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| **FPR agonist Cmpd17b induces dilation and opposes constriction of pulmonary arteries ex vivo in a preclinical model of pulmonary hypertension** |
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| **Introduction/Aim:** Current treatments for pulmonary hypertension (PH) consist of vasodilators that do not effectively target the vascular remodelling that drives the disease. The small molecule formyl peptide receptor (FPR) agonist Cmpd17b dilates arteries and inhibits pro-inflammatory cytokine release from naïve mouse precision-cut lung slices (PCLS), and attenuates fibrosis in models of murine cardiac disease and diabetes, offering a potential dual-action therapeutic benefit. Here, the PCLS preparation is utilised to assess vasodilator effects of Cmpd17b in lungs from mice with Sugen/hypoxia-induced pulmonary hypertension *ex vivo*. **Methods:** PH was induced in 9-week-old male C57BL/6J mice via weekly s.c. injections with 20mg/kg Sugen 5416, in addition to 4 weeks of hypoxia (10% O2) exposure (SuHx). Normoxia controls (NmOx) were kept at 21% O2 and administered a vehicle. PCLS were sliced at 200μm thickness. Concentration-response (C-R) curves to dilators were performed in intrapulmonary arteries (<150μm diameter), pre-contracted with 3μM 5HT. PCLS were also pre-treated with either 3μM Cmpd17b or vehicle for 10 minutes, before C-R curves to 5HT were performed. Images were captured at the end of each drug addition period and lumen area was measured to calculate level of artery contraction.

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|  | **Dilation to Cmpd17b (n=6)** | **Dilation to Sildenafil (n=4)** | **Contraction to 5-HT (n=6)** |
|  | **Fitted Max (%)** | **pEC50** | **Fitted Max (%)** | **pEC50** | **Fitted Max (%)** | **pEC50** |
| **NmOx** | 90 ± 8  | 6.1 ± 0.3 | 98 ± 2 | 4.5 ± 0.2 | 13 ± 2 | 6.5 ± 0.2 |
| **SuHx** | 98 ± 1 | 7.8 ± 0.8 | 98 ± 2 | 5.0 ± 0.5 | 16 ± 7 | 6.0 ± 0.2 |

**Results:** Cmpd17b and sildenafil elicited complete vasodilation in both NmOx and SuHx PCLS, with similar efficacy and potency between groups. SuHx did not alter 5HT-mediated contraction. In the presence of 3μM Cmpd17b, the concentration-response to serotonin was completely abolished in both SuHx and NmOx mice, hence efficacy and potency could not be calculated. Statistics reported as mean ± SEM.**Conclusion:** Cmpd17b-mediated both vasodilation and inhibition of contraction in PCLS from NmOx and SuHx mice, with comparable potency and efficacy to sildenafil. These results support the development of FPR-based therapy against excessive pulmonary artery contraction and vascular remodelling in PH. Future research should explore chronic anti-inflammatory and anti-remodelling effects of Cmpd17b and other FPR agonists to support clinical translation for PH therapies.**Grant Support:** RTP Stipend NHMRC Funding**Declaration of Interest:**The authors declare no conflict of interest. |