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Renal vascular K$^+$-channels

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Abstract

The control of renal vascular tone is important for the regulation of salt and water balance, blood pressure and the protection against damaging elevated glomerular pressure. The K^+ conductance is a major factor in the regulation of the membrane potential (V_m) in vascular smooth muscle (VSMC) and endothelial cells (EC). The vascular tone is controlled by V_m via its effect on the opening probability of voltage operated Ca^{2+} channels (VOCC) in VSMC. When K^+ conductance increases V_m becomes more negative and vasodilation follows, while deactivation of K^+ channels leads to depolarization and vasoconstriction. K^+ channels in EC indirectly participate in the control of vascular tone by endothelium derived vasodilation. Therefore, by regulating the tone of renal resistance vessels, K^+ channels have a potential role in the control of fluid homeostasis and blood pressure as well as in the protection of the renal parenchyma. The main classes of K^+ channels (calcium activated (K_{Ca}), inward rectifier (K_{ir}), voltage activated (K_v) and ATP sensitive (K_{ATP})) have been found in the renal vessels. In this review, we summarize results available in the literature and our own studies in the field. We compare the ambiguous *in vitro* and *in vivo* results. We discuss the role of single types of K^+ channels and the integrated function of several classes. We also deal with the possible role of renal vascular K^+ channels in the pathophysiology of hypertension, diabetes mellitus and sepsis.

Keywords: vasodilation, vasoconstriction, afferent arteriole, *in vivo*, *in vitro,* RVR*,* RBF

1. Introduction

The control of renal vascular tone has a dual purpose. Firstly, it participates in the regulation of renal blood flow (RBF) and glomerular filtration rate (GFR). Since the renal excretion of Na^+ and water is controlled by GFR and tubular reabsorption, the renal vascular tone is crucial for the maintenance and regulation of body fluid volume and blood pressure. Secondly, it has a protective function by governing intra-glomerular pressure. The importance of this function is illustrated by the renal microvascular and glomerular damage in several diseases among them hypertension and diabetes [1, 2]. Thus, impaired renal vascular control could lead to rapid deterioration of arteriolar and glomerular tissue and decreased renal function eventually causing renal failure.

As in other vascular beds, the constriction of renal vascular smooth muscle cells (VSMC) is controlled by the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) in parallel with Ca^{2+} independent mechanisms [3]. VSMC $[Ca^{2+}]_i$ is in turn determined by a balance between release and uptake from and to intracellular stores (e.g. the sarcoplasmatic reticulum) combined with entry from and efflux to the extracellular space.

Although Ca^{2+} entry via voltage independent Ca^{2+} channels may play a role in the regulation of renal vascular tone, the entry largely occurs via voltage-operated Ca^{2+} channels (VOCC) [4, 5]. These channels are activated by depolarization of the VSMC cell membrane and are thus under control of the cell membrane potential (V_m). The dominating VOCC in most vascular beds, among them renal, is the dihydropyridine sensitive L-type channel ($Ca_V1.2$) [3, 6, 7]. Furthermore, T-type channels have been found in several vascular beds including renal pre- and postglomerular arterioles [7-10] but their role is debated and remains to be fully elucidated [8, 11-13]. As renal VSMC V_m is mainly determined by K^+ channels in these cells, they may have an important impact on the salt and water balance and thus blood pressure. There are four main classes of vascular K^+ channels: calcium activated (K_{Ca}), inward rectifier (K_{ir}), voltage activated (K_v), and ATP sensitive (K_{ATP}). The K2P channels are also found in the vasculature but their role is less explored [14]. V_m is determined by the ion gradients and their relative conductances over the VSMC membrane. In addition, endothelial cells may affect VSMC V_m via myoendothelial gap junctions [15]. Primarily, it is the intra- and extracellular concentrations of K^+, Na^+ and Cl^- ions and their membrane conductances that control V_m. Thus, V_m can be derived from the chord conductance equation:

$$V_m = \frac{E_K\, g_K + E_{Na}\, g_{Na} + E_{Cl}\, g_{Cl}}{g_K + g_{Na} + g_{Cl}}$$

Here E_x is the equilibrium potential for the specific ion x and g_x is its conductance. E for the ion is calculated by the Nernst equation (here adjusted for body temperature, 37° C, and converted to $\log_{10}$):

$$E_{ion} \approx \frac{61.5\ mV}{z}\log\frac{[ion]_{out}}{[ion]_{in}}$$

z is the valence of the particular ion.

Significant changes in V_m involve changes in conductances of K^+, Na^+ and /or Cl^- ions. As K^+ channels are the dominant cation channels in VSMC [16] V_m is largely determined by E_K. With normal extra- and intracellular concentrations of K^+,, calculated as above E_K is ~ - 90 mV. Owing to the effect of the other ions involved, V_m is more positive. Accordingly, V_m of afferent arteriolar VSMC has been found to be between -55 and -40 mV at normal blood pressure ranges measured in hydronephrotic kidneys [17-19]. Membrane potentials in this range are close to the L-type Ca^{2+} channel activation potential but more positive than that for T-type Ca^{2+} channels [19, 20].

Changes in g_K thus affect the tone of the renal vessels. A decreased general K^+ conductance depolarizes the cell membrane inducing vasoconstriction. An increased K^+ conductance has the opposite effect [21, 22]. In this review, we summarize the current literature on the role of K^+ channels in the renal vasculature. We deal with studies investigating the integrated renal vascular bed as well as *in vitro* results originating from intra-renal arteries and arterioles. In addition, we discuss the possible interaction between several classes of K^+ channels in the control of renal vascular tone as well as the role of K^+ channels in the communication between endothelial cells (EC) and VSMC. The role of renal vascular K^+ channels in renovascular pathology is also discussed.

