PPARbeta/delta agonists GW0742 and GW501516 induce vasodilatation of human pulmonary artery

LS Harrington, W Wright, T Gatheral, TD Warner, JA Mitchell

Pulmonary arterial hypertension is defined as a mean pulmonary artery pressure of greater than 25mmHg at rest. Current therapies modulate or mimic endogenous hormones released by endothelial cells that regulate vascular tone. These include prostacyclin (IP) receptor agonists (e.g. treprostinil sodium), 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 PPARbeta/delta agonist GW0742 induces vasodilatation of mouse and rat pulmonary arteries (Harrington et al 2010; Li et al 2012). However, the effect of PPARbeta/delta agonists on human pulmonary vessels has not been tested. Here we investigated the effects of two PPARbeta/delta agonists on human pulmonary artery tone in vitro using resting pressures in line with those seen in patients with pulmonary hypertension.

Human pulmonary arteries dissected from human lung samples were loaded on to Mulvany myographs and normalised to an effective pressure of 4kPa (equivalent to 30mmHg). Following equilibration, arteries were exposed to $3x10^{-8}$M U46619 followed by increasing concentrations of GW0742 (10^{-6} to $3x10^{-5}$M), GW501516 (10^{-6} to $3x10^{-5}$M), or the mixed IP/PPARbeta/delta agonist treprostinil sodium (10^{-9} to 10^{-6}M). The drug vehicle, DMSO plus bovine serum albumin (BSA; maximum bath concentration of 0.033% for both) was added to control tissues.

All agonists tested induced reductions in tone induced by U46619 with a range of potencies: GW0742, EC_{50} $1.4x10^{-5}$M; max response, change in induced tone, -71±9%: GW501516, EC_{50} $9.6x10^{-6}$M; max response -76±7%: treprostinil sodium, EC_{50} $1.74x10^{-8}$; max response -67±9%: n=3 for all. Addition of vehicle had minimal effect on vascular tone (max change in induced tone, -9±7%).

Two chemically distinct PPARbeta/delta agonists induced vasodilatation in human pulmonary artery with similar efficacies to that of treprostinil sodium. These results support the idea that PPARbeta/delta agonists could have therapeutic utility in the treatment of pulmonary arterial hypertension.

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