

Selective inhibition of the PI3K isoform p110alpha using BYL719 protects against tyrosine kinase-mediated processes in PASMCs and reduces experimental pulmonary hypertension in mice and rats

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Rationale: Pulmonary arterial hypertension (PAH) is a vascular disease characterized by chronic increases in pulmonary vascular resistance (PVR), pulmonary arterial pressure (PAP), and right ventricular (RV) hypertrophy. Increased activation of receptor tyrosine kinase (RTK) -mediated signaling pathways leads to increased proliferation and migration of pulmonary smooth vascular muscle cells (PASMCs) which promote vascular remodeling processes. We identified the catalytic subunit p110alpha of phosphatidylinositol-3-kinase as a key enzyme for these processes and showed that both genetic ablation of p110alpha in SMCs and pharmacological inhibition can prevent experimental PH. Here, the effects of the orally bioavailable p110alpha selective PI3K inhibitor BYL719 on the RTK-mediated proliferation and chemotaxis of PASMCs, as well as the effects in the hypoxia-induced mouse and in the Sugen / hypoxia (SuHx) -induced rat model of PH were investigated.

Methods: Human and murine PASMCs were pretreated with different concentrations of BYL719 and stimulated with a mixture of growth factors (PDGF [30ng/ml], EGF [0,5ng/ml], bFGF [2ng/ml], insulin [0,5ng/ml], and FBS [5%]). Proliferation was investigated using a BrdU incorporation ELISA assay (Roche). Chemotaxis was quantified using modified Boyden chambers.

Male BL/6 mice were subjected to hypoxia (10% O₂) for 21 days. Treatment with BYL719 (or vehicle) was carried out via daily gavage of 50mg/kg bodyweight.

In addition, a therapeutic approach was investigated using male Sprague Dawley rats in the SuHx model, which were treated with BYL719 (20 mg / kg body weight) or vehicle for 2 weeks after a three-week hypoxia phase. The RV pressure (RVSP) was measured using a Millar® or liquid-filled catheter. The RV hypertrophy is shown as the quotient of the weights of the RV to the LV + septum (RV / (LV + S)).

Results: Growth factor-induced proliferation and chemotaxis of the PASMCs were significantly and concentration-dependently inhibited by BYL719. The exposure to hypoxia led to an increase of the RVSP (24.5±0.95 to 35.2±1.28 mmHg) and the development of right ventricular hypertrophy (RV / LV + S 0.24±0.01 to 0.37±0.073), which was significantly reduced in the BYL719 treated group (RVSP 31.4±0.53 mmHg; RV / LV + S 0.31±0.01) (p<0.05). In addition, SuHx led to a robust increase of the RVSP (129.2±5.4 mmHg) and pronounced RV hypertrophy (RV / (LV + S): 0.86±0.04), which were significantly reduced by the therapeutic BYL719 treatment (102.0±6.1 mmHg or 0.64±0.03).

Conclusion: These results show that inhibition of p110alpha using the BYL719 reduced growth factor-mediated pathological processes in PASMCs in vitro, as well as hypoxia-induced (mouse) and already established SuHx-induced PH (rat). Thus, the inhibition of p110a using BYL719 represents a promising approach for the treatment of PAH.