Renal vascular K^+ channels

The nomenclature for vascular K^+ channels used in this review is based on the International Union of Basic and Clinical Pharmacology (IUPHAR). Table 1 provides a comparison between the IUPHAR classification and the colloquial names for channels dealt with in this review. The K^+ channels are distributed into four subfamilies: 1. Calcium activated (K_{Ca}), 2. Inwardly rectifying (K_{ir}), 3. Voltage gated (K_V), 4. Two-pore domain (K2P) channels. Based on their permeability, K_{Ca} channels are further subdivided into large, intermediate and small conductance calcium-activated potassium channels (BK_{Ca}, IK_{Ca} and SK_{Ca}, respectively). The K_{ATP} channels are composed of $K_{ir}6.1$ or $K_{ir}6.2$ subunits and thus they belong to the inward rectifier super family [23]. To our knowledge, the possible significance of K2P channels in the renal vasculature has never been investigated. However, considering the diversity of K^+ channels, it is highly possible that classes of K^+ channels which have not yet been described in the renal vasculature participate in the regulation of renal hemodynamics [24].

K⁺ channels in renal vascular smooth muscle

BK_{Ca} channels in VSMC

The conductance of BK_{Ca} channels is in the range of 100-200 pS [25-27]. In addition to their Ca^{2+}- sensitivity, they are also sensitive to electrical potential [25]. At negative membrane potentials (-50 to -70 mV) close to normal resting potentials measured in vivo in VSMC [28], activation is reported to require intracellular $[Ca^{2+}]$ in the range of 1-10 µM [29, 30]. Therefore, it is not totally clarified to what extent BK_{Ca} channels contribute to the normal resting V_m [29]. Physiologically, BK_{Ca} may be modulated by protein kinases. Although there are a few exceptions [31], most reports indicate that they are activated by protein kinase A [32] and/or G [33, 34] (PKA and PKG, respectively; Fig. 2) and inhibited by protein kinase C (PKC; Fig. 1) [35, 36]. Nitric oxide (NO) stimulates the PKG pathway. Therefore activation of the NO system potentially may lead to increased activity of BK_{Ca} channels (Fig. 2) [37]. Likewise, it is suggested that vasoconstrictors could act via PKC mediated inhibition of BK_{Ca} channels (Fig. 1) [35, 36]. BK_{Ca} channels are pharmacologically inhibited by tetraethylammonium (TEA), charybdotoxin or more specifically by iberiotoxin. They are stimulated by NS 1619 [38].

Function

BK_{Ca} channels may have a buffering function on vasoconstrictor responses (Fig. 1) [39]. The depolarization and increase in VSMC $[Ca^{2+}]_i$, resulting from agonist stimulation or myogenic activation activates BK_{Ca} channels, initiating a hyperpolarizing current that attenuates depolarization and opposes vasoconstriction [40]. There is evidence that a complex formed by BK_{Ca} channels and VOCC might provide a basis for the control of BK_{Ca} channel activation [41]. Accordingly, in several vascular beds it is shown that BK_{Ca} channels open simultaneously with the L-type Ca^{2+} channels [29, 42]. Furthermore, ryanodine-sensitive Ca^{2+} release from intracellular stores may also buffer vasoconstriction via BK_{Ca} channel activation [43].

Renal function

We and others have found evidence for the expression of BK_{Ca} channels in rat preglomerular vessels utilizing RT-PCR and immunofluorescence [44, 45]. Their presence has also been suggested in rat mesangial cells and an iberiotoxin sensitive current has been identified in rat juxtaglomerular cells [45 46, 47].

TEA is reported to induce an elevated basal perfusion pressure in the isolated perfused rat kidney which suggests that BK_{Ca} channels contribute to the basal renal vascular tone. [48, 49]. These results should be interpreted with caution as the TEA concentration used in these studies were between 2 and 10 mM, concentrations where TEA is not specific for the BK_{Ca}

channel but is reported to also inhibit both K_v channels and K_{ATP} channels [50, 51]. Nevertheless, a lower concentration of TEA (1mM) has been reported to constrict the afferent arteriole using the blood perfused juxtamedullary nephron preparation [52, 53]. Using the same technique it was shown that stimulation with the BK_{Ca} channel opener NS 1619 (30 µM) increased afferent arteriolar diameter, an effect that was abolished by TEA (1mM) [54]. At these concentrations the authors assumed NS 1619 and TEA to be specific for the BK_{Ca} channels. It should, however, be kept in mind that even at these concentrations NS 1619 and TEA has been shown to affect K_V channels [55-58]. We found that TEA, at an estimated plasma concentration of 1 mM infused directly into the rat renal artery *in vivo* reduced baseline RBF by ~10 %. Meanwhile the more specific BK_{Ca} channel blocker iberiotoxin, at an estimated plasma concentration of 100 nM, had no effect [44]. Furthermore, we found that NS 1619 (estimated plasma concentration 30 µM) had no effect on rat RBF *in vivo* [44]. These results indicate a limited role for BK_{Ca} channels in the regulation of renal vascular tone under resting conditions *in vivo* and are in contrast to the *in vitro* results emanating from the blood perfused juxtamedullary nephron preparation. The discrepancy between the *in vivo* and the *in vitro* studies might be explained by different $[Ca^{2+}]_i$ or Ca^{2+}-sensitivity. The effect of NS 1619 is Ca^{2+} dependent and it is possible that *in vivo* $[Ca^{2+}]_i$ in renal VSMC is not sufficient to allow activation by NS1619 [38].Thus, it is unclear whether BK_{Ca} channels have a role in the maintenance of the normal resting potential of renal VSMC and therefore in renal vascular tone.

