Role of vascular potassium channels in the regulation of renal hemodynamics

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Sorensen CM, Braunstein TH, Holstein-Rathlou N-H, Salomonsson M. Role of vascular potassium channels in the regulation of renal hemodynamics. Am J Physiol Renal Physiol 302: F505–F518, 2012. First published December 14, 2011; doi:10.1152/ajprenal.00052.2011.—K+ conductance is a major determinant of membrane potential (V_m) in vascular smooth muscle (VSMC) and endothelial cells (EC). The vascular tone is controlled by V_m through the action of voltage-operated Ca2+ channels (VOCC) in VSMC. Increased K+ conductance leads to hyperpolarization and vasodilation, while inactivation of K+ channels causes depolarization and vasoconstriction. K+ channels in EC indirectly participate in the control of vascular tone by several mechanisms, e.g., release of nitric oxide and endothelium-derived hyperpolarizing factor. In the kidney, a change in the activity of one or more classes of K+ channels will lead to a change in hemodynamic resistance and therefore of renal blood flow and glomerular filtration pressure. Through these effects, the activity of renal vascular K+ channels influences renal salt and water excretion, fluid homeostasis, and ultimately blood pressure. Four main classes of K+ channels [calcium activated (KCa), inward rectifier (Kir), voltage activated (KV), and ATP sensitive (KATP)] are found in the renal vasculature. Several in vitro experiments have suggested a role for individual classes of K+ channels in the regulation of renal vascular function. Results from in vivo experiments are sparse. We discuss the role of the different classes of renal vascular K+ channels and their possible role in the integrated function of the renal microvasculature. Since several pathological conditions, among them hypertension, are associated with alterations in K+ channel function, the role of renal vascular K+ channels in the control of salt and water excretion deserves attention.

vasodilation; vasoconstriction; afferent arteriole; in vivo; in vitro

The renal excretion of Na+ and water is determined by the balance between glomerular filtration rate (GFR) and tubular reabsorption. The primary determinants of the glomerular filtration rate are the single-nephron blood flow, the glomerular capillary hydrostatic pressure, and the plasma oncotic pressure (134). Except for the latter, these variables are direct consequences of microcirculatory function. Tubular reabsorption requires uptake of the reabsorbate into the peritubular capillaries. This is driven by the Starling forces, i.e., the hydrostatic and oncotic pressures in the peritubular capillaries and the interstitium. Again, these variables will be directly influenced by changes in the renal microcirculation. It is therefore not surprising that many experiments have demonstrated that changes in blood flow and pressure within renal vessels have marked effects on Na+ and water excretion (134) and that control of renal vascular tone is essential for the maintenance of body fluid homeostasis and blood pressure.

The tone of renal vascular smooth muscle cells (VSMC), and therefore the hemodynamic resistance in the renal microcirculation, is controlled by Ca2+-independent and -dependent mechanisms. The intracellular Ca2+ concentration ([Ca2+]i) in VSMC is dependent on Ca2+ entry via voltage-operated Ca2+ channels (VOCC) (153). The activity of these channels is influenced by the membrane potential (V_m), and through their influence on the V_m, K+ channels may have an impact on the salt and water balance and thus blood pressure (80). In addition to the direct effects on VSMC function, K+ channels in the endothelial cells may indirectly influence the activity of VSMC through several mechanisms, e.g., release of nitric oxide (NO) and endothelium-derived hyperpolarizing factor (EDHF) (46). K+ channels are also present in the tubular epithelium in several nephron segments (60, 75). An altered channel activity in the tubule will directly affect renal potassium excretion and thus have an impact on salt and water balance and therefore also blood pressure (80). Tubular K+ channels will not be dealt with in the present review.

The available information regarding the role of the main classes of vascular K+ channels [calcium activated (KCa), inward rectifier (Kir), voltage activated (KV), and ATP sensitive (KATP)] in the control of the renal vasculature is largely based on results from in vitro experiments. While in vitro experiments are necessary for investigating the characteristics and the regulation of individual channels, they are often inad-
equate in determining the physiological function of a class of ion channels in a given organ or tissue. It is mandatory that the in vitro data are supplemented by experiments performed in the integrated system in question, e.g., the renal microcirculation. Results originating from in vivo experiments also have to be interpreted with caution as these techniques are associated with several pitfalls. Measuring renal blood flow (RBF) responses during administration of test agents directly into the renal artery (113, 114, 161, 163) will avoid some of the systemic effects, but there are still several associated problems. Some agents might need an exposure time that inevitably leads to systemic effects, for example, on the nervous system. The distribution of the agent might be uneven within the renal vasculature, leading to different concentrations at different locations. The filtration of the test agent might have tubular effects that affect signaling from the tubule to the vasculature (e.g., via the tubuloglomerular feedback mechanism). In addition, it is impossible to discriminate between effects on the VSMC and the endothelium. Finally, the inevitable use of anesthetic agents might have an effect on K⁺ channels in the VSMC and endothelial cell (EC) membranes. Neither approach by itself, that is in vitro or in vivo, can provide the information necessary to understand the physiological roles of a given class of K⁺ channels.

The purpose of the present review is therefore to attempt to develop an understanding of the physiological functions of renal vascular K⁺ channels by combining the knowledge obtained from in vitro experiments with that from corresponding in vivo experiments. We focus on studies investigating the activation of VOCC (81, 92). In VSMC, depolarization of the membrane decreases the electrochemical gradient for Ca²⁺, but the increased Ca²⁺ permeability, due to opening of the VOCC, will lead to increased Ca²⁺ entry and the net result will be an increase in [Ca²⁺]. Accordingly, vasoconstriction might be mediated via inactivation of K⁺ channels (93). A lack of VOCC was originally reported for the VSMC of the efferent arteriole (26). Later reports have, however, revealed T-type VOCC in efferent arterioles and L-type VOCC in juxtaglomerular efferent arterioles (54, 68, 138). The role of voltage-dependent Ca²⁺ entry remains unclear for efferent arteriolar VSMC.

In cells without VOCC, such as EC, inactivation of K⁺ channels will still cause depolarization. In contrast to the situation in the VSMC, the result will be a decreased influx of Ca²⁺ as the depolarization of the cell membrane decreases the inwardly directed electrochemical gradient for Ca²⁺.

In addition to K⁺ channels, Cl⁻ channels might participate in the regulation of Vm. In VSMC the Vm is normally more negative than ECl, and the opening of Ca²⁺-activated Cl⁻ channels (ClCa) has been shown to mediate agonist-induced depolarization (2, 100). However, available results are conflicting and differ in experimental setup and use of blockers (25, 86, 163, 168). Using niflumic acid, one of the most specific inhibitors of ClCa, no evidence for a role for ClCa in the control of basal renal vascular tone or the action of vasoactive agonists was found in vivo or in vitro (163).

