Apelin Deficient Mice Demonstrate Worsening Pulmonary Hypertension in a Nitric Oxide Dependent Manner

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Abstract:
Our recent studies have shown high expression of the GPCR APJ and its ligand apelin in the pulmonary vasculature, implicating its role in pulmonary hypertension. It was hypothesized that disruption of the pathway leads to worsening of pulmonary hypertension in the apelin deficient model, and that this pathway is autonomously regulated in patients with pulmonary arterial hypertension (PAH). Apelin deficient (KO) mice were used to assess right ventricular systolic pressures after 2 weeks of hypoxia. Lungs were perfused with formalin, and sections were stained with Masson's trichrome and CD31. Mice were treated with apelin to determine whether apelin could improve pulmonary hypertension in response to hypoxia compared to control group. All mice underwent two rounds of hypoxic exposure at 2 weeks of age.

Results:
Mice lacking apelin develop worse pulmonary hypertension in response to hypoxia. Apelin KO mice have increased levels of serum NO and have lower expression of eNOS in the lung, as determined by both RT-PCR and western blotting. The authors concluded that apelin could improve pulmonary hypertension in response to hypoxia compared to control group. All mice underwent two rounds of hypoxic exposure at 2 weeks of age.

Introduction:
The apelin receptor and its G-protein-coupled receptor (GPR) works as a signaling pathway that is involved in cardiovascular and pulmonary function. The apelin receptor (APJ) is expressed in the lung and has been shown to bind to angiotensin receptor (AT1) and angiotensin II receptor (AT2). The authors hypothesize that apelin deficiency leads to worsening of pulmonary hypertension. It was observed that apelin KO mice have increased levels of serum NO and have lower expression of eNOS in the lung, as determined by both RT-PCR and western blotting. The authors concluded that apelin could improve pulmonary hypertension in response to hypoxia compared to control group. All mice underwent two rounds of hypoxic exposure at 2 weeks of age.

Methods:
- In a controlled study, apelin KO mice were evaluated under baseline conditions and using an established in vivo model of pulmonary hypertension. The authors hypothesize that apelin deficiency leads to worsening of pulmonary hypertension. It was observed that apelin KO mice have increased levels of serum NO and have lower expression of eNOS in the lung, as determined by both RT-PCR and western blotting. The authors concluded that apelin could improve pulmonary hypertension in response to hypoxia compared to control group. All mice underwent two rounds of hypoxic exposure at 2 weeks of age.

Summary:
- Apelin deficient mice develop worsening pulmonary hypertension in response to hypoxia.
- Anatomic changes include increased small vessel muscularization, increased vessel tortuosity.
- Decreased serum NO levels and pulmonary eNOS expression suggest defective NO signaling as a possible mechanism.
- Patients with PAH have decreased serum apelin levels.
- Ongoing work to further define the mechanism of eNOS regulation by apelin.
- Potential therapeutic target for the treatment of PAH.