Gut Mechanics During Stress: How Feed Efficiency and Growth Can be Influenced

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Focus of Talk: Gut Health

- Components of gut health
- How gut health is impacted by stressors
  - Specific production stressors
  - Pathophysiology
- Implications for feed efficiency
Poor Gut Health is a Major Contributor to Economic Losses in Animal Production

GI Disease

Suboptimal feed efficiency

Infectious Enteric disease

subclinical

clinical
Factors Influencing Gut Health

- Environment
- GI Disease
- Pathogen
- Stress
- Host
Stressors in Animal Production

- Crowding stress
- Transport stress
- Nutrition stress
- Cold Stress
- Heat Stress
- Weaning
- Antigen Toxin Stress
- Mixing Stress
Stress is a Major Factor in the Onset and Exacerbation of GI Disease in Animals and People

The biological mechanisms by which stress adversely impacts gut health is poorly understood.
Gastrointestinal Stress Biology Laboratory

**GSL Objectives:** To gain a fundamental understanding of how stress causes GI disease and to optimize GI Health in animals and people through basic science discovery, management and nutrition.

- Early Life stress and GI development
- Mechanisms of Stress-induced disruption of GI immune and epithelial barriers
- Interaction between nutrition, stress, and GI disease

http://cvm.msu.edu/research/faculty-research/moeser
The Gastrointestinal Barrier: The Largest Interface Between Us and the Outside World
Components of The Intestinal Barrier

- Intestinal Lumen
  - HCO₃⁻
  - Cl⁻
  - Antimicrobial peptides
  - Mucus
  - H₂O
  - Nutrients
  - Antigens
  - Microbiota
  - Tight Junctions
  - IgA

- Epithelial Cells
  - Intestinal Lumen
  - Lamina Propria
  - Enteric nervous system
  - Circulation
  - Immune System

- Pathogens
- Toxins
Consequences of Intestinal Barrier Breakdown

- Fluid Loss
- Nutrients
- Antigens
- Pathogens
- Toxins

Intestinal Lumen: H₂O, Cl⁻, HCO₃⁻

Epithelial Cells: Chronic Stages

Lamina Propria: Immunosuppression
Mechanisms of Intestinal Absorption and Secretion: Importance of Barrier Function
Impaired Barrier Function and Disease Pathogenesis

- Infectious Disease Pathogenesis
- Feed Efficiency
- Endocrine/Metabolic Diseases
- Endotoxemia Sepsis
- Inflammatory Bowel Diseases
- Food Allergy/Anaphylaxis
- Microbiome Dysbiosis
What is the Impact of Stress on the Intestinal Barrier?
Measurement of Barrier Function: Ussing Chamber Method
Measurement of Barrier Function: 
Ussing Chamber Method

- **3H-Mannitol**
- **14C-Inulin**
- **FITC Dextran**

- Mucosal
- Serosal

High Flux Rate
- Impaired Barrier Function

Low Flux Rate
- Intact Barrier Function
Impact of Heat and Mixing Stress on Feed:Gain

Control
Mixing crowding stress

Feed intake: Not significant (P=0.6)
ADG: p<0.01

Control
Chronic Heat Stress

Feed intake: Not significant (restricted feed intake)
ADG: p<0.01

Manuscripts in preparation
Impact of Chronic Crowding Stress on Intestinal Barrier and Absorptive Function

Intestinal Permeability

Control
Crowding + Mixing Stress

Intestinal Glucose Absorptive Response

Control
Crowding + Mixing Stress

7 d of mixing and crowding stress
Impact of Chronic Heat Stress on Intestinal Barrier and Absorptive Function

10 d of Heat stress

Intestinal Permeability

- Control
- Chronic Heat Stress

Intestinal Glucose Absorptive Response

- Control
- Chronic Heat Stress
Weaning Stress

- Maternal separation
- Alteration in environment
- Antimicrobial resistance in diet
- Increased exposure to pathogens
- Maternal separation
- Alteration in environment
- Increased exposure to pathogens
- Maternal separation
- Alteration in environment
- Increased exposure to pathogens
Weaning Stress is Linked with Impaired Gut Function and Enteric Disease

Does weaning impact intestinal barrier function?
Weaning Induces Breakdown of the Intestinal Barrier

Moeser et al. Am J Physiol Gastrointest Liver Physiol. 292:G173-81
Intestinal Barrier Response to Weaning Stress: Effects of Wean Age

Moeser et al. Am J Physiol Gastrointest Liver Physiol. 293:G413-21
Long-Term Effects of Early Weaning Stress on Intestinal Permeability

$^{3}H$-mannitol flux, $\mu$mol.cm$^{-2}$.h

- **LW**
- **EWS**

Time (Days Post-weaning)

* * *
Does Early Weaning Stress Impact Subsequent GI Stress Responses?

