concentration. The activity of BK_{Ca} channels increases with membrane depolarization with an increase in the intracellular calcium concentration [72].

An important physiological role of BK_{Ca} channels is that they provide a negative feedback regulation of arterial myogenic tone. It is known that ryanodine receptors (RyRs) of the sarcoplasmic reticulum adjoin to BK_{Ca} channels in the smooth muscle cell outer membrane [73,74]. Moreover, BK_{Ca} channels are co-localized with voltage-dependent calcium channels in the caveolae of arterial smooth muscle cells [75,76]. Thus, a local increase in the calcium concentration as a result of calcium sparks or activation of voltage-dependent calcium channels causes a short-term increase in the activity of BK_{Ca} channels, the efflux of potassium ions from the cell, hyperpolarization and, as a result, relaxation.

3.5.2. The Vasomotor Role of BK_{Ca} Channels Increases during Postnatal Development

Most studies have demonstrated that the contribution of BK_{Ca} channels to the regulation of vascular tone in systemic circulation increases with age.

In rat cerebral arteries, the effects of BK_{Ca} channel blockade became more pronounced with age—the BK_{Ca} channel blocker, iberiotoxin, caused a contraction and an increase in the intracellular calcium concentration in arteries of adult (12–14 weeks old), but not newborn, rats (1–2 days old) [77]. Similarly, iberiotoxin led to an increase in basal tone and sensitivity to the α_1-adrenoceptor agonist methoxamine in saphenous arteries of adult (2–3 months old), but not of young (10–15 day old), rats [45,46]. The effects of iberiotoxin on the contraction of sheep middle cerebral arteries also increased with age [40]. Later, this group also demonstrated an increase in the contractile responses of the carotid artery of adult sheep, but not fetuses, to 5-HT in the presence of iberiotoxin [78]. The effects of tetraethylammonium (TEA), another—albeit less selective—blocker of BK_{Ca} channels, also intensified with age: TEA caused more pronounced contractions of the aortic segments of 8- and 12-week-old rats compared to newborns and 4-week-old animals [38]. In addition, TEA enhanced contractile responses to the noradrenaline of the aorta of 8–12 week old, but not neonatal, rats [38]. These authors also demonstrated that the average density of the outward potassium current in isolated smooth muscle cells from the rat aorta increased with age. This was achieved by a considerable increase in the contribution of the calcium-dependent potassium current to the total outward potassium current between the age of 4 and 8 weeks [38]. In accordance with this, various blockers of BK_{Ca} channels (TEA, charybdotoxin and paxillin) had a suppressive effect on the outward potassium current in isolated smooth muscle cells from adult, but not newborn, aorta [38,39].

The more pronounced contribution of BK_{Ca} channels to the regulation of arterial tone in the adult organism may be due to several reasons. First, negative feedback regulation of vascular tone, as described above, requires co-localization of sarcoplasmic reticulum ryanodine receptors, voltage-gated calcium channels and BK_{Ca} channels in the plasma membrane. Although ryanodine receptors and BK_{Ca} channels are expressed in smooth muscle cells at newborn age, they are not yet organized into clusters; therefore, BK_{Ca} channels cannot function properly [77]. Indeed, a considerable part of calcium sparks does not activate BK_{Ca} channels in smooth muscle cells of newborn animals [79].

Second, the frequency of calcium sparks in the smooth muscle cells of newborn animals is considerably lower than in adults [77] and the amount of ryanodine receptors increases with age in, at least, the rat saphenous artery [80]. Probably, as a compensation for limited calcium availability, BK_{Ca} channels of immature arteries have a lower set point for calcium (the calcium concentration required for half-maximum activation at a membrane

potential of 0 mV) as it was demonstrated in isolated smooth muscle cells of sheep cerebral arteries [81]. It was suggested that BK_{Ca} channels of fetal sheep arteries have a greater sensitivity to calcium because they are more phosphorylated by the protein kinase G [82,83].

Third, the expression of BK_{Ca} channels in smooth muscle cells can change as the organism matures. It was demonstrated that the mRNA expression of both the pore-forming α1- and the regulatory β1-subunits, where the latter has a positive effect on channel activity [84,85], increases with age [45,46]. In addition, the level of labeled charybdotoxin (a ligand of BK_{Ca} channels) binding was considerably lower in the aorta of 4-week-old compared to 12-week-old rats [38].

Finally, the biophysical properties of BK_{Ca} channels may vary at different developmental stages. BK_{Ca} channels of adult aortic smooth muscle cells remain open almost 10 times longer than the channels of fetal cells [86]. In addition, currents mediated by BK_{Ca} channels in isolated smooth muscle cells of the middle cerebral artery of adult female baboons activated faster at lower membrane potential values than in fetal cells [87]. Probably the differences in the biophysical properties of the BK_{Ca} channel between an adult and an immature organism correlate with the expression of the regulatory β1-subunit, which has a positive regulatory effect on BK_{Ca} channel function [84,85].

