Angiotensin II promotes Kv7.4 channels degradation through reduced interaction with HSP90

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Questions. Angiotensin II (Ang II) modulates vascular smooth muscle cell (VSMCs) contractility and the expression of potassium (K+) channels. Among them, voltage gated K+ channels belonging to Kv7 family modulate arterial contractility and mediate the responses to several endogenous vasorelaxants. In particular, Kv7.4 protein is down-regulated in several arterial beds in different models of hypertension. In this study we evaluated the effects of Ang II on vascular Kv7.4 expression and function**.**

Methods. Whole mesenteric artery (MA), as well as isolated VSMCs from Wistar rats were incubated with 100nM Ang II. Subcellular localisation of Kv7.4 subunits was assessed by immunofluorescence experiments. RNA and protein levels were measured by quantitative PCR and western blot. Functional effects were evaluated by wire myography. Proximity Ligation Assays were performed to measure protein:protein interactions.

Results. Ang II reduced Kv7.4 localisation at the plasma membrane in VSMCs, and decreased protein expression in MA without a concomitant reduction of mRNA levels. In addition, Ang II impaired the vasorelaxation produced by the Kv7.4 activator ML213 in pre-contracted MA. Proteasome-inhibitor MG132 prevented Ang II-induced reduction of Kv7.4 protein levels and function. Ang II decreased the number of interactions of Kv7.4 with the chaperone protein HSP90, and increased the interaction with the E3 ubiquitin ligase CHIP. Inhibition of HSP90 with 17-AAG reduced Kv7.4 protein levels and increased its interaction with CHIP.

Conclusions. Ang II alters Kv7.4 protein stability by decreasing its interaction with HSP90. This determines Kv7.4 degradation via the proteasome, possibly by an increased activity of CHIP.