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Oral presentation

Analysis of BK_{Ca} channel deficient mice

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The large-conductance, voltage and Ca^{2+}-dependent K^+ (BK) channel links membrane depolarization and local increases in cytosolic Ca^{2+} to hyperpolarizing K^+ outward currents and has been proposed as an important effector of the cGMP/cGMP kinase pathway in the control of vascular and smooth muscle tone.

Deletion of the pore-forming BK channel α subunit leads to a significant blood pressure elevation. In smooth muscle from small arteries, deletion of the BK channel leads to a depolarized membrane potential, a complete lack of membrane hyperpolarizing spontaneous K^+ outward currents, and an attenuated cGMP vasorelaxation associated with a reduced suppression of Ca^{2+} transients by cGMP. However, the $BK^{-/-}$ mice also exhibit a hyperaldosteronism accompanied with decreased serum K^+ levels as well as increased vascular tone in small arteries. The high level of BK channel expression observed in wild-type adrenal glomerulosa cells, together with unaltered serum renin activities and corticotropin levels in mutant mice, suggests that the hyperaldosteronism results from abnormal adrenal cortical function in $BK^{-/-}$ mice. The urinary bladder phenotype in $BK^{-/-}$ comprises an overactive bladder associated with an increased intravesical pressure and frequent micturitions. This phenotype was traced back to hyperactivity of the detrusor muscle caused by depolarized membrane potential, as well as disruption of cGMP-dependent modulation of the frequency of rhythmic contractions. In $BK^{-/-}$ detrusor, however, cGMP efficiently reduced the contractility of the muscle, while cGMP did not affect the contractility of wild-type detrusor. It appears that the BK channel deficiency activates or up-regulates cGMP-sensitive mechanisms that are responsible for the inhibitory effect of cGMP on muscle contractility in the $BK^{-/-}$ genotype.

These results identify previously unknown roles of BK channels in blood pressure regulation and raise the possibility that BK channel dysfunction may underlie specific forms of hyperaldosteronism. Further, the results identify BK channels as predominant regulator of urinary bladder smooth muscle contractility. The modulatory role of cGMP for urinary bladder rhythmic contractions switches from frequency control in wild-type towards contractility regulation in $BK^{-/-}$ detrusor.