

Deletion Of Repressor Activator Protein 1 Modulates Vascular Function In Mouse Aorta

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Introduction. Repressor activator protein 1 (Rap1) is a telomeric protein which resides within the shelterin complex and docks at chromosomal ends. Besides maintaining chromosome integrity, it also participates in metabolic regulation and body-weight homeostasis. Its role, if any, in vascular responsiveness is unknown.

Aims. The present study investigated whether or not Rap1 deletion affects vascular responsiveness.

Methods. Female Rap1 knockout and wild-type littermates on a C57BL/6N background were used in the experiments (Aged 13-15 weeks, n=5-6). All mice were kept on standard chow. The thoracic aortae from the two groups of mice were dissected and rings with or without endothelium were suspended in wire myographs to determine contractions and relaxations to increasing concentrations of phenylephrine (10^{-9} - 10^{-4} mol/L) and acetylcholine (10^{-10} - 10^{-4} mol/L; during contractions to 10^{-6} mol/L phenylephrine), respectively. Contractions were expressed as percentage to the reference response obtained with 60mmol/L potassium solution at the beginning of the experiment. Relaxations were expressed as percentage of the pre-contraction to phenylephrine.

Results. Relaxations to acetylcholine were diminished significantly in Rap1 knockout compared to wild type aortae with endothelium (pEC₅₀: 8.13 ± 0.14 vs 7.61 ± 0.08 , $P < 0.001$). The E_{max} of contractions induced by phenylephrine was increased in Rap1 knockout aortae with endothelium (E_{max}: $72.51\% \pm 2.60$ vs $79.54\% \pm 1.69$, $P < 0.05$). In the absence of endothelium, the contractions to phenylephrine were reduced significantly in Rap1 knockout aortae (pEC₅₀: 6.97 ± 0.13 vs 6.38 ± 0.15 , $P < 0.005$).

Discussion. These results demonstrate that Rap1 modulates vascular responsiveness in the mouse aorta. Deletion of Rap1 appears to result in impaired basal and acetylcholine-stimulated release of nitric oxide.

Differential Effects Of GPR55 On Cardiac Adrenoceptor Subtypes In Mice

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Introduction. Increased cardiac sympathetic activity in heart failure (HF) leads to chronic stimulation and subsequent loss of cardiac β_1 -adrenoceptors (β_1 -ARs) and reduced AR mediated inotropy [1]. We have previously shown reduced contractile reserve following dobutamine administration in GPR55^{-/-} mice [2]

Aims. To identify the AR subtype(s) affected by GPR55 gene deletion and determine their role in the cardiac decompensation.

Methods. Mice (WT and GPR55^{-/-}; 3months old) were anaesthetised with ketamine/xylazine (120mg/kg & 16mg/kg i.p.) and a 1.4-Fr pressure conductance catheter inserted into the left ventricle to measure pressure volume loops (PVL). Responses to dobutamine (10 μ g/kg; $\alpha_1/\beta_1/\beta_2$ -AR agonist; n=9), procaterol (0.02-2 μ g/kg; β_2 -AR agonist; n=7-8), A-61603 (0.2-20 μ g/kg; α_1 -AR agonist; n=9) and dobutamine (1-10 μ g/kg) plus prazosin (α_1 -AR antagonist) and ICI 118,551 (β_2 -AR antagonist, both 1mg/kg i.p; n=9) were assessed in both strains.

Results. GPR55^{-/-} mice exhibited reduced contractile responses to dobutamine alone. GPR55^{-/-} mice exhibited significantly attenuated β_1 -AR mediated (dobutamine in the presence of prazosin/ICI 118,551) pressor (ESP; 4 ± 1 vs. 14 ± 1 mmHg), lusitropic (dP/dt_{min}; -82 ± 174 vs. -1013 ± 175 mmHg/ μ L), and inotropic (dP/dt_{max}; 1354 ± 128 vs. 2047 ± 145 mmHg/ μ L) & ejection fraction (2 ± 1.2 vs. $12 \pm 4\%$) responses compared to WT mice (all $P < 0.05$). In GPR55^{-/-} mice, A-61603, induced significantly greater pressor (ESP; 77 ± 6 vs. 60 ± 2 mmHg), lusitropic (dP/dt_{min}; -3013 ± 312 vs. 205 ± 100 mmHg/ μ L), and inotropic (dP/dt_{max}; 5759 ± 469 vs. 3450 ± 256 mmHg/ μ L) responses compared to WT mice (all $P < 0.05$). Procaterol had minimal effects on cardiac function in either strain..

Discussion. Our findings demonstrate that GPR55 influences adrenoceptor function in the heart and may play a role in the altered adrenoceptor signalling characteristic of heart failure.

- (1) Mohl *et al.* (2011) Cardiovasc Res **91**: 310-319.
- (2) Walsh *et al.* (2014) PLoS One **9**:e108999