K⁺ Channel Classification

More than 75 genes coding for K⁺ channels have been identified in the human genome (52). They are divided into four superfamilies: Kca, Kir, Kv, and two-pore domain (K2p) channels (Table 1). Kca channels are further subdivided into large-, intermediate-, and small-conductance calcium-activated potassium channels (BKCa, IKCa, and SKCa, respectively). Kv, IKCa, and SKCa channels possess six transmembrane domains, whereas K2p, BKCa, and Kir have seven, four, and two transmembrane domains, respectively (117). The KATP channel belongs to the inward rectifier superfamily as it is composed of Kir6.1 or Kir6.2 subunits (183). In addition to the pore-forming domain, K⁺ channels are usually associated with regulatory subunits determining the characteristics of the channel. K⁺ channels are highly selective due to a conserved K⁺ recognition sequence in the pore (41, 187, 189). No consistent nomenclature is used for K⁺ channels in the cardiovascular field, and Table 1 provides the International Union of Basic and Clinical Pharmacology nomenclature and the aliases commonly used in the literature for vascular K⁺ channels as well as in this review.

BKCa Channels

The BKCa channel is coded for by a single gene. A tetramer of the pore-forming α-subunits is necessary for basic BKCa channel function. Alternative splicing and association with β-subunits contribute to a large diversity in BKCa channels with regard to regulation and function (110). The BKCa chan-
nel is also known as KCa1 or Slo (52) (Table 1). Their conductance is in the range of 200–250 pS. These channels are voltage sensitive, and the voltage sensitivity is modulated by \([Ca^{2+}]_{i}\). In addition, they are activated by protein kinases including cAMP- and cGMP-dependent protein kinase (PKA and PKG) (Table 1) (121, 162, 188). As NO stimulates the cGMP/PKG pathway, activation of NO synthase might lead to increased BKCa activity (see Fig. 2) (8). However, it has been suggested that the effect of NO in the renal vasculature is independent of \([Ca^{2+}]_{i}\) channels (95). Also, carbon monoxide (CO) has been reported to activate BKCa channels via a PKG-dependent mechanism or by binding to a heme group on the channel (74, 83, 149). Most studies indicate that PKC inhibits BKCa channels (12, 37, 99), but one study has shown that PKC via cGMP activates BKCa (12). Pharmacologically, they are inhibited by tetraethylammonium (TEA), charybdotoxin, and iberiotoxin (IBT) and stimulated by NS 1619 (Table 1) (81).

**Function of vascular BKCa.** It is still controversial whether BKCa channels are active at resting \(V_m\) and VSMC \([Ca^{2+}]_{i}\) (20). At negative \(V_m\), activation requires \([Ca^{2+}]_{i}\) in the range of 1–10 \(\mu M\) (150), which exceeds that found in the bulk cytoplasm under resting conditions. It is therefore doubtful whether they are active in VSMC under resting conditions. It is suggested that BKCa channels have an important function by buffering vasoconstrictor responses (Fig. 1) (126). The increase in \([Ca^{2+}]_{i}\), resulting from agonist stimulation or activation of the myogenic mechanism, activates BKCa channels, attenuates depolarization, and opposes vasoconstriction (82). The increase in \([Ca^{2+}]_{i}\), necessary for activating BKCa, need not be global, but may be restricted to so-called microdomains within the cell (42). \(Ca^{2+}\) recruitment via entry and release from intracellular stores may cause localized elevations in \([Ca^{2+}]_{i}\), so-called \(Ca^{2+}\) sparks, able to activate BKCa channels (Fig. 1). Recent evidence shows that BKCa channels and

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PKA, protein kinase A; PKG, protein kinase G; NO, nitric oxide; TEA, tetraethylammonium; IBT, iberiotoxin; ChTx, charybdotoxin; PKC, protein kinase C; TRAM-34, 1-[(2-chlorophenyl)diphenylmethyl]-1H-pyrazole; Gli, glibenclamide; 4-AP, 4-aminopyridine. Shown are the International Union of Basic and Clinical Pharmacology (IUPHAR) nomenclature, members expressed in renal and cardiovascular tissue, some of the common aliases, the effect of \([Ca^{2+}]_{i}\) and voltage, and some of the relevant activators and inhibitors.

**Fig. 1.** Different pathways lead to vasoconstriction via inactivation of K⁺ channels in vascular smooth muscle cells. See text for details. Grey arrow indicates effect; red arrow, inhibition; green arrow, activation. VOCC, voltage-activated calcium channel; \(V_m\), membrane potential; SR, sarcoplasmic reticulum; PKC, protein kinase C; IP₃, inositol trisphosphate; 20-HETE, 20-hydroxyeicosatetraenoic acid.
VOCC form complexes in the cell membrane which could provide an efficient mechanism for attaining local Ca\(^{2+}\) concentrations of a magnitude necessary to activate BK\(_{Ca}\) channels (16). In isolated coronary and cerebral arterial myocytes from rabbits, it is shown that BK\(_{Ca}\) channels open simultaneously with the L-type Ca\(^{2+}\) channels (20, 66). Also, Ca\(^{2+}\) released via ryanodine-sensitive Ca\(^{2+}\) channels in the sarcoplasmic reticulum attenuates vasoconstriction via activation of BK\(_{Ca}\) channels (181). It is reported that vasoconstrictors could exert their effect by PKC-mediated inhibition of BK\(_{Ca}\) channels (Fig. 1) (37, 99).

**Endothelial BK\(_{Ca}\) channels.** It has been suggested that endothelial BK\(_{Ca}\) channels participate in the regulation of NO production (129). Activation of BK\(_{Ca}\) channels will hyperpolarize the EC membrane, causing an increased Ca\(^{2+}\) influx and an increase in [Ca\(^{2+}\)]\(_i\), which will activate endothelial NO synthase (eNOS) (Fig. 2) (19, 123, 129). It is also possible that K\(^+\) released by endothelial BK\(_{Ca}\) channels activates VSMC K\(_a\) channels and/or Na-K-ATPase and thereby acts as an EDHF (Fig. 2) (46). Although a function for endothelial BK\(_{Ca}\) channels has been suggested in the larger renal artery, there are to our knowledge no reports that endothelial BK\(_{Ca}\) channels have a function in the regulation of renal hemodynamics (19).

**Renal vascular BK\(_{Ca}\) channels: expression and function.** In rat juxtaglomerular cells an IBT-sensitive current has been identified in patch-clamp experiments (57). To our knowledge, there are no other reports of BK\(_{Ca}\) current in renal vascular resistance vessels. Evidence for the expression of BK\(_{Ca}\) channels in rat preglomerular vessels has been provided by RT-PCR and immunofluorescence. (57, 113). Their presence has also been suggested in rat mesangial cells (164, 165).

