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Ion channel TRPM4 modulates RV remodeling under right ventricular pressure load in rat

Uhl S. (1,2), Frede W. (1,2), Medert R. (2), Freichel M. (2), Gorenflo M. (1)
Department Pediatric and Congenital Cardiology, University Medical Center, Heidelberg, Germany (1); Institute of Pharmacology, University Medical Center, Heidelberg, Germany (2)

Objectives: The survival of children with congenital heart defects including increased right ventricular pressure load (i.e. Tetralogy of Fallot, TOF) or pulmonary arterial hypertension (PAH) is dependent on the function of the right ventricle (RV). RV remodeling under pressure load has several adaptive and maladaptive effects with progressive transition from compensated status to heart failure. Transient receptor potential melastatin 4 (TRPM4) forms calcium-activated nonselective cation channels expressed in myocardium of human, rat and mouse, which was shown to modulate left ventricular hypertrophy in mice. Aim of this study was to identify the cardiac role of TRPM4 regarding right ventricle in healthy rats and under Monocrotaline (MCT)-induced pressure load.
Methods: We performed experiments with untreated adult rats and under MCT-induced pressure load. RV function was characterized by echocardiographic measurements and contractility measurements of isolated papillary muscles. Hypertrophy was investigated by echocardiography and by organ weight measurements. Expression of TRPM4 in human and rat RV was detected by western blot. Brain natriuretic peptide (BNP) level was evaluated in rat by enzyme-linked immune assay.
Results: TRPM4 was detected in RV of a child with TOF and in rat. In healthy rats, no difference was seen between wild type (WT) and TRPM4-deficient (TRPM4−/−) rats concerning cardiac function or RV diameter. In rats with MCT-induced RV pressure load (42 days after MCT-injection) TRPM4 expression was reduced by 67% (TRPM4/Calnexin, p 0.002). Both genotypes showed increased RV hypertrophy and subsequently improved basal contractility in isolated papillary muscles ([mN±SEM]: WT untreated 10.1±0.3, treated 13.8±1.0, p0.04; TRPM4−/− untreated 10.0±0.5, treated 16.2±1.4, p<0.001), but TRPM4−/− rats showed significantly increased hypertrophy in comparison to WT (echocardiography: RVAWd [mm] TRPM4−/− 0.89±0.06, WT 0.63±0.05, p0.002; RV weight/ tibia length [mg/mm]: TRPM4−/− 11.6±0.5; WT 8.6±0.7, p<0.001). Cardiac contractility (echocardiography RVFAC [%]: TRPM4−/− 33±2, WT 37±1; papillary muscle contractility after application of 100 µm Isoprenaline [mN]: WT 19.3±1.5, TRPM4−/− 20.3±1.9) as well as survival rate and BNP level were comparable in TRPM4−/− and WT rats.
Conclusion: TRPM4 modulates right ventricular pressure-load-mediated hypertrophy in rats representing a potential candidate for pharmacological approach of right ventricular remodeling.