RP5063 Prevents Monocrotaline-Induced Pulmonary Arterial Hypertension in Rats

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Poster #A7286

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive, fatal disease characterized by increase in pulmonary vascular resistance that leads to right ventricular failure.[1] Changes in serotonin synthesis, receptor activation and uptake via the serotonin transporter (SERT) have been reported in experimental and clinical PAH. Synthesis of serotonin can occur in pulmonary artery endothelial cells, which activates vascular smooth muscle (VSM), serotonin (5-HT_{2A}, 5-HT_{2B}) receptors and SERT to cause constriction and proliferation of pulmonary VSM cells.[2,3]

The present study aimed at determining RP5063 efficacy for PAH in the monocrotaline (MCT) induced PAH rat model. RP5063 is a novel multimodal modulator of dopamine and serotonin receptors with high binding affinity for 5-HT_{2B} (0.19nM), 5-HT_{2A} (2.5nM), 5-HT_{1A} (1.5nM) and 5-HT_{7} (2.7nM), and moderate affinity for SERT (107nM).

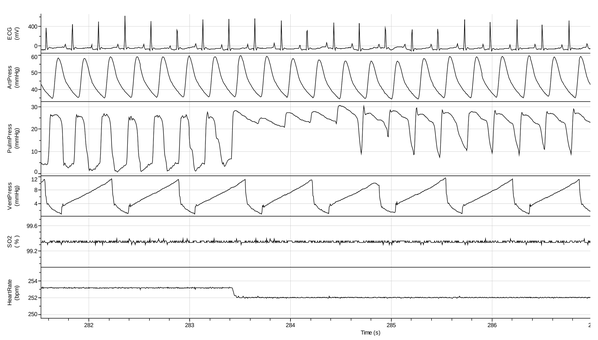
METHODS

Induction of pulmonary arterial hypertension:
Adult male Sprague-Dawley rats were given a single s.c. injection of 50 mg/kg monocrotaline on Day 0. The animals were pair-housed in cages ventilated with normoxic filtered air. The animals were monitored for 28 days while PAH symptoms progressed. 10 animals per group received either vehicle, 1 mg/kg, 3 mg/kg, or 10 mg/kg RP5063, b.i.d. or 50 mg/kg sildenafil, b.i.d. by oral gavage for 28 days. Functional observations and body weight were monitored and blood samples were taken weekly. The animals had access to food and water *ad libitum* throughout the induction period.

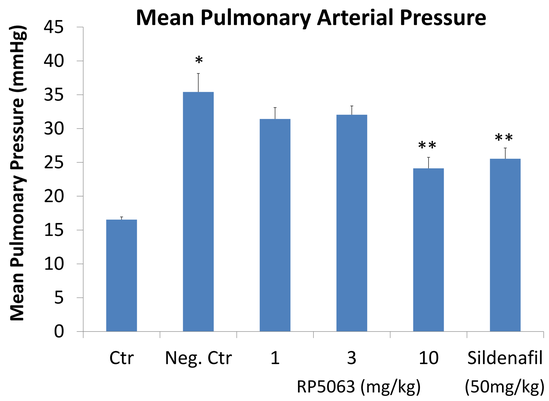
Surgery procedures:
At the end of the treatment period, the rats were anesthetised with a mixture of 2 to 2.5 % isoflurane USP (Abbot Laboratories, Montreal Canada) in 95% O_2 and 5% CO_2, and placed on a heating pad to maintain body temperature. Rats were then tracheotomized to allow mechanical ventilation and monitoring of respiratory pressure. Lead II ECG electrodes were placed on the rats to monitor their depth of anesthesia and record heart rate and arrhythmias. Oxygen saturation was monitored by pulse oximetry. A catheter connected to a transducer was inserted in the left femoral artery to measure the systemic arterial blood pressure. Following a sternotomy, a second catheter connected to a pressure transducer was inserted into the right ventricle for 5 seconds to record the right ventricular pressure. The same catheter was pushed further into the pulmonary artery for pulmonary artery pressure (PAP) recording.

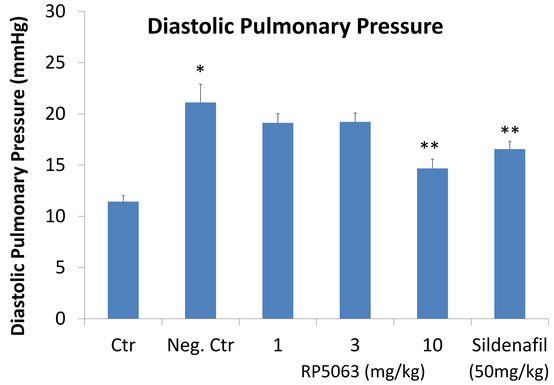
The lungs and heart were withdrawn and fixed in 10% formalin, and stained by H&E for histological examination.

Screen capture of the functional monitoring on surgery day:

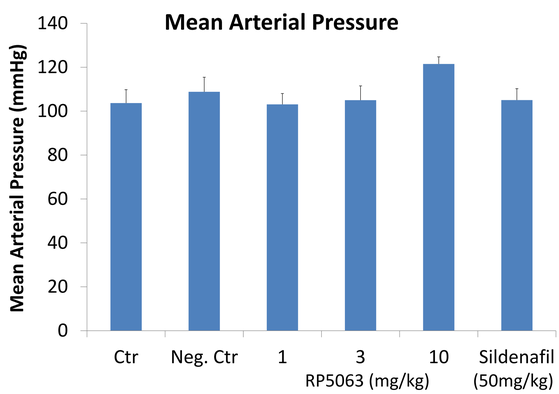


RESULTS

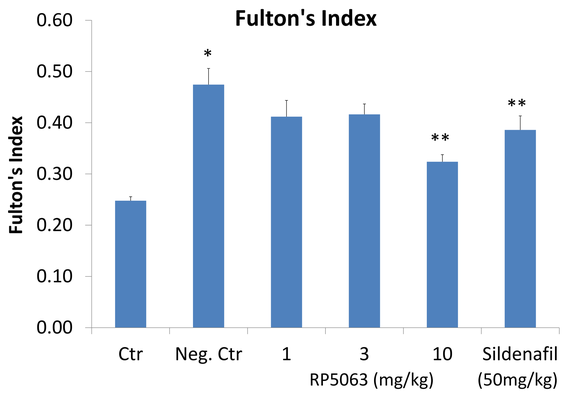




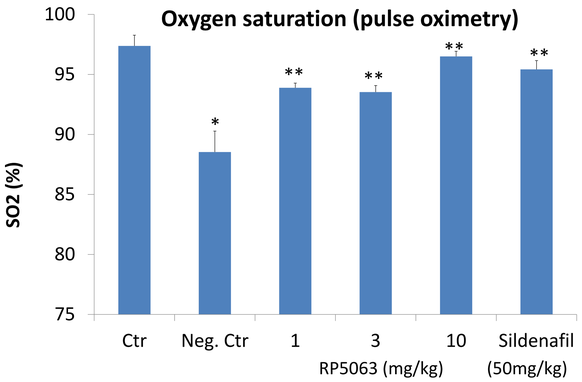
Monocrotaline increased pulmonary diastolic and systolic pressures from 11.4 to 21.1 and 26.7 to 64.0 mmHg, resp. RP5063 (10mg/kg) significantly lowered the pulmonary diastolic and systolic pressures to 14.7 and 43.0 mmHg, respectively.



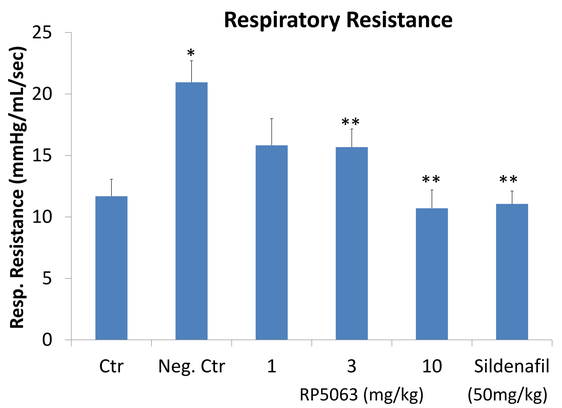
The diastolic and mean arterial pressures remain unchanged in the RP5063 treated animal groups. The systolic arterial pressure was increased 19% in the animals treated 10mg/kg RP5063. The heart rate remained unchanged in the RP5063 treated animals.



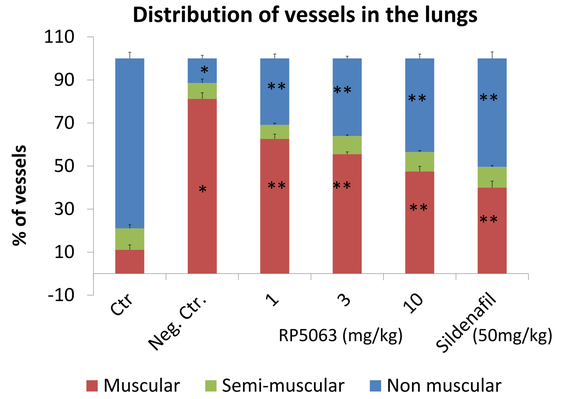
The Fulton's index was statistically lower (32%) in 10mg/kg RP5063 group compared to negative control MCT-only supporting the hypothesis that RP5063 successfully prevented RV hypertrophy associated with PAH.

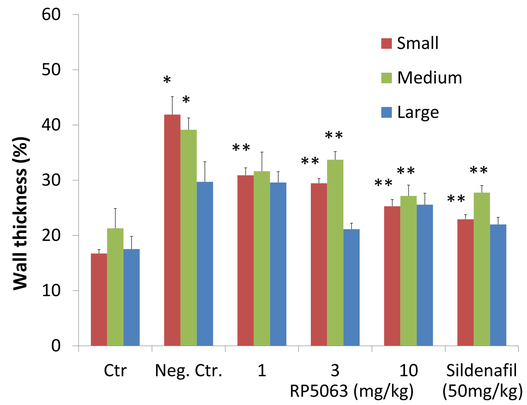


RP5063 (10mg/kg) brought the oxygen saturation inside the range considered normal (95 and 100%).



RP5063 (10mg/kg) lowered respiratory resistance from 20.9 to 10.7 mmHg/mL/sec, suggesting that RP5063 decreased pulmonary edema and fibrosis.





The percentage of muscular vessels was significantly lower in RP5063 treated animals; from 81% in negative control MCT-only treated animals to 62%, 55% and 47% in RP5063 1, 3, and 10mg/kg bid treated animals, respectively. The wall thickness in small and medium lung vessels in RP5063 treated animals was significantly smaller when compared to the negative control MCT-only treated animals.

DISCUSSION / SUMMARY

- Alveolar macrophage infiltrations and oedema/fibrosis observed in the RP5063 treated animals at all three doses were lower than in negative control MCT-only treated animals, suggesting that RP5063 could prevent the onset of lung fibrosis/oedema associated with PAH.
- The gross pathology performed on the surgery day revealed that the liver, spleen, stomach, intestines and lungs of RP5063 treated animals were normal.
- RP5063 also showed similar efficacy results in sugen-hypoxia induced PAH in rats.[4]
- To summarize, combined with the morphometric evidence of limited lung remodeling, these results indicate that RP5063 may provide therapeutic benefit for patients with PAH.

REFERENCES

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