Hydrochlorothiazide Reduces Cardiac Hypertrophy, Fibrosis and Rho-Kinase Activation in DOCA-Salt Induced Hypertension

- Mondaca-Ruff D.[a],
- Araos P.[a, b],
- Yañez C.E.[a],
- Novoa U.F.[c],
- Mora I.G.[a],
- Ocaranza M.P.[a, d, e]
- Jalil J.E.[a, e]

Abstract

Background: Thiazides are one of the most common antihypertensive drugs used for hypertension treatment and hydrochlorothiazide (HCTZ) is the most frequently used diuretic for hypertension treatment. The Rho/Rho-kinase (ROCK) path plays a key function in cardiovascular remodeling. We hypothesized that in preclinical hypertension HCTZ reduces myocardial ROCK activation and consequent myocardial remodeling. Methods: The preclinical model of deoxycorticosterone (DOCA)-salt hypertension was used (Sprague–Dawley male rats). After 3 weeks, in 3 different groups: HCTZ, the ROCK inhibitor fasudil or spironolactone was added (3 weeks). After 6 weeks myocardial hypertrophy and fibrosis, cardiac levels of profibrotic proteins, mRNA levels (RT PCR) of pro remodeling and pro oxidative molecules and ROCK activity were determined. Results: Blood pressure, myocardial hypertrophy and fibrosis were reduced significantly by HCTZ, fasudil and spironolactone. In the heart, increased levels of the pro-fibrotic proteins Col-I, Col-III and TGF-β1 and gene expression of pro-remodeling molecules TGF-β1, CTGF, MCP-1 and PAI-1 and the pro-oxidative molecules gp91phox and p22phox were significantly reduced by HCTZ, fasudil and spironolactone. ROCK activity in the myocardium was increased by 54% ($P < 0.05$) as related to the sham group and HCTZ, spironolactone and fasudil, reduced ROCK activation to control levels. Conclusions: HCTZ reduced pathologic LVH by controlling blood pressure, hypertrophy and myocardial fibrosis and by decreasing myocardial ROCK activation, expression of pro remodeling, pro fibrotic and pro oxidative genes. In hypertension, the observed effects of HCTZ on the myocardium might explain preventive outcomes of thiazides in hypertension, specifically on LVH regression and incident heart failure. © The Author(s) 2021.

Author keywords

cardiac remodeling; hydrochlorothiazide; hypertension; hypertrophy; Rho-kinase