In vitro studies utilizing the blood-perfused juxtaglomerular nephron preparation reported a TEA-induced constriction of the afferent arteriole (49, 78, 173). TEA (1 mM) had no effect on efferent arteriolar diameter (49). In the same study, it was shown that stimulation with the BK\(_{Ca}\) channel opener NS 1619 (30 μM) increased efferent arteriolar diameter (49). In the isolated, perfused rat kidney, TEA produced an elevation in the basal perfusion pressure (96, 145). These results suggest that BK\(_{Ca}\) participates in the regulation of basal renal vascular tone. However, in these studies TEA concentrations of 2 and 10 mM were used. This makes interpretation of the results somewhat difficult as TEA in these concentrations is not specific for the BK\(_{Ca}\) channel but also may inhibit K\(_i\) and K\(_{ATP}\) channels (132, 167).

Loutzenhiser and Parker (109) found that TEA (1 mM) augmented the afferent arteriolar myogenic response, indicating a role for BK\(_{Ca}\) channels as a buffer against myogenic vasoconstriction in vitro.

We investigated the BK\(_{Ca}\) channel in vivo (113) and found that TEA (estimated plasma concentration 1 mM) infused directly into the rat renal artery reduced RBF by ~10%. IBT (estimated plasma concentration 100 nM), which is considered to be a specific BK\(_{Ca}\) channel blocker, did not affect baseline RBF in our in vivo experimental setting (113). This suggests that part of the TEA effect may be unspecific and due to blockade of other K\(^+\) channels, and that the activity of BK\(_{Ca}\) channels in vivo may be low under resting conditions. This is supported by the lack of effect on RBF of the BK\(_{Ca}\) channel stimulator NS 1619 (estimated plasma concentration 30 μM) in vivo (113). In contrast, Fallet et al. (49) found that superfusion with NS 1619 (30 μM) caused a concentration-dependent dilation of the afferent arteriole in vitro. 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 NS 1619 (131). Another possible explanation for the discrepancy between the in vivo and the in vitro studies could be that in vivo we investigated the effect on the integrated renal circulation while in the in vitro study a single vessel type (i.e., the juxtaglomerular afferent arteriole) was investigated. It has indeed been shown that subpopulations of BK\(_{Ca}\) channels exhibit different Ca\(^{2+}\) sensitivity (154). Finally, superfusion of agents will primarily affect channels on the VSMC, while infusion into the renal artery will elicit an initial effect on the EC. However, the significance of this for the observed discrepancies is difficult to evaluate.

In agreement with Fallet et al. (49), we found that ANG II-induced renal vasoconstriction was attenuated by stimulation with NS 1619 (113). This attenuation was reversed by TEA or IBT, indicating that the attenuation is by stimulation of BK\(_{Ca}\) channels. This finding supports the notion that the ability of NS 1619 to open BK\(_{Ca}\) is significant only when [Ca\(^{2+}\)]\(_i\) is elevated under ANG II stimulation.

**Role in renal vasodilation.** Mice lacking a regulatory β-subunit of the BK\(_{Ca}\) channel (Mβ1) are moderately hypertensive, but no differences in renal function were found between these...
mice and wild-type mice under euvelomic conditions. However, during acute volume expansion the increase in GFR was impaired in the MB1−/− mice (137). This finding indicates a role for the β1-subunit of BKCa channels in the renal response to acute volume loading. The precise location of these channels cannot be determined based on this study, but a preglomerular vasodilatory action of BKCa channels is in agreement with the findings.

One of many actions of cAMP is to activate BKCa channels (Fig. 2). Activation of adenylate cyclase could therefore lead to renal vasodilation (171, 188). We were not able to confirm this in vivo as the renal vasodilation induced by forskolin, an activator of adenylate cyclase, was not attenuated by IBT (113).

In isolated VSMC from rat preglomerular vessels, the NO donor sodium nitroprusside reduced the [Ca2+]i response to 50 mM KCl. IBT restored this response, which suggests a role for BKCa channels in NO-induced renal vasodilation (53). It is, however, difficult to understand how activation of BKCa channels would cause sufficient hyperpolarization to inactivate VOCC in the presence of 50 mM KCl. According to Nernst’s equation, $E_K$ is in this situation far more positive than the activation level of L-type VOCC, and opening of BKCa channels cannot make $V_{in}$ more negative than $E_K$. Also, in perfused hydrolephotic rat kidneys TEA has only a minor effect on the ACh-induced afferent arteriolar vasodilation (178). As this and other studies indicate that the renal response to ACh is to a large extent mediated by NO, this finding does not support a role for BKCa channels in NO-induced renal vasodilation (10, 133, 178).

Epoxidecatrienoic acid (EET) has been suggested to function as an EDHF (47), and recent evidence shows that EETs act as vasodilators also in the renal microcirculation (77). Imig et al. (77) found that an 11,12-EET analog caused dilation of the afferent arteriole and, to a lesser extent, of the efferent arteriole (77). The EETs elicited afferent arteriolar vasodilation via activation of BKCa channels as the vasodilation was abolished by IBT, while inhibitors of SKCa and IKCa channels were without effect. Furthermore, this study suggests that BKCa channels are activated via a protein phosphatase 2-dependent pathway (77). In this regard, it has also been suggested that the afferent arteriolar vasodilation by bradykinin may rely partly on activation of BKCa channels by EETs (179).

In addition to NO, CO has been suggested to elicit vasodilation through activation of soluble guanylate cyclase (149). Ryan et al. (149) found that IBT completely blocked the vasodilatory effect of a CO-releasing molecule in pressurized mouse renal interlobar arteries, indicating that the CO-mediated vasodilation is partly mediated by activation of BKCa channels.

**Role in renal vasoconstriction.** A role for BKCa channels has been proposed in vasoconstriction as closure of these channels causes depolarization and opening of VOCC (37, 71, 81, 99, 140) (Fig. 1). Stimulation with ANG II causes increased 20-HETE production in preglomerular vessels, which might inhibit BKCa channels in these vessels (36, 78). Another mechanism to mediate closure of BKCa channels is via phosphorylation by PKC (Fig. 1) (120). The in vitro responses to TEA support the concept that closure of BKCa channels causes sufficient depolarization to elicit a renal vasoconstriction (49, 78, 96, 173). In vivo we found that the specific inhibitor IBT had no effect on RBF and that TEA only had a small effect (113). NS 1619 reduced the ANG II-induced reduction of RBF in vivo, an effect inhibited by IBT (113). This finding could be explained if the renal vascular BKCa channels are blocked by ANG II administration. However, as IBT failed to cause renal vasoconstriction, it is more likely that only during ANG II administration is [Ca2+]i sufficient to allow NS 1619-induced activation of BKCa channels (see Renal vascular BKCa channels: expression and function).

