Potassium Channel Function in Vascular Disease

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Abstract—Potassium ion (K⁺) channel activity is a major regulator of vascular muscle cell membrane potential (Em) and is therefore an important determinant of vascular tone. There is growing evidence that the function of several types of vascular K⁺ channels is altered during major cardiovascular diseases, such as chronic hypertension, diabetes, and atherosclerosis. Vasoconstriction and the compromised ability of an artery to dilate are likely consequences of defective K⁺ channel function in blood vessels during these disease states. In some instances, increased K⁺ channel function may help to compensate for increased vascular tone. Endothelial cell dysfunction is commonly associated with cardiovascular disease, and altered activity of nitric oxide, prostacyclin, and endothelium-derived hyperpolarizing factor could also contribute to changes in resting K⁺ channel activity, Em, and K⁺ channel-mediated vasodilatation. Our current knowledge of the effects of disease on vascular K⁺ channel function almost exclusively relies on interpretation of data obtained by using pharmacological modulators of K⁺ channels. As further progress is made in the development of more selective drugs and through molecular approaches such as gene targeting technology in mice, specific K⁺ channel abnormalities and their causes in particular diseases should be more readily identified, providing novel directions for vascular therapy. (Arterioscler Thromb Vasc Biol. 2001;21:28-38.)

Key Words: hypertension ■ depolarization ■ endothelium-derived hyperpolarizing factor ■ hypercholesterolemia ■ hyperpolarization

When a potassium ion (K⁺) channel opens in the vascular smooth muscle cell membrane, K⁺ efflux increases, causing membrane potential (Em) hyperpolarization, closure of voltage-activated calcium (Ca²⁺) channels, decreased Ca²⁺ entry, and vasodilatation (Figure 1). Conversely, closure of a K⁺ channel causes Em depolarization, opening of voltage-activated Ca²⁺ channels, increased cytosolic Ca²⁺ concentration, and vasoconstriction (Figure 1). As a major regulator of vascular muscle cell Em, K⁺ channel activity is therefore an important determinant of vascular tone and blood vessel diameter.¹

The physiological roles and properties of K⁺ channels in arterial smooth muscle have recently been comprehensively reviewed.¹–⁶ This Brief Review will provide a short description of the functional characteristics of the 4 main types of vascular K⁺ channels and the likely physiological importance of these channels, as well as the phenomenon of K⁺ channel–mediated, endothelium-dependent vascular hyperpolarization. The majority of this review will then examine the evidence for altered K⁺ channel function in blood vessels in 3 major cardiovascular disease states.

While molecular biological studies are revealing a large diversity in the subtypes of K⁺ channels that are normally expressed in vascular muscle,² it is noteworthy that there is still very little information available at the molecular level regarding regulation of K⁺ channel expression and function in vascular disease. Hence, our current knowledge of the effects of disease on vascular K⁺ channel expression is somewhat indirect and almost exclusively relies on interpretation of functional or electrophysiological data (eg, recordings of vessel tone or diameter, vascular muscle cell Em, or whole-cell or single-channel currents in isolated myocytes under voltage-clamp conditions) obtained in the presence of pharmacological modulators of K⁺ channels.

Calcium-Activated K⁺ Channels

Large conductance Ca²⁺-activated K⁺ (BKCa) channels are activated by intracellular Ca²⁺ and also by Em depolarization and are particularly abundant in vascular smooth muscle cells.¹,⁸ Physiological activation of vascular BKCa channels may be an important buffering mechanism to counteract vessel depolarization and constriction in response to some vasoconstrictors and to increased intravascular pressure. Because of the large conductance of BKCa channels, the activity of relatively few channels can exert a relatively large influence on Em. Vasodilators that increase intracellular levels of cAMP or cyclic GMP,¹,⁵ carbon monoxide,⁹ and epoxides of arachidonic acid¹⁰ may activate BKCa channels. Focal increases in subsarcolemma Ca²⁺ levels (“Ca²⁺ sparks”) due to Ca²⁺ released through ryanodine receptors in the sarcoplasmic reticulum appear to play a fundamental role in regulating BKCa channel activity and hence, Em and vascular tone.¹¹,¹² Pharmacological agents commonly used to inhibit BKCa channels include tetraethylammonium ion (≤1 mmol/L),

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dil, and pinacidil. This phenomenon provides functional exceptions to this (eg, see References 3, 6, and 11). Pharmacological agents that can induce glibenclamide-sensitive vasodilatation (vasoconstriction). Left: Activation (opening) of a K⁺ channel (gray) in the cell membrane allows K⁺ to flux out of the cell, causing a decrease in Eᵶ (depolarization) and consequent inhibition (closure) of voltage-activated Ca²⁺ channels (white) and a decrease in cytosolic Ca²⁺ levels, resulting in vascular muscle relaxation (vasodilatation). Right: In the reverse case, inhibition of a vascular muscle K⁺ channel decreases K⁺ efflux and hence, increases Eᵶ (depolarization). Voltage-activated Ca²⁺ channels will open in response to the increased Eᵶ, allowing Ca²⁺ to enter the cell and to increase cytosolic Ca²⁺ levels resulting in vascular contraction (vasoconstriction).

charybdotoxin, and ibierotoxin. Based on the constrictor responses elicited by these inhibitors, it is thought that BKCa channel activity may be greater in large arteries versus microvessels under normal resting conditions.

