Gut Integrity – Implications for health and performance

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Heat Stress (HS) is **Not** a Fever

When ambient temperature approaches body temperature, cooling mechanisms are impaired.

Fever vs. Hyperthermia

Key Biological Differences
Heat Stress is a Global Problem

January 2003, NASA

July 2003, NASA
# Heat Stress: Animal Agriculture

<table>
<thead>
<tr>
<th>Industry</th>
<th>Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Dairy Industry</td>
<td>897 million - $1.5 billion</td>
</tr>
<tr>
<td>American Swine Industry</td>
<td>&gt;$350 million annually</td>
</tr>
<tr>
<td></td>
<td>(St-Pierre et al., 2003 J. Dairy Sci. E52-E77)</td>
</tr>
<tr>
<td>Grow - Finishing</td>
<td>$450 million/year</td>
</tr>
<tr>
<td></td>
<td>(Dr. Steve Pollmann)</td>
</tr>
<tr>
<td>Sow - Repro</td>
<td>$450 million/year</td>
</tr>
<tr>
<td></td>
<td>(Dr. Steve Pollmann)</td>
</tr>
<tr>
<td>Almost double the economic impact of PRSS</td>
<td></td>
</tr>
<tr>
<td>Largest impediment to food security:</td>
<td>Chinese Government</td>
</tr>
</tbody>
</table>
Heat Stress: Economics and Food Security

- **Cost:** (lost productivity, mortality, product quality, health care etc.)
  - American Agriculture: > $3 billion/year
  - Global Agriculture: > $100 billion/year
- Heat abatement is the primary strategy to mitigate heat stress
  - But production remains suboptimal during the summer
- Heat stress one of the largest impediments to efficient animal agriculture (even in developed countries)
- Threatens global food security
- Regionalizes animal agriculture

St. Pierre et al., 2003; Baumgard and Rhoads, 2013
HS will Become More an Issue in the Future if:

- Climate change continues as predicted
- Genetic selection continues to emphasis heat generating processes
  - Lean tissue accretion
    - Increased muscle mass increases basal heat production
  - Piglets/litter
    - Gestational heat
    - Lactation heat
- Increased basal heat increases susceptibility to heat stress

Baumgard and Rhoads, 2013
Heat Stress and Industry Issues

- Don’t “finish”
- Increased variability in market weight
- Packing issues with “seam fat”/“flimsy fat”/“watery fat”
- Seasonal infertility
  - Wean to estrous; Failure to express estrous; Conception rate
  - Failure to maintain pregnancy… “slipped liters”
- Mortality
  - Especially late gestation
    - The pig with the biggest investment
- Farrowing parameters
  - Pigs born alive, birth weight, weaning weight
- Decreased Efficiency
  - Feed
  - Production/Facility/Barn (decreased market weights or increased time to market weight)
Etiology of Heat Stress Symptoms
Marked diversion of blood flow to skin and extremities….in an attempt to maximize radiant heat dissipation

Coordinated vasoconstriction in intestinal tissues
- Reduced nutrient and oxygen delivery to enterocytes
- Hypoxia increases reactive oxygen species (ROS)

Reduced nutrient uptake increases intestinal osmolarity
- Multiple reasons for increased osmotic stress
Etiology of Heat Stress

Heat Storage

Cardiovascular Responses
- Gut Constricts
- Skin Dilates
- Muscle Dilates

- Ischemia, ROS & RNS
- NO
- Cytokine Release (IL-1, IL-6, IL-10, TNF)
- Increased Intestine Permeability
- Endotoxemia

Cell Heat Shock & Ischemia
- (Intestine, Hepatic, Renal, Endothelium, Brain, Muscle, Heart)
- Injury
- Inflammation
- Death
- Apoptosis
- Necrosis

Heat Stroke
CNS & multi-organ damage via fever, shock, hemorrhage, stroke & muscle breakdown

Sawka & Young Adv. Exerc. Physiol 2006
Heat Stress and Gut Integrity

- Endotoxin (aka. Lipopolysaccharide: LPS)
- Component of bacteria cell wall
- When bacteria die, LPS is released into intestine
- Normally LPS is prevented from entering through GIT tight junctions
- During HS some LPS enters blood stream
Blood stream