Renal buffer function

As in Fallet et al. [54], we found that renal vasoconstriction induced by Ang II in vivo was impaired by NS 1619 [44]. The effect was reversed by TEA and iberiotoxin indicating that the attenuation is caused by stimulation of BK_{Ca} channels. Possibly the elevated $[Ca^{2+}]_i$ under Ang II stimulation facilitates the action of NS 1619. The attenuating effect of NS 1619 on the ANG II responses indicates that the renal BK_{Ca} channels may have a buffering function on vasoconstrictor responses (Fig. 1). The activation of BK_{Ca} channels may also play a role in renal vasodilation. However, TEA and iberiotoxin did not augment the juxtamedullary afferent arteriolar diameter reduction *in vitro or in vivo* in response to vasoconstrictors [44, 54]. On the other hand Loutzenhiser & Parker found that TEA elevated myogenic response of afferent arterioles which indicates that renal myogenic vasoconstriction might be buffered by opening of BK_{Ca} channels [59].

Activation of adenylate or guanylate cyclase and subsequent increases in cAMP or cGMP, respectively, followed by increased kinase activity may induce activation of BK_{Ca} channels and vasodilation [33, 60]. We did not find support *in vivo* for cAMP stimulation of BK_{Ca} channels leading to vasodilation. Renal vasodilation induced by forskolin, an activator of adenylate cyclase, was not affected by iberiotoxin in rats [44]. However, cAMP stimulates several other K^+-channels. We cannot exclude the possibility that the vasodilation was caused by activation of several classes of these channels, including BK_{Ca} channels. BK_{Ca} channel β-subunits contribute to a large diversity in BK_{Ca} channel function. Mice lacking the subunit Mbeta1 are mildly hypertensive. During acute volume expansion, the increase in GFR seen in wild type mice was decreased in the Mbeta1-/- mice indicating a role for the beta1-subunit of BK_{Ca} channels in the renal vasodilatory response to acute volume loading [61 62].

NO causes renal vasodilation and based on studies on isolated VSMC from rat preglomerular vessels, it is suggested that activation of BK_{Ca} channels may be involved. It was shown that the NO donor sodium nitroprusside reduced the increase in $[Ca^{2+}]_i$ in response to 50 mM KCl and that iberiotoxin reestablished this response [63]. This suggests a role for BK_{Ca} channels in NO induced renal vasodilation. On the other hand, it is somewhat challenging to comprehend how activation of BK_{Ca} channels would cause sufficient hyperpolarization to inactivate VOCC in the presence of 50 mM KCl. Nernst´s equation show that E_K in this condition is much more positive than the activation level of L-type VOCC. As opening of BK_{Ca} channels would not cause V_m to become more negative than E_K, a substantial effect on VOCC activity cannot be predicted. In addition, TEA has only a slight effect on the afferent arteriolar vasodilation in response to acetylcholine (ACh) as shown in the perfused hydronephrotic rat kidney [64]. This finding does not support a BK_{Ca} channel mediated NO induced renal vasodilation as the ACh response is largely mediated by NO [64-66]. On the other hand, BK_{Ca} channels may mediate the effect of other vasodilators. Epoxyeicosatrienoic acid (EET), which has been suggested to participate in endothelial derived hyperpolarization (EDH), causes afferent arteriolar vasodilation that is inhibited by iberiotoxin, indicating a role for BK_{Ca} channels in this setting [67] (Fig. 2). It has also been suggested that EETs may mediate the afferent arteriolar vasodilation induced by bradykinin via activation of BK_{Ca} channels [68]. In summary, renal BK_{Ca} channels do not seem to affect renal vascular resistance *in vivo* even though *in vitro* results suggests this. BK_{Ca} channels do however seem to act as buffers in response to agonist- or pressure induced vasoconstriction.

IK_{Ca} and SK_{Ca} channels in VSMC

Only few studies suggest the presence of IK_{Ca} and SK_{Ca} channels in renal VSMC. One study shows the presence of an apamin-sensitiv K^+ channel with a conductance of 68 pS in VSMC isolated from preglomerular arterioles [69]. However, functional evidence for a role in regulation of renal blood flow is lacking. In the isolated blood perfused juxtamedullary nephron preparation no change in afferent arteriolar diameter was seen after treatment with 100 nM apamin [52] and intrarenal infusion of apamin (0.5 µM) had no effect on RBF *in vivo* [10].

K_{ir} channels in VSMC

The single channel conductance of the classic K_{ir} channel ($K_{ir}2$) is ~ 20 pS [16]. In the vascular system, K_{ir} channels predominantly reside in VSMC from microvessels where the main isoform is $K_{ir}2.1$ [70-73]. They are named "inward rectifier" channels since they carry larger inward (at potentials negative to E_K) than outward currents K_{ir} (Fig. 3). As V_m is more positive than E_K under physiological conditions, K_{ir} channels carry a small outward hyperpolarizing K^+ current [74]. This current is sensitive to extracellular K^+ concentration ($[K^+]_o$) [75]. A small increase (~5 – 12 mM) in $[K^+]_o$ increases the outward current at membrane potentials measured in afferent arteriolar VSMC [17] (Fig. 3). The mechanism might be mediated by interaction of K^+ ions with polyamines or Mg^{2+} in the channel pore causing increased opening probability [76, 77]. When $[K^+]_o$ is increased to > ~20mM, the depolarizing effect of the increased $[K^+]_o$ according to the Nernst equation, becomes dominant and the net effect is depolarization. K_{ir} channels may also function as an amplifier of hyperpolarization if V_m becomes more hyperpolarized and thus reaches a voltage range with larger conductance and thus elevated outward current [78-81]. At concentrations lower than 100 µM, Ba^{2+} is considered to be specific for K_{ir} channels with a reported half maximal inhibition concentration of 2.2 µM at -60 mV [82].

