Hypertension, or sustained elevation in systemic arterial blood pressure, is a major risk factor for diseases like stroke and myocardial infarction and affects around 25% of the adult population in the Western world. The pathogenesis of hypertension is largely unknown, although clinical intervention with regimens to lower blood pressure (BP) significantly reduces morbidity and mortality associated with stroke. Thus a considerable research effort has been directed toward elucidating the mechanisms controlling BP. In this issue of Circulation Research, Amberg and Santana have put forward a novel concept that down-regulation of the β1 subunit of the large-conductance, Ca2+-activated K+ (BK) channel may be an integral component in the development of vascular dysfunction during genetically induced hypertension. To understand the implications of the present findings, we will first summarize the current concepts about the role of the BK channel in regulating vascular tone and its contribution to the pathogenesis of hypertension.

Regulation of Vascular Tone
Ca2+ influx through plasmalemmal voltage-dependent Ca2+ channels (VDCCs) is an important regulator of arterial tone in resistance vessels, the major determinant of BP. The open-state probability (P0) of VDCCs is low around the resting membrane potential (Em), which in pressurized arteries ranges between −55 and −40 mV, and rises steeply with membrane depolarization. Thus, it is not surprising that agents influencing Em will have profound effects on blood vessel diameter. Indeed, opening of BK channels causes K+ efflux and membrane hyperpolarization, which underlies relaxation to a variety of endogenous vasodilators. Conversely, inhibition of K+ channels is commonly observed with vasoconstrictor agents.

BK Channels as Negative-Feedback Regulators of Vascular Tone
BK channels are by far the most abundant K+ channels expressed in vascular smooth muscle, and their importance as a physiological regulator of cerebral blood flow has long been recognized. Specific blockers of these channels, most notably iberiotoxin, depolarize and constrict pressurized but not resting arteries, leading to the notion that BK channels act as a compensatory mechanism to regulate arterial tone when Ca2+ levels are elevated. Activation of BK channels paradoxically arises from the highly localized Ca2+ release (Ca2+ sparks) from ryanodine receptors which are located in the sarcoplasmic reticulum (SR) at close proximity to these channels, thus resulting in vascular relaxation. In isolated smooth muscle cells, Ca2+ sparks give rise to spontaneous transient outward K+ currents (STOCs), the magnitude and frequency of which can be increased by several factors, including membrane depolarization, SR Ca2+ load, and Ca2+ influx through VDCCs.

BK channels are typically composed of four pore-forming α subunits and an unknown number of auxiliary β subunits. The α subunit arises from a single gene, although extensive alternative splicing and posttranslational modification can give rise to variation in channel gating and trafficking defects. There are at least four β subunits, although β1 appears principally expressed in vascular smooth muscle. While α subunits can form a K+ selective pore, coexpression with β1 subunits dramatically increases Ca2+ and voltage sensitivity of the channel as well as slowing activation and deactivation kinetics. The presence of the β1 subunit is also required for channel activation by dehydrosoyasaponin and estrogen agonists. Genetic studies have been instrumental in identifying the β1 subunit as a physiological regulator of vascular tone. Mice lacking this gene develop systemic hypertension, and their arteries show vascular hyperreactivity to agonists and defective coupling of Ca2+ sparks to BK channel activation at the resting Em. These observations raise the possibility that changes in β1 expression may contribute to the development of hypertension.