**Voltage-Dependent (Delayed Rectifier) K⁺ Channels**

Voltage-dependent (Kᵥ) channels in vascular smooth muscle are activated by membrane depolarization in the physiological range for Eᵶ (approximately −35 to −55 mV) and are therefore also thought to serve an important buffering function against depolarization and vasoconstriction. 1,5 Amino-pyridine is widely used as a pharmacological blocker of Kᵥ channels. 4-Aminopyridine causes arterial depolarization and constriction, suggesting that Kᵥ channel activity exists in some blood vessels under basal conditions. 13–16 cAMP 17,18 and nitric oxide (NO)/cyclic GMP 19,20 may activate Kᵥ channels in some blood vessels, and these channels may be inhibited by protein kinase C. 21

**ATP-Sensitive K⁺ Channels**

ATP-sensitive K⁺ (KₐTP) channels are inhibited by intracellular ATP and are therefore likely to have a very low open probability in most vascular smooth muscle cells under normal conditions. Thus, glibenclamide, which is widely used as a selective inhibitor of KₐTP channels, generally has no effect on vascular Eᵶ or tone, although there are examples of exceptions to this (eg, see References 3, 6, and 11). Pharmacological agents that can induce glibenclamide-sensitive vascular relaxation by directly activating KₐTP channels include cromakalim, levcromakalim (lemakalim), aprikalim, nicorandil, and pinacidil. 1,5 This phenomenon provides functional evidence that KₐTP channels are present in vascular muscle and can be activated to influence Eᵶ and vascular tone. Endogenous vasodilator stimuli, such as hypoxia, acidosis, and mediators that increase intracellular cAMP levels (eg, adenosine, prostacyclin, and norepinephrine), may also exert their vascular effects, in part via activation of KₐTP channels. 1,5

**Inwardly Rectifying K⁺ Channels**

When vascular myocyte Eᵶ is varied experimentally by using electrophysiological techniques, one type of K⁺ channel displays “inward rectification.” That is, because of the blocking effects of intracellular polyamines and magnesium ions, these inwardly rectifying K⁺ (KᵢR) channels conduct K⁺ current into cells much more readily than they conduct outward K⁺ current. 1,3,22 Importantly though, at physiological Eᵶ, a small increase above the normal extracellular K⁺ concentration of 3 to 5 mmol/L leads to an increase in the resting outward K⁺ current through KᵢR channels. Hence, a modest increase in extracellular K⁺ (eg, by <10 mmol/L), as may occur during neuronal or muscle activation, can paradoxically lead to substantial vascular hyperpolarization and vasorelaxation due to K⁺ efflux through KᵢR channels. 26–31 Reasonably selective block of KᵢR channels can be achieved pharmacologically by using ≥100 μmol/L barium ion (Ba²⁺), and because this inhibitor causes vascular depolarization and constriction, 26,28,29,31 it is thought that vascular KᵢR channels may be active under resting conditions. Recent findings in gene-targeted mice indicate that Ba²⁺-sensitive, K⁺-induced vasorelaxation is mediated by activation of the KᵢR.2,1 channel 30 (see below).

**Endothelium-Dependent Hyperpolarization**

Vascular smooth muscle relaxation in response to a signal initiated by stimulation of overlying endothelium is known as “endothelium-dependent relaxation” and involves the release of at least 1 “endothelium-derived relaxing factor” (EDRF). There appear to be several important EDRFs, the 2 most well understood of these being NO and prostacyclin. It is now well established that endothelium-dependent vascular relaxation is often accompanied by K⁺ channel–mediated hyperpolarization of the vascular smooth muscle. Because both NO and prostacyclin are known to be able to elicit vascular relaxation, at least in part, through activation of K⁺ channels 1,5 (Figure 2), endothelium-dependent hyperpolarization may often simply reflect part of the mechanism of relaxation produced by NO and/or prostacyclin. 32

