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Commentary

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Hypertension: β testing

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A new study (see the related article beginning on page 717) demonstrates that angiotensin-induced hypertension results in a marked decrease in expression of the β subunit of the BK channel, suggesting a role for this critical subunit in the regulation of vascular tone.

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Hypertension, a silent killer, affects more than 40 million Americans, approximately a third of whom are not aware of their condition, resulting in an increased risk of heart attack, stroke, and kidney disease. The prevalence and severity of hypertension increases markedly with age, and some estimates suggest that as many as 90% of adults will suffer from systolic hypertension by the age of 80. Despite these daunting statistics, the root causes of progressive hypertension remain elusive. One important component of the regulation of vascular tone, a major determinant of blood pressure, has been identified within the last several years, however, and several findings now suggest that this signaling system may play an important role in systemic hypertension.

Increases in arterial vascular smooth muscle tone narrow the arteries and lead to chronic increases in systemic blood pressure. Evidence suggests that a major signaling system within myocytes serves to hyperpolarize and relax arterial smooth muscle. This system consists of intracellular Ca^{2+} channels (ryanodine receptor) expressed on the sarcoplasmic reticulum, and large conductance Ca^{2+}-activated K^+ (BK) channels. As shown in Figure 1, the gating of ryanodine receptors releases Ca^{2+} ions close to the myocyte membrane, resulting in the activation of a few BK channels, and a small hyperpolarizing current, producing (1). These events occur in single arterial myocytes at a frequency of approximately 1 Hz, contributing a tonic hyperpolarization throughout the electrically coupled arterial smooth muscle. Thus, alterations in the activity of this signaling pathway could have important consequences on arterial tone and systemic blood pressure.

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Nonstandard abbreviations used: Ca^{2+}-activated K^+ (BK); angiotensin II type 1 (AT1); sarcoplasmic reticulum (SR).

BK channels regulate vascular tone

BK channels are made up of pore-forming α and regulatory β subunits. While a single gene encodes the α subunit, which is expressed ubiquitously, there are four distinct β subunits that show marked tissue specific expression and account for much of the functional diversity of the channel complexes observed in different cell lineages (for review see ref. 2). The β1 subunit (3), which is selectively expressed in smooth muscle and which markedly increases the Ca^{2+} sensitivity of the channel complex, has received substantial attention recently regarding its role in the regulation of vascular tone. Binding of steroid hormones such as estradiol to the β subunit activates BK channels and relaxes smooth muscle (4), thereby providing a non-genomic mechanism for vasorelaxant actions of these hormones. Further, two recent studies of β1 knockout mice have documented that loss of expression of this subunit results in disrupted coupling between Ca^{2+} release and the activation of hyperpolarizing BK currents, result-

ciated role in the pathogenesis and susceptibility to hypertension. Thus, regulation of expression of the β subunit of the BK channel may be a critical element in the development of hypertension, through mechanisms that are at present unclear.

