

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 (PGI₂) and thromboxane (TxA₂), regulate vessel tone; PGI₂ mediates vasodilation and platelet inhibition, and TxA₂ opposes this. PGI₂ therapies are used in pulmonary arterial hypertension (PAH). Endogenous TxA₂/PGI₂ 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^{-/-} and COX-2^{-/-} 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 TxA₂ mimetic, U46619. Relaxation to PGI₂ receptor or PPARβ/δ agonists was also similar in all PAs. However, COX-1^{-/-} and, to a lesser extent, COX-2^{-/-} PA had impaired vasodilation to acetylcholine (ACh), which stimulates endothelial nitric oxide (NO) release, and COX-1^{-/-} 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.*

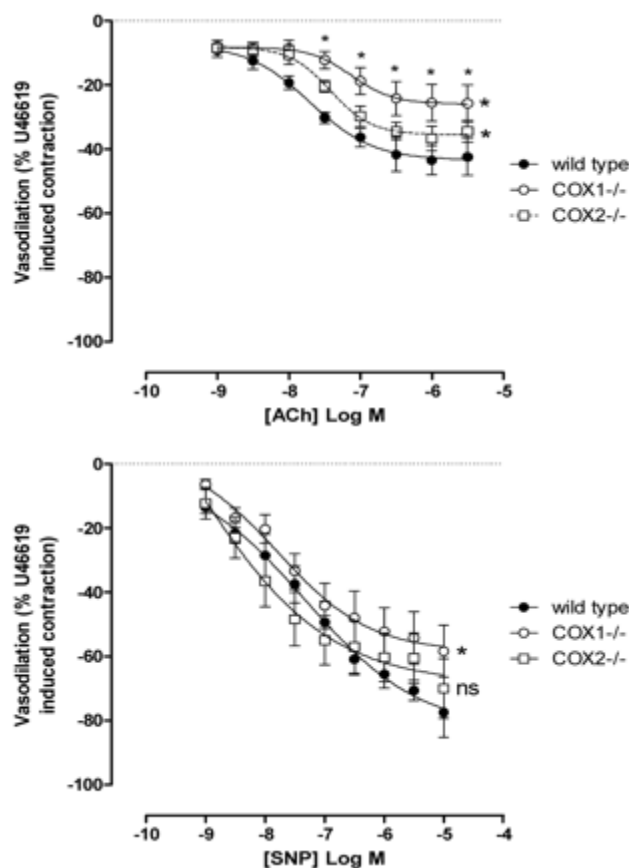


Figure 1 ACh (A) and SNP (B) vasodilation in U46619 contracted PA segments from WT (A n=5; B n=3), COX-1^{-/-} (A n=4; B n=5) and COX-2^{-/-} (A n=6; B n=5) mice. Data are mean ± SEM. Statistical significance was determined by two-way ANOVA with Bonferroni's post-test (* p < 0.05). Best-fit curves represent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