**Vasodilation induced by PPARβ/δ agonists is greater at higher pressures than lower pressures in rat pulmonary arteries**

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Pulmonary arterial hypertension (PAH) is defined as a mean pulmonary artery pressure of greater than 25mmHg at rest, and advanced PAH as 50-60mmHg. Current therapies include prostacyclin (IP) receptor agonists (e.g. iloprost and beraprost), phosphodiesterate type 5 inhibitors (e.g. sildenafil), and endothelin receptor antagonists (e.g. bosentan). However, none of these drugs cure the condition, and new therapeutic approaches are currently under investigation. We and others have recently shown that the PPARβ/δ agonist GW0742 induces vasodilatation of mouse and rat pulmonary arteries (Harrington et al 2010; Li et al 2012). However, the effects of pressure on the vasodilatory effects of PPARβ/δ agonists have not been tested. Here we investigated vasodilation induced by PPARβ/δ agonists in rat pulmonary arteries at different resting pressures in line with those seen in patients with PAH.

Male Sprague Dawley rats (250g) were killed by $CO_2$, and segments of the main intra-pulmonary artery dissected out and loaded onto isometric wire myographs. Arteries were normalised to an effective pressure of 4kPa or 7.5kPa (equivalent to 30mmHg and 56mmHg respectively). To test vasodilatory responses, arteries were pre-contracted with an $EC_{80}$ U46619 ($3x10^{-8}$M) followed by increasing concentrations of GW0742 ($10^{-6}$ to $3x10^{-5}$M), GW501516 ($10^{-6}$ to $3x10^{-5}$M), or the IP agonists iloprost and beraprost ($10^{-9}$ to $10^{-6}$M). The drug vehicle, DMSO (maximum bath concentration of 0.333%) was added to control tissues.

Table 1 Vasodilation to PPARβ/δ and IP agonists; * indicates significance by two way ANOVA, $p<0.01$.

| | 4kPa | 7.5kPa | 4kPa | 7.5kPa | |
|---|---|---|---|---|---|
| | $EC_{50}$ | $EC_{50}$ | max dilation | max dilation | n= |
| GW0742 | $9.7x10^{-6}$M | $7.0x10^{-6}$M | -76.2±9.3%* | -98.6±7.1%* | 4 |
| GW501516 | $9.0x10^{-6}$M | $5.2x10^{-6}$M | -81.2±8.0%* | -101.3±2.5%* | 3 |
| iloprost | $2.7x10^{-6}$M | $2.24x10^{-6}$M | -54.5±3.7% | 59.9±7.9% | 4 |
| beraprost | $1.6x10^{-5}$M | $8.03x10^{-6}$M | -28.3±9.7% | 33.8±14.1% | 4 |
| vehicle control | | | -5.27±7.7% | -11.83±6.1% | 8 |

Both PPARβ/δ agonists induced greater vasodilatory responses than the IP agonists. The maximum dilation induced by PPARβ/δ agonists was greater in arteries at 7.5kPa than in those at 4kPa (Table 1), whereas there were no pressure related differences in the dilations induced by the IP agonists.

These data show that the PPARβ/δ agonists induce greater dilations of rat pulmonary arteries than IP agonists, and that their effects are greater at pressures in line with advanced pulmonary artery hypertension. These data support the idea PPARβ/δ agonists could have therapeutic utility in the treatment of pulmonary arterial hypertension.

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