In addition, in many normal vascular preparations, a component of agonist-induced, endothelium-dependent relaxation appears to be mediated by a non-NO, nonprostanoid, hyperpolarization-related mechanism that involves activation of K⁺ channels 32 (Figure 2). The chemical nature of this mediator(s), termed endothelium-derived hyperpolarization factor (EDHF), has still not been definitively identified, nor has the particular type(s) of K⁺ channel(s) activated by EDHF, but inhibition of its action appears to require coapplication of charybdotoxin and apamin, which may implicate a role for small conductance KᵢC, intermediate conductance KᵢR, and/or BKCa channels. 33 This particular combination of inhibitors may be necessary to block release of EDHF from endothelial cells, rather than to block the action of EDHF on vascular smooth muscle. 34 EDHF may play a greater role in the smaller resistance arteries of animals 35–37 and humans 38,39 and might therefore normally modulate systemic arterial pressure. It has been suggested that the vascular activity of EDHF is normally inhibited by NO, such that when NO synthesis is impaired in cardiovascular disease, EDHF production and/or function may increase 40,41 (Figure 2). How-
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NO, EDHF(s), and prostacyclin (PGI2), each of which can induce release of several endothelium-derived relaxing factors. These include acetylcholine (ACh), bradykinin (BK), and substance P (SP) may cause release of endothelial cell receptors by agonists such as acetylcholine mediated, endothelium-dependent hyperpolarization. Stimulation of endothelial cell receptors by agonists such as acetylcholine leads to vasodilatation, as described in Figure 1. Because all 3 endothelial factors may normally activate vascular K+ channels, in the case of NO and PGI2, this may involve the intracellular accumulation of a second messenger (cyclic GMP and cAMP, respectively). Like EDHF, NO may activate K+ channels directly. The production of EDHF may depend on the bioavailability of NO, such that EDHF release may be more significant under conditions in which NO production is impaired. The hyperpolarization occurring in response to K+ channel activation leads to vasodilatation, as described in Figure 1. Because all 3 endothelial factors may normally activate vascular K+ channels, endothelial dysfunction occurring during cardiovascular disease states may result in vascular depolarization and/or abnormal K+ channel function, leading to increased vascular tone and reduced blood flow.

ever, there is also evidence against this proposal in hypertension and diabetes (see the following sections).

Use of Gene Targeting to Study Vascular K+ Channels

The biology of K+ channels is extremely complex, and we now know that there is enormous diversity at the molecular level in mammalian cells. The use of traditional pharmacological inhibitors has been invaluable for our initial understanding of the functional importance of major K+ channel types. However, this approach is likely to be of limited value in future research that will seek to discriminate between the functional roles of different K+ channel subtypes. Instead, it is likely that a great deal more information will be gained by using the powerful approach of gene targeting in mice. The first example of such work was published recently by Zaritsky et al., who found that K+ -induced cerebral artery hyperpolarization and relaxation are absent in mice lacking the gene to express Kir2.1 channels but are normal in Kir2.2 channel–deficient mice, confirming that the Kir2.1 channel isoform is critically and exclusively involved in K+ -induced cerebral vasodilator responses. Although a number of studies of vascular function have already been performed in genetically altered mice, most have focused on the role of the endothelium, and this landmark study is the first in which gene-targeted mice were used to examine the role of any ion channel in blood vessels.

K+ Channels in Vascular Diseases

Altered vascular K+ channel function under pathological conditions could be either a cause (ie, involved in the pathogenesis) or an effect (ie, a secondary phenomenon or compensatory mechanism) of the disease. Vasoconstriction and the compromised ability of an artery to dilate are likely consequences of defective K+ channel function in blood vessels and may be due to a change in the number, unitary conductance, and/or open probability of the channel(s). Information at this level regarding K+ channel expression can currently be provided only by studies with molecular and/or patch-clamp approaches and hence, are restricted to studies of blood vessels or myocytes removed from their physiological environment. For this reason, where feasibility allows (ie, with the future availability of selective pharmacological tools or appropriate genetically modified animals), it will remain important to verify such findings with data regarding vascular K+ channel function obtained in the integrated physiological environment in vivo.

Very few published studies have so far examined the impact of disease states on the biophysical characteristics of K+ channels or channel subtypes. By contrast, as mentioned above, most of our knowledge of the effects of diseases on vascular K+ channel expression remains indirect and dependent on interpretation of the experimental data obtained by using K+ channel modulators that are thought to be relatively selective pharmacological agents. The following sections will review current evidence for the effects of 3 major cardiovascular diseases on the expression and function of K+ channels in blood vessels.

Chronic Hypertension

Chronic hypertension has been the most extensively studied cardiovascular disease state in terms of its effects on vascular K+ channel function, and there is now evidence for abnormal functioning of each of the 4 major K+ channel types during hypertension (Figure 3).

Figure 2. Some potential mechanisms involving K+ channel–mediated, endothelium-dependent hyperpolarization. Stimulation of endothelial cell receptors by agonists such as acetylcholine (ACh), bradykinin (BK), and substance P (SP) may cause release of several endothelium-derived relaxing factors. These include NO, EDHF(s), and prostacyclin (PGI2), each of which can induce relaxation of underlyng vascular muscle through activation of K+ channels. In the case of NO and PGI2, this may involve the intracellular accumulation of a second messenger (cyclic GMP and cAMP, respectively). Like EDHF, NO may activate K+ channels directly. The production of EDHF may depend on the bioavailability of NO, such that EDHF release may be more significant under conditions in which NO production is impaired. The hyperpolarization occurring in response to K+ channel activation leads to vasodilatation, as described in Figure 1. Because all 3 endothelial factors may normally activate vascular K+ channels, endothelial dysfunction occurring during cardiovascular disease states may result in vascular depolarization and/or abnormal K+ channel function, leading to increased vascular tone and reduced blood flow.