4. Conclusions

Taken together, the data described above demonstrate that the pattern of potassium channel expression and function in arterial smooth muscle changes dramatically while the organism matures (Figure 1, Table 1). Importantly, such alterations do not seem to be dependent on the embryological origin of the particular vascular bed, since similar patterns of changes were observed in the proximal part of the aorta and smaller arteries [88]. BK_{Ca} channels acquire an important role in the regulation of vascular tone with maturation, but their role in developing arteries is limited. BK_{Ca} channel activation by calcium sparks is weak in the newborn organism due to an unfinished co-localization process with RyRs of the sarcoplasmic reticulum and a low calcium spark frequency. Less calcium-dependent potassium channel types (K_v1, K_v7, TASK-1 and $K_{ir}2$) play the main role in counteracting vasocontraction at early postnatal life. Indeed, contraction of the arterial smooth muscle depends much more on calcium in the adult age than in the early postnatal period. Therefore, while the vascular remodeling in postnatal development proceeds (including the formation of BK_{Ca}/RyRs clusters), a switch of the potassium channels from less to more calcium-dependent ones occurs. Conditions affecting arterial smooth muscle potassium channels expressed at high levels during the early postnatal period, especially Kv7 and TASK-1 channels, may disturb the developmental switch of potassium channel contribution to arterial tone regulation. This may possibly lead to disturbances in potassium channel function in childhood. The latter in its turn may cause the development of cardiovascular disorders, including hypertension [3,89–94], the occurrence of which is steadily increasing in childhood [95].

Table 1. Alterations in the contribution of potassium channels to the regulation of vascular tone during maturation.

Channel Type		Alteration with Maturation	Objects Studied	Pharmacological Agent	References
K_v	K_v	Decrease	Rat aorta, segments and SMCs	4-AP (5 mM)	[38]
		Decrease	SMCs from rat aorta	4-AP (20 mM)	[39]
	K_v1	Decrease	Rat saphenous artery	DPO-1 (1 μM)	[45]
	K_v2	No change	Rat saphenous artery	ScTx (0.1 μM)	[45]
	K_v7	Decrease	Rat saphenous artery	XE991 (3 μM), Linopirdine (10 μM)	[45]
		Decrease	Rat saphenous artery	XE991 (3 μM)	[46]
	K_v	Increase	Sheep middle cerebral artery	4-AP (1 and 5 mM)	[40]
TASK-1		Decrease	Rat saphenous artery	AVE1231 (1 μM)	[24]

Table 1. *Cont.*

Channel Type	Alteration with Maturation	Objects Studied	Pharmacological Agent	References
K_{ir}	Decrease	Sheep middle cerebral artery	$BaCl_2$ (10 μM)	[64]
$K_{ir}2$	Decrease	Rat saphenous artery	$BaCl_2$ (30 μM)	[45]
	No change	Sheep middle cerebral artery	$BaCl_2$ (10 μM)	[40]
	No change	Sheep middle cerebral artery	Glib (0.1 mM–30 μM)	[64]
$K_{ir}6(K_{ATP})$	No change	Rat saphenous artery	Glib (30 μM)	[45]
	Increase *	Sheep middle cerebral artery	Lemakalim * (0.01 nM–1 mM)	[71]
	Increase *	Sheep middle cerebral artery	Pinacidil * (1 nM–10 mM)	[64]
BK_{Ca}	Increase	Rat cerebral arteries	IbTx (100 nM)	[77]
	Increase	Rat aorta, segments and SMCs	TEA (1–10 mM)	[38]
	Increase	Rat aortic SMCs	Paxilline (1 μM)	[39]
	Increase	Rat saphenous artery	IbTx (100 nM)	[45]
	Increase	Rat saphenous artery	IbTx (100 nM)	[46]
	Increase	Sheep middle cerebral artery	IbTx (100 nM)	[40]
	Increase	Sheep carotid artery	IbTx (100 nM)	[78]
	Decrease	SMCs from sheep cerebral arteries	IbTx (100 nM)	[81]
	No change	Sheep middle cerebral artery	IbTx (100 nM)	[64]

* An increase in K_{ATP} functional contribution was shown with the use of the activators lemakalim and pinacidil. All other substances listed above are blockers of potassium channels: 4-AP—4-aminopyridine; DPO-1—diphenyl phosphine oxide-1; Glib—glibenclamide; IbTx—iberiotoxin; ScTx—stromatoxin; TEA—tetraethylammonium.

