L-type Ca^{2+} channel activation is sensitized in renal resistance arteries in response to renal denervation

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Perivascular innervation is a determinant of vascular smooth muscle cell (VSMC) phenotype. Neonatal sympathectomy causes depolarization of VSMC membrane potential (MP) in rat renal resistance arteries which increases their sensitivity to vasoconstrictor stimuli including facilitated L-type Ca^{2+} channel activation. We tested if local renal denervation in young adult rats sensitizes renal resistance arteries to L-type Ca^{2+} channel activation and if increased sensitivity to L-type Ca^{2+} channel activation as well as noradrenaline (NA) supersensitivity can be abolished by hyperpolarizing VSMC MP in vessels from denervated kidneys. We further investigated the effects of L-type Ca^{2+} channel activation on basal and of K_{ATP} channel activation on NA-induced vascular tone in human renal resistance arteries.

Eight-week-old rats underwent bilateral renal denervation or sham denervation under ketamine/xylazine anesthesia at 100/10 $mg*kg^{-1}$, i.p. At the age of 12 weeks, kidneys were removed under pentobarbital anesthesia (60 mg/kg, i.p.) and third generation renal artery branches were dissected for myograph and mRNA expression studies. Tissue samples from human kidneys were obtained from patients who underwent nephrectomy.

L-type Ca^{2+} channel activator S-(-)-BayK8644 induced tension was higher in arteries from denervated than in arteries from sham-denervated rat kidneys (60 vs. 30% of K^+-induced tension; $p < 0.01$). K_{ATP} channel activator levcromakalim blocked S-(-)-BayK8644-induced vasoconstriction in arteries from denervated and sham-denervated rats. S-(-)-BayK8644 increased vascular tension to 100% of K^+-induced tension in human renal resistance arteries which was blocked by levcromakalim. Arteries from denervated kidneys showed higher NA sensitivity than arteries from sham-denervated kidneys (logEC50 -6.62 vs. -6.12 mol/l; $p < 0.01$). In both groups, levcromakalim similarly shifted the NA concentration response curves rightward. Levcromakalim also shifted the NA concentration response curves rightward in human renal resistance arteries. K_{ATP} channel blockade did not affect basal and NA-induced vascular tone in rat and human intrarenal arteries. Transcriptome analyses did not reveal statistically significant effects of renal denervation on K^+ channel mRNA abundances. PCR analyses showed that mRNAs of all K_{ATP} channel constituents are present in human renal resistance arteries.

Local renal denervation sensitizes renal resistance arteries to L-type Ca^{2+} channel activation suggesting that VSMC MP is depolarized compared to VSMC MP of innervated intrarenal arteries. A depolarized membrane potential does not contribute to NA supersensitivity in denervated renal resistance arteries. K_{ATP} channels are functional in rat and human renal resistance arteries. They do not contribute to basal and NA-induced vascular tone.