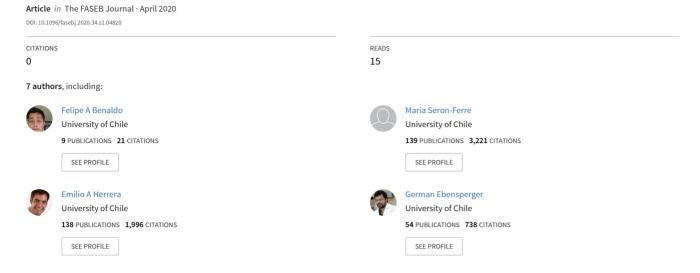
## Cinaciguat Reduces Prolyl Hydroxylase 2 (PHD2) Protein Expression in Chronically Hypoxic and Pulmonary Hypertensive Newborn Lambs



Some of the authors of this publication are also working on these related projects:



Modeling the epigenetic programming of vascular dysfunction by oxidative stress in the Intrauterine Growth Restricted fetus: role of prenatal antioxidants in preventing long-term vascular dysfunction View project



Time-course modeling of the vascular epigenetic programming by fetal growth restriction: role of endothelial-derived miRNAs on hypoxia- and oxidative stress-induced responses View project

## Cinaciguat Reduces Prolyl Hydroxylase 2 (PHD2) Protein Expression in Chronically Hypoxic and Pulmonary Hypertensive Newborn Lambs.

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Newborn lambs at high altitudes (3,600 m) develop pulmonary hypertension due to a sustained hypoxic vasoconstriction followed by a pathological remodeling of small pulmonary arteries (SPA). The latter is produced by several agents, including the transcription factor Hypoxia Inducible Factor-1α (HIF-1α). HIF-1α increases the pulmonary vascular remodeling in chronic hypoxia and the enzyme PHD-2 is a key factor participating in the degradation of HIF-1a. Cinaciguat an activator of sGC is able to decrease HIF-1α, in adults, and increase HO-1 in neonatal lambs. This enzyme reduces reactive oxygen species (ROS) and cytokines, whereas no information in PHD-2 and cinaciguat is available. Therefore, we use two groups of 6 newborn lambs each, that were catheterized under general anesthesia and a Swan Ganz catheter was placed into the pulmonary artery, to measure pulmonary arterial pressure (mPAP), cardiac output (CO) and calculate pulmonary vascular resistance (PVR). The groups received, either the activator of sGC (cinaciguat 35 µg kg<sup>-1</sup>) or vehicle (DMSO: NaCl 0,9%, 1:10), for seven days. Additionally, we took lung samples to perform histology (muscle & adventitia layers in small pulmonary arteries, SPA) and western blots (HIF-1α and PHD-2). Fortyeight hour after the end of treatment, euthanasia was accomplished. All procedures were approved by the local Bioethical Committee (CBA#0643 FMUCH). Cinaciguat did not change the mPAP but did vary the PVR. Mean PAP was not modified because CO increased. Concordant with the lower PVR there was a reduction of the muscular and adventitia layers in SPA. Further, cinaciguat did not modify the HIF-1α protein expression but showed a decrease in PHD-2 in pulmonary hypertensive newborn lambs. If ROS and cytokines are diminished (unmeasured) by cinaciguat, both factors could generate a reduction in HIF-1α, that could lessen PHD-2 (feedforward). The latter should produce a decrease in HIF-1α hydroxylation and therefore a reduced destruction in the proteasome, which would lead to an increase in HIF-1α availability, and eventually to its initial state (feedback). HIF-1α did not decrease because has a short half-life in contrast with PHD-2 that has a half-life over 48h. In conclusion, the decrease in PHD-2 could be the consequence of an initial HIF-1α reduction, producing a diminution in muscle and adventitia layers in small pulmonary arteries consistent with a lesser PVR. The reduction of HIF-1α could be considered a useful tool to treat the pulmonary hypertension of the

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