Bronchopulmonary dysplasia (BPD), the chronic lung disease that follows respiratory care and oxygen therapy after premature birth, occurs in nearly 15,000 infants per year in the United States alone.

BPD is characterized by abnormal lung structure due to decreased alveolar and vascular growth, leading to chronic respiratory disease, recurrent hospitalizations, asthma, exercise intolerance and pulmonary hypertension.

Past laboratory studies suggest that disruption of endothelial function and impaired angiogenesis contributes to BPD, partly due to decreased nitric oxide (NO) activity and disruption of NO-cGMP signaling.

Whether pharmacologic treatment with new agents that augment cGMP can stimulate endothelial cell growth and angiogenesis in the developing lung is unknown.

**Background**

**Hypotheses**

- Augmentation of cGMP signaling with Cinaciguat, an sGC activator, and Sildenafil, a PDE5 inhibitor, will increase PAEC growth and angiogenesis;
- These effects of cGMP agonists are dependent on protein kinase G (PKG) stimulation and are mediated by MAPK activation.

**Methods**

- PAECs harvested from late-gestation fetal sheep characterized by cobblestone appearance and (+) staining for standard EC markers. Studies performed at passages 4-6.
- **Study drugs:**
  - Cinaciguat (soluble guanylate cyclase activator; 10 µM)
  - Sildenafil (PDE5 inhibitor; 1 nM)
  - KT5823 (protein kinase G inhibitor; 1 µM)
  - SB203580 (P38 MAP kinase inhibitor; 100 µM)
  - PD98059 (MEK1 inhibitor; 25 µM)
- **Tube Formation Assay:**
  - PAECs were plated on rat tail collagen for 18-24 hrs in the presence or absence of Cinaciguat (Cin), Sildenafil (Sil), and inhibitors (KT, SB, PD) in room air.
  - Quantified by branch point counting

**Results**

- Cinaciguat and Sildenafil increase fetal PAEC growth and tube formation in vitro.
- MEK1 inhibition decreases fetal PAEC growth and tube formation.
- Cinaciguat-induced stimulation of PAEC growth and tube formation are attenuated by PKG and MAPK inhibition.
- Sildenafil-induced stimulation of PAEC growth is attenuated by PKG and MAPK inhibition, whereas tube formation was attenuated by treatment with MAPK, PKG and P38 inhibitors.

**Conclusions**

- Cinaciguat and Sildenafil increase fetal PAEC growth and tube formation.
- These cGMP-dependent effects are mediated by PKG and MAPK activation.

**Speculation**

- We speculate that therapies that enhance cGMP activity may provide a novel strategy for promoting angiogenesis and preventing chronic lung disease in preterm newborns.

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