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Title: TRAM-34 ameliorates hypoxia-induced pulmonary arterial hypertension in rats

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Body: Objectives: Pulmonary arterial hypertension(PAH) is a life-threatening disease characterized by remodelling of pulmonary vasculature. This study aimed to investigate the therapeutic effects of TRAM-34, a selective blocker of the intermediate-conductance Ca^{2+}-activated K^+ channel (Kca3.1), on hypoxia-induced PAH in rats. Methods: Pulmonary artery smooth muscle cells(PASMCs) were used to measure Kca3.1 mRNA and protein expression in response to normoxia(21%O_2) and hypoxia(2%O_2) for 24 hours. Flow cytometry was performed after administering TRAM-34.In vivo experiment, TRAM-34(i.p.-injection) was administered daily to Wistar rats over a period of 3 weeks starting on the day of hypoxia(10%O_2, 23h/d). Mean pulmonary artery pressure(mPAP) and right ventricle hypertrophy index(RVHI)were assessed. Tissue samples were collected for histological analysis. Result: Quantitative real-time PCR and western blot showed that Kca3.1 mRNA and protein expression were increased in PASMCs after hypoxia.The difference was significant($p<0.05$) respectively.Hypoxia reduced the proportion of PASMCs in the G0/G1 phase(65%vs 76.2%). TRAM-34 inhibited PASMCs proliferation by G0/G1 arrest. In the hypoxia group,TRAM-34 intervention reduced the mPAP(20±1mmHg vs 17±1mmHg,$p<0.05$) and RVHI(41.5%±3.8% vs 33.6±3.2%,$p<0.05$).The ratio of wall area and lumen area attenuated after TRAM-34 administration.The difference was significant($p<0.05$) compared with the normoxia group. Conclusion: TRAM-34 attenuates hypoxia induced PASMCs proliferation, and reduces pulmonary artery remodelling in vivo. These findings raise the possibility that blocking the Kca3.1 channel will attenuate hypoxia-induced PAH, and thus TRAM-34 offer a new approach to PAH therapy.