Vascular Dysfunction in Diabetes Mellitus
Large Conductance Calcium-Activated Potassium Channels as Part of a Subsarcolemmal Signaling Soirée

D.D. Gutterman, M.J. Durand

Vascular smooth muscle membrane potential is a key determinant of vessel tone primarily through regulation of voltage-dependent calcium channels (VDCCs). The opening probability of VDCCs is increased by membrane depolarization, facilitating influx of calcium and producing contraction of vascular smooth muscle cells (VSMCs). Control of membrane potential and VDCC activity is orchestrated by a complex series of signals that occur just below the sarcolemmal membrane.

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Large-conductance calcium-activated potassium channels (also known as maxi-K or BK channels) play a pivotal role in modulating vasomotor tone in both health and disease. BK channels, expressed on VSMCs, act as breaks for the increase in vascular tone that occurs after membrane depolarization and elevation of cytosolic calcium. An intracellular rise in cytosolic calcium through VDCC leads to activation of ryanodine receptors that release quanta of calcium from the sarcoplasmic reticulum (calcium sparks). It is these intracellularly generated sparks that elevate local submembrane concentrations of calcium and activate BK channels which increase potassium conductance and lower membrane potential. This reduces calcium influx, thus attenuating the myogenic contraction.

A classic example of BK channel modulation of vascular tone is the attenuation of myogenic vasoconstriction. An increase in intraluminal pressure depolarizes the VSMC membrane eliciting calcium influx and myogenic contraction. The calcium influx triggers opening of previously quiescent BK channels resulting in increased potassium conductance, hyperpolarization of the smooth muscle membrane, and a reduction in calcium influx, thus attenuating the myogenic contraction.

BK channels are comprised of homotetrameric α subunits with a potassium-selective pore region. The channel complex is flanked by β subunits that enhance calcium sensitivity. Gain of function mutations of the β1 subunit in humans are associated with a low prevalence of hypertension and coronary disease, whereas genetic loss of function mutations in the α subunit or reductions in the β1 subunit produce increases in blood pressure and cardiovascular disease. Conversely, gain of function polymorphisms of the β subunit reduce diastolic blood pressure and may reduce the risk of cardiovascular events.

In diabetes mellitus, the action of BK channels is reduced, in part by decreased calcium sensitivity from a reduction in β1 subunit expression. Interestingly, the nature of the reduced activity changes over time. Early in the Zucker high-fat diet–induced model of diabetes mellitus (8 weeks), vascular dysfunction and reduced BK currents are observed in VSMCs. By 4 to 6 months, BK channels still open to voltage changes but calcium sensitivity is reduced. At this more advanced stage, the Zucker high-fat diet–induced model of diabetes mellitus rat also demonstrates abnormal biophysical properties of the BK channel, not observed at earlier time points, including impaired calcium sensitivity, more prolonged closed times, and shortened opening times.

It is easy to see how BK channels play a central role in vasodilation and development of vascular disease. However, little is known about how these channels are regulated. Which intracellular pathways are responsible for modulating BK channel activity and expression? Nystoriak et al in the current issue provide new findings that link the calcineurin–nuclear factor of activated T cells, c3 isoform (NFATc3) pathway to BK channel expression in an animal model of diabetes mellitus. The scaffolding protein A-kinase anchoring protein 150 is critical in linking calcineurin with L-type calcium channels (Figure). Calcineurin, the calmodulin-dependent serine/threonine phosphatase, is activated by elevations in intracellular calcium leading to dephosphorylation of NFATc3 which enhances nuclear translocation. There, NFATc3 blocks expression of the BK channel β1 subunit. Strong evidence is provided that in diabetes mellitus, activation of calcineurin dephosphorylates NFATc3, allowing it to move into the nucleus, reduce transcription of the BK channel β1 subunit, thereby decreasing calcium sensitivity of the BK channel. As a result, BK opening probability is impaired at any given level of calcium spark activity, leading to larger intracellular calcium levels and enhanced vasomotor tone. This was convincingly demonstrated by an elevation in intracellular calcium, reduced opening probability of BK channels in vascular myocytes, an elevation in blood pressure in animals with a constitutively active form of NFATc3, and normal calcium sensitivity in VSMCs from diabetic animals with reduced levels of NFATc3. Calcium spark activity did not change.

The NFATc3 pathway’s influence on vascular ion channels is not unique to the BK channel because nuclear localization of NFATc3 in response to angiotensin II downregulates Kv2.1 channel expression. Thus, NFATc3 may engage multiple complementary pathways of vasodilation in disease. Indeed, like BK, Kv channel activity is reduced and expression is...
Reciprocally, protein kinase Cα, calcineurin, and subsarcolemmal calcium signaling complex in that hydrogen peroxide, thought to be the primary redox signaling derivative of superoxide, is a potent inhibitor of calcineurin.26,27 which would be expected to prevent BK β1 downregulation via NFATc3.

In summary, BK channels are an integral part of the subsarcolemmal calcium signaling complex that regulates vascular tone. Understanding how this modulating influence on vasoconstriction is impaired in disease may open new pathways for treating cardiovascular complications of diabetes mellitus, hypertension, and heart failure. The present study takes the first step by establishing that the calcineurin–NFATc3 pathway contributes to hypertension in diabetes mellitus by downregulating expression of the calcium-sensitizing β1 subunit of the BK channel.

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None.

References


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