The β_1 subunit of the Ca^{2+}-sensitive K^+ channel protects against hypertension

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Previous animal studies have demonstrated that the loss of the β_1 subunit of the large-conductance Ca^{2+}-activated K^+ (BK) channel leads to hypertension. A new study (see the related article beginning on page 1032) demonstrates that a gain in β_1 subunit function is associated with protection against diastolic hypertension in humans, underscoring the importance of the β_1 subunit and the BK channel in the regulation of vascular resistance.

Elevated blood pressure — hypertension — is a major risk factor for brain, heart, and kidney diseases and affects at least 50 million people in the USA, and about 1 billion people worldwide. Despite the devastating consequences of this disease, the underlying cause is not known in 90 to 95% of all cases. The known genetic causes of hypertension involve mutations that disrupt salt regulation (1).

Blood pressure is determined by the amount of blood ejected by the heart (cardiac output) and by the resistance to blood flow, which is regulated by the vasculature. Blood pressure exhibits characteristic fluctuations that correspond to the initial ejection (systolic) and filling (diastolic) phases of cardiac contractions. Blood pressures below 120 mmHg systolic and 80 mmHg diastolic are considered desirable.

Mice have been engineered in which genes key to blood vessel development and the regulation of vascular resistance have been deleted. For example, ablation or suppression of the genes for eNOS (2, 3), cyclic GMP–dependent kinase I (4), an isoform — SK3 — of the small-conductance Ca^{2+}-activated potassium (SK) channel (5), or the β_1 subunit of the large-conductance Ca^{2+}-activated K^+ (BK) channel (6–8) leads to a chronic elevation of blood pressure. The β_1 subunit of the BK channel is particularly interesting, since it appears to be exclusively expressed in smooth muscle (6, 9, 10), where it acts to increase the apparent Ca^{2+}- and voltage-sensitivity of the BK channel (11).

Nonstandard abbreviations used: human BK channel α subunit (hSlo1); intracellular Ca^{2+} ion ($[Ca^{2+}]_i$); large-conductance Ca^{2+}-activated K^+ (BK); small-conductance Ca^{2+}-activated K^+ (SK).

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β_1 subunit of the BK channel regulates vascular tone

BK channels, which are activated by both intracellular Ca^{2+} ions ($[Ca^{2+}]_i$) and membrane potential depolarization, regulate the membrane potential of arterial smooth muscle cells. BK channels are activated in arterial smooth muscle by local Ca^{2+} release events ("Ca^{2+} sparks") caused by the opening of a cluster of ryanodine receptors in the sarcoplasmic reticulum membrane adjacent to the cell membrane (12). In pressurized arteries under normal physiological membrane potentials (~–40 mV) and $[Ca^{2+}]_i$ (~200 nM) these channels have an exceedingly low activity. A Ca^{2+} spark increases the activity of nearby BK channels 10^4- to 10^6-fold, resulting in an efflux of K^+ that is sufficient to hyperpolarize the membrane potential by 10 to 20 mV (13–15). Blocking BK channels or ryanodine receptors in arterial smooth muscle can cause membrane potential depolarization, an elevation of arterial wall Ca^{2+}, and vasoconstriction (12, 16). The Ca^{2+} spark–BK channel pathway thus functions as a negative feedback loop to limit membrane depolarization and contraction (12, 14) (Figure 1A).

A wide variety of vasodilators exert their actions through activation of BK channels (17–19). BK channels in smooth muscle are regulated by multiple second messenger signaling pathways, including cAMP- and cGMP-dependent protein kinases (PKA and PKG, respectively). PKA and PKG activate BK channels directly through channel phosphorylation, but also activate BK channels indirectly through an elevation of Ca^{2+} spark frequency and amplitude (14).

The BK channel in smooth muscle is composed of α pore-forming subunits and β_1 subunits (Figure 1A). The β_1 subunit is highly expressed in smooth muscle, but not in other tissues (6, 10). The β_1 subunit has been shown to increase the apparent voltage- and Ca^{2+}-sensitivity of the pore-forming α subunit in heterologous expression systems (20–22). The importance of the β_1 subunit in arterial smooth muscle physiology is just emerging (6). Disruption of the gene encoding the β_1 subunit (*Kcnmb1*) in mice functionally uncouples Ca^{2+} sparks from activation of BK channels, leading to membrane potential depolarization, vasoconstriction, an elevation of blood pressure, and left ventricular hypertrophy (6–8). In commonly used rat models of hypertension, including spontaneously hypertensive rats and rats made hypertensive by chronic angiotensin II infusion, elevated blood pressure is associated with a downregulation of the β_1 subunit, but not the α subunit, of the BK channel (23, 24). Significantly, blocking the BK channel has a diminished effect on vasoconstriction in these models, suggesting that the observed decrease in expression is functionally relevant. Estradiol has also been shown to activate BK channels through binding to the β_1 subunit (25), an observation that may provide a mechanistic basis for well-characterized gender differences in resting vascular tone and myogenic responses. Collectively, these studies support the concept that the β_1 subunit of BK channels plays an important role in regulating vascular resistance.

