Nitric oxide-dependent vasodilation is compromised in isolated pulmonary arteries from COX knockout mice

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Cyclooxygenase (COX) has two isoforms and is essential for prostanoid synthesis. COX–1 is constitutive whilst COX–2 is induced in inflammation. Two COX products, prostacyclin (PGI\textsubscript{2}) and thromboxane (TxA\textsubscript{2}), regulate vessel tone; PGI\textsubscript{2} mediates vasodilation and platelet inhibition, and TxA\textsubscript{2} opposes this. PGI\textsubscript{2} therapies are used in pulmonary arterial hypertension (PAH). Endogenous TxA\textsubscript{2}/PGI\textsubscript{2} has been linked to PAH in animal models, but the mechanism and isoform involved is debated. We hypothesized that pulmonary artery (PA) from COX–1\textsuperscript{−−} and COX–2\textsuperscript{−−} mice would have altered vasodilatory function compared with wild-type (WT; C57Bl6) mice. Vasomotor responses to contractile and relaxant agents were measured by myography. PA from all mice responded similarly to contraction by high potassium or the TxA\textsubscript{2} mimetic, U46619. Relaxation to PGI\textsubscript{2} receptor or PPAR\textsubscript{β/δ} agonists was also similar in all PAs. However, COX–1\textsuperscript{−−} and, to a lesser extent, COX–2\textsuperscript{−−} PA had impaired vasodilation to acetylcholine (ACh), which stimulates endothelial nitric oxide (NO) release, and COX–1\textsuperscript{−−} PA also dilated less to sodium nitroprusside (SNP); an NO donor that works on smooth muscle (Fig 1). These data indicate an interaction between COX and NO sensing pathways in pulmonary vessels, and have implications for our understanding of PAH. Research funded by the Wellcome Trust. WRW receives a NHLI foundation studentship.

![Figure 1 ACh (A) and SNP (B) vasodilation in U46619 contracted PA segments from WT (A n=5; B n=3), COX–1\textsuperscript{−−} (A n=4; B n=5) and COX–2\textsuperscript{−−} (A n=6; B n=5) mice. Data are mean ± SEM. Statistical significance was determined by two-way ANOVA with Bonferroni’s post-test (* p < 0.05). Best-fit curves represent non-linear regression analysis.](image-url)