Submucosa

Healthy TJs

Compromised TJs

Hypoxia

HIF-1α

TLR4

PGE2

TNFα

IL-1β

IL-16

INFγ

APP

P

65

NFκB

IkB

P

60

Actin

Myosin

MLCK

Lumen
↑ Immune response
↑ Inflammatory response
↑ Acute Phase Proteins:
- Serum Amyloid A
- Haptoglobin
- LBP
Heat Stress and Gut Health

- LPS causes liver damage
  - May impair gluconeogenesis capability
  - May impair ability to export VLDL (fatty liver)
  - May impair ability to secrete anabolic hormones
- LPS stimulates the immune system and inflammatory cytokine production
  - TNFα, IL-1 etc..
    - Reduced appetite
    - Stimulates fever
    - Causes muscle breakdown
    - Induces lethargy
    - ....reduces productivity
Heat Stress and Bioenergetics
Heat Stress Increases Lipid and Decreases Carcass Lean Content

- **Pigs**
  - Close et al., 1971; Verstegen et al., 1978; Stahly et al., 1979; Heath, 1983, 1989; Bridges et al., 1998; Collin et al., 2001

- **Chickens**
  - Geraert et al., 1996; Yunianto et al., 1997

- **Rodents**
  - Schmidt and Widdowson, 1967; Katsumata et al., 1990

- **But, normally growing animals on a restricted-diet prioritize lean tissue accretion and deemphasize fat synthesis** (Le Dividich et al., 1980; Oresanya et al., 2008)

- **Heat Stress alters the nutrient partitioning hierarchy**
Pig Heat Stress Questions

- Direct vs. Indirect Effects of Heat
  - Indirect effects mediated by reduced feed intake
  - Production
  - Metabolism
  - Leaky Gut?

- *In Utero* Heat Stress
  - Future body temperature
  - Future performance
    - Body composition
Pig Heat Stress Experiments

- Utilized pair-feeding model
- Eliminates the confounding effect of dissimilar feed intake
- Need to appreciate the difference between direct and indirect effects of heat stress in order to develop mitigation strategies.
Daily Feed Intake

46% Decrease

Pearce et al., 2013
Rectal Temperature

Pearce et al., 2013

39.3 vs. 40.9 °C
Pigs: Change in Body Weight

Pearce et al., 2013
Pigs: Plasma Energetics

Insulin

- TN
- HS
- PFTN

NEFA

- TN
- HS
- PFTN

Glucose

- TN
- HS
- PFTN

BUN

- TN
- HS
- PFTN

Pearce et al., 2013
Insulin Secretion Variables

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**Insulin**

- **Trt*Day** $P = 0.03$

**C-peptide**

- **Trt*Day** $P < 0.01$

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Sanz-Fernandez et al., 2013
Intestinal Morphology

Thermal Neutral  Heat Stress  Pair-fed

Pearce et al., 2013
The effects are rapid!
Plasma LPS & LBP

Pearce et al., 2015
Almost all of these metabolic/physiological effects occur during heat stress.
LPS and the Immune System

- Marked activation of the innate immune system.

- Activated immune has a large nutrient requirement
  - Energy and amino acids
Glucose and the Immune System

- At rest, immune cells can oxidize multiple fuels
- Once activated, immune cells become obligate glucose utilizers
- How much glucose does the immune system use?
LPS can Induce Lethal Hypoglycemia