Figure 3. Altered vascular K+ channel function during chronic hypertension. Experimental evidence suggests that expression and/or activity of BKCa channels is enhanced during hypertension, whereas the function of KATP, Kir, and Kq channels may be reduced. Increased activity of protein kinase (PKC) and increased cytosolic Ca2+ levels may inhibit activation of KATP and Kir channels, as part of their proconstrictor effects, as shown. Inhibition of Kir channel activity is likely to cause Er depolarization, which together with increased cytosolic Ca2+ levels, causes increased activity of BKCa channels. Increased function of BKCa channels will help to restrict increases in vascular tone and hence, arterial pressure.
Effects of Hypertension on $E_m$

The resting $E_m$ of vascular smooth muscle cells is reported to be more depolarized in arteries from hypertensive versus normotensive animals\(^{43-49}\) (Figure 3). Increased vascular depolarization is associated with enhanced myogenic tone in arteries from hypertensive animals.\(^{50,51}\) The effect of hypertension on $E_m$ may be more profound in smaller resistance vessels, especially in vascular beds that play a significant role in the regulation of peripheral resistance.\(^{52}\)

**BKCa Channels in Hypertension**

There is strong evidence that the functional role of BK\(_{Ca}\) channels is enhanced in vascular muscle during chronic hypertension. For example, pharmacological inhibitors of these channels cause augmented depolarization and constriction of arteries from hypertensive animals. This phenomenon occurs similarly in vessels from various anatomic regions, including aorta,\(^{53-56}\) carotid artery,\(^{57-59}\) and the mesenteric,\(^{58}\) femoral,\(^{58,60}\) and cerebral\(^{51,62}\) vascular beds. Because increases in both Ca\(^{2+}\) influx and BK\(_{Ca}\) channel activity can be detected even in prehypertensive spontaneously hypertensive rats (SHRs),\(^{60}\) genetic factors may play at least some role in these changes. However, increased BK\(_{Ca}\) channel function may also be a consequence of elevated blood pressure, as it can be induced over several weeks by surgical or pharmacological interventions that cause hypertension.\(^{53,61}\) and it can be reversed by antihypertensive therapy.\(^{54}\) Therefore, BK\(_{Ca}\) channel function may be increased in arterial smooth muscle cells as a protective mechanism against progressive increases in blood pressure and may provide a negative-feedback mechanism that helps to restrict the increased pressure and vascular tone. Such a mechanism would therefore act to limit pressure-induced vasoconstriction and to preserve local blood flow.

Electrophysiological measurements obtained under voltage-clamp conditions in arterial myocytes isolated from hypertensive animals have confirmed that the whole-cell K\(^{+}\) current through BK\(_{Ca}\) channels is enhanced in comparison with currents recorded from normotensive myocytes.\(^{52,53,63}\) A comprehensive molecular, electrophysiological, and functional study in the cerebral circulation of SHRs has provided strong evidence for greater expression of BK\(_{Ca}\) channels per myocyte rather than any change in channel unitary conductance or open probability.\(^{62}\) Liu et al\(^{62}\) found that a 2- to 4-fold greater constriction of SHR versus Wistar-Kyoto rat (WKY) cerebral arteries in vivo in response to iiberiotoxin was associated with a 4.7-fold higher density of BK\(_{Ca}\) channels in SHR cerebral arteries.\(^{62}\) A similar phenomenon may exist in cerebral arteries after subarachnoid hemorrhage (SAH), a cerebral vascular disease state that is also associated with vascular depolarization\(^{68-70}\) and increased intracellular Ca\(^{2+}\) levels\(^{71}\) and in which K\(_{Ca}\) channel function also appears to be impaired.\(^{18}\)

Paracrine influences potentially underlying altered K\(^{+}\) channel activity in hypertension have not yet been extensively explored and could be numerous. One recent report suggested that parathyroid hypertensive factor, a circulating substance originating in the parathyroid gland and associated with some forms of experimental and human hypertension, inhibits K\(_{Ca}\) channels and causes depolarization of myocytes from rat tail artery.\(^{72}\) Parathyroid hypertensive factor is thought to increase Ca\(^{2+}\) influx into vascular muscle cells via L-type, voltage-activated Ca\(^{2+}\) channels (probably due to K\(_{Ca}\) channel inhibition) and consequently to enhance vascular responses to depolarizing and constrictor stimuli in vitro\(^{73}\) and in vivo.\(^{74}\) In an analogous manner, decreased K\(_{Ca}\) channel function in the pulmonary circulation is reported to cause depolarization and vasoconstriction in patients with primary pulmonary hypertension.\(^{75}\) Because NO may activate K\(_{Ca}\) channels in some arteries,\(^{15,19,76,77}\) impaired bioavailability of endothelium-derived NO in hypertension and other cardiovascular disease states could lead to vascular depolarization and contraction that are partly due to inhibition or closure of K\(_{Ca}\) channels. Thus, increased knowledge of mediators that modulate K\(_{Ca}\) channel function could provide important insight into the mechanisms of increased vascular tone during chronic hypertension and may reveal novel targets for pharmacological prevention of vascular dysfunction.