**Buffering of renal vasoconstriction.** Increased [Ca2+]i, in VSMC has been suggested to activate BKCa channels and thus act as a buffer to vasoconstriction (126). As mentioned above, complexes of VOCC and BKCa channels have been suggested to play a role in this regard (16). This hypothesis is not supported by an earlier report in which TEA failed to affect the juxtaglomerular afferent arteriolar diameter reduction in vitro in response to ANG II or AVP (49). Also, in vivo the rat renal vasoconstriction induced by NE or ANG II was unaffected by TEA or IBT (113). If there was a significant BKCa channel-dependent buffering of the renal vasoconstrictor responses, they should be augmented during BKCa channel blockade.

**SKCa and IKCa Channels**

Four isoforms of SKCa are known, SK1–SK4 (15), but only one isoform of IKCa (Table 1). Both types of channels have six transmembrane-spanning domains. SKCa typically have a conductance of 10 pS and are blocked by apamin at nanomolar concentrations (123, 129). IKCa has a conductance of 30–80 pS and is blocked by charybdoxotoxin and TRAM-34 (123, 129). Both channels are stimulated by NS 309 (166), and unlike the BKCa channels, they are not voltage sensitive (Table 1).

**Function of vascular SKCa and IKCa channels.** Support for the existence and functional role for SKCa and IKCa channels in VSMC is limited. There are, however, reports that indicate the presence of SKCa channels in rat afferent arterioles and rabbit aorta (58, 59). In EC, stimulation by agonists such as ACh and bradykinin activate SKCa and IKCa via inositol 1,4,5-trisphosphate stimulation of intracellular Ca2+ release, and this is assumed to initiate hyperpolarization (Fig. 2) (116). As there is no substantial presence of VOCC in EC, the hyperpolarization leads to Ca2+ entry followed by production of vasodilating compounds such as NO and EDHFs. This Ca2+ entry takes place via non-voltage-sensitive Ca2+ channels, possibly of transient receptor potential (TRP) type (98, 129).

The hyperpolarization exerted by the opening of endothelial SKCa and IKCa channels might also be transmitted to the VSMC via myoendothelial gap junctions and thus lead to hyperpolarization of VSMC, inactivation of VOCC, and vasodilation (Fig. 2) (33, 48). Finally, it has been proposed that activation of endothelial SKCa and IKCa causes secretion of K+ into the restricted space between the EC and the VSMC (46). The increased extracellular concentration of K+ ([K+]o) could then lead to hyperpolarization and relaxation of the VSMC through activation of K+ channels and/or the Na-K-ATPase.

**Renal vascular IKCa and SKCa channels: expression and function.** Patch-clamp experiments utilizing freshly isolated VSMC from rat preglomerular arterioles indicate the existence of a 68-pS KCa channel that is blocked by apamin (59). We have detected positive staining for SK2 and SK3 KCa channels in VSMC and EC of rat preglomerular arterioles (161).
There is support for a role for both IK\textsubscript{Ca} and SK\textsubscript{Ca} channels in renal vasodilation, where they primarily seem to act in the endothelium (Fig. 2). Apamin caused a small increase in renal vascular resistance in the isolated, perfused kidney (96). It is also reported that apamin does not affect basal afferent arteriolar diameter in the in vitro blood-perfused juxtamedullary nephron (173).

ACh or bradykinin has been used to elicit endothelium-dependent renal vasodilation (144, 145, 178, 179). Endothelium-dependent vasodilation is due to the release of NO, prostacyclin (PGI\textsubscript{2}), and EDHF. The response that remains following blockade of the NO and prostaglandin systems is by definition assumed to be mediated by EDHF (51, 115, 151). The nature of EDHF is not fully clarified, but it is clear that different mechanisms are responsible for the EDHF response depending on the vascular bed and experimental conditions (46, 143). EDHF has been suggested to be 1) K\textsuperscript{+} released from the EC through IK\textsubscript{Ca} and/or SK\textsubscript{Ca} channel, 2) H\textsubscript{2}O\textsubscript{2}, 3) EETs, or 4) transmission of hyperpolarization from EC to VSMC via myoendothelial gap junctions (47, 77). EDHF might be stimulated by endothelial Ca\textsuperscript{2+} entry following endothelial hyperpolarization induced by IK\textsubscript{Ca} and/or SK\textsubscript{Ca} channel activation (Fig. 2).

Several in vitro studies report a renal vasodilatory effect of bradykinin that is attenuated by SK\textsubscript{Ca} and/or IK\textsubscript{Ca} inhibition (11, 145, 179). Charybdotoxin attenuated the renal EDHF-mediated response to bradykinin while IBT or leiurotoxin, a putative inhibitor of SK\textsubscript{Ca}, had no effect, indicating an exclusive role of IK\textsubscript{Ca} channels (145). Wang et al. (179) showed that the EDHF-mediated response to bradykinin was attenuated by \(-\text{50}\%\) by a combination of charybdotoxin and apamin. The same laboratory reported that either charybdotoxin or apamin attenuated an EDHF-mediated, ACh-induced transient afferent arteriolar vasodilation and abolished it when administrated simultaneously (178). Similar results were obtained by Ozawa et al. (133) utilizing the isolated, perfused hydronephrotic rat kidney. They also found that the sustained ACh-induced afferent arteriolar vasodilation was unaffected by SK\textsubscript{Ca} and IK\textsubscript{Ca} inhibition. On the other hand, blockade of these channels reduced the peak response to ACh. The peak response (2–5 min) to ACh in the afferent arterioles was unaffected by NO blockade while the sustained (10 min) response was attenuated by \(-\text{70–90}\%\). Taken together, these results indicate that the non-NO-mediated part of endothelium-dependent renal vasodilation is more reliant on hyperpolarization via SK\textsubscript{Ca} and IK\textsubscript{Ca} channel activation than the NO-mediated part (133). In isolated, perfused rabbit afferent arterioles, a combination of apamin and charybdotoxin had no effect on the ACh-induced afferent arteriolar vasodilation while this response was abolished by these K\textsuperscript{+} channel inhibitors in the presence of \(\text{NNA}\) (177). It should be noted that these authors did not discriminate between the initial and sustained response, but followed the preparation for 7–10 min. In another study using the isolated, perfused hydronephrotic rat kidney, Wang and Loutzenhiser (178) found that SK\textsubscript{Ca} and IK\textsubscript{Ca} blockade attenuated the NO-dependent sustained (~10 min) response to ACh. There is no obvious explanation for the discrepancy between the studies of Ozawa et al. (133) and Wang and Loutzenhiser (178). It is possible that the higher ACh concentrations used in the latter study could induce intracellular Ca\textsuperscript{2+} release. Taken together, the results of the in vitro studies mentioned above also indicate that the EDHF-mediated part of endothelium-dependent renal vasodilatory responses to ACh and bradykinin is transient in nature while the sustained response is dependent on NO (133, 145, 177, 178).

