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THE ROLE OF CALCIUM IN UROMODULIN EXPRESSION AND SECRETION FROM RENAL MEDULLARY EPITHELIAL CELLS OF HYPERTENSIVE AND NORMOTENSIVE RATS

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BACKGROUND AND AIMS: Uromodulin (UMOD) is the most abundantly secreted protein found within the urine, primarily produced by medullary thick ascending limb (mTAL) epithelial cells of the kidneys. There is accruing genetic evidence implicating UMOD in blood pressure regulation and consequently hypertension. The molecular signaling induced by calcium in the kidney and its influence on blood pressure are not well understood. The aim of this study was to investigate the potential role of extracellular calcium and the calcium-sensing receptor (CaSR) in mTAL on UMOD production and secretion in TAL cells with the hope of defining novel clinical targets for the treatment of hypertension.
METHOD: Kidneys were harvested from normotensive Wistar-Kyoto (WKY) and stroke-prone spontaneously hypertensive (SHRSP) female rats. To determine the effect of extracellular calcium on UMOD secretion, mTAL tubules were incubated in media with and without 1mM calcium, nifedipine (10μM), NPS2143 (1 or 5 μM) and spermine (2mM). Extracellular and intracellular UMOD protein levels were detected by Western blot. Gene expression of Umod was determined by qRT-PCR.
RESULTS: Calcium increased mTAL tubule UMOD secretion in WKY and SHRSP. Nifedipine slightly decreased UMOD secretion in WKY without calcium. In both strains, NPS2143 increased calcium-induced UMOD secretion, with an enhanced effect in SHRSP. Stimulation of CaSR with spermine decreased UMOD secretion in WKY. Analysis of intracellular UMOD levels in these conditions demonstrated increased accumulation when extracellular secretion was low, and vice versa. Incubation of primary mTAL cells with calcium confirmed increased localisation of UMOD at the membrane compared to the cytosol, without any major differences in cell morphology. The Umod mRNA level changes were not statistically significant among conditions.
CONCLUSION: Trafficking of UMOD in the mTAL is influenced by the type of CaSR ligand and the biased nature of G-protein coupled CaSR signalling. Unravelling the signalling events post-calcium will be necessary for identification of key regulators of UMOD secretion and provide new sites for therapeutic intervention in hypertension.