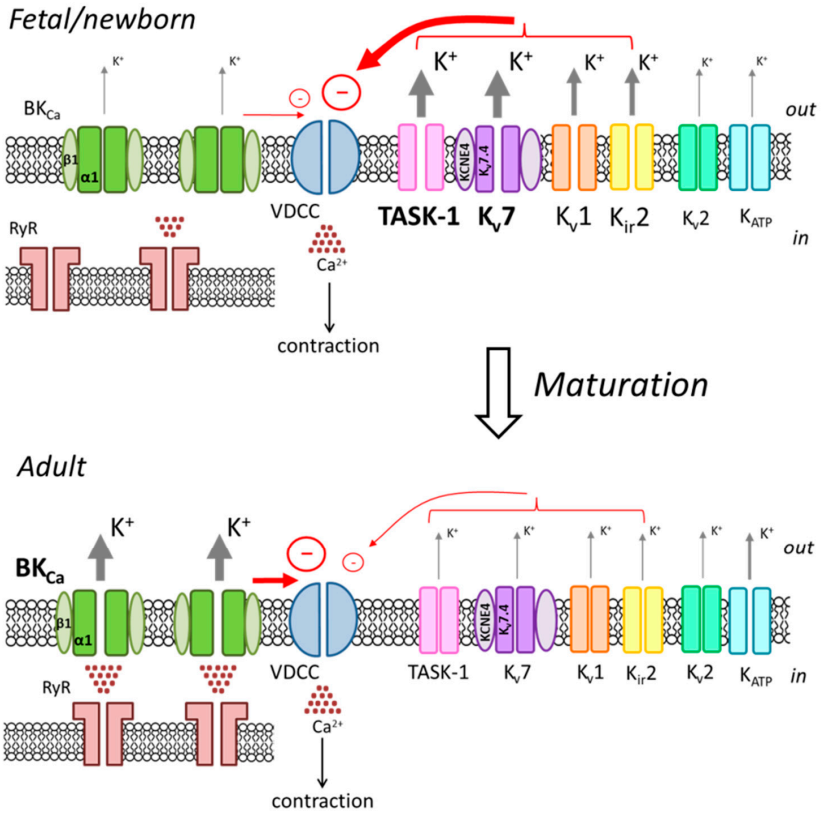

Figure 1. The switch of the leading role in the regulation of vascular tone from $K_{ir}2$, K_v1, K_v7 and TASK-1 channels to BK_{Ca} channels with maturation. The activation of potassium channels leads to K^+ efflux and hyperpolarization of the membrane, which in turn suppresses the opening of voltage-dependent calcium channels (VDCC) and counteracts vasocontraction. The arrow thickness represents the functional impact of the channel in this process.

Author Contributions: A.A.S., D.K.G., R.S. and O.S.T. wrote the manuscript together. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the Russian Science Foundation (Grant N 20-75-00027).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interests.

References

1. Hirst, G.D.S.; Edwards, F.R. Sympathetic neuroeffector transmission in arteries and arterioles. *Physiol. Rev.* **1989**, *69*, 546–604. [CrossRef]
2. Mulvany, M.J.; Aalkjaer, C. Structure and function of small arteries. *Physiol. Rev.* **1990**, *70*, 921–961. [CrossRef]
3. Amberg, G.C.; Bonev, A.D.; Rossow, C.F.; Nelson, M.T.; Santana, L.F. Modulation of the molecular composition of large conductance, Ca2+ activated K+ channels in vascular smooth muscle during hypertension. *J. Clin. Investig.* **2003**, *112*, 717–724. [CrossRef]
4. Nieves-cintrón, M.; Navedo, M.F.; Syed, A.U.; Nystoriak, M.A. Regulation of voltage-gated potassium channels in vascular smooth muscle during hypertension and metabolic disorders. *Microcirculation* **2018**, *25*, e12423. [CrossRef] [PubMed]
5. Gollasch, M.; Welsh, D.G.; Schubert, R. Perivascular adipose tissue and the dynamic regulation of Kv7 and Kir channels: Implications to resistant hypertension. *Microcirculation* **2017**, *25*, e12434. [CrossRef]
6. Jackson, W.F. Potassium channels in regulation of vascular smooth muscle contraction and growth. *Adv. Pharmacol.* **2017**, *78*, 89–144. [CrossRef]
7. Nelson, M.T.; Patlak, J.B.; Worley, J.F.; Standen, N.B. Calcium channels, potassium channels, and voltage dependence of arterial smooth muscle tone. *Am. J. Physiol.* **1990**, *259*, C3–C18. [CrossRef] [PubMed]
8. Tykocki, N.R.; Boerman, E.M.; Jackson, W.F. Smooth muscle ion channels and regulation of vascular tone in resistance arteries and arterioles. *Compr. Physiol.* **2017**, *7*, 485–581. [CrossRef]
9. Nelson, M.T.; Quayle, J.M. Physiological roles and properties of potassium channels in arterial smooth muscle. *Am. J. Physiol. Physiol.* **1995**, *268*, C799–C822. [CrossRef]
10. Jackson, W.F. Potassium channels in the peripheral microcirculation. *Microcirculation* **2005**, *12*, 113–127. [CrossRef]
11. Gurney, A.; Manoury, B. Two-pore potassium channels in the cardiovascular system. *Eur. Biophys. J.* **2009**, *38*, 305–318. [CrossRef]