Function

As K_{ir} channels are sensitive to small elevations in $[K^+]_o$, they may participate in K^+ induced vasodilation as a part of the metabolic regulation of blood flow [83-85]. Furthermore, they may have a role in the EDH response via K^+ released from endothelial IK_{Ca} and SK_{Ca} channels (Fig. 2) [86]. It is possible that part of the K^+ induced hyperpolarization/vasodilation is mediated by activation of Na/K ATPase [87].

Renal function

In the renal vasculature, $K_{ir}2.1$ channels are expressed in both VSMC and EC of rat afferent and efferent arterioles [88, 89]. In the rat descending vasa recta, both the endothelial cells and the pericytes express $K_{ir}2.1$, $K_{ir}2.2$, and $K_{ir}2.3$ channels [90, 91]. K_{ir} currents have been identified in the afferent and efferent arterioles and the distal rat interlobular artery (ILA) while they are absent in the proximal part of the same vessel [90, 92-94].

At concentrations supposed to be specific for K_{ir} channels (≤ 100 µM), Ba^{2+} reduced afferent arteriolar diameter [18]. Likewise renal vascular resistance (RVR) was increased in isolated perfused kidneys after Ba^{2+} treatment [48]. We found that infusion of Ba^{2+} into the rat renal artery, at an estimated final plasma concentration of 20 µM, caused a small (6–13%) transient elevation of baseline RVR *in vivo* [89]. These studies indicate a role for K_{ir} channels in the basal RVR.

K^+ induced renal vasodilation

An increase in plasma $[K^+]$ has been reported to decrease RVR, increase GFR, urine flow and Na^+ excretion in several species [95-97, 98]. These findings are in accord with the notion of a K^+ induced renal vasodilation [97]. It is possible that such a mechanism is relevant when plasma K^+ increases following metabolic stress where K^+ induced renal vasodilation may have a protective function. As high dietary K^+ is correlated with a decreased risk for cardiovascular disease it may also be speculated that the slightly increased plasma $[K^+]$ that follows high K^+ intake mediates renal vasodilation and decreased arterial blood pressure via stimulation of renal vascular K_{ir} channels [97, 99]. In this regard it is interesting that small physiologic changes in K^+ concentration have been reported to participate in the control of renal medullary blood flow via K_{ir} channels located in vasa recta [90, 91].

The K^+ induced renal vasodilation may be caused by activation of either Na^+/K^+ -ATPase or K_{ir} channels with subsequent VSMC hyperpolarization [18, 88, 100]. K^+ induced vasodilation of afferent arterioles was blocked by Ba^{2+} [18, 88]. In the larger rabbit, arcuate artery vasodilation was blocked by ouabain, an inhibitor of the Na^+/K^+ -ATPase [100]. This is in line with the notion of a more pronounced activity for K_{ir} channels in smaller vessels. Chilton et al. have shown that the K^+ induced vasodilation of the interlobular artery was correlated to vessel diameter [92]. The distal interlobular artery (ILA) dilated in response to 15 mM K^+ while this response was absent in the proximal ILA. The response was inhibited by 100 µM Ba^{2+} but not by ouabain [92]. Different results might be obtained when the integrated response of the intact renal circulation is under investigation. Accordingly, in isolated perfused rat kidneys, Ba^{2+} or ouabain attenuated the K^+ induced renal vasodilation. This indicates a role for both

K_{ir} channels and Na/K ATPase in this process [97]. Our laboratory has confirmed this *in vivo* in normotensive rats while the effect of ouabain was not significant in hypertensive rats [89].

Voltage-gated K^+ channels in VSMC

Voltage-gated K^+ (K_V) channels exhibit conductances between ~4 and 70 pS depending on subtype, preparation and experimental conditions [16, 101-104]. They are strongly voltage dependent and cell membrane depolarization leads to activation of K_V channels (Fig. 1) and thus an increased hyperpolarizing outward K^+ current that deactivates VOCC channels and consequently decreases VSMC tone [16, 39, 85, 105] (Fig. 2).

Function

K_V channels may contribute to the regulation of resting membrane potential by buffering membrane depolarization to maintain resting vascular tone [39]. In addition to the classical 4-aminopyridine (4-AP) sensitive K_V 1.1 - 1.7 channels, K_V7 channels have recently been described in VSMC from several vascular beds among them renal [106-112]. Prolonged depolarization leads to inactivation of K_V channels which is a slower process than that of activation. Thus, the steady state current via these channels is determined by the balance between activation and inactivation [16, 34, 39, 113, 114]. Like other K^+ channels, K_V1.x channels are activated by the cAMP/PKA and cGMP/PKG pathway [115, 116] (Fig. 2) and the activity is reduced by PKC (Fig. 1) [36, 117-120]. Specifically, it is reported that PKA increases open probability of 4-AP sensitive single channels [119].

