Deletion of repressor activator protein 1 modulates vascular function in mouse aorta

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The 1st Joint Scientific Meeting of the Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists (ASCEPT) and the British Pharmacological Society (BPS), The University of Hong Kong, Hong Kong, China, 19-21 May 2015. In Oral Abstracts, p. 40, abstract no. 303

2015

http://hdl.handle.net/10722/214271

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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 β₁-adrenoceptors (β₁-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-/-; 3 months 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 (10⁻⁹-10⁻⁶ mol/L; β₁-AR agonist; n=9), procaterol (0.02-2 μg/kg; β₂-AR agonist; n=7-8), A-61603 (0.2-20 μg/kg; α₁-AR agonist; n=9) and dobutamine (1-10 μg/kg) plus prazosin (α₁-AR antagonist) and ICI 118,551 (β₂-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 β₁-AR mediated (dobutamine in the presence of prazosin/ICI 118,551) pressor (pEC50: 8.13±0.14 vs 7.61±0.08, P<0.001). The E₅₀ of contractions induced by phenylephrine was increased in Rap1 knockout aortae with endothelium (E₅₀: 72.51±2.60 vs 79.54±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. 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.