12. Thorneloe, K.S.; Nelson, M.T. Ion channels in smooth muscle: Regulators of intracellular calcium and contractility. *Can. J. Physiol. Pharmacol.* **2005**, *83*, 215–242. [CrossRef]
13. Martínez, A.C.; Pagán, R.M.; Prieto, D.; Recio, P.; García-Sacristán, A.; Hernández, M.; Benedito, S. Modulation of noradrenergic neurotransmission in isolated rat radial artery. *J. Pharmacol. Sci.* **2009**, *111*, 299–311. [CrossRef]
14. Pagán, R.M.; Martínez, A.C.; Martínez, M.P.; Hernández, M.; García-Sacristán, A.; Correa, C.; Prieto, D.; Benedito, S. Endothelial and potassium channel dependent modulation of noradrenergic vasoconstriction in the pig radial artery. *Eur. J. Pharmacol.* **2009**, *616*, 166–174. [CrossRef] [PubMed]
15. Puzdrova, V.A.; Kudryashova, T.V.; Gaynullina, D.K.; Mochalov, S.V.; Aalkjaer, C.; Nilsson, H.; Vorotnikov, A.V.; Schubert, R.; Tarasova, O.S. Trophic action of sympathetic nerves reduces arterial smooth muscle Ca2+ sensitivity during early post-natal development in rats. *Acta Physiol.* **2014**, *212*, 128–141. [CrossRef]
16. Reho, J.J.; Zheng, X.; Benjamin, J.E.; Fisher, S.A. Neural programming of mesenteric and renal arteries. *Am. J. Physiol. Circ. Physiol.* **2014**, *307*, H563–H573. [CrossRef]
17. Sandow, S.L.; Goto, K.; Rummery, N.M.; Hill, C.E. Developmental changes in myoendothelial gap junction mediated vasodilator activity in the rat saphenous artery. *J. Physiol.* **2004**, *556*, 875–886. [CrossRef] [PubMed]
18. Mochalov, S.V.; Tarasova, N.V.; Kudryashova, T.V.; Gaynullina, D.K.; Kalenchuk, V.U.; Borovik, A.S.; Vorotnikov, A.V.; Tarasova, O.S.; Schubert, R. Higher Ca2+-sensitivity of arterial contraction in 1-week-old rats is due to a greater Rho-kinase activity. *Acta Physiol.* **2018**, *12*, e13044. [CrossRef] [PubMed]
19. Todd, M.E. Development of adrenergic innervation in rat peripheral vessels: A fluorescence microscopic study. *J. Anat.* **1980**, *131*, 121–133. [PubMed]
20. Akopov, S.E.; Zhang, L.; Pearce, W.J. Developmental changes in the calcium sensitivity of rabbit cranial arteries. *Biol. Neonate* **1998**, *74*, 60–71. [CrossRef]
21. Sandoval, R.J.; Injeti, E.R.; Gerthoffer, W.T.; Pearce, W.J. Postnatal maturation modulates relationships among cytosolic Ca2+, myosin light chain phosphorylation, and contractile tone in ovine cerebral arteries. *Am. J. Physiol. Hear. Circ. Physiol.* **2007**, *293*, 2183–2192. [CrossRef]
22. Gaynullina, D.; Lubomirov, L.T.; Sofronova, S.I.; Kalenchuk, V.U.; Gloe, T.; Pfitzer, G.; Tarasova, O.S.; Schubert, R. Functional remodelling of arterial endothelium during early postnatal development in rats. *Cardiovasc. Res.* **2013**, *99*, 612–621. [CrossRef] [PubMed]