**K\(_{ATP}\) Channels in Hypertension**

Findings from several studies suggest that the function of vascular K\(_{ATP}\) channels is impaired during hypertension. Synthetic K\(_{ATP}\) channel activators are less potent dilators in vivo in both large\(^{78,79}\) and small\(^{80}\) cerebral vessels of chronically hypertensive rats. This alteration seems likely to involve an impaired membrane hyperpolarization response to these agents, as analogous findings from patch-clamp studies indicate that a glibenclamide-sensitive K\(^{+}\) current activated by levromakalim is decreased in mesenteric artery smooth
The vasodilator response associated with cerebral blood flow autoregulation during systemic hypertension, which is mediated by K\textsubscript{ATP} channel activation,\textsuperscript{84-86} is impaired in chronically hypertensive rats.\textsuperscript{78} Thus, although most studies of vascular K\textsubscript{ATP} channel function during hypertension have examined the effects of synthetic channel openers, these findings\textsuperscript{86,87} suggest that the K\textsubscript{ATP} channel dysfunction may also interfere with vascular responsiveness to endogenous vasodilator stimuli.

Impaired K\textsubscript{ATP} channel–mediated vascular effects may not necessarily occur for all endogenous K\textsubscript{ATP} channel activators, however, because responses to some vasodilators that increase intracellular cAMP levels (ie, forskolin and norepinephrine) are preserved in the basilar artery of hypertensive rats.\textsuperscript{78} Thus, a defect in only a particular aspect of K\textsubscript{ATP} channel function could account for the abnormal responses during hypertension. Moreover, increased effects of angiotensin II and protein kinase C are associated with various forms of chronic hypertension, and both mediators may inhibit K\textsubscript{ATP} channel function in vascular smooth muscle\textsuperscript{88-91} (Figure 3). An important goal of future studies will be to investigate the molecular basis for K\textsubscript{ATP} channel dysfunction in hypertension. Importantly, several studies have clearly demonstrated that impairment of K\textsubscript{ATP} channel–mediated vascular responses can be restored to near-normal levels by long-term treatment of high blood pressure.\textsuperscript{80-82,87} These findings emphasize the importance of antihypertensive therapy for correcting many abnormalities in vascular smooth muscle function.

There is very little information currently available on the effects of hypertension on K\textsubscript{ATP} channel function in human blood vessels, with data from just 1 study reporting preserved dilator responses of isolated mesenteric arteries to cromakalim.\textsuperscript{92} Some studies of mesenteric arteries from hypertensive animals have also reported unchanged effects of K\textsubscript{ATP} channel openers.\textsuperscript{47,93} It will be especially important to clarify whether this phenomenon occurs in humans; if it is restricted to certain vascular beds, this knowledge may then be critical in predicting the viability of using K\textsubscript{ATP} channel openers as a potential new class of antihypertensive therapy.

Surprisingly, K\textsubscript{ATP} channel function is augmented in cerebral vessels after exposure to subarachnoid blood,\textsuperscript{70,79,94} and this is particularly pronounced in hypertensive animals.\textsuperscript{79} Furthermore, although responses to many vasodilators are generally impaired in cerebral arteries after SAH, the effects of calcitonin gene–related peptide (which activates K\textsubscript{ATP} channels) are preserved or augmented,\textsuperscript{84-97} and treatment with calcitonin gene–related peptide can prevent development of cerebral vasospasm after experimental SAH.\textsuperscript{98,99} K\textsubscript{ATP} channel openers may therefore represent a promising therapeutic strategy for treatment of depolarized and spastic cerebral arteries after SAH, which is up to 8 times more likely to occur in the presence of hypertension.\textsuperscript{100}

**K\textsubscript{ATP} Channels in Hypertension**

There is indirect evidence that vascular K\textsubscript{ATP} channel function may be altered during chronic hypertension. McCarron and Halpern\textsuperscript{101} reported that Ba\textsuperscript{2+}-sensitive vasodilator responses to >7 mmol/L K\textsuperscript{+} were impaired in posterior cerebral arteries isolated from stroke-prone SHRs in comparison with vessels from WKYs, perhaps suggesting impaired K\textsubscript{ATP} channel function in the cerebral circulation during hypertension. Earlier studies reported that K\textsuperscript{+}-induced vascular relaxation was either augmented\textsuperscript{85,102} or impaired\textsuperscript{103} in several models of hypertension. Our laboratory has recently found that dilator responses of the basilar artery to K\textsuperscript{+} in vivo, which are largely Ba\textsuperscript{2+} sensitive in normotensive rats,\textsuperscript{31} are moderately enhanced and Ba\textsuperscript{2+} insensitive in SHRs (S. Chrissobolis et al, unpublished observations, 1999). Thus, it is possible that chronic hypertension leads to decreased expression and/or function of vascular K\textsubscript{ATP} channels (Figure 3) and expression of a compensatory vasodilator mechanism(s) that is upregulated. K\textsubscript{ATP} channel–mediated dilatation of cerebral arteries is also reported to be impaired after cerebral ischemia and reperfusion.\textsuperscript{104}

