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## **Serotonin 2B receptor potentiates erythropoietin-induced mobilization of endothelial progenitor cells: contribution to hypoxic pulmonary arterial hypertension?**

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**Introduction:** Pulmonary arterial hypertension (PAH) is characterized by increased pulmonary vascular resistance leading to right ventricular failure. Chronic hypoxia increases plasma levels of erythropoietin (Epo), a hormone that has been shown to promote mobilization of endothelial progenitor cells (EPCs). During hypoxia, the 5-HT<sub>2B</sub> receptor-mediated mobilization of EPCs from the bone-marrow contributes to PAH [1]. In the present work, we tested the hypothesis that (i) Epo recapitulates features of hypoxic PAH and (ii) serotonin and Epo interact together in the bone marrow to mobilize EPCs leading to PAH.

**Material and methods:** (i) In wild-type (Htr2B<sup>+/+</sup>) mice, we compared the effects of recombinant human Epo (3 injections of 3500 UI/kg per week, 2 weeks) and hypoxia (2 weeks normobaric 10% FiO<sub>2</sub>), on hemodynamics, pulmonary vascular remodeling, hematological analysis and mobilization of EPCs. (ii) In Htr2B<sup>+/+</sup> and knockout (Htr2B<sup>-/-</sup>) mice, we compared the blood mobilization of EPCs by FACS, after the stimulation of 5-HT<sub>2B</sub> receptors by nordexfenfluramine (1 mg/kg/day, 14 days) and/or Epo stimulation. Erythropoiesis (blood cells count) and pulmonary vascular remodeling were also evaluated.

**Results:** In normoxia, Epo recapitulates all hemodynamic and structural alterations of hypoxia-induced PAH (increase of right ventricular pressure, pulmonary vascular remodeling, increase of red blood cells count and hematocrit). Then, nordexfenfluramine and Epo increase EPCs count 5–10 times in Htr2B<sup>+/+</sup> mice blood. The mobilization of EPCs is potentiated by the 5-HT<sub>2B</sub> and Epo receptors simultaneous stimulation in Htr2B<sup>+/+</sup> mice, whereas it is prevented in Htr2B<sup>-/-</sup> mice blood. Concerning erythropoiesis, Epo treatment induces similar increase of red blood cells count, hematocrit and hemoglobin levels in Htr2B<sup>+/+</sup> and Htr2B<sup>-/-</sup> mice. The analysis of pulmonary vascular remodeling is currently under investigation.

**Discussion/Conclusion:** These data further emphasize the contribution of EPCs mobilization in the mechanisms of PAH, and confirm that serotonin and EPO both trigger EPCs mobilization. A pharmacological synergism between EPO and 5-HT<sub>2B</sub> receptors is suggested and will be investigated. Blockade of serotonin 5-HT<sub>2B</sub> receptors could be a therapeutic target to prevent Epo-induced PAH, without affecting the erythropoiesis response.

### **Reference**

[1] Launay J.M. et al. Serotonin 5-HT<sub>2B</sub> receptors are required for bone-marrow contribution to pulmonary arterial hypertension. *Blood* (2012) 119 1772–1780.