23. Sofronova, S.I.; Borzykh, A.A.; Gaynullina, D.K.; Kuzmin, I.V.; Shvetsova, A.A.; Lukoshkova, E.V.; Tarasova, O.S. Endothelial nitric oxide weakens arterial contractile responses and reduces blood pressure during early postnatal development in rats. *Nitric Oxide* **2016**, *55–56*, 1–9. [CrossRef]
24. Shvetsova, A.A.; Gaynullina, D.K.; Schmidt, N.; Bugert, P.; Lukoshkova, E.V.; Tarasova, O.S.; Schubert, R. TASK-1 channel blockade by AVE1231 increases vasocontractile responses and BP in 1- to 2-week-old but not adult rats. *Br. J. Pharmacol.* **2020**, *177*, 5148–5162. [CrossRef]
25. Kent, A.L.; Kecskes, Z.; Shadbolt, B.; Falk, M.C. Normative blood pressure data in the early neonatal period. *Pediatr. Nephrol.* **2007**, *22*, 1335–1341. [CrossRef]
26. Yeung, S.Y.M.; Pucovský, V.; Moffatt, J.D.; Saldanha, L.; Schwake, M.; Ohya, S.; Greenwood, I.A. Molecular expression and pharmacological identification of a role for Kv7 channels in murine vascular reactivity. *Br. J. Pharmacol.* **2007**, *151*, 758–770. [CrossRef] [PubMed]
27. Cox, R.H.; Fromme, S. Functional expression profile of voltage-gated K+ channel subunits in rat small mesenteric arteries. *Cell Biochem. Biophys.* **2016**, *74*, 263–276. [CrossRef]
28. Jackson, W.F. Kv channels and the regulation of vascular smooth muscle tone. *Microcirculation* **2018**, *25*, e12421. [CrossRef]
29. Mackie, A.R.; Byron, K.L. Cardiovascular KCNQ (Kv7) potassium channels: Physiological regulators and new targets for therapeutic intervention. *Mol. Pharmacol.* **2008**, *74*, 1171–1179. [CrossRef] [PubMed]
30. Fancher, I.S.; Butcher, J.T.; Brooks, S.D.; Rottgen, T.S.; Skaff, P.R.; Frisbee, J.C.; Dick, G.M. Diphenyl phosphine oxide-1-sensitive K+ channels contribute to the vascular tone and reactivity of resistance arteries from brain and skeletal muscle. *Microcirculation* **2015**, *22*, 315–325. [CrossRef] [PubMed]
31. Amberg, G.C.C.; Santana, L.F.F. Kv2 channels oppose myogenic constriction of rat cerebral arteries. *Am. J. Physiol. Cell Physiol.* **2006**, *291*, C348–C356. [CrossRef]
32. Zhong, X.Z.; Abd-Elrahman, K.S.; Liao, C.-H.; El-Yazbi, A.F.; Walsh, E.J.; Walsh, M.P.; Cole, W.C. Stromatoxin-sensitive, heteromultimeric Kv2.1/Kv9.3 channels contribute to myogenic control of cerebral arterial diameter. *J. Physiol.* **2010**, *588*, 4519–4537. [CrossRef] [PubMed]
33. Yeung, S.Y.M.; Greenwood, I.A. Electrophysiological and functional effects of the KCNQ channel blocker XE991 on murine portal vein smooth muscle cells. *Br. J. Pharmacol.* **2005**, *146*, 585–595. [CrossRef]
34. Khanamiri, S.; Soltysinska, E.; Jepps, T.A.; Bentzen, B.H.; Chadha, P.S.; Schmitt, N.; Greenwood, I.A.; Olesen, S.P. Contribution of Kv7 channels to basal coronary flow and active response to ischemia. *Hypertension* **2013**, *62*, 1090–1097. [CrossRef] [PubMed]
35. Zhong, X.Z.; Harhun, M.I.; Olesen, S.P.; Ohya, S.; Moffatt, J.D.; Cole, W.C.; Greenwood, I.A. Participation of *KCNQ* (Kv7) potassium channels in myogenic control of cerebral arterial diameter. *J. Physiol.* **2010**, *588*, 3277–3293. [CrossRef] [PubMed]