Association between genetic variants of the β_1 subunit (*KCNMB1*) gene and human hypertension

The human gene that encodes the β_1 subunit of the BK channel, *KCNMB1*, maps to chromosome 5q34 and had not been linked to human hypertension (26). In this issue of the *JCI*, a report based on the results of a large genetic epidemiological study (3,876 participants) by Fernández-Fernández et al. describes a new single nucleotide substitution (G352A) in the third exon of the *KCNMB1* gene (27). The resulting mutant protein (β_{1E65K}) contains a glutamic acid to lysine substitution at position 65 in the β_1 subunit. Interestingly, the investigators found that the frequency of the β_{1E65K} polymorphism is dramatically lower (3.2%)

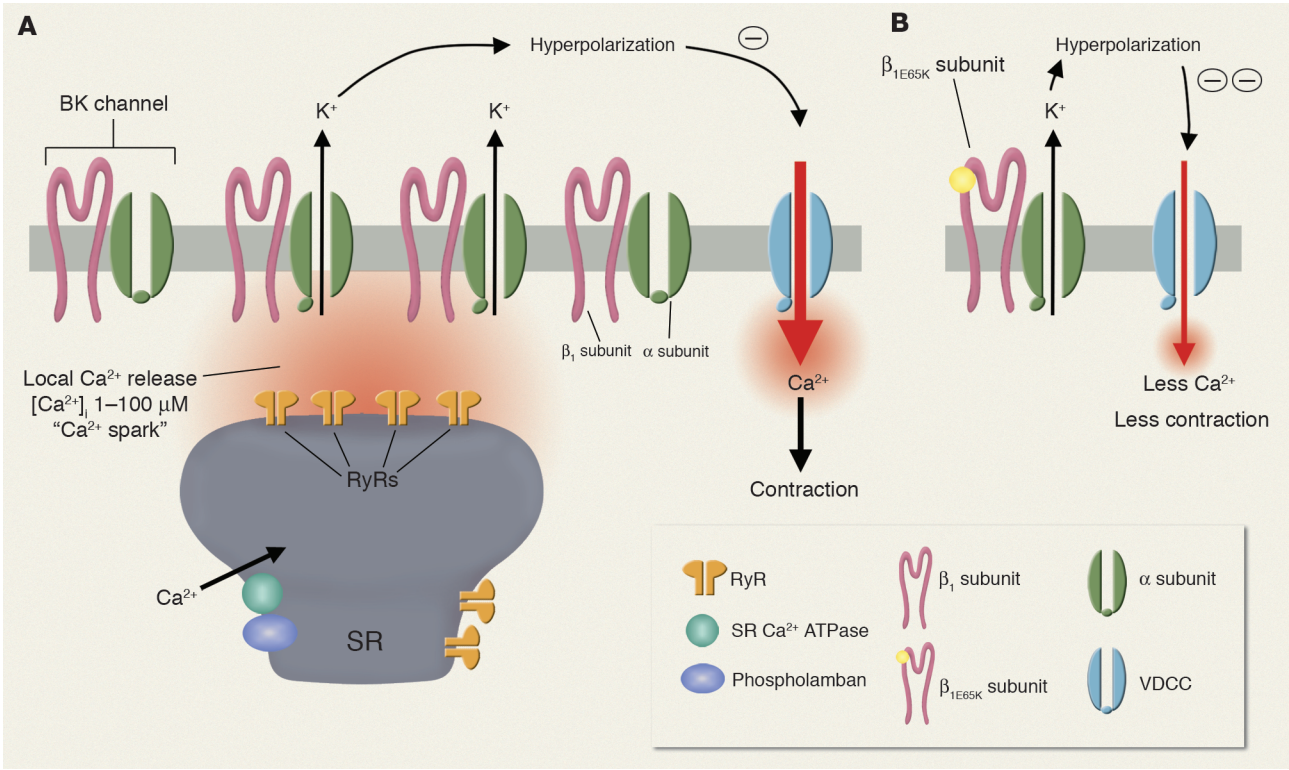

Figure 1
Proposed role for the β_{1E65K} subunit, resulting from a single point mutation in the β_1 subunit and leading to a gain-of-function of the BK channel and vasodilation. (**A**) The BK channels in smooth muscle are composed of α pore-forming subunits and β_1 subunits. Local Ca^{2+} release (Ca^{2+} sparks) through a cluster of ryanodine receptors (RyRs) in the sarcoplasmic reticulum (SR) membrane activates nearby BK channels leading to membrane potential hyperpolarization, decreased influx of Ca^{2+} through voltage-dependent Ca^{2+} channels (VDCCs), and less contraction. β_1 subunits play a crucial role in the Ca^{2+} spark–BK channel negative feedback loop, since they increase the Ca^{2+}-sensitivity of the pore-forming α subunit of the BK channel. (**B**) The mutant form of the β_1 subunit, the β_{1E65K} subunit, which reflects a single amino acid substitution, has an even higher efficacy in enhancing the Ca^{2+}-sensitivity of BK channels resulting in their gain-of-function. Hence, the mutant β_{1E65K} subunit enhances the role of the Ca^{2+} spark–BK channel negative feedback mechanism in limiting vasoconstriction and effectively provides protection against diastolic hypertension.

among individuals in the population with severe elevations in diastolic blood pressure (>110 mmHg) compared to that in the normotensive population (21.6%). There was no relationship between β_{1E65K} allele frequency and systolic blood pressure. These results suggest that the β_{1E65K} variant provides a protective effect against diastolic hypertension, which would be consistent with a gain-of-function of the BK channel that increases opposition to constriction of resistance arteries.