There is a paucity of information regarding the role of SK\textsubscript{Ca} and IK\textsubscript{Ca} in the regulation of renal hemodynamics in vivo. Edgley et al. (43) found that ACh- or bradykinin-induced renal vasodilation in vivo in rats was largely dependent on NO. After inhibition of NO and prostaglandin synthesis, only the initial phase of ACh- or bradykinin-induced renal vasodilation remained. This EDHF-mediated part was inhibited by intrarenal infusion of a combination of charybdotoxin and apamin. Edgley et al. did not observe a reduction in basal renal tone in vivo after blocking the IK\textsubscript{Ca} and SK\textsubscript{Ca} channels with apamin and charybdotoxin. When all the results are viewed together, there appears to be experimental support for the role of IK\textsubscript{Ca} and SK\textsubscript{Ca} channels in the renal EDHF response. However, the underlying mechanism is not resolved and awaits further investigations.

\(K_{ir}\) Channels

Six families of \(K_{ir}\) channels are known (\(K_{ir}1–6\)), where \(K_{ir}2\) is the classic inward rectifier channel (Fig. 3) and \(K_{ir}6\) is the ATP-sensitive channel (107) (see below and Table 1). The \(K_{ir}\) channels are tetramers where each \(\alpha\)-subunit has two transmembrane domains (107). These are bridged by an extracellular pore loop containing the selective K\textsuperscript{+} recognition sequence (107).

The single-channel conductance of the \(K_{ir}\) channels is reported to be \(\sim\) 20 pS (92). They are coined “inward rectifier” channels because of their propensity for carrying current in the inward direction (Fig. 3). Under physiological conditions, \(V_m\) is more positive than \(E_K\) and the \(K_{ir}\) channels carry a small outward hyperpolarizing K\textsuperscript{+} current. A unique feature of \(K_{ir}\) channels is that small increases (~5–12 mM) in [K\textsuperscript{+}]\textsubscript{i} increases the outward current (Fig. 3). This mechanism is mediated by interaction of K\textsuperscript{+} with polyamines and/or Mg\textsuperscript{2+} in the channel pore (67, 105). An increase in the single-channel conductance has recently been suggested to also contribute to the increased outward current (104). The Nernst equation (see above) predicts that increased [K\textsuperscript{+}]\textsubscript{i} leads to a less negative \(E_K\) and thus a depolarization of the cell membrane is to be expected, but as the small elevation in [K\textsuperscript{+}]\textsubscript{i} also increases the outward K\textsuperscript{+} current, the net effect is a hyperpolarization of the membrane.

\[E_K = -\frac{RT}{zF} \ln \left(\frac{[K^+]_{o}}{[K^+]_{i}}\right)\]

\[V_m = E_K - I_{K_{ir}} R\]

Fig. 3. Current-voltage relationship for \(K_{ir}\) channels at two different extracellular K\textsuperscript{+} concentrations. \(E_K\) is calculated from the Nernst equation (see the text) using [K\textsuperscript{+}]\textsubscript{o} = 5 or 12 mM and [K\textsuperscript{+}]\textsubscript{i} = 130 mM. \(V_m\) covers the range of measured values (~55 to ~40 mV) in afferent arteriolar VSMC (21, 108).
the cell membrane (Fig. 3). If \([K^+]_o\) is increased further (more than \(\sim 20 \text{ mM}\)), the depolarizing effect dominates. From Fig. 3 it is also clear that a hyperpolarization (e.g., due to opening of other \(K^+\) channels or conducted responses) might be amplified by \(K_{ir}\) channels if \(V_{in}\) attains a voltage range where there is a larger outward current (64, 84, 147, 157). \(Ba^{2+}\) is a general blocker of \(K^+\) channels, but at concentrations <100 \(\mu\text{M}\) it is considered to be specific for \(K_{ir}\) channels with a reported half-maximal inhibition concentration of 2.2 \(\mu\text{M}\) at \(-60 \text{ mV}\) (142).

Function of vascular \(K_{ir}\) channels. \(K_{ir}\) channels are found predominantly in VSMC from microvessels, and the main isoform found is \(K_{ir}^2.1\) (18, 44, 141, 185). In accord with the sensitivity to \([K^+]_o\) described above, \(K_{ir}\) channels might participate in \(K^+\) induced vasodilation described in the metabolic regulation of blood flow (45, 81, 91) and in the EDHF response elicited by \(K^+\) release via \(IK_{Ca}\) and \(SK_{Ca}\) channels (Fig. 2) (46). It is also possible that part of the \(K^+\) induced hyperpolarization/vasodilation is mediated by activation of Na-K-ATPase (180). In addition to VSMC, \(K_{ir}\) channels are found in endothelial cells (81, 126) where \(K_{ir}^2.1\) is supposed to be the main isoform (56).

Renal vascular \(K_{ir}\) channels: expression and function. \(K_{ir}^2.1\) channels have been found in rat afferent and efferent arterioles in both VSMC and EC (29, 114). Patch-clamp experiments indicate inwardly rectifying and \(Ba^{2+}\)-sensitive currents in myocytes from both vessels. Inwardly rectifying currents, originating from \(K_{ir}^2.1\) and 2.2 channels, have been characterized in the renin-producing juxtaglomerular cells, located in the media of the distal afferent arteriole (97, 101). Furthermore, Chilton et al. (31) identified \(K_{ir}\) currents in the distal rat interlobular artery (ILA), while they were absent in the proximal part of the same vessel. In the rat descending vasa recta, both the endothelial cells and the pericytes expressed \(K_{ir}^2.1, K_{ir}^2.2,\) and \(K_{ir}^2.3\) channels (22, 23). \(Ba^{2+}\)-sensitive inwardly rectifying currents are also reported in the rat descending vasa recta EC (23).

\(Ba^{2+}\) at low concentrations (\(<100 \mu\text{M}\)) has been reported to reduce afferent arteriole diameter, indicating a role for \(K_{ir}\) channels in basal renal vascular resistance (30). In isolated, perfused kidneys, \(Ba^{2+}\) increased renal vascular resistance (96).