Stoakes, Abuajamieh, and Baumgard, 2012 unpublished data
Can we quantify this amount of glucose?
<table>
<thead>
<tr>
<th>Min</th>
<th>Blood Sample</th>
<th>[Glucose] (mg/dL)</th>
<th>Glucose Rate (mL/hr)</th>
<th>Tr (F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 (1 hr)</td>
<td>✔️</td>
<td>96</td>
<td>0</td>
<td>101.3</td>
</tr>
<tr>
<td>70</td>
<td></td>
<td>84</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td></td>
<td>79</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>✔️</td>
<td>91</td>
<td>0</td>
<td>100.8</td>
</tr>
<tr>
<td>100</td>
<td></td>
<td>98</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>110</td>
<td></td>
<td>116</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>120 (2 hr)</td>
<td>✔️</td>
<td>115</td>
<td>0</td>
<td>101.2</td>
</tr>
<tr>
<td>130</td>
<td></td>
<td>102</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>140</td>
<td></td>
<td>87</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>150</td>
<td>✔️</td>
<td>68</td>
<td>0</td>
<td>100.9</td>
</tr>
<tr>
<td>160</td>
<td></td>
<td>49</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>170</td>
<td></td>
<td>54</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>180 (3 hr)</td>
<td>✔️ ✔️</td>
<td>55</td>
<td>75</td>
<td>100.7</td>
</tr>
<tr>
<td>190</td>
<td></td>
<td>56</td>
<td>75</td>
<td></td>
</tr>
</tbody>
</table>

Stoakes et al., 2015
Study Limitations

- Glucose uptake by other tissues
  - ↓ insulin sensitivity in adipose
    - (Song et al., 2006, Shi et al., 2006, Poggi et al., 2007)
  - ↓ insulin sensitivity in muscle
    - Conclusion: 78 g/h or 1880 g/d is underestimated!

- Glucose output by liver
  - Increased
    - (Lang et al., 1993, McGuinness et al., 1993, Ling et al., 1994)
Why does heat stress increase insulin??

- Why increase the most anabolic hormone during a hypercatabolic condition?
- Direct or Indirect effects?
- Indirect: associated/caused by heat compromised gastrointestinal track barrier function?
I.V. LPS Challenge to Pigs

- Glucose
- Insulin

**Figure Details:**
- Insulin concentration (ng/mL) increases over time.
- Glucose concentration (mg/dL) decreases over time.
- The graph shows temperature changes: 101.8°F and 103.2°F.

**Reference:** Baumgard unpublished
LPS and Insulin

- LPS stimulates or at least augments glucose stimulated insulin secretion….
- LPS activates the immune system
- Insulin promotes adipose tissue accretion
- Partitions nutrients away from muscle and lactation
Can the Feed or Animal Health Industry do anything about leaky gut? 

Targets:
- Direct action at intestine
- Indirect via:
  - Increased feed intake
Potential nutritional strategies to ameliorate intestinal permeability

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Presumed Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicarbonate</td>
<td>Acidosis prevention</td>
</tr>
<tr>
<td>Glutamine</td>
<td>↑ intestine integrity</td>
</tr>
<tr>
<td>Zinc</td>
<td>↑ intestine integrity, antioxidant</td>
</tr>
<tr>
<td>Dairy Products</td>
<td>↑ intestine integrity</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Antioxidant</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Antioxidant</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Antioxidant</td>
</tr>
<tr>
<td>Selenium</td>
<td>Antioxidant</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>↑ intestine integrity</td>
</tr>
<tr>
<td>Betaine</td>
<td>Osmotic regulation; CH₃ donor</td>
</tr>
<tr>
<td>Conjugated Linoleic Acid</td>
<td>↑ Energy balance</td>
</tr>
<tr>
<td>Chromium</td>
<td>↑ Feed Intake</td>
</tr>
<tr>
<td>Yeast, yeast extract/DFM</td>
<td>Acidosis prevention &amp; ↑ Feed Intake</td>
</tr>
<tr>
<td>Ionophores</td>
<td>Acidosis prevention</td>
</tr>
<tr>
<td>β-glucan</td>
<td>Immune modulation</td>
</tr>
<tr>
<td>Mannanoligosaccharide</td>
<td>↑ intestine integrity</td>
</tr>
<tr>
<td>Rehydration therapy</td>
<td>↑ intestine integrity &amp; ↑ Feed Intake</td>
</tr>
<tr>
<td>Butyrate</td>
<td>↑ intestine integrity</td>
</tr>
<tr>
<td>Mycotoxin binders</td>
<td>↑ intestine integrity</td>
</tr>
</tbody>
</table>
Human Gut Health and Zinc

Results: Ileum Permeability

San Fernandez et al., 2014
Previous experiment evaluated just increasing amounts of Zinc.

Objectives of next experiment: compare Zinc source

Treatments:
- Control: 120 ppm ZnSO\(_4\