EWS
LWC

Post-Weaning
Mixing Stress
54d

Barrier function measured 3hr post-stress

Wean 16d
Wean 28d

Pohl et al. Manuscript in preparation
Early Weaning Stress Leads to Exacerbated Intestinal Injury Responses to Subsequent Stressors

$3^H$-mannitol flux, $\mu$mol.cm$^{-2}$.h$^{-1}$

- **Control**
- **Mixing Stress**

**Fecal Score**

- **Control**
- **Mixing Stress**

*Pohl et al. Manuscript in preparation*
What is the Impact of Early Weaning Stress on Intestinal Responses to Subsequent Infectious Challenges?
Early Weaning Stress Leads to Heightened Clinical Disease in Response to Subsequent Enterotoxigenic *E. coli* Challenge

McLamb et al., 2013 PLoS One. 8:e59838
Early Weaned Pigs Exhibit Dampened Mucosal Immune Response to ETEC challenge

McLamb et al., 2013 PLoS One. 8:e59838
Impact of Production Stressors on Gut Barrier Health in Pigs

- Impaired feed efficiency
  - Independent of feed intake
- Immediate and long-lasting disturbances in intestinal barrier function
- Impaired nutrient transport mechanisms
  - Not associated with changes in absorptive area or morphology
- Heightened responses to later life stress challenges
- Heightened responses to later life infectious challenges
- Suppressed immune response to later life infectious challenges
Mechanisms of Stress-Induced Intestinal Dysfunction
Histopathological Analysis of the Early Weaned Pig Intestine

No Differences in H&E Histology
Increased Mast Cell Numbers and Activation in EWS Pigs

*Smith et al. Am J Physiol Gastrointest Liver Physiol 2010;298:G352-G363
*Pohl et al, manuscript in preparation
Mast Cell Release Preformed and Synthesized Mediators

Prestored Mediators
- Histamine
- Proteases
- TNF

Synthesized Mediators
- Cytokines
- Chemokines
- Neuropeptides
- Lipid Mediators

Degranulation
Heightened Mast Cell Degranulation is a Driving Mechanism in GI Disease

- Increased Intestinal permeability (Barbara et al, 2004, Gastroenterology) – correlation with visceral hypersensitivity/abdominal pain in IBS patients

- Association with and Activation of enteric neurons

- Secretion/diarrhea

- Increased Intestinal permeability

(Barbara et al 2004, Gastroenterology) – correlation with visceral hypersensitivity/abdominal pain in IBS patients
Does Inhibition of Mast Cells Improve Intestinal Barrier Function in EWS Pigs?

Smith et al. Am J Physiol Gastrointest Liver Physiol 2010;298:G352-G363
How does stress induce intestinal mast cell activation and intestinal barrier dysfunction?
The Corticotropin Releasing Factor (CRF) System is a Major Regulator of the Stress Response
Early Weaning Stress and Intestinal Permeability is Mediated by Activation of the CRF System

Overman et al., PLoS One 2012;7:e39935
Smith et al. Am J Physiol Gastrointest Liver Physiol 2010;298:G352-G363
CRF Receptor Activation in Linked with Intestinal Barrier Function and Mast Cell Activity

Overman et al., PLoS One 2012;7:e39935
Smith et al. Am J Physiol Gastrointest Liver Physiol 2010;298:G352-G363
How do Mast Cells Increase Intestinal Permeability in Response to Stress?

Increased Intestinal Permeability

Corticotropin Releasing Factor (CRF)

The Mechanistic Link Between Stress and GI Disease

- Activation of the CRF system
- Intestinal Mast Cell Activation
- Intestinal Permeability

Pohl, Medland, and Moeser 2015; Am J Physiol-GI
Implications: Stress, GI Function, and FE

- Common production stressors have a marked, deleterious influence on intestinal barrier function
  - Increased intestinal permeability
  - Immune cell activation
  - Hypersecretion

- Stress and impaired intestinal barrier function can negatively influence FE
  - Impaired digestive and absorptive processes
  - Persistent GI immune system activation
  - Changes in microbiota

- Further elucidation of the mechanisms of stress-induced regulation of gut health and barrier function could have important implications for improving FE
Acknowledgements

Moeser GI Stress Biology Laboratory

• Saru Ayyadurai, Research Associate
• Kristen Bagley
• Susan D’Costa, Research Associate
• Laura Edwards RLATG
• Shellsea Frandsen BS
• Amelia Gibson PhD
• Liz Lennon, DVM DACVIM
• Julia Medland MS
• Emily Mackey, DVM/PhD student
• Beth Overman, PhD
• Calvin Pohl DVM, PhD student
• Ashwin Poopal, MS
• Mrigendra Rajput, PhD
• Laura Sommerville, Post Doc
• Yihang Li, Post Doc
• Vandana Zaman, PhD

Collaborators

• Soman Abraham PhD, Duke University (Mast Cell Biology)
• Jean Rivier PhD, The Salk Institute, La Jolla, CA (CRF receptor compounds)
• Aditi Bhargava PhD, UCSF (CRF$_2$-/- mice)
• Richard Neubig MD PhD, MSU (GPCR mechanisms)

Lab Funding

• American Gastroenterological Association (AGA)
• National Institutes of Health grants
  – NIH R01 HD072968
  – NIH R03 DK097462
  – NIH K08 DK097462
• National Pork Board
• NC Pork Council
• USDA
• UNC Chapel Hill Center for Gastrointestinal Biology and Disease

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