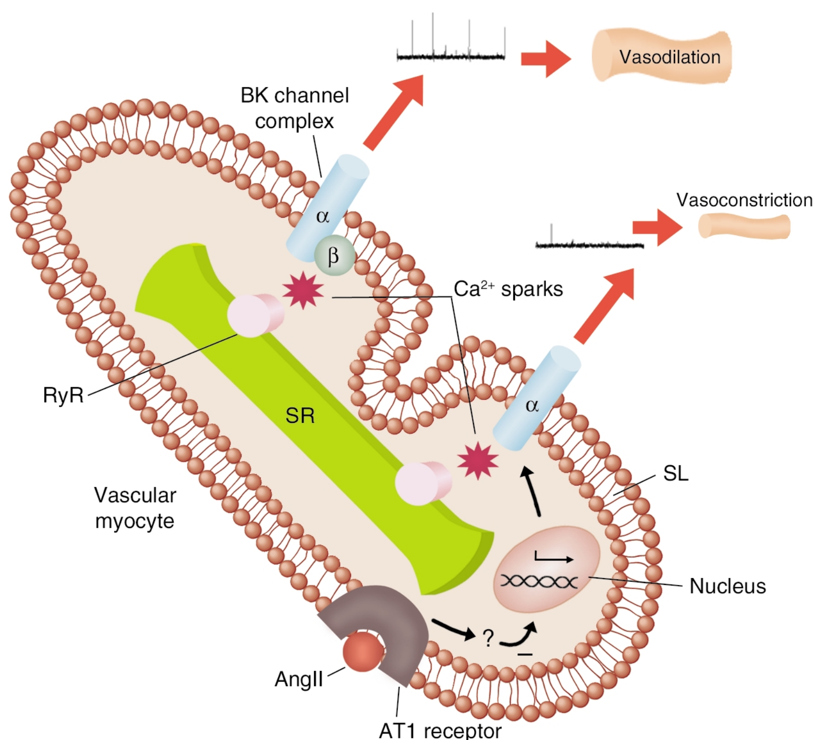

Figure 1
The β subunit tunes the coupling of BK channels to RyR Ca^{2+} release. Gating of ryanodine receptors (RyR) in the sarcoplasmic reticulum (SR) results in brief, localized increases in Ca^{2+}, termed Ca^{2+} sparks (red stars). These Ca^{2+} sparks activate a few BK channels in the sarcolemma (SL), resulting in spontaneous transient outward currents, or STOCs (currents shown above), which hyperpolarize and relax the myocyte, leading to vasodilation. The β subunit of the BK channel plays a critical role in regulating the sensitivity of the BK channel complex to Ca^{2+} ions, and Amberg et al. (7) now establish a link between hypertension, produced by a chronic infusion of angiotensin (AngII), and this channel subunit. Equivalent Ca^{2+} sparks produce smaller and less frequent STOCs in hypertensive mice, and this appears to result from a decrease in expression of the β1 subunit following angiotensin infusion. The results focus attention on transcriptional regulation of the β subunit and how this may be affected by activation of AT1 receptors.

ing in systemic hypertension (5, 6). These studies raise the possibility that changes in β1 subunit expression may occur in and contribute to the development of human hypertension.

Decreased expression of the β subunit of BK channels in hypertension

The paper by Amberg et al. in this issue of the *JCI* (7) examines the role of this critical subunit in hypertension from a somewhat different perspective. The question is asked as to whether acquired hypertension results in regulatory shifts in β1 subunit expression and attendant alterations in coupling between sarcoplasmic reticulum (SR) Ca^{2+} release and the activation of hyperpolarizing currents. The authors report that in rats chronically infused with angiotensin II at levels sufficient to raise systolic blood pressure by approximately 90 mmHg, expression of the β1, but not the α, subunit is markedly decreased. Consistent with this finding, equivalent Ca^{2+} sparks, the spatially localized SR Ca^{2+} release events, produce smaller hyperpolarizing currents, without a loss in the average number of expressed channels. This large increase in systolic blood pressure is, of course, in excess of the commonly seen age-related increases of 10 to 40 mmHg (although such increases are seen in a minority of patients with severe hypertension), but the demonstrated mechanism serves to highlight a potentially important adaptive response. A second implication of this finding is that differences in β subunit expression, perhaps associated with variations in the promoter sequence, may play an as yet unappreciated role in the pathogenesis and susceptibility to hypertension. Thus, regulation of expression of the β subunit of the BK channel may be a critical element in the development of hypertension, through mechanisms that are at present unclear.

Genetics of human hypertension

The gene encoding the β1 subunit of BK channels (*Kcnmb1*) maps to human chromosome 5q34 (Genbank accession number U25138), whereas the gene for the α subunit is situated on chromosome 10q 22-23. If abnormalities in the β subunit were important for control of blood pressure, one might predict that linkage to this region might be seen in studies examining the genetic basis of hypertension in humans. Several genome screens on relevant populations have now been performed, but in common with other complex diseases the results have been rather disappointing, with most studies failing to report loci achieving genome-wide significance. Of particular relevance to the present study, the majority of screens have failed to identify even suggestive evidence for linkage on chromosome 5, although in the most recent British Genetics of Hypertension study (known as BRIGHT) (8) a suggestive logarithm of the odds score (maximum 1.85) was obtained on 5q, the nearest marker being D5S2019. However, this region is a long distance centromeric to the region containing the *Kcnmb1* gene. To date there have been no association studies examining markers in the *Kcnmb1* region and control of blood pressure.

