Diuretics prevent Rho-kinase activation and expression of profibrotic/oxidative genes in the hypertensive aortic wall

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Abstract

Background:

Diuretics are current antihypertensive drugs since they reduce blood pressure and cardiovascular risk. Increased vascular tone is modulated in a relevant way by the RhoA/Rho-kinase (ROCK) pathway, by acting on vascular smooth muscle cell contraction. This pathway has also proremodeling vascular effects. There are few data on the role of diuretics on both vascular ROCK activation and on proremodeling effects. We assessed the effects of hydrochlorothiazide (HCTZ) and spironolactone (spiro) alone and in combination with the ROCK inhibitor fasudil (FAS) on ROCK activation, gene expression of proremodeling markers and on hypertrophy in the aortic wall of hypertensive rats.

Methods:

Deoxycorticosterone acetate (DOCA)-salt hypertensive rats (male, Sprague–Dawley) were randomized to the specific ROCK inhibitor FAS, HCTZ, spiro or the combinations of FAS/HCTZ or FAS/spiro for 3 weeks. At the end of the study, ROCK activation (by western blot), gene expression of proremodeling markers (by reverse transcription polymerase chain reaction, RT-PCR) and vascular hypertrophy (by morphometry) were determined in the aortic wall.

Results:

All treatments significantly reduced blood pressure. In the DOCA rats the p-myosin phosphatase target protein-1 (MYPT1)/t-MYPT1 ratio, index of ROCK activation was higher by 2.8 fold (p < 0.05) compared with control rats. All treatments reduced ROCK activation in the aortic wall to control levels (p < 0.05). Besides, significantly increased protein levels of transforming growth factor β1 (TGF-β1), gene expression of TGF-β1, connective tissue growth factor (CTGF), p22 phox and gp91 phox subunits of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, as well as increased media thickness and aortic media area/lumen area (AM/LA) in the untreated hypertensive rats were significantly reduced (p < 0.05) to control levels by all treatments. Similar effects were observed using both diuretics alone or in combination with FAS.

Conclusions:

In the aortic wall, both HCTZ and spiro in antihypertensive doses reduce ROCK activation, subsequent expression of genes that promote vascular remodeling and hypertrophy in this experimental model of hypertension. These effects could explain some of their clinical benefits in hypertensive patients.

Keywords Deoxycorticosterone acetate, Diuretics, Fasudil, Hydrochlorothiazide, Hypertension, Remodeling, Rho-kinase, Spironolactone