To test this hypothesis, the investigators examined the effects of β_{1E65K} on the Ca^{2+}- and voltage-activation of human BK channel α subunit (hSlo1), expressed in HEK-293 cells (27). As has been previously shown, expression of the wild-type β_1 subunit increased the apparent Ca^{2+}- and voltage-sensitivity of the pore-forming α subunit. Remarkably, β_{1E65K} alone or in combination with wild-type β_1 subunits further increased the apparent α- and voltage-sensitivity (Figure 1B). This effect was equivalent to a negative 30 mV shift in the activation curve of the BK channel in the presence of 10 μM Ca^{2+}, a concentration that the BK channel would experience during a Ca^{2+} spark. Furthermore, the E65K mutation had a dominant-positive effect in combination with the wild-type β_1 subunit. Finally, the authors used the allosteric model of Horrigan and Aldrich (28) to explain the increase in apparent Ca^{2+}- and voltage-sensitivity, without a change in channel kinetics.

Future directions

In mouse studies, the loss of the BK channel β_1 subunit leads to an increase in vascular tone and hypertension. The study by Fernández-Fernández et al. (27) provides an exciting complementary view, demonstrating that a gain-of-function BK channel β_1 subunit variant exerts a protective effect against diastolic hypertension in humans. The combined use of human genetic epidemiological studies and functional studies on exogenously expressed channels in vitro has established the basic mechanism that connects BK channel function with a form of human hypertension. An examination of vascular tone control and BK channel function in resistance arteries from people exhibiting the β_{1E65K} variant is the next logical step. Additional insights might also be gained by exploring the effects of the E65K mutation on β_1 subunit modulation of BK channel function, vascular tone, and blood pressure control in a mouse model. Nonetheless, this study elevates the potential importance of the β_1 subunit and the BK channel in the regulation of blood pressure, and provides significant motivation for the development of BK channel–regulating therapeutic agents that specifically target the β_1 subunit.

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Functional obstruction: the renal pelvis rules

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Failure in the peristaltic mechanism that conducts urine from the kidney to the bladder can lead to hydronephrosis, a common birth defect associated with obstructive nephropathy. New animal models reveal molecular pathways important for peristalsis and point to the central role of the renal pelvis in urine transport (see the related article beginning on page 1051).

Hydronephrosis, enlargement of a kidney as a result of urine collection in the renal pelvis or calyces, is present in about 1% of newborns and can lead to obstructive nephropathy (1, 2). Often caused by static anatomic occlusion (e.g., by stones) or by failure of the peristaltic mechanism, the underlying genetic and cellular defects at play in obstructive nephropathy are not well understood. Urine is transported out of the papilla by a peristaltic process to the pelvis and ureters and then is stored in the bladder. Peristalsis is initiated in the renal pelvis and is propagated along the urinary tract by smooth muscle cells in the ureter coat. Hydronephrosis is associated with a number of congenital abnormalities including vesico-ureteral reflux and hydroureter, which can be caused by physical obstruction. Despite their different appearances, these malformations most likely stem from a common defect: failure of ureters to join the bladder properly (Figure 1A) (3). Ectopically terminating ureters can join the bladder outside the normal position in the trigone or can join the sex ducts or urethra or end blindly. However, in many congenital cases of hydronephrosis or hydroureter, no physical obstruction can be demonstrated (Figure 1B). The cause of these conditions is thought to be abnormalities in the smooth muscle of the urinary outflow tract (renal pelvis, ureters, or bladder) or impaired peristalsis. An elegant study by Chang et al. in this issue of the *JCI* describes a new mouse model of obstructive nephropathy in which the gene encoding the calcineurin B type1 isoform (*Cnb1*) has been deleted from mesenchyme lining the urinary outflow tract (4). These animals develop hydronephrosis due to impaired pyeloureteral peristalsis, most likely caused by a failure in the outgrowth of the renal pelvis. This new study points to the crucial role of the renal pelvis as a regulator of peristalsis in the urinary outflow tract.

Effective urine transport depends on formation of proper connections between the kidney and ureters

Development of the metanephric kidney is initiated by the ureteric bud, an epithelial sprout that forms at the base of the Wolf-

Nonstandard abbreviations used: cytoplasmic nuclear factor of activated T cells (NFATc).

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