36. Zavaritskaya, O.; Zhuravleva, N.; Schleifenbaum, J.; Gloe, T.; Devermann, L.; Kluge, R.; Mladenov, M.; Frey, M.; Gagov, H.; Fésüs, G.; et al. Role of KCNQ channels in skeletal muscle arteries and periadventitial vascular dysfunction. *Hypertension* **2013**, *61*, 151–159. [CrossRef] [PubMed]
37. Gutman, G.A.; Chandy, K.G.; Grissmer, S.; Lazdunski, M.; McKinnon, D.; Pardo, L.A.; Robertson, G.A.; Rudy, B.; Sanguinetti, M.C.; Stühmer, W.; et al. International Union of Pharmacology. LIII. Nomenclature and molecular relationships of voltage-gated potassium channels. *Pharmacol. Rev.* **2005**, *57*, 473–508. [CrossRef]
38. Gomez, J.P.; Ghisdal, P.; Morel, N. Changes of the potassium currents in rat aortic smooth muscle cells during postnatal development. *Pflugers Arch. Eur. J. Physiol.* **2000**, *441*, 388–397. [CrossRef] [PubMed]
39. Belevych, A.; Beck, R.; Tammaro, P.; Poston, L.; Smirnov, S. Developmental changes in the functional characteristics and expression of voltage-gated K+ channel currents in rat aortic myocytes. *Cardiovasc. Res.* **2002**, *54*, 152–161. [CrossRef]
40. Teng, G.Q.; Nauli, S.M.; Brayden, J.E.; Pearce, W.J. Maturation alters the contribution of potassium channels to resting and 5HT-induced tone in small cerebral arteries of the sheep. *Dev. Brain Res.* **2002**, *133*, 81–91. [CrossRef]
41. Khammy, M.M.; Kim, S.; Bentzen, B.H.; Lee, S.; Choi, I.; Aalkjaer, C.; Jepps, T.A. 4-aminopyridine: A pan voltage-gated potassium channel inhibitor that enhances Kv7.4 currents and inhibits noradrenaline-mediated contraction of rat mesenteric small arteries. *Br. J. Pharmacol.* **2018**, *175*, 501–516. [CrossRef]
42. Petkova-Kirova, P.; Gagov, H.; Krien, U.; Duridanova, D.; Noack, T.; Schubert, R. 4-Aminopyridine affects rat arterial smooth muscle BKCa currents by changing intracellular pH. *Br. J. Pharmacol.* **2000**, *131*, 1643–1650. [CrossRef]
43. Escoubas, P.; Diochot, S.; Célérier, M.-L.; Nakajima, T.; Lazdunski, M. Novel tarantula toxins for subtypes of voltage-dependent potassium channels in the Kv2 and Kv4 subfamilies. *Mol. Pharmacol.* **2002**, *62*, 48–57. [CrossRef]
44. Lagrutta, A.; Wang, J.; Fermini, B.; Salata, J.J. Novel, potent inhibitors of human Kv1.5 K+ channels and ultrarapidly activating delayed rectifier potassium current. *J. Pharmacol. Exp. Ther.* **2006**, *317*, 1054–1063. [CrossRef]
45. Shvetsova, A.A.; Gaynullina, D.K.; Tarasova, O.S.; Schubert, R. Negative feedback regulation of vasocontraction by potassium channels in 10- to 15-day-old rats: Dominating role of Kv7 channels. *Acta Physiol.* **2019**, *225*, 1–18. [CrossRef]
46. Ma, D.; Gaynullina, D.; Schmidt, N.; Mladenov, M.; Schubert, R. The functional availability of arterial Kv7 channels is suppressed considerably by large-conductance calcium-activated potassium channels in 2- to 3-month old but not in 10- to 15-day old rats. *Front. Physiol.* **2020**, *11*, 1–18. [CrossRef]
47. Jepps, T.A.; Carr, G.; Lundegaard, P.R.; Olesen, S.-P.; Greenwood, I.A. Fundamental role for the KCNE4 ancillary subunit in Kv7.4 regulation of arterial tone. *J. Physiol.* **2015**, *593*, 5325–5340. [CrossRef] [PubMed]