β Subunit expression and hypertension

While definitive linkage analysis and association data are not available, it is worthwhile to observe that inter-individual variability in blood pressure control due to altered regulation of BK by the β subunit could potentially be driven by genetic variability in the expression or function of the β subunit itself, or could be explained by altered subunit expression as a consequence of variability in other controlling pathways such as the renin-angiotensin system. Although only minimal characterization of

KCNMB1 transcriptional regulation has been performed (9,10), the genomic structure of the promoter appears to share elements with other smooth muscle specific genes, which contain important regulatory elements in a large first intron (11,12). Exposure of vascular myocytes to pressors such as angiotensin, used here to produce hypertension, results in transcriptional activation of numerous genes, through angiotensin II type 1 receptor (AT1) activation (13). Whether these target genes include pore-forming or regulatory ion channel subunits is yet to be determined.

The β test described here by Amberg et al. (7) further highlights the unique, localized Ca^{2+} signaling mechanism in vascular myocytes and the role of the β subunit in tuning the Ca^{2+} sensitivity of the BK channel complex. Functional changes in coupling between the SR and the sarcolemma, resulting from the altered expression of BK β subunits, may be a key mechanism underlying variations in vascular tone in vivo. This idea, and the mechanism by which angiotensin and perhaps other pressors regulate β subunit expression, will undoubtedly be the subject of considerable future investigation.

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The host response to anthrax lethal toxin: unexpected observations

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***Bacillus anthracis*, the causative agent of anthrax, is believed to induce disease and death in humans in an endotoxic shock–like manner. A comprehensive study (see the related article beginning on page 670) of the effects of anthrax toxin in mice demonstrates that toxin-induced death is mediated not by cytokine release, as previously thought, but by hypoxia-induced liver failure. The study strongly suggests that the therapies developed for treatment of cytokine-mediated septic shock will not be appropriate for the treatment of anthrax.**

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Anthrax is an ancient disease now believed to be the cause of two of the plagues of Egypt described in the Old Testament. It was further characterized by the Romans in the writings of Virgil in 28–27 B.C. (1), and studied in a systematic fashion by the preeminent 19th-century scientists Robert Koch and Louis Pasteur (2). The first anthrax vaccine was produced by Pasteur in 1881 for use in cattle and was the predecessor to the more immunogenic attenuated strain of *Bacillus anthracis* developed in the 1930s by Sterne (3). As early as the 19th century there were insights into the immunodominant and protective antigens expressed by the organism. The essential virulence factors of *B. anthracis* are known and well characterized (4); the bacterial adhesin has been identified, its binding domain mapped, and its crystal structure determined at a resolution of 2 Å (5). The anthrax toxin receptor (ATR), an integral membrane protein, has been identified (6). The genomic DNA of *B. anthracis* has been sequenced; critical domains of the major virulence factors are mapped, and much of the molecular biology of the major virulence determinants of anthrax is well established, at least in vitro. Yet, despite the long history of *B. anthracis* as a human and animal pathogen and its notoriety as an agent of biological warfare, exactly how anthrax kills the host is unclear. In an exhaustive pathological study presented in this issue of the *JCI*, observations from the laboratory of Stephen Leppla and colleagues provide major new insights into the pathogenesis of anthrax (7).

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Nonstandard abbreviations used: anthrax toxin receptor (ATR).

Pathogenesis of anthrax: plasmid-mediated expression of essential virulence factors

Through the work of many investigators it has been well established that virulent *B. anthracis* expresses two plasmids, pXO1 and pXO2. The plasmid pXO1 expresses the anthrax toxins