**EDHF in Hypertension**

Endothelium-dependent vascular relaxation is impaired in many animal models of hypertension and in hypertensive humans, and this is thought to be due, at least in part, to impaired endothelial NO production or activity.\textsuperscript{105,106} Consistent with the idea that EDHF may compensate during impaired vascular production of NO (Figure 2), findings made in endothelial NO synthase–deficient mice (which are moderately hypertensive\textsuperscript{107}) suggest that EDHF(s) mediates endothelium-dependent relaxation of saphenous, mesenteric, and skeletal muscle arterioles, whereas the same functional responses are mediated by NO in normal mice.\textsuperscript{108,109} This phenomenon may be specific to certain vascular beds, however, because no such compensation by EDHF occurs in aorta or the carotid, pulmonary, cerebral, or coronary arteries of endothelial NO synthase–mutant mice\textsuperscript{107,110-113} or in cerebral arterioles\textsuperscript{114} of normal mice treated with inhibitors of NO synthase or soluble guanylate cyclase.

Interestingly, impaired production of EDHF, and not NO, may sometimes contribute to reduced endothelium-dependent vascular relaxation during chronic hypertension, and in some instances, basal NO synthesis may be upregulated.\textsuperscript{115} There are now several reports that the contribution of EDHF to endothelium-dependent vasorelaxation is greatly reduced, whereas that of NO is preserved or increased, in a number of models of genetic and nongenetic hypertension.\textsuperscript{47-49,93,116-118} Thus, more work is clearly needed, not only to clarify the chemical identity of EDHF(s) and the molecular details of its K\textsuperscript{+} channel–mediated mechanism of hyperpolarization, but also to understand the relationship between the bioavailability and function of EDHF and NO in normal and diseased arteries.

**Diabetes**

There is a 2- to 4-fold increase in the risk of coronary heart disease, cerebrovascular disease, congestive heart failure, and
other cardiovascular complications due to diabetes. Moreover, abnormalities of vascular function are thought to contribute to the etiology of many diabetic complications, including neuropathy, retinopathy, and myopathy. Functional changes occurring in blood vessels during diabetes include endothelial cell dysfunction but may also involve altered ion channel function in vascular smooth muscle.

**K<sub>ATP</sub> Channels in Diabetes**

Most information currently available regarding vascular K<sup>+</sup> channel function in diabetes concerns K<sub>ATP</sub> channels. As for chronic hypertension, there are now several reports of impaired vascular relaxant responses to synthetic openers of K<sub>ATP</sub> channels in long-term diabetes. These studies have mostly utilized the streptozotocin-injected rat model of diabetes and have examined vessels at 2.5 to 4 months after streptozotocin treatment. In this model in which plasma glucose levels are increased 3- to 4-fold, impaired relaxation of the isolated aorta and mesenteric vascular bed and reduced dilatation of large and small cerebral arteries in vivo typically develop. These changes are thought to be the result of a decreased number of vascular K<sub>ATP</sub> channels and/or reduced sensitivity of these channels to synthetic openers. Nonspecific cytotoxic effects of streptozotocin seem an unlikely cause of these changes because, like other manifestations of vascular dysfunction, abnormal vasodilator responses to K<sub>ATP</sub> channel openers are prevented by treatments that prevent or reverse the hyperglycemia. Streptozotocin-induced diabetes may also alter the functional response of K<sub>ATP</sub> channels in other tissues, including pancreatic β-cells and ventricular myocytes, indicating that hyperglycemia-induced impairment of K<sub>ATP</sub> Channels is not restricted to the vasculature. Because diabetes is associated with elevated plasma levels of LDL cholesterol and triglycerides, it is conceivable that some vascular abnormalities of diabetes are not directly related to hyperglycemia per se but could instead be a consequence of an altered plasma lipid profile.

The period of experimental hyperglycemia appears to be an important determinant of the observed effects of diabetes on vascular K<sub>ATP</sub> channel function because, by contrast, responses to K<sub>ATP</sub> channel activation are reported to be enhanced in the early diabetic state. For example, cromakalim-induced dilatation of large coronary arteries in the dog are augmented 1 week after treatment with alloxan, and responses of the small coronary arteries are unaltered. Similarly, only 2 weeks after streptozotocin injection, activators of K<sub>ATP</sub> channels cause enhanced dilatator responses of rat isolated renal afferent arterioles. Moreover, because glibenclamide may cause marked constriction of those vessels, increased expression and basal activation of K<sub>ATP</sub> channels may both occur in the renal circulation early during diabetes. This condition could contribute to the increases in glomerular filtration rate and renal plasma flow (ie, “hyperfiltration”), which occur in early stages of diabetes in both clinical and experimental settings. An increased K<sub>ATP</sub> channel activity at this time may therefore reflect a very high metabolic state (ie, low ATP levels) of vascular smooth muscle cells relatively soon after the initiation of hyperglycemia. Increased K<sub>ATP</sub> channel activity in blood vessels during metabolic stress, such as during ischemia, could be beneficial for maintaining tissue perfusion. Hence, tissues could be more susceptible to ischemic damage after extended periods of diabetes owing to impaired function of K<sub>ATP</sub> channels.