48. Gurney, A.M.; Osipenko, O.N.; MacMillan, D.; McFarlane, K.M.; Tate, R.J.; Kempsill, F.E.J. Two-pore domain K channel, TASK-1, in pulmonary artery smooth muscle cells. *Circ. Res.* **2003**, *93*, 957–964. [CrossRef]
49. Gardener, M.J.; Johnson, I.T.; Burnham, M.P.; Edwards, G.; Heagerty, A.M.; Weston, A.H. Functional evidence of a role for two-pore domain potassium channels in rat mesenteric and pulmonary arteries. *Br. J. Pharmacol.* **2004**, *142*, 192–202. [CrossRef]
50. Goldstein, S.A.; Bockenhauer, D.; O'Kelly, I.; Zilberberg, N. Potassium leak channels and the KCNK family of two-P-domain subunits. *Nat. Rev. Neurosci.* **2001**, *2*, 175–184. [CrossRef]
51. Dedman, A.; Sharif-Naeini, R.; Folgering, J.H.A.; Duprat, F.; Patel, A.; Honoré, E. The mechano-gated K2P channel TREK-1. *Eur. Biophys. J.* **2009**, *38*, 293–303. [CrossRef] [PubMed]
52. Renigunta, V.; Schlichthörl, G.; Daut, J. Much more than a leak: Structure and function of K2P-channels. *Pflügers Arch. Eur. J. Physiol.* **2015**, *467*, 867–894. [CrossRef] [PubMed]
53. Ma, L.; Roman-Campos, D.; Austin, E.D.; Eyries, M.; Sampson, K.S.; Soubrier, F.; Germain, M.; Trégouët, D.-A.; Borczuk, A.; Rosenzweig, E.B.; et al. A novel channelopathy in pulmonary arterial hypertension. *N. Engl. J. Med.* **2013**, *369*, 351–361. [CrossRef] [PubMed]
54. Antigny, F.; Hautefort, A.; Meloche, J.; Belacel-Ouari, M.; Manoury, B.; Rucker-Martin, C.; Péchoux, C.; Potus, F.; Nadeau, V.; Tremblay, E.; et al. Potassium channel subfamily K member 3 (KCNK3) contributes to the development of pulmonary arterial hypertension. *Circulation* **2016**, *133*, 1371–1385. [CrossRef]
55. Lambert, M.; Capuano, V.; Boet, A.; Tesson, L.; Bertero, T.; Nakhleh, M.K.; Remy, S.; Anegon, I.; Pechoux, C.; Hautefort, A.; et al. Characterization of Kcnk3-mutated rat, a novel model of pulmonary hypertension. *Circ. Res.* **2019**, *125*, 678–695. [CrossRef]
56. Kiper, A.K.; Rinné, S.; Rolfes, C.; Ramírez, D.; Seebohm, G.; Netter, M.F.; González, W.; Decher, N. Kv1.5 blockers preferentially inhibit TASK-1 channels: TASK-1 as a target against atrial fibrillation and obstructive sleep apnea? *Pflugers Arch. Eur. J. Physiol.* **2015**, *467*, 1081–1090. [CrossRef] [PubMed]
57. Sakmann, B.; Trube, G. Conductance properties of single inwardly rectifying potassium channels in ventricular cells from guinea-pig heart. *J. Physiol.* **1984**, *347*, 641–657. [CrossRef] [PubMed]
58. Matsuda, H.; Saigusa, A.; Irisawa, H. Ohmic conductance through the inwardly rectifying K channel and blocking by internal Mg2+. *Nature* **1987**, *325*, 156–159. [CrossRef]
59. Lopatin, A.N.; Makhina, E.N.; Nichols, C.G. Potassium channel block by cytoplasmic polyamines as the mechanism of intrinsic rectification. *Nature* **1994**, *372*, 366–369. [CrossRef] [PubMed]
60. Zaritsky, J.J.; Eckman, D.M.; Wellman, G.C.; Nelson, M.T.; Schwarz, T.L. Targeted disruption of Kir2.1 and Kir2.2 genes reveals the essential role of the inwardly rectifying K+ current in K+-mediated vasodilation. *Circ. Res.* **2000**, *87*, 160–166. [CrossRef]
61. Smith, P.D.; Brett, S.E.; Luykenaar, K.D.; Sandow, S.L.; Marrelli, S.P.; Vigmond, E.J.; Welsh, D.G. KIR channels function as electrical amplifiers in rat vascular smooth muscle. *J. Physiol.* **2008**, *586*, 1147–1160. [CrossRef]
62. Yang, Y.; Chen, F.; Karasawa, T.; Ma, K.T.; Guan, B.C.; Shi, X.R.; Li, H.; Steyger, P.S.; Nuttall, A.L.; Jiang, Z.G. Diverse Kir expression contributes to distinct bimodal distribution of resting potentials and vasotone responses of arterioles. *PLoS ONE* **2015**, *10*, 1–26. [CrossRef]
63. Schubert, R.; Krien, U.; Wulfsen, I.; Schiemann, D.; Lehmann, G.; Ulfig, N.; Veh, R.W.; Schwarz, J.R.; Gagov, H. Nitric oxide donor sodium nitroprusside dilates rat small arteries by activation of inward rectifier potassium channels. *Hypertension* **2004**, *43*, 891–896. [CrossRef]
64. Long, W.; Zhang, L.; Longo, L.D. Cerebral artery K(ATP)- and K(Ca)-channel activity and contractility: Changes with development. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2000**, *279*, R2004–R2014. [CrossRef]
65. Dunne, M.J.; Petersen, O.H. Intracellular ADP activates K+ channels that are inhibited by ATP in an insulin-secreting cell line. *FEBS Lett.* **1986**, *208*, 59–62. [CrossRef]
66. Beech, D.J.; Zhang, H.; Nakao, K.; Bolton, T.B. K channel activation by nucleotide diphosphates and its inhibition by glibenclamide in vascular smooth muscle cells. *Br. J. Pharmacol.* **1993**, *110*, 573–582. [CrossRef] [PubMed]
67. Berwick, Z.C.; Payne, G.A.; Lynch, B.; Dick, G.M.; Sturek, M.; Tune, J.D. Contribution of adenosine A2A and A2B receptors to ischemic coronary dilation: Role of Kv and KATP channels. *Microcirculation* **2010**, *17*, 600–607. [CrossRef] [PubMed]
68. Holdsworth, C.T.; Copp, S.W.; Ferguson, S.K.; Sims, G.E.; Poole, D.C.; Musch, T.I. Acute inhibition of ATP-sensitive K^+ channels impairs skeletal muscle vascular control in rats during treadmill exercise. *Am. J. Physiol. Circ. Physiol.* **2015**, *308*, H1434–H1442. [CrossRef]
69. Wei-Wei, S.; Yang, Y.; Yun, S.; Chun, J. KATP channel action in vascular tone regulation from genetics to diseases. *Acta Physiol. Sin.* **2012**, *29*, 997–1003.
70. Foster, M.N.; Coetzee, W.A. KATP channels in the cardiovascular system. *Physiol. Rev.* **2016**, *96*, 177–252. [CrossRef] [PubMed]
71. Pearce, W.J.; Elliott, S.R. Maturation enhances the sensitivity of ovine cerebral arteries to the ATP-sensitive potassium channel activator lemakalim. *Pediatr. Res.* **1994**, *35*, 729–732. [CrossRef]
72. Cui, J.; Yang, H.; Lee, U.S. Molecular mechanisms of BK channel activation. *Cell. Mol. Life Sci.* **2009**, *66*, 852–875. [CrossRef]
73. Nelson, M.T.; Cheng, H.; Rubart, M.; Santana, L.F.; Bonev, A.D.; Knot, H.J.; Lederer, W.J. Relaxation of arterial smooth muscle by calcium sparks. *Science* **1995**, *270*, 633–637. [CrossRef]
74. Knot, H.J.; Standen, N.B.; Nelson, M.T. Ryanodine receptors regulate arterial diameter and wall [Ca2+] in cerebral arteries of rat via Ca2+-dependent K+ channels. *J. Physiol.* **1998**, *508*, 211–221. [CrossRef]