In the late 1950s, \(K^+\)-induced renal vasodilation was reported by Scott et al. (155). Adequate theories behind the \(K^+\)-induced vasodilation were lacking at that time, but the phenomenon was described for several vascular beds. In the renal vasculature, both the Na-K ATPase and the \(K_{ir}\) channels have been suggested to mediate \(K^+\)-induced vasodilation (29, 30, 139). The discrepancy between studies might originate from the fact that different renal vascular segments were studied. The \(K^+\)-induced vasodilation in afferent arterioles was blocked by \(Ba^{2+}\) at concentrations considered specific for \(K_{ir}\) channels (\(<100 \mu\text{M}\)) (29, 30) whereas the vasodilatory effect of \(K^+\) in the larger rabbit arcuate artery was blocked by ouabain, indicating a major effect of the Na-K ATPase (139). This is in accord with studies reporting a more pronounced activity for \(K_{ir}\) channels in smaller vessels. As mentioned above, a recent study by Chilton et al. (31) indicates that this is the case also in the renal vasculature. Utilizing the in vitro perfused hydronephrotic rat kidney preparation, these authors found that the \(K^+\)-induced vasodilation of the ILA was correlated to vessel diameter. While the distal ILA exhibited a pronounced vasodilation to 15 mM \(K^+\), this response was absent in the proximal ILA. The intermediary ILA showed a modest vasodilatory response to 15 mM \(K^+\). These responses were inhibited by 100 \(\mu\text{M}\) \(Ba^{2+}\) but insensitive to ouabain (31). In isolated, perfused and preconstricted rat kidneys, it was shown that both \(Ba^{2+}\) (100 \(\mu\text{M}\)) and ouabain (10 \(\mu\text{M}\)) attenuated \(K^+\)-induced renal vasodilation, indicating a role for both \(K_{ir}\) channels and Na-K ATPase in this process (124). A recent in vivo report from our laboratory has confirmed this in normotensive rats (114). In spontaneously hypertensive rats (SHR), the blocking effect of ouabain was not significant. This indicates that, while the \(K^+\)-induced vasodilation in individual renal vessel segments from normotensive rats relies on one of the mechanisms (either \(K_{ir}\) channels or Na-K-ATPase), the integrated response of the intact renal circulation is affected by both.

It is suggested that \(K^+\) released from the endothelial cells might act as an EDHF in endothelium-mediated vasodilation by activating VSMC \(K_{ir}\) (35, 46). Evidence for such a function in the renal vasculature is lacking. On the contrary, \(Ba^{2+}\) has no effect on the EDHF component of \(ACh\)-induced vasodilation, arguing against a role of \(K^+\) as a renal EDHF (178).

Plasma \([K^+]_o\) and renal vasodilation. High dietary \(K^+\) intake is associated with a decreased risk for cardiovascular events (13). Furthermore, increased plasma \([K^+]_o\) is correlated to decreased renal vascular resistance, increased glomerular filtration rate, urine flow, and \(Na^+\) excretion (73, 124, 184). It could be speculated that the slightly increased plasma \([K^+]_o\) that follows high dietary \(K^+\) intake mediates renal vasodilation via stimulation of renal vascular \(K_{ir}\) channels. This could underlie the beneficial health effects via decreased arterial blood pressure (124). Murphy and Cohen (124) reported a \(K^+\)-induced renal vasodilation in kidneys from normotensive and hypertensive rats. The vasodilation was augmented after high-\(K^+\) feeding for 8 wk both in hypertensive and normotensive rats (124). However, the blood pressure in the study by Murphy and Cohen was not significantly decreased after high-\(K^+\) diet, which puts into question the clinical importance of the mechanism. Nevertheless, it is possible that such a mechanism is relevant when plasma \(K^+\) increases following metabolic stress where \(K^+\)-induced renal vasodilations may have a protective function. To our knowledge, there are no reports of measurements of renal \([K^+]_o\) under such conditions. However, a doubling of extracellular \(K^+\) has been reported under metabolic stress in brain tissue as well as in venous blood (136, 156, 160). In particular, physiological changes in \([K^+]_o\) has been suggested to participate in the control of renal medullary blood flow via \(K_{ir}\) channels in vasa recta pericytes and endothelial cells (22, 23).

\(K_V\) Channels

\(K_V\) channels consist of four \(\alpha\)-subunits, each subunit consisting of six transmembrane sequences (94). Each of the four \(\alpha\)-subunits is associated with an additional \(\beta\)-subunit influencing the characteristics of the channel (103, 172). Conductances between \(~4\) and 70 pS have been reported for single \(K_V\) channels depending on preparation and experimental conditions (32, 92, 159, 176, 190). The main isoforms found in VSMC are \(K_V^1.1–1.6\), although there is support in the literature for the expression of several other isoforms in these cells.
such as the Kv2 and Kv7 families (7, 28, 34, 88, 170, 186). To our knowledge, only a role for the Kv1 family has so far been described in the control of the renal vascular tone.

Kv channels exhibit strong voltage dependence. Cell membrane depolarization leads to activation of Kv channels and an increased hyperpolarizing outward K+ current (Fig. 2). The resulting hyperpolarization of the VSMC inactivates VOCC channels and consequently decreases VSNC tone (81, 92, 126). The threshold for activation of Kv channels is approximately −50 mV. Sustained depolarization leads to inactivation of Kv channels. Inactivation is slower than activation, and the steady-state current via these channels is determined by the balance between these processes. Thus the open probability (P_open) of these channels is a product of the probability that they are available (not inactivated) and the probability that they are activated (17, 62, 92, 126, 162). In addition to depolarization, Kv channels are activated by the cAMP/PKA pathway (Fig. 2) and inactivated by PKC (Fig. 1) as well as by a decreased pH (3–5, 14, 37). Furthermore, Rho kinases have been reported to suppress Kv currents in rat cerebral arteries (111).

The classic inhibitor of Kv1.x channels is 4-aminopyridine (4-AP) with a reported half-maximal inhibition concentration of 0.3–1.1 mM (92, 126, 130). In addition, the snake venom dendrotoxin blocks Kv1.1 and Kv1.2 channels in the nanomolar range, and other blockers used to identify Kv1 channels are the scorpion toxins agitoxin and correolide (6, 38, 69).

**Function of vascular Kv channels.** Kv channels may contribute to the regulation of the resting membrane potential and thus the tone of VSMC (28, 81, 92). It is suggested that the physiological role of Kv channels is to buffer membrane depolarization to maintain resting vascular tone (126). The presence of Kv channels in EC has been indicated, but their precise role in the control of EC function has yet to be clarified (28, 40, 50, 72).

**Renal vascular Kv channels: expression and function.** There is immunohistochemical evidence for the expression of Kv1.2 and Kv1.4 channels in rat ILA and arcuate artery (55). In addition, we have localized Kv1.4 channels to rat and mice afferent arteriolar VSMC by immunofluorescence staining (161).