In contrast to the 4-AP sensitive channels which are activated at -20 mV, the K_V7 channels, which are insensitive to 4-AP, activate at a more negative membrane potential. This potential is in the range of the resting membrane potential of renal arteriolar VSMC (-60 mV to -40 mV) [17, 121, 122]. It is therefore likely that the physiological role of K_V7 channels is different from that of the 4-AP sensitive K_V channels. K_V7 channels could have a larger impact on normal resting potential while K_V1 channels may exhibit more of a buffering function [85, 122]. K_V7.x channels are pharmacologically inhibited by XE991 or linordipine and K_V7.2-5 channels are stimulated by flupirtine or retigabine [122, 123].

Renal function

We and others have identified the expression of Kv1.2 and Kv1.4 channels in rat interlobar and arcuate arteries [124] and K_V1.4 channels in rat and mice afferent arteriolar VSMC [10]. Using patch clamp, 4-AP sensitive currents have been detected in VSMC from rat renal arcuate and interlobar arteries [114, 125]. However, in rabbit arcuate arteries K_V channels did not

participate in maintenance of normal tone but seemed to have a buffering effect against depolarization in these vessels [126]. An intermediate conductance K^+ current sensitive to 4-AP has been reported in VSMC from rat preglomerular vessels [127]. Furthermore, a functional role for 4-AP sensitive K_V channels has been suggested based on studies in the blood perfused juxtamedullary nephron preparation [52] or the isolated perfused rat kidney [48]. In both these studies, 4-AP induced renal vasoconstriction.

K_V7 channels have been found in the rat renal artery and in the isolated perfused rat kidney [112]. In that study it was found that linopirdine contracted isolated rat renal arteries. This is in accord with a recent report from our laboratory [111]. Using imunofluorescence, we revealed the expression of $K_V7.4$ channels in rat afferent arterioles. Our results also pointed to a role for these channels in the maintenance of basal RVR. Namely, intrarenal XE991administration led to a reduction of rat RBF *in vivo* as well as a reduction in mouse afferent arteriolar diameter as assessed by the blood perfused juxtamedullary nephron technique. These effects were abolished by nifedipine indicating that inhibition of K_V7 channels led to depolarization and activation of L-type Ca^{2+} channels. In addition flupirtine caused relaxation of isolated rat interlobar arteries in the wire myograph as well as an increase of RBF *in vivo*. In chronically instrumented conscious rats, retigabine caused transient renal vasodilatation in normotensive rats. This effect was augmented after Ang II induced acute hypertension [128]. These findings suggest a therapeutic potential for K_V7 channel stimulation in the treatment of unfavorable renal vasoconstriction in vascular disease states.

Renal buffer function

In addition to contributing to the basal renal tone, it was found that K_V7 channels partly mediate β-adrenoceptor–mediated renal vasodilation [112]. Furthermore, the RBF responses to the renal vasoconstrictors NE or Ang II were not affected by pretreatment with XE991 or flupirtine [111]. Surprisingly, XE991 pretreatment caused a minor augmentation of the ACh induced increase in RBF. Thus, K_V7 channels do not seem to mediate or buffer agonist induced renal vasoconstriction or vasodilation.

ATP-sensitive K^+ channels in VSMC

The ATP-sensitive K^+ channel (K_{ATP}) comprises four transmembrane domains emanating from the K_{ir} channel family (Kir6.1 or Kir6.2; table 1) which forms the pore, and four additional subunits of sulfonylurea receptors (SUR1, SUR2A and SUR2B) exhibiting a regulatory function [23]. The single channel conductance for K_{ATP} channels shows a substantial

variation between different tissues as values from 15 pS to 258 pS have been reported for VSMC [23, 39, 129]. These channels are inhibited physiologically by elevated intracellular ATP (Fig. 1) and stimulated by ADP [39]. As the ATP/ADP ratio regulates their activity, they have the potential to adapt the vascular tone to the metabolic needs of the tissue [130]. In addition, they are stimulated by PKA (Fig. 2) and/or PKG and inhibited by PKC [16, 85]. Pharmacologically, they are inhibited by sulfonylureas such as glibenclamide and stimulated by drugs such as cromakalim, pinacidil and diazoxide [131].

Renal function

Lorenz et al. found a K^+ channel in rabbit afferent arteriolar myocytes with an unusually high conductance (258 pS) which was inactivated by 1 mM ATP [129]. The authors also reported that the K_{ATP} channel opener diazoxide dilated rabbit isolated afferent arterioles *in vitro* while these vessels were constricted by the K_{ATP} channel inhibitor glibenclamide [129]. Binding studies and in situ hybridization histochemistry have revealed the existence of K_{ATP} channels in smaller rat renal arteries and arterioles [132].

Jensen et al. found in the isolated perfused rat kidney that cromakalim caused a renal vasodilation that was attenuated by glibenclamide [133]. It has also been shown, using the blood-perfused juxtamedullary nephron preparation, that pinacidil caused afferent arteriolar vasodilation whereas glibenclamide had little effect on afferent arteriolar tone [134]. Several *in vivo* studies have found that different K_{ATP} channel stimulators increase RBF in rats and dogs [135-139] whereas glibenclamide had no effect on RBF in rats [10]. K_{ATP} channels and glibenclamide sensitive currents has also been described in the rat descending vasa recta [140].

Metabolic vasodilation

Lowered glucose concentrations led to vasodilation in isolated rabbit afferent arterioles, an effect that was reversed by glibenclamide. This supports the notion of regulation of renal blood flow by intracellular levels of ATP [129]. Furthermore, glibenclamide constricted while pinacidil dilated afferent arterioles from rats with streptozotocin-induced diabetes implicating K_{ATP} channels in the hyperfiltration seen in diabetes [134].

