Prostaglandin production by COX-1 and COX-2-deficient mouse hearts

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Introduction It is widely held that COX-2 is the primary source of the protective metabolite prostacyclin (PGI2), in the cardiovascular system because selective COX-2 and non-selective COX-1/COX-2 inhibitors lower urinary levels of PGI2 metabolites to the same degree (McAdam et al. PNAS. 1999). Despite this, in healthy endothelial cells, and many other tissues, COX-2 protein is rare in comparison to COX-1. We sought to clarify the role of COX-1 and COX-2 in prostaglandin release in endocardium and whole mouse heart by comparing COX activity in wild type mice and those deficient in each COX isoform.

Methods PGI2 production was measured in intact pieces of free left ventricular wall (~10mg), homogenates of whole hearts, or the interior of ex vivo cannulated left ventricles. All were freshly isolated from wild type (WT), COX-1−/− and COX-2−/− mice. Ventricle wall pieces and cannulated hearts were allowed to equilibrate for 60mins in DMEM before replacement of the media and incubation for a further 30mins. PGI2 accumulation was then measured as its stable metabolite, 6-keto-PGF1α. Separate hearts were homogenised and then incubated for 20min before determination of the PGE2 content of the supernatant. Data were analysed by 1-way ANOVA with Dunnett’s post-hoc test.

Results All preparations of hearts from WT mice yielded detectable levels of the prostaglandins measured. In incubations of intact pieces of left ventricular wall (n=6) 6-keto-PGF1α accumulation was not altered by COX-2-deficiency (WT: 3.56±0.80ng/ml; COX-2: 4.84±0.71ng/ml; p>0.05) but was almost abolished by COX-1-deficiency (0.19±0.02ng/ml; p<0.01). In perfused left ventricle preparations (n=6) 6-keto-PGF1α accumulation was also similar between WT (1.71±0.40ng/ml) and COX-2−/− mouse hearts (1.30±0.31ng/ml; p>0.05), but significantly reduced in those from COX-1−/− mice (0.03±0.01ng/ml; p<0.01) mice. Similarly, PGE2 release by whole heart homogenates (n=4) was reduced in COX-1−/− (WT: 0.69±0.18ng/ml; COX-1: 0.14±0.07ng/ml; p<0.05) but not COX-2−/− mice (1.13±0.15ng/ml; p>0.05).

Conclusion The primary COX isoform responsible for PGI2 and PGE2 production in whole mouse heart and within the left ventricle is COX-1 with COX-2 providing little contribution in these healthy tissues.