On the other hand, mixed effects on K<sub>ATP</sub> channel function are reported to occur at ~4 to 8 weeks after induction of hyperglycemia, presumably in part reflecting a gradual deterioration of vascular mechanisms during progression of the disease. For example, Bouchard et al reported that vasorelaxant responses to lemakalim are impaired in coronary resistance vessels, but not in the mesenteric vascular bed or the aorta, after 2 months of hyperglycemia. Likewise, pinacidil-induced hyperpolarization of the mesenteric artery was reported to be preserved after 8 to 12 weeks. Zimmerman et al reported that dilator responses to K<sub>ATP</sub> channel openers were impaired in cerebral arteries from 4- to 8-week-diabetic rats as a consequence of reduced basal release of endothelium-derived NO. K<sub>ATP</sub> channel function could be restored in those diabetic vessels by application of an NO donor drug. However, such a mechanism of endothelial NO-dependent K<sub>ATP</sub> channel activation may not always occur in other preparations, as others have found no evidence of a role for NO in the dilator responses of rat cerebral vessels to K<sub>ATP</sub> channel openers in vivo and K<sub>ATP</sub> channel–mediated relaxant responses are impaired even in endothelium-denuded vessels after slightly longer periods of diabetes.

**Other K<sup>+</sup> Channels in Diabetes**

Information is still generally lacking regarding the effects of diabetes on the function of other types of K<sup>+</sup> channels. Diabetes, like several other vascular diseases, is recognized as a condition in which there is increased oxidant stress. Hence, with increased production of reactive oxygen species in the vascular wall and consequently, a decreased bioavailability of NO (eg, due to inactivation of NO by superoxide anion), activation of BK<sub>Ca</sub> or K<sub>IR</sub> channels by NO/cyclic GMP might be expected to be decreased under resting or stimulated conditions. Moreover, there is recent evidence that peroxynitrite, which is formed by the reaction of superoxide anion with NO, can cause vasoconstriction (and presumably, E<sub>m</sub> depolarization) by inhibition of BK<sub>Ca</sub> channels in cerebral vascular muscle cells. Consistent with this notion, there is evidence that E<sub>m</sub> is more depolarized than normal in cerebral arteries of genetic and nongenetic models of diabetes, although it is not altered in mesenteric arteries of streptozotocin-injected rats. A reduced hyperpolarizing influence of basally released endothelium-derived NO may contribute to cerebrovascular depolarization in some cases.

In addition, there is preliminary evidence for an overall decrease in the outward K<sup>+</sup> current in cerebral myocytes from spontaneously diabetic BB rats, which may involve decreased BK<sub>Ca</sub> channel function and increased K<sub>IR</sub> channel function. Finally, K<sup>+</sup>-induced relaxation is impaired in mesenteric arteries from diabetic rats, perhaps reflecting an altered K<sub>IR</sub> channel function.

**EDHF in Diabetes**

Recent findings suggest that the role of EDHF may be diminished in diabetic arteries. The component of endothelium-dependent relaxation that is resistant to NO synthase inhibition but sensitive to vascular depolarization is reduced...
in mesenteric vessels from diabetic rats, whereas the NO-mediated component is preserved or augmented.\textsuperscript{130} Consistent with this finding, direct measurements of $E_{\text{m}}$ in vascular muscle cells have confirmed that the endothelium-dependent hyperpolarization by EDHF is markedly reduced in mesenteric arteries from diabetic rats.\textsuperscript{134} Thus, impaired production and/or effects of EDHF may account for the diminished endothelium-dependent relaxant responses of diabetic mesenteric arteries.

**Hypercholesterolemia and Atherosclerosis**

It is well established that vascular dysfunction occurs in hypercholesterolemia and atherosclerosis. In particular, this disease is associated with impairment of endothelial function, and reduced vascular activity of endothelium-derived NO is likely to play a major role in the development of atherosclerosis.\textsuperscript{141} As a consequence, arteries may exhibit an increased vascular tone under basal conditions and may respond inadequately to endothelium-dependent vasodilator agonists. Under such conditions of altered vascular reactivity, K$^+$ channel activity or function may also be abnormal.

