Effect of COX-1 or COX-2 gene deletion on prostacyclin formation in the heart

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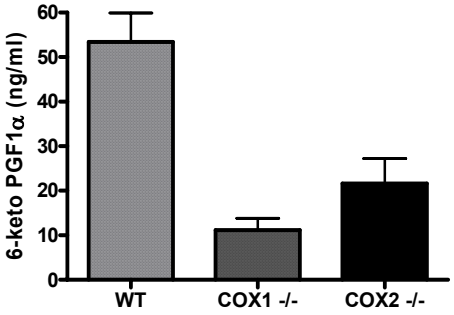
Background: Prostacyclin is an anti-thrombotic hormone released by a range of cell types, most notably endothelial cells. Prostacyclin is formed by the concerted action of cyclo-oxygenase (COX) and prostacyclin synthase. COX exists in two isoforms; COX-1, generally expressed constitutively, and COX-2, expressed at sites of inflammation and at discrete sites constitutively. Analysis of controlled trials and real world use indicate the use of COX-2 selective inhibitors is associated with an increased risk of thrombotic events (1). However, in almost all vascular tissue from healthy mammals COX-1 predominates greatly over COX-2 (2). Interestingly, Wang et al recently demonstrated that cardiomyocyte selective deletion of COX-2 altered cardiac rhythm and function (3). Here we have investigated the relative roles of COX-1 and COX-2 in the production of prostacyclin by mouse hearts.

Methods: Whole hearts from C57Bl6 wild-type (WT), COX-1 deficient (COX-$1^{-/-}$) and COX-2 deficient (COX-$2^{-/-}$) mice were homogenized in a ratio of 1:5 weight:volume in 50mM Tris buffer (pH 7.4) and incubated for 20 min at 37°C. COX activity was then stopped by addition of 1mM diclofenac. Incubates were then centrifuged and supernatants collected for measurement by radioimmunoassay of the stable prostacyclin metabolite, 6-keto$PGF_{1\alpha}$, as a marker of COX activity.

Results: COX activity was greatest in hearts of WT mice, and was significantly different (one way ANOVA, Dunnett's post-test) to that in hearts from both COX-$1^{-/-}$ ($p<0.01$) and COX-$2^{-/-}$ ($p<0.05$) animals (Figure 1, n=8 for all).

Figure 1. COX activity in the Heart



Discussion: These data suggest that both COX-1 and COX-2 support prostacyclin production healthy mouse hearts.

References:

1.Bresalier *et al*. (2005) *N Engl J Med* 352(11)**:**1092-102.
2.Mitchell *et al*. (2006) *Nat Rev Drug Discov* 5(1)**:**75-86.
3. Wang *et al*. (2009) *Proc Natl Acad Sci U S A* 106(18)**:**7548-52.