It has also been suggested that K_{ATP} channels mediate the vasomotor response to changes in oxygen tension in different vascular beds [21, 130]. The rat afferent arteriolar myogenic response was attenuated via activation of K_{ATP} by low oxygen tension (PO_2 20 mm Hg). This myogenic response was restored by glibenclamide [59]. These findings suggest that K_{ATP} channels have a function in the adaptation of renal perfusion to hypoxia. As the cortex

normally has a low arterio-venous PO_2 difference, one could speculate that this mechanism is more important in the medullary circulation with its lower oxygen tension.

Based on results obtained in the perfused hydronephrotic rat kidney, it is suggested that afferent arteriolar vasodilation induced by calcitonin gene-related peptide (CGRP) or activation of A2a adenosine receptors is mediated via activation of K_{ATP} channels [141, 142].

K$^+$ channels in renal endothelium

BK_{Ca} channels in EC

BK_{Ca} channels are present in endothelial cell of some vascular beds [143, 144]. Hyperpolarization of EC following activation of BK_{Ca} channels can increase the electrochemical gradient for Ca^{2+} thus increasing the Ca^{2+} influx to modulate NO production [144-146]. In addition, release of K^+ from endothelial BK_{Ca} channels have been suggested to function as an endothelial derived hyperpolarizing factor (EDHF) by activation of K_{IR} channels or Na^+/K^+-ATPases on VSMC [86, 147].

BK_{Ca} channels in renal EC

BK_{Ca} channels have been identified in EC from renal arteries [145] whereas expression in EC from smaller arteries was not confirmed [44]. A functional role in regulation of renal hemodynamics has not been shown.

SK_{Ca} and IK_{Ca} channels in EC

Small conductance potassium channels (SK_{Ca}) and intermediate conductance potassium channels (IK_{Ca}) have been found in most endothelial cells in the vasculature including the renal vasculature. The IK_{Ca} and SK_{Ca} channels are activated by increased $[Ca^{2+}]_i$ within the physiological range and they are not voltage sensitive [148]. The SK_{Ca} and IK_{Ca} channels have conductances of 10 pS and 40 pS, respectively [149, 150]. SK_{Ca} channels are inhibited by apamin and the IK channels by TRAM-34 and the less specific charybdotoxin [144, 146]. Both IK_{Ca} and SK_{Ca} channels are stimulated by NS 309 [151].

IK_{Ca} channels are mostly located in the vicinity of myoendothelial junctions (MEJ) whereas the SK_{Ca} channels are distributed more evenly over the endothelial surface [152-154]. However, this distribution remains to be quantified in renal arteries and arterioles.

In endothelial cells, activation of IK_{Ca} and SK_{Ca} channel by Ca^{2+} involves activation of a G-coupled receptor and an IP_3 mediated increase in cytosolic Ca^{2+} [155]. $[Ca^{2+}]_i$ can also be modulated by the opening of endothelial TRP channels [146, 156]. TRP channel activity has directly been linked to IK_{Ca} opening in the MEJ [157]. It is suggested that the location of IK_{Ca}

channels in the MEJ creates a signaling micro-domain that allows Ca^{2+} to be elevated only in the MEJ and thereby specifically activate the IK_{Ca} channels here [158, 159].

SK_{Ca} and IK_{Ca} channels in renal EC

Endothelial IK_{Ca} and SK_{Ca} channels are expressed in the renal vasculature [10, 69]. Apamin-induced inhibition of SK_{Ca} channels increases RVR in the isolated perfused kidney [48]. In contrast, it does not affect baseline rat afferent arteriolar diameter in the blood-perfused juxtamedullary model [52] or RBF in anesthetized rats [10].

Renal EDH

Endothelium derived hyperpolarization (EDH) is defined as the endothelial mediated vasodilation elicited by ACh or bradykinin that remains when NO and prostacyclin production is inhibited [160]. The current generated by the activation of IK_{Ca} and SK_{Ca} channels is suggested to initiate a hyperpolarizing current into the VSMC via MEGJ. Furthermore, IK_{Ca} and SK_{Ca} channel activation may increase the K^+ concentration in the extracellular space between EC and VSMC. This in turn leads to activation of VSMC K_{ir} channels and Na^+/K^+-ATPases and to hyperpolarization of these cells [15, 86, 161-163]. The exact mechanisms behind EDH remain unclear and may depend on the vascular bed and the arterial segment [160, 164-166]. This might explain some of the different results that have been obtained in vitro with renal arteries and arterioles [43, 61, 137, 167]. Some have shown a major role of IK_{Ca} and SK_{Ca} channels in renal EDH whereas others have suggested a minor role. Boettcher et al [168] showed that in a. gracilis under isometric conditions lack of connexin 40 reduced the EDH response whereas under isobaric conditions the EDH response was unaffected. This difference between isobaric and isometric setups might also provide an explanation for the discrepancy.

In the renal vasculature, *in vitro* studies have shown that the EDH-response can be abolished by co-treatment with apamin and charybdotoxin [64, 163, 169]. In the hydronephrotic rat kidney, Wang et al showed that inhibition of either the IK_{Ca} or SK_{Ca} channel with charybdotoxin or apamin respectively reduced the EDH response and a combination abolished the EDH response [64, 68]. Under isometric conditions, we found that the EDH mediated vasodilation in rat renal interlobar arteries was inhibited by a combination of TRAM-34 and apamin. Also, inhibition of Na^+/K^+-ATPase and K_{ir} channels reduced the magnitude of EDH [15].

In vivo, the renal EDH is commonly quantified as changes in RBF. In wistar rats renal EDH was reduced when the IK_{Ca} and SK_{Ca} channels were inhibited with charybdotoxin and apamin [170]. In Sprague-Dawley rats we found that the EDH response was absent when inhibiting the IK_{Ca} and SK_{Ca} channels with a combination of TRAM-34 and apamin [15]. This suggests that IK_{Ca} and SK_{Ca} channels are crucial for renal EDH, but that the complete mechanism is not

clarified [15]. In contrast to the *in vitro* results, we found *in vivo* that inhibition of Na^+/K^+-ATPase and K_{ir} channels did not reduce the magnitude of EDH [15].

K_{ir} channels in EC

K_{ir} channels are also found in EC [171] where K_{ir}2.1 seems to be the dominating isoform [172]. In renal vessels, K_{ir} is found in EC in afferent and efferent arterioles [88, 89], in the renin-secreting cells [94] and in the EC and pericytes of the decending vasa recta [90, 91]. Inhibition of renal K_{ir} channels induce vasoconstriction both in vitro [18, 48] and in vivo [89] but whether this is caused by K_{ir} channels expressed in EC or VSMC is hard to distinguish. In small mesenteric arteries, only EC express K_{ir} and inhibition of these significantly reduces vasodilation in response to ACh [173] and flow-induced vasodilation [174].

K_V and K_{ATP} channels in EC

Although both K_V and K_{ATP} channels have been shown in EC, their exact role in regulation of renal vascular tone has not yet been clarified.

Renal vascular K^+ channels in integrated renal hemodynamics.

Several blockers of K^+ channels have a constrictor effect on renal vessels *in vitro* [48] and in vivo [10, 89]. Specifically BK_{Ca}, K_{ir}, K_V1, K_V7 and K_{ATP} channels have been shown to affect baseline renal vascular resistance in vitro whereas K_{ir}, K_V7 and K_{ATP} affect RBF in vivo. However, the constrictor effect seems to be additive as blockage of a single group of channels elicits a smaller change than inhibition of several channels [10, 48] suggesting a considerable overlap in function. Closure of the K^+ channels causes depolarization of VSMC and opening of VOCC followed by vasoconstriction. Conversely, opening of K^+ channels leads to hyperpolarization and renal vasodilation. However, adding individual stimulators as well as a cocktail of K^+ channel openers in vivo only elicits minor effects on basal RBF, while the same cocktail attenuated the RBF responses to AngII and norepinephrine by 60 % and 33 %, respectively [10].

In the kidney, BK_{Ca} channels in VSMC has been proposed to function as a buffer during agonist induced vasoconstriction [27, 35, 36, 85, 126] (Fig. 1). In addition, the BK_{Ca} channel opener NS 1619 attenuated Ang II induced reductions of RBF *in vivo* and this effect was reversed by iberiotoxin [44]. BK_{Ca} channels also act as a buffer during the renal myogenic response [59].

As in other vascular beds, SK_{Ca} and IK_{Ca} channels in renal EC are suggested to induce endothelial derived hyperpolarization. This hyperpolarization can transfer to VSMC via myoendothelial gap junction. Furthermore,, the K^+ released from EC via SK_{Ca} and IK_{Ca} channels can active K_{IR} channels and Na^+/K^+-ATPases on VSMC to induce hyperpolarization and renal vasodilation. Renal K_{IR} channels also play a role in K^+ induced vasodilation to elicit increases in RBF, GFR and sodium excretion possibly reducing arterial blood pressure during high potassium intake [99].

Renal vessels express both K_V1 and K_V7 channels and K_V7 are suggested to mediate β-adrenergic renal vasodilation.

Inactivation of several classes of K^+ channels might be mediated by PKC induced phosphorylation [16, 36, 85, 175]. Blockade of PKC attenuates the Ang II or norepinephrine induced increase in afferent arteriolar VSMC $[Ca^{2+}]_i$ [176] suggesting that activation of PKC leads to depolarization via inhibition of K^+ channels [4]. In addition, renal afferent arteriolar myogenic activity is attenuated by PKC inhibition [177]. This effect was reversed by 4-AP suggesting that PKC has an inhibitory effect on K_V channels (Fig. 1). As PKC inhibits several other classes of K^+ channels, it is likely that K^+ channels other than K_V channels are involved in this response [16, 85].

Renal vascular K^+ channels in disease.

Hypertension

K^+ channel function is altered in hypertension [178]. However, the manner of alteration may differ between channels. While K_{ATP} and K_{ir} channel function is supposed to be reduced in hypertension, BK_{Ca} channel function is up-regulated [16, 178, 179]. IK_{Ca} channel expression is also up-regulated during hypertension [180]. On the other hand, other authors reported a reduced expression of both SK_{Ca} and IK_{Ca} channels during Ang II-induced hypertension [181]. Likewise our laboratory has found that mRNA of SK_{Ca} and IK_{Ca} channels were significantly down-regulated in obese fructose/fat fed rats with elevated blood pressure [182]. Regarding the renal vascular system, information is scarce. Comparing VSMC from renal interlobar arteries from WKY, SD, SHR and DOCA rats Martens and Gelband found an upregulation in K_V channels activity and a down-regulation in K_{Ca} channel activity [183]. It has also been reported that K_{ATP} channel function is down-regulated in hypertension [139, 184]. Activation of BK_{Ca} in renal arteries from SHR was reduced compared to WKY possibly caused by a decrease in NO production [185]. Furthermore, expression of $K_V7.4$ in renal arteries from SHR is significantly

reduced [112]. However, there is an urgent need for studies dealing with altered renal vascular K^+ channels function in different forms of hypertension.

Diabetes

In diabetes mellitus (DM), elevated K_{ATP} and K_{ir} channel function may contribute to preglomerular vasodilation and hyperfiltration [52, 134, 186]. Kir1.1 and/or Kir3.x channels contribute to the afferent arteriolar dilation seen in DM [52]. The same study showed that the effect of TEA on afferent arteriolar diameter was similar in control rats and DM rats indicating that BK_{Ca} channel function is not altered [52]. Also, glibenclamide constricted afferent arterioles from rats with DM while the effect was absent in normal rats [134]. Thus, increased K_{ATP} channel function may contribute to the early DM hyperfiltration [186]. In addition, oxidative stress may contribute to the exaggerated vasodilating actions of Kir1.1, Kir2.1, and K_{ATP} channels on afferent arteriolar tone during DM [187]. On the other hand, using clearance methods, Vallon et al. were unable to find any renal vascular effect of the K_{ATP} channel blocker U37883A in rats with DM [188]. It is clear that there is a need for more research to fully elucidate a possible role for renal vascular K^+ channels in early diabetic hyperfiltration.

Sepsis

Activation of vascular BK_{Ca} or K_{ATP} channels may be involved in the hypotension associated with sepsis [189-192]. However, treatment with blockers or lack of these channels has not shown any beneficial effects [193-195]. Levosimendan, a K_{ATP} channel activator, exhibited protection against lipopolysaccharide -induced acute renal failure [189]. This is in line with a study demonstrating that despite the fact that glibenclamide or iberiotoxin increased blood pressure and vascular reactivity to vasoconstrictors in septic animals, the treatment led to a substantial reduction in RBF especially after treatment with drugs, such as norepinephrine and phenylephrine putting renal perfusion at risk [190].

Concluding remarks

It is clear that renal vascular K^+-channels play a significant role in the regulation of renal vascular tone. In the literature, there is a considerable volume of information available regarding the role of the individual classes of renal vascular K^+-channel in a variety of *in vitro* settings. However, studies characterizing K^+ currents in renal resistance vessels are

sparse as are studies investigating these channels in *in vivo* settings. Information regarding the role of these channels in different disease conditions is especially scarce. An increased knowledge about renal vascular K^+-channel function in physiology and during pathophysiological conditions such as hypertension, DM and sepsis may increase the potential for renoprotection in these conditions.

Acknowledgements

Conflict of Interest

None

Table legends

Table 1. The four super families of K^+ channels. Shown are the International Union of Basic and Clinical Pharmacology (IUPHAR) nomenclature for relevant members expressed in renal vascular tissue, the gene names and some of the common aliases.

Table 1: K^+ channels

Family	Subtype	Renal vascular members	Gene name	Alias
Ca^{2+} activated (KCa)	KCa1	$K_{Ca}1.1$	KCNMA1	BK_{Ca} or Slo
	KCa2	$K_{Ca}2.1-2.3$	KCNN1-3	SK_{Ca} or SK1-3
	KCa3	$K_{Ca}3.1$	KCNN4	IK_{Ca}
Inwardly rectifying (K_{ir})	$K_{ir}1-6$	$K_{ir}1.1$	KCNJ1	ROMK
		$K_{ir}2.1-2.2$	KCNJ2/12	K_{ir}
		$K_{ir}6.1-6.2$	KCNJ8/11	K_{ATP}
Voltage gated (K_V)	K_V1-12	$K_V1.1-1.8$	KCNA1-7; 10	K_V Shaker-related
		$K_V7.1-7.5$	KCNQ1-5	KCNQ
Two-P	K2P	$K_{2P}2.1$	KCNK2	TREK-1
		$K_{2P}3.1$	KCNK3	TASK-1

KCa nomenclature: [196]
K_{ir} nomenclature: [197]
K_V channel nomenclature: [198]
K2P nomenclature: [199]

Figure legends

Figure 1. Pathways leading to vasoconstriction via deactivation of K^+ channels in vascular smooth muscle cells (shown with red arrows). The following depolarization and increase in $[Ca^{2+}]_i$ can activate K^+ channels to buffer the vasoconstriction (shown with green arrows). See text for details. Blue arrow = effect; Red arrow = deactivation; Green arrow = activation. VOCC: voltage activated calcium channel, V_m: membrane potential, SR: sarcoplasmatic reticulum, PKC: protein kinase C, IP_3: inositol trisphosphate, 20-HETE: 20-Hydroxyeicosatetraenoic Acid

Figure 2. Pathways leading to vasodilation via activation of K^+ channels in endothelial cells or vascular smooth muscle. See text for details. Blue arrow = effect; Red arrow = inhibition; Green arrow = activation.
ER: endoplasmatic reticulum, Cyt P450: cytochrome P450, NOS: nitric oxide synthase, V_m: membrane potential, EET: Epoxyeicosatrienoic acids, MEGJ: myoendothelial gap junctions, K^+_{EC}: K^+ released from the endothelial cell, cGMP: cyclic GMP, PKG: protein kinase G, VOCC: voltage activated calcium channel, PKA: protein kinase A

Figure 3. Current-voltage relationship for K_{ir} channels at three different extracellular K^+ concentrations. The curves are calculated using the equations for the Kir channel in Edwards et al [74]. E_K used is calculated from the Nernst equation using $[K^+]_{out}$ = 5 mM, 12 mM or 20 mM and $[K^+]_{in}$=130 mM. V_m covers the range of measured values (-55 mV - -40 mV) in afferent arteriolar VSMC [17, 121].

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