The KCNQ (Kv7) potassium channel activator flupirtine attenuates elevated right ventricular pressure in 2 models of pulmonary hypertension

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Pulmonary arterial hypertension (PAH) is characterised by elevated PA pressure, pulmonary vascular remodelling and right heart failure and is associated with an extremely poor prognosis. Mice over expressing the 5-hydroxytryptamine transporter (5-HTT) (5-HTT+ mice) develop spontaneous PAH and are more susceptible to hypoxia-induced PAH (MacLean et al., 2004). Down regulation of voltage gated potassium channels (Kv) occurs in chronic hypoxia-induced PAH (Osipenko et al., 1998). Recent evidence suggests that KCNQ potassium (Kv7) channels play a functional role in pulmonary artery smooth muscle and KCNQ channel blockers are potent pulmonary arterial vasoconstrictors (Joshi et al., 2006).

Here we investigate the effects of the KCNQ K+ channel activator, flupirtine, in chronic hypoxia induced PAH in wild-type (WT) mice and in mice that over-express the 5-HTT (5-HTT+). Female mice (C57BL/6 x CBA, WT and 5-HTT+, 5-6 months) were dosed daily for 16 days with vehicle (1% carboxymethylcellulose) or flupirtine at 30mg/kg by oral gavage. On day 3 of the dosing regimen, some of the WT mice were subjected to 14 days of hypobaric hypoxia (10% O2). Under isoflurane anaesthesia, right ventricular pressure (RVP) was obtained by transdiaphragmatic right ventricular cannulation. Right ventricular (RV) / left ventricle+septum (LV+S) ratio was determined as described previously (MacLean et al., 2004). Statistical comparisons were made by one-way ANOVA with a Neuman-Keuls multiple comparison test. Data are expressed as mean ± s.e.mean.

Hypoxia induced an increase in mean RVP (mRVP) (21.6 ± 2.0 mmHg vs normoxic: 13.4 ± 0.9mmHg, n=8, P<0.01) and right ventricular hypertrophy (RV/LV+S ratio = 0.293 ± 0.010 vs normoxia: 0.216 ± 0.005, n=6-7; P<0.001) in WT mice. Treatment with flupirtine attenuated the elevation in both mRVP (14.7 ± 0.7mmHg; n=9; P<0.01 versus hypoxia) and right ventricular hypertrophy (RV/LV+S ratio = 0.241 ± 0.02, n=8; P<0.05 vs hypoxia). mRVP was markedly elevated in normoxic 5-HTT+ mice (29.9 ± 2.7, n=6; P<0.001 versus WT) and treatment with flupirtine attenuated this response (mRVP = 17.1 ± 1.9, n=6; P<0.001). Right ventricular hypertrophy was observed in the 5-HTT+ mice (RV/LV+S ratio = 0.251 ± 0.007, n=6; P<0.01 versus WT) and this was slightly attenuated by flupirtine treatment (RV/LV+S ratio = 0.226 ± 0.004, n=6; P<0.05 versus 5-HTT+).

The Kv7 activator flupirtine markedly attenuates the elevated right ventricular pressure observed in chronic hypoxic mice and in mice over expressing the 5-HTT. This, and other drugs that activate Kv7 channels may be of benefit in the treatment of PAH.

