The ppargamma agonist pioglitazone reverses pulmonary arterial hypertension (PAH) and prevents right heart failure through fatty acid oxidation (fao)

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Background. Pulmonary arterial hypertension (PAH) has a mortality rate of 25-60% within 5 years after diagnosis, with right ventricular (RV) failure being the leading cause of death.

Purpose. So far, no intervention could fully reverse PAH or even prevent pressure overload heart failure, in the well-established SuHx rat model that closely resembles human disease. We hypothesized that the PPAR? agonist pioglitazone (Pio) reverses angio-obliterative PAH and prevents heart failure in RV pressure overloaded rats.

Methods. We measured ventricular function and PA acceleration time (PAAT) in mice with deletion of PPAR? in cardiomyocytes (cmPPAR? -/-) by MRI and ECHO. In addition, SD rats were divided into 4 groups, injected either with no agent, vehicle (DMSO), or the VEGFR2 inhibitor SU5416: control normoxia (ConNx); control/hypoxia (ConHx, 1x s.c. DMSO, 3wks room air); SU5416/hypoxia (SuHx, SU5416 20mg/kg/dose s.c. x 1, 3wks Hx, 6wks Nx); SU5416/hypoxia treated with Pio (SuHx + Pio, SU5416 s.c. x1, 3wks Hx, 6wks Nx, including 5wks of Pio treatment 20mg/kg/day p.o.). Hemodynamics, RV/LV mass and volumes were assessed by cardiac catheterization, MRI, ECHO, RV/LV+S mass ratio. Mitochondrial integrity and lipid accumulation were assessed by 2D/3D electron microscopy and cardiac MR spectroscopy. RNA expression studies (mRNASeq, single/array miRNA qPCR) were performed on rat RV and LV (N=3/group), and on laser-capture microdissected explanted heart and lung tissue of IPAH HLTx patients or donors (N=7-10). We measured Pio-regulated mitochondrial function (FAO, ATP production) in rat neonatal ventricular cardiomyocytes (NRCM) by Seahorse.

Results. cmPPAR? -/- mice developed biventricular systolic dysfunction vs. controls, in the absence of PAH (PAAT n.s. different). SuHx rats developed severe PAH and overt RV failure vs. ConNx and ConHx. PAH was fully reversed and RV failure prevented by Pio administration (SuHx+Pio): RVSP (91 in SuHx vs. 29 vs. 32 vs. 34 mmHg). EM showed abnormal mitochondrial and T-tubule/SR couplon morphology, and large vacuoles (lipid vacuoles) in SuHx rats. MR spectroscopy unraveled intracellular lipid accumulation in failing RVs, which was not present in controls or SuHx+Pio rats. Consistently, Pio induced FAO and ATP production in cultured NRCM. RNASeq revealed 104 genes with differential expression in SuHx RVs, and 67 genes to be Pio-regulated. Several miRNAs were altered in SuHx RVs and regulated by Pio. Accordingly, we found altered miRNA expression in human plexiform lesions vs. small pulmonary arteries, and RVs of HLTx IPAH patients vs.
Conclusions. PPAR? deficiency in cardiomyocytes leads to biventricular systolic dysfunction in mice. PPAR? activation by pioglitazone is the first intervention that fully reverses angio-obliterative PAH/PVD and prevents heart failure in a robust animal model of PAH/RV failure, and as such is an attractive treatment option for clinical PAH that regulates lipid metabolism.