The presence and possible functional role of Kv channels has been studied in larger renal vessels such as the ILA and arcuate artery (17, 55, 63, 140). 4-AP-sensitive currents have been found in VSMC from rat renal vessels (i.e., arcuate artery and ILA), and it has been reported that this current is inhibited by activation of endothelin A receptors (17, 63). In the rabbit arcuate artery, Kv channels did not participate in maintenance of normal tone, but appeared to prevent the VSMC from depolarizing past −30 mV (140). However, it is doubtful whether these larger vessels significantly contribute to the regulation of renal hemodynamics.

Regarding renal resistance vessels, an intermediate-conductance K+ channel (46.3 pS) blocked by 5 mM 4-AP was found in VSMC from rat preglomerular vessels (191). A functional role of Kv channels has been suggested based on experiments utilizing the blood-perfused juxtamedullary nephron technique (173). In this study, 3 mM 4-AP decreased afferent arteriolar diameter by 23%. In another study using the isolated, perfused rat kidney, renal vascular resistance increased by 10.2 ± 0.3 mmHg when 10^{-3} M 4-AP (81) was added.

It is reported that renal afferent arteriolar myogenic activity is attenuated by PKC inhibition (89). This attenuation is reversed by 4-AP, which suggests that PKC has an inhibitory effect on Kv (Fig. 1) (89) similar to what has been reported for other Kv channels (92). In this regard, it is reported that the afferent arteriolar [Ca^{2+} ], response to agonists such as NE and ANG II is attenuated by PKC blockade (152). Taken together, these observations indicate that PKC could mediate or potentiate agonist-induced pregloemular constriction by inhibiting Kv channels (Fig. 1).

**K_ATP Channels**

K_ATP channels consist of eight protein subunits; four α-subunits from the Kv family (Kir6.1 or Kir6.2) forming the pore and four regulatory subunits which belong to the family of sulfonylurea receptors (SUR1, SUR2A, and SUR2B) (183).

The single-channel conductance for K_ATP channels varies between different tissues, indicating different compositions of the subtypes in different tissues. As reviewed by Yokoshiki et al. (183), single-channel conductances of ~15–50 pS have been reported for VSMC. Larger-conductance (~130 pS) K_ATP channels have also been found in mesenteric, tail artery, and aorta VSMC (126). An even larger conductance (258 pS) has been reported for an ATP-sensitive K+ current in rabbit afferent arteriolar VSMC (106). As no other K_ATP channel with this large conductance has been reported subsequently, a possible explanation for this finding could be inhibition of BKCa channels by chelation of Ca^{2+} by ATP (90).

K_ATP channels are inhibited by intracellular ATP (Fig. 1) and stimulated by ADP (126). Thus the ATP/ADP ratio is a major factor determining channel activity. They are pharmacologically inhibited by sulfonyl ureas like glibenclamide and stimulated by, for example, pinacidil, cromakalim, and diazoxide (125).

**Function of vascular K_ATP channels.** K_ATP channels could be controlled by cell metabolism via the concentration of ATP and/or the ATP/ADP ratio, and it is possible that they have a role in the adaptation of vascular tone to the metabolic needs and PO2 of the tissue (128). Furthermore, since the channels are inhibited by PKC there is a potential for mediation of the effect of vasoconstrictors like NE and ANG II (Fig. 1) (81, 92). Outward currents by these channels are stimulated by PKA (Fig. 2) and/or PKG, and it is suggested in some studies that this pathway mediates the vasodilatory action of adenosine (81, 92).

EC also express K_ATP channels (125) and may participate in shear stress- and hyperosmolarity-mediated vasodilation (81, 92). However, their general significance for endothelial function remains to be investigated.

**Renal vascular K_ATP channels: expression and function.** A binding study utilizing a K_ATP channel agonist indicated the presence of K_ATP channels in afferent arterioles (118). In addition, Kir 6.1 and SUR2B mRNA were shown in smaller rat renal arteries and arterioles using in situ hybridization histochemistry (102). As mentioned above, Lorenz et al. (106) found a K+ channel in rabbit afferent arteriolar myocytes with a conductance of 258 pS which was largely inactivated by 1 mM ATP. Lorenz et al. reported that diazoxide, a K_ATP channel activator, dilated rabbit isolated afferent arterioles in vitro while...
the K\textsubscript{ATP} blocker glibenclamide constricted them (106). They also reported that lowered glucose concentration caused glibenclamide-sensitive vasodilation in rabbit afferent arterioles, supporting the notion of an ATP-inhibited hyperpolarizing current in these vessels (106). In the isolated, perfused rat kidney, Jensen et al. (85) found that cromakalim caused renal vasodilation, an effect attenuated by glibenclamide. Using the blood-perfused juxtamedullary nephron preparation, Ikenaga et al. (76) reported that glibenclamide had almost no effect on the tone of afferent arterioles from control rats while it constricted afferent arterioles from rats with streptozotocin-induced diabetes, implicating K\textsubscript{ATP} channels in the hyperfiltration seen in diabetes (see below). They also showed that pinacidil caused afferent arteriolar vasodilation (76). In accord with this, it has in vivo been found that different K\textsubscript{ATP} channel stimulators increase RBF in rat and dog (39, 87, 122, 174, 182).

Based on results obtained using the in vitro perfused hyporeninemic nephropathic rat kidney, it is suggested that high-affinity adenosine A\textsubscript{2A} receptors elicit afferent arteriolar vasodilation by activating K\textsubscript{ATP} channels (146, 169). In another study from the same laboratory, it was found that pinacidil attenuated the ANG II-induced constriction of afferent arterioles by 59% while pressure-induced constriction was attenuated by 97% (146). After pressure-induced afferent arteriolar vasoconstriction, calcitonin gene-related peptide (CGRP) also elicited an afferent arteriolar vasodilation which was attenuated by glibenclamide. On the other hand, CGRP-induced vasodilation after preconstriction with ANG II was not affected by glibenclamide (146), a finding the authors attribute to a possible inhibition of K\textsubscript{ATP} channel activation by ANG II.

It is suggested that K\textsubscript{ATP} channels mediate the vasomotor response to change in PO\textsubscript{2} in different vascular beds (79, 128). Loutzenhiser and Parker (109) found that hypoxia (PO\textsubscript{2} 20 mmHg) via activation of K\textsubscript{ATP} channels attenuated the rat afferent arteriolar myogenic response. The hypoxia-induced attenuation of the myogenic afferent arteriolar vasoconstriction was restored by addition of 1 \textmu M glibenclamide (109). This indicates a role for K\textsubscript{ATP} channels in the adaptation of renal perfusion to hypoxia. As the kidneys normally have a low arteriovenous PO\textsubscript{2} difference, and thus are overperfused relative to their metabolic needs, the physiological relevance for such a mechanism is not clear. K\textsubscript{ATP} channels could be of interest in the control of the medullary circulation, as conditions in this region are hypoxic. This possibility is supported by the finding of K\textsubscript{ATP} channels and glibenclamide-sensitive currents in rat descending vasa recta (24).