75. Cheng, X.; Jaggar, J.H. Genetic ablation of caveolin-1 modifies Ca2+ spark coupling in murine arterial smooth muscle cells. *Am. J. Physiol. Heart Circ. Physiol.* **2006**, *290*, H2309–H2319. [CrossRef]
76. Suzuki, Y.; Yamamura, H.; Ohyac, S.; Imaizumi, Y. Caveolin-1 facilitates the direct coupling between large conductance Ca2+-activated K+(BKCa) and Cav1.2 Ca 2+ channels and their clustering to regulate membrane excitability in vascular myocytes. *J. Biol. Chem.* **2013**, *288*, 36750–36761. [CrossRef]
77. Gollasch, M.; Wellman, G.C.; Knot, H.J.; Jaggar, J.H.; Damon, D.H.; Bonev, A.D.; Nelson, M.T. Ontogeny of local sarcoplasmic reticulum Ca2+ signals in cerebral arteries: Ca2+ sparks as elementary physiological events. *Circ. Res.* **1998**, *83*, 1104–1114. [CrossRef]
78. Thorpe, R.B.; Stockman, S.L.; Williams, J.M.; Lincoln, T.M.; Pearce, W.J. Hypoxic depression of PKG-mediated inhibition of serotonergic contraction in ovine carotid arteries. *AJP Regul. Integr. Comp. Physiol.* **2013**, *304*, R734–R743. [CrossRef] [PubMed]
79. Li, A.; Adebiyi, A.; Leffler, C.W.; Jaggar, J.H. KCa channel insensitivity to Ca2+ sparks underlies fractional uncoupling in newborn cerebral artery smooth muscle cells. *Am. J. Physiol. Heart Circ. Physiol.* **2006**, *291*, H1118–H1125. [CrossRef]
80. Gaynullina, D.; Dweep, H.; Gloe, T.; Tarasova, O.S.; Sticht, C.; Gretz, N.; Schubert, R. Alteration of mRNA and microRNA expression profiles in rat muscular type vasculature in early postnatal development. *Sci. Rep.* **2015**, *5*, 1–12. [CrossRef]
81. Lin, M.T.; Hessinger, D.A.; Pearce, W.J.; Longo, L.D. Developmental differences in Ca2+-activated K+ channel activity in ovine basilar artery. *Am. J. Physiol. Heart Circ. Physiol.* **2003**, *285*, H701–H709. [CrossRef]
82. Lin, M.T.; Longo, L.D.; Pearce, W.J.; Hessinger, D.A. Ca2+-activated K+ channel-associated phosphatase and kinase activities during development. *Am. J. Physiol. Heart Circ. Physiol.* **2005**, *289*, H414–H425. [CrossRef] [PubMed]
83. Lin, M.T.; Hessinger, D.A.; Pearce, W.J.; Longo, L.D. Modulation of BK channel calcium affinity by differential phosphorylation in developing ovine basilar artery myocytes. *Am. J. Physiol. Heart Circ. Physiol.* **2006**, *291*, H732–H740. [CrossRef] [PubMed]
84. Cox, D.H.; Aldrich, R.W. Role of the β1 subunit in large-conductance Ca2+-activated K+ channel gating energetics. *J. Gen. Physiol.* **2000**, *116*, 411–432. [CrossRef]
85. Bao, L.; Cox, D.H. Gating and ionic currents reveal how the BKCa channel's Ca2+ sensitivity is enhanced by its β1 subunit. *J. Gen. Physiol.* **2005**, *126*, 393–412. [CrossRef] [PubMed]
86. Bregestovski, P.D.; Printseva, O.; Serebryakov, V.; Stinnakre, J.; Turmin, A.; Zamoyski, V. Comparison of Ca2+-dependent K+ channels in the membrane of smooth muscle cells isolated from adult and foetal human aorta. *Eur. J. Physiol.* **1988**, *413*, 8–13. [CrossRef]
87. Bisen, S.; Simakova, M.N.; Dopico, A.M.; Bukiya, A.N. Large conductance voltage- and calcium-gated potassium channels (BK) in cerebral artery myocytes of perinatal fetal primates share several major characteristics with the adult phenotype. *PLoS ONE* **2018**, *13*, e0203199. [CrossRef]
88. Gurung, R.; Choong, A.M.; Woo, C.C.; Foo, R.; Sorokin, V. Genetic and epigenetic mechanisms underlying vascular smooth muscle cell phenotypic modulation in abdominal aortic aneurysm. *Int. J. Mol. Sci.* **2020**, *21*, 6334. [CrossRef] [PubMed]
89. Bratz, I.N.; Dick, G.M.; Partridge, L.D.; Kanagy, N.L. Reduced molecular expression of K+ channel proteins in vascular smooth muscle from rats made hypertensive with Nω-nitro-L- arginine. *Am. J. Physiol. Hear. Circ. Physiol.* **2005**, *289*, 1277–1283. [CrossRef]
90. Kiyoshi, H.; Yamazaki, D.; Ohya, S.; Kitsukawa, M.; Muraki, K.; Saito, S.-Y.; Ohizumi, Y.; Imaizumi, Y. Molecular and electrophysiological characteristics of K+ conductance sensitive to acidic pH in aortic smooth muscle cells of WKY and SHR. *AJP Hear. Circ. Physiol.* **2006**, *291*, H2723–H2734. [CrossRef]
91. Chadha, P.S.; Zunke, F.; Zhu, H.L.; Davis, A.J.; Jepps, T.A.; Olesen, S.P.; Cole, W.C.; Moffatt, J.D.; Greenwood, I.A. Reduced KCNQ4-encoded voltage-dependent potassium channel activity underlies impaired β-adrenoceptor-mediated relaxation of renal arteries in hypertension. *Hypertension* **2012**, *59*, 877–884. [CrossRef] [PubMed]
92. Liu, B.; Shi, R.; Li, X.; Liu, Y.; Feng, X.; Chen, X.; Fan, X.; Zhang, Y.; Zhang, W.; Tang, J.; et al. Downregulation of L-type voltage-gated Ca2+, voltage-gated K+, and large-conductance Ca2+-Activated K+ channels in vascular myocytes from salt-loading offspring rats exposed to prenatal hypoxia. *J. Am. Heart Assoc.* **2018**, *7*, 1–13. [CrossRef]
93. Yang, Y.; Li, P.Y.; Cheng, J.; Mao, L.; Wen, J.; Tan, X.Q.; Liu, Z.F.; Zeng, X.R. Function of BKCa channels is reduced in human vascular smooth muscle cells from han chinese patients with hypertension. *Hypertension* **2013**, *61*, 519–525. [CrossRef] [PubMed]
94. Cheng, J.; Mao, L.; Wen, J.; Li, P.Y.; Wang, N.; Tan, X.Q.; Zhang, X.D.; Zeng, X.R.; Xu, L.; Xia, X.M.; et al. 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*, 1–11. [CrossRef]
95. Flynn, J.T. High blood pressure in the young: Why should we care? *Acta Paediatr.* **2018**, *107*, 14–19. [CrossRef] [PubMed]