Ion Channel Dysfunction in Genetic Hypertension
As a means to investigate genetic hypertension, a strain of spontaneously hypertensive rats (SHR) developed from a colony of normotensive Wistar-Kyoto rats (WKY), have consistently been used, with WKY acting as the traditional control for both SHR and stroke-prone SHR (SHR-SP). Recent studies suggest that WKY, because of random breeding with certain suppliers, exist as different genetic strains, with some having borderline hypertension and high salt sensitivity (WKY/J-l-tf). SHR develop hypertension within 6 weeks of age and is fully established by 12 to 16 weeks. Using these SHR models, numerous patch-clamp studies have reported increased amplitude of currents through VDCCs in several vascular beds, including the cerebral circulation, resulting from both upregulation of the channel and membrane depolarization (see Reference 3). Since a good corre-
loration between current density and systemic BP was found at different ages in WKY and SHR, this has led to the hypothesis that increased VDCC function resulting in elevated intracellular Ca\textsuperscript{2+} is a fundamental component of genetic hypertension. Substantial evidence exists to suggest that hypertension is associated with altered expression of K\textsuperscript{+} channels. Voltage-gated (Kv) current density is suppressed in many models of hypertension, and this may result from Ca\textsuperscript{2+} inhibition of channel activity. Since Kv currents are a major determinant of Em, this may explain depolarized potentials reported in cells from hypertensive animals. Furthermore, increased contraction to BK channel inhibitors is observed in cerebral vessels from SHR or SHR-SP, suggesting an upregulation of BK function in hypertension. This is consistent with the observation that BK currents are larger in cerebral, mesenteric, and aortic cells from SHR, and this can in part be accounted for by increased \(\alpha\) subunit protein levels. Therefore, one could argue from these studies that BK channels provide a crucial counterregulatory mechanism to preserve normal levels of blood flow. However, the situation may be different in other forms of hypertension. For example, in rat (Dahl) genetic salt-sensitive hypertension, BK function was unaffected in cerebral arteries compared with their appropriate control. In the authors’ own recently published study, angiotensin II–induced hypertension was shown to be associated with a depressed \(\beta 1\) subunit expression resulting in BK channels that had a reduced ability to respond to Ca\textsuperscript{2+} sparks and modulate vascular tone in cerebral arteries. With this in mind, Amberg and Santana\textsuperscript{2} set out to examine whether uncoupling of BK from Ca\textsuperscript{2+} sparks is a general feature of hypertension, and if so, whether such dysfunction occurs early on in hypertension. To investigate this, BK channel function was assessed in young (12- to 16-week-old) normotensive Sprague-Dawley (SD) rats (systolic BP [SBP] 117 mm Hg) and compared with an age-matched borderline hypertensive Sprague-Dawley (SD) rats (systolic BP [SBP] 117 mm Hg) and SHR (SBP 117 mm Hg) and compared with an age-matched borderline hypertensive rats. As observed in angiotensin-induced hypertension, BK function was unaffected in cerebral arteries measured from STOC activity at \(-40\) mV was reduced by half in both WKY and SHR compared with SD rats. They went on to show that both Ca\textsuperscript{2+} spark frequency and amplitude were similar in all groups, thus suggesting that Ca\textsuperscript{2+} activation of the BK channel was somehow impaired. Indeed, BK single-channel analysis showed a lower Ca\textsuperscript{2+} sensitivity and \(P_c\), recorded from WKY and SHR. Unlike cells from SD rats, no activation of these channels was observed with the xenoestrogen tamoxifen, further supporting the idea that \(\beta 1\) subunit function is depressed. In the last part of the study, real-time PCR was used to compare mRNA levels of \(\alpha\) and \(\beta 1\) subunits in all rat strains. Thus the authors found that while message levels for \(\alpha\) were comparable, message levels for \(\beta 1\) were down by 70% in both WKY and SHR, as was \(\beta 1\)-associated immunofluorescence in single cells. The authors conclude that an early impairment in the coupling between BK channels and Ca\textsuperscript{2+} sparks may mediate the initial elevation in arterial tone and may represent a common feature in hypertension. The intriguing question posed by this study is whether \(\beta 1\) subunit defects in hypertension translate into depressed BK channel function at the level of the intact artery and whether such defects extend to systemic arteries involved in BP regulation. Clearly, both issues need to be addressed in future studies. If the authors are indeed correct with their interpretation, then one would expect diminished contractile effects of iberiotoxin in pressurized arteries from hypertensive animals, as observed in angiotensin-induced hypertension. Another prediction would be a decrease in the magnitude of whole-cell BK current and insensitivity to agonists working through the \(\beta 1\) subunit. However, it is worth pointing out that contractions to BK antagonists in SHR do not depend solely on SR Ca\textsuperscript{2+} release but also involve SR-independent Ca\textsuperscript{2+} elevation, with varying contribution in different blood vessels. Thus, BK channels could potentially regulate tone in the event of uncoupling of Ca\textsuperscript{2+} sparks to BK channels through an action of global Ca\textsuperscript{2+} on the \(\alpha\) subunit. Perhaps a scenario more in keeping with data already published is that depressed \(\beta\) function might be compensated for by an upregulation in the \(\alpha\) subunit either at the protein level or as a consequence of higher intracellular Ca\textsuperscript{2+} associated with sustained membrane depolarization. However, based on unchanged mRNA levels, the authors infer that the pore-forming \(\alpha\) subunit protein levels do not change. Without evidence from Western blotting and immunofluorescent studies, such a conclusion may be a little premature, particularly since Liu et al\textsuperscript{13} reported increased expression of \(\alpha\) protein without changes in mRNA levels in SHR. So we are left wondering if the results presented in the present study are in direct conflict or indeed concur with the numerous studies showing upregulation of BK function in hypertension.

What therefore might be the physiological significance of changes in the level of BK \(\alpha\) and \(\beta 1\) subunit expression? One possibility might be to reset arterial tone to a higher level within a range where blood flow can be autoregulated, but without the potential adverse effects (excessive dilation or pulsatile flow) associated with exacerbated Ca\textsuperscript{2+} sparks. Indeed, previous studies have shown that SR Ca\textsuperscript{2+} pools are higher in SHR compared with WKY, which coupled to a higher Ca\textsuperscript{2+} influx would lead one to the supposition that Ca\textsuperscript{2+} spark function is enhanced during established hypertension. Thus, it is somewhat surprising that in the present study, no difference in Ca\textsuperscript{2+} handling was observed between normotensive and hypertensive rats.

Finally, perhaps a more difficult issue to tackle is whether the normotensive strain used as a control (SD) in this study is appropriate. One possibility is that the changes in the molecular characteristics of BK channels are strain-dependent, rather than representing real changes associated with hypertension per se. In this vein, it is not clear why the authors chose SD rats over other strains of WKY that have been shown to be normotensive and salt resistant, such as WKY/1j-cr, having a similar SBP (\(\approx 118\) mm Hg) to SD themselves.9

Concluding Remarks

Hypertension is a complex polygenic disease that probably results from several independent defects, each imposing a
small cumulative effect on BP. Thus, the $\beta_1$ subunit of the BK channel is likely to be one of many proteins whose expression is altered either as a cause or consequence of hypertension. Indeed knock out of other genes can cause an increase in BP, such as endothelial nitric oxide synthase and the atrial natriuretic peptide receptor. These studies may assist in elucidating the molecular mechanisms underlying the pathogenesis of hypertension and may identify novel targets for therapeutic intervention and development of more specific/selective antihypertensive drugs.

References

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