**BK$_{Ca}$ Channels in Hypercholesterolemia and Atherosclerosis**

Najibi and colleagues\textsuperscript{142,143} have reported functional evidence of an enhanced role for BK$_{Ca}$ channels in the vasodilator responses of carotid arteries from hypercholesterolemic rabbits. These investigators found that although the magnitude of endothelium-dependent relaxation was preserved, the responses of hypercholesterolemic but not of normal arteries were sensitive to charybotoxin.\textsuperscript{142} Similarly, acetylcholine-induced relaxation is inhibited by charybotoxin in aortic rings of atherosclerotic but not of normal mice.\textsuperscript{78} Initially, the findings of Najibi et al were interpreted as being evidence for upregulation of an EDHF-mediated compensatory component during impaired NO production in hypercholesterolemia.\textsuperscript{142} However, subsequent studies by those workers revealed that the mechanism of the vasorelaxant response to exogenous NO becomes charybotoxin sensitive despite an impaired production of cyclic GMP after cholesterol feeding,\textsuperscript{143} suggesting that the functional role of BK$_{Ca}$ channels in vascular muscle is markedly increased during hypercholesterolemia. These observations could be explained, in part, by a lower level of basal BK$_{Ca}$ channel activity (and hence, increased BK$_{Ca}$ channel availability for opening) under conditions of impaired activity of endothelium-derived NO. Analogous evidence for an increased role of BK$_{Ca}$ channels in vasodilator responses to NO has been reported in cerebral arteries during NO synthase inhibition\textsuperscript{136} and after SAH.\textsuperscript{144} Interestingly, recent patch-clamp studies have found that the activity of BK$_{Ca}$ channels is significantly higher in smooth muscle cells from human coronary atherosclerotic plaques than in medial smooth muscle cells, possibly suggesting a role for BK$_{Ca}$ channels in the development of human atherosclerosis.\textsuperscript{145}

**K$_v$ Channels in Hypercholesterolemia and Atherosclerosis**

4-Aminopyridine induces contraction and rhythmic activity of aortic rings from atherosclerotic but not control mice.\textsuperscript{76} Because it is thought that basal NO release from endothelial cells may activate K$_v$ channels on vascular smooth muscle\textsuperscript{15,19,20} and that NO activity is reduced in atherosclerotic arteries,\textsuperscript{141} it was suggested that the findings were evidence for reduced basal K$_v$ channel activity in atherosclerotic vessels.\textsuperscript{76} An alternative interpretation might be that increased effects of a K$_v$ channel inhibitor reflect an increased basal influence of these channels during atherosclerosis, whereby inhibition of channel activity might be expected to have an increased influence on vascular muscle $E_{\text{m}}$ and tone. In another study, 4-aminopyridine was found to inhibit endothelium-dependent, NO-mediated relaxation in response to acetylcholine in normal rabbit cerebral arteries, but it had no effect on the impaired responses to acetylcholine in vessels from cholesterol-fed rabbits,\textsuperscript{77} consistent with a reduced role for K$_v$ channels in the relaxant responses of atherosclerotic vessels.

**EDHF in Hypercholesterolemia and Atherosclerosis**

Few studies have so far tested the effects of hypercholesterolemia and atherosclerosis on EDHF function. Lysophosphatidylcholine, which is elevated in oxidatively modified LDL, is reported to inhibit different components of endothelium-dependent relaxation mediated by either NO or EDHF,\textsuperscript{151} suggesting that responses to both endothelium-derived factors may be sensitive to hypercholesterolemia. Similarly, EDHF-mediated relaxation of human isolated gastroepiploic arteries was reduced during hypercholesterolemia.\textsuperscript{38} By contrast, EDHF-mediated (ie, NO synthase– and cyclooxygenase-independent), endothelium-dependent relaxation of the rabbit renal artery was increased during hypercholesterolemia despite an impaired endothelium-dependent relaxant response overall in the absence of inhibitors, consistent with an enhanced role for EDHF in helping to maintain vascular function during reduced NO activity\textsuperscript{152} (Figure 2).
Concluding Remarks and Future Directions
As we have seen, many complex alterations in vascular K⁺ channel functions have been described in several major diseases. Although there is no firm evidence that vascular K⁺ channel dysfunction is genetic in origin, the progression of human cardiovascular disease states—which are probably caused by complex interactions between genetic and environmental factors—may nevertheless lead to secondary effects on K⁺ channel function that could perhaps be protective or that may further exacerbate the consequences of the disease. Only a very modest amount of data currently exists at the molecular level regarding vascular K⁺ channel function in disease. As further progress is made, particularly through molecular and electrophysiological approaches, in unraveling the relationship between K⁺ channel structure and function, we will obtain a clearer picture of the ways in which channel expression and function are normally regulated. We can then use this information in seeking to identify specific K⁺ channel abnormalities and their causes in particular diseases. Increased appreciation of the diversity of vascular cell types present throughout the circulation and the relevance of specific K⁺ channel functions in different cell types and in different segmental regions may prove very important for understanding vascular K⁺ channel biology as well as pathology. With the development of more selective pharmacological modifiers, activation of vascular K⁺ channels would seem to be a very promising direction for therapy in numerous vascular disease states associated with vascular constriction and depolarization. In particular, the utilization of gene targeting technology in mice will very likely provide major advances in our understanding of the function of vascular K⁺ channel subtypes in isolated vessel preparations (as in Reference 30) and ultimately, in the intact circulation in vivo in both health and disease.

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