Restricted Postnatal Feeding Reduces the PPARγ-Setd8-Wnt Pathway in the Lung of Chronically Ventilated Preterm Lambs


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Disclosure

Synneva Hagen-Lillevik has nothing to disclose
Introduction

- Preterm neonates who develop chronic lung disease (CLD) often fail to thrive
  - Feeding intolerance
  - Limited nutrition to the neonate

- Effects of limited nutrition on lung development is not well understood

- Preterm lamb model of CLD provides an opportunity to test the role of limited nutrition
Introduction

- **Preterm Delivery**
  - **HFNV 21 days**
    - **Control**
      - *ad libitum*
      - Adequate Growth
      - Good Lung Outcomes
    - **Restricted Feeding**
      - 75% of Control Group
      - Poor Growth
      - Poor Lung Outcomes
PPARγ and Wnt Signaling

Ligand → PPARγ → Setd8 → Wnt Signaling

β-catenin
Wnt11
LEF1

MMP9

PPARγ: Peroxisome proliferator receptor gamma; Setd8: Histone-lysine N-methyltransferase
LEF1: Lymphoid enhancer-binding factor 1; MMP9: Matrix metallopeptidase 9
Docosahexanoic Acid (DHA)

✦ Physiologically relevant
  • Human preterm infants who develop CLD have reduced plasma DHA

✦ Limited nutrition on DHA status remain unknown
Hypothesis

Restricted feeding will decrease plasma DHA and reduce flux through the:

- PPARγ
- Setd8
- Wnt Signaling
  - β-catenin
  - Wnt11
  - LEF1
- MMP9
Methods-Preterm Lambs

Antenatal Steroids

Delivered at ~131 days

(Term is ~150 days)

Intubated and treated with surfactant and caffeine citrate

Intermittent Mandatory Ventilation (IMV) ~3 hours
Methods - Preterm Lambs

Extubated

↓

HFNV

(Percussionaire® ventilator)

Restricted Feeding
(mL/Kg/d matched to historical MV)

Control (increased to *ad libitum*)

21 days
Methods-Preterm Lambs

- Respiratory gas parameters-
  - $\text{PaO}_2$: 60 to 90 mmHg
  - $\text{PaCO}_2$: 45 to 60 mmHg
  - pH range: 7.25-7.45

- Enteral feedings within 3-4h of delivery
  - Colostrum
  - Mature ewe milk
Methods-Data collection

- Mass spectrometry was used to measure levels of plasma DHA
- Western blotting or real-time RT PCR was used to measure components of the PPARγ-Setd8-Wnt signaling pathway
RESULTS
Restricted feeding decreases plasma DHA levels

Plasma DHA (mol% of total fatty acids)

Mean ± SD; n=4

HFNV
Restricted feeding decreases lung PPARγ protein abundance

Mean ± SD; n=4
Restricted feeding decreases lung Setd8 protein abundance

Mean ± SD; n=4

Setd8 (% Total Protein)

Restricted  Control

HFNV
Restricted feeding decreases lung β-catenin protein abundance

β-catenin (% Total Protein)

Mean ± SD; n=4
Restricted feeding decreases lung Wnt11 protein abundance

Mean ± SD; n=4
Restricted feeding decreases lung LEF1 mRNA transcript levels.

Mean ± SD; n=4 HFNV
Restricted feeding decreases lung MMP9 mRNA transcript levels.
## Summary

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<thead>
<tr>
<th>Restricted Feeding</th>
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<tbody>
<tr>
<td>Plasma DHA</td>
</tr>
<tr>
<td>PPARγ</td>
</tr>
<tr>
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</tr>
<tr>
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*As compared to control*
Speculation

- Poor postnatal nutrition contributes to the development of chronic lung disease

- Restoration of plasma DHA levels may normalize PPARγ-Setd8-Wnt signaling and indices of alveolar formation under conditions of restricted feeding
Thank You

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