

Insights: Publications

Gut Pathology and Its Rescue by ACE2 (Angiotensin-Converting Enzyme 2) in Hypoxia-Induced Pulmonary Hypertension

Hypertension, Vol. 76, No. 1

May 18, 2020

Written by **Marianthi M. Karas**

Therapeutic advances for pulmonary hypertension (PH) have been incremental because of the focus on the pulmonary vasculature in PH pathology. Here, we evaluate the concept that PH is, rather, a systemic disorder involving interplay among multiorgan systems, including brain, gut, and lungs. Therefore, the objective of this study was to evaluate the hypothesis that PH is associated with a dysfunctional brain-gut-lung axis and that global overexpression of ACE2 (angiotensin-converting enzyme 2) rebalances this axis and protects against PH. ACE2 knockin and wild-type (WT; C57BL/6) mice were subjected to chronic hypoxia (10% FIO₂) or room air for 4 weeks. Cardiopulmonary hemodynamics, histology, immunohistochemistry, and fecal 16S rRNA microbial gene analyses were evaluated. Hypoxia significantly increased right ventricular systolic pressure, sympathetic activity as well as the number and activation of microglia in the paraventricular nucleus of the hypothalamus in WT mice. This was associated with a significant increase in muscularis layer thickening and decreases in both villi length and goblet cells and altered gut microbiota. Global overexpression of ACE2 prevented changes in hypoxia-induced pulmonary and gut pathophysiology and established distinct microbial communities from WT hypoxia mice. Furthermore, WT mice subjected to fecal matter transfer from ACE2 knockin mice were resistant to hypoxia-induced PH compared with their controls receiving WT fecal matter transfer. These observations demonstrate that ACE2 ameliorates these hypoxia-induced pathologies and attenuates PH. The data implicate dysfunctional brain-gut-lung communication in PH and provide novel avenues for therapeutic interventions.

Related People



Marianthi M. Karas

t 310.777.3732

mkaras@ktslaw.com