Other K\textsuperscript{+} Channels

Considering the diversity of K\textsuperscript{+} channels, it is possible that some of the classes of K\textsuperscript{+} channels which have not yet been investigated in the renal vasculature, partly due to lack of appropriate pharmacological agents, may participate in the regulation of renal hemodynamics (1). For example, both K\textsubscript{2p} and KCNQ/HERG (K\textsubscript{V}7.x) channels have been reported to play a role in the function of other vascular beds (65, 93, 127). These channels have a current-voltage relationship such that they are active during normal V\textsubscript{m} (93, 112). The possible significance of these channels in the renal vasculature has, to our knowledge, never been investigated.

The Review

Integrated Effect of K\textsuperscript{+} Channels in the Renal Vasculature

Some in vivo studies concerning K\textsuperscript{+} channels in renal vascular function have already been dealt with above (9, 39, 43, 113, 122, 174, 182). The information regarding the integrated role of renal vascular K\textsuperscript{+} channels in vivo is sparse. By reviewing studies dealing with the effect of individual K\textsuperscript{+} channel blockers, it is clear that several of these blockers have a constrictor effect on renal vessels in vitro. For example, Kurtz et al. (96) found that Ba\textsuperscript{2+}, 4-AP, TEA, or apamin caused a significant increase in renal vascular resistance in the isolated, perfused rat kidney. Using the same individual blockers, only negligible or no effect was found in vivo (113, 114, 161). Adding a cocktail of these K\textsuperscript{+} channel blockers into the isolated, perfused rat kidney, Kurtz et al. (96) observed an almost 100% increase in basal renal vascular resistance. Using a similar cocktail in vivo, we observed a 43% decrease in RBF (161). By adding glibenclamide to the cocktail, we attained an 86% decrease in RBF. Using the blood-perfused juxtamedullary nephron technique, we also found that the same cocktail reduced the mouse afferent arteriolar diameter by 22% (161). These data indicate that in vivo it may be necessary to block several classes of K\textsuperscript{+} channels to elicit a depolarization sufficient to activate VOCC. Also, a cocktail of K\textsuperscript{+} channel blockers had only a minor effect on basal RBF in vivo while the same cocktail attenuated the responses to ANG II and NE by 60 and 33%, respectively (161). Taken together, these findings are in accord with the hypothesis that agonist-induced renal vasoconstriction in vivo is mediated by inhibition of several classes of K\textsuperscript{+} channels (Fig. 1).

Regarding the discrepancies between the in vivo and in vitro findings, it should be mentioned that a direct comparison between the results obtained in vivo and those originating from the isolated, perfused kidney is not uncomplicated. This is due to the fact that there is a low vascular resistance in the latter preparation and a constant flow system is utilized.

Simultaneous inactivation of several classes of K\textsuperscript{+} channels might be mediated by PKC-induced phosphorylation (37, 81, 92, 120). It is shown that blockade of PKC by chelerytrine attenuates the ANG II- or NE-induced increase in afferent arteriolar VS\textsubscript{M} [Ca\textsuperscript{2+}] (152). Furthermore, it was reported in the same study that the response to ANG II was attenuated to a larger extent than the response to NE (152). This observation is in accord with the notion that activation of PKC leads to depolarization via inhibition of K\textsuperscript{+} channels as the response to ANG II is more dependent on VOCC than that to NE (153). In this regard, it is also reported that ANG II inhibits TEA-, Ba\textsuperscript{2+}, and glibenclamide-sensitive currents in rat vasa recta pericytes (24, 135). It is also possible that activation of several K\textsuperscript{+} channel classes might participate in renal vasodilation and that the cAMP/PKA pathway is a common pathway activating the main classes of K\textsuperscript{+} channels (81, 92).

Renal Vascular K\textsuperscript{+} Channels in Pathology

Hypertension. It is reported that K\textsuperscript{+} channel function is altered under pathological conditions such as hypertension (158). K\textsubscript{Ca}, K\textsubscript{ATP}, and K\textsubscript{r} channel function is supposed to be reduced in hypertension while BK\textsubscript{Ca} channel function is up-regulated in this condition (92, 148, 158, 158). It is also reported that IK\textsubscript{Ca} channel expression is upregulated during hypertension (61). On the other hand, other authors reported a
reduced expression of both SKCa and IKCa channels during ANG II-induced hypertension (70). There is a paucity of information as to whether this also holds true for the renal vascular bed; however, a few studies suggest that renal KATP channel function is downregulated in hypertension (87, 119).

**Diabetes.** Elevated KATP and K+ channel function was found to contribute to the preglomerular vasodilation in early diabetes mellitus (27, 76, 173). The effect of TEA on afferent arteriolar diameter was similar in control rats and rats with streptozotocin-induced diabetes showing that diabetes does not change the role of BKCa channels (173). In the same study, it was reported that Kir1.1 and/or Kir3.x channels contribute to the afferent arteriolar dilatation seen in diabetes mellitus (173).

As mentioned above, glibenclamide constricted afferent arterioles from rats with diabetes while it had almost no effect in normal rats (76). This suggests that increased activation and availability of KATP channels contribute to the glomerular hyperfiltration observed in early diabetes mellitus (27). In contrast, using standard clearance methods, Vallon et al. (175) did not find any effect of the KATP channel blocker U37883A on renal hemodynamics in rats with diabetes (175), arguing against a substantial role for KATP channels in the basal control of renal hemodynamics in both nondiabetic and diabetic rats. Obviously, there is a need for more extensive investigations to fully elucidate a possible role for KATP channels in diabetic hyperfiltration.

**Conclusion**

While there is a substantial amount of information available regarding the role of the individual classes of renal vascular K+ channels in a variety of in vitro settings, patch-clamp studies characterizing K+ currents in renal resistance vessels are rare. Similarly, there is still insufficient knowledge regarding their function in the integrated organ. Also, knowledge of the role of these channels in different pathophysiological conditions is limited and information is only available for the most commonly investigated classes of K+ channels (i.e., KCa, KIR, Kv, and KATP channels). However, renal vascular K+ channels do seem to play a significant role in the regulation of renal vascular tone both during control conditions (as reviewed in Figs. 1 and 2) and during pathophysiological conditions.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

C.M.S. and M.S. drafted manuscript; C.M.S., T.H.B., N.-H.H.-R., and M.S. edited and revised manuscript; C.M.S., T.H.B., N.-H.H.-R., and M.S. approved final version of manuscript; T.H.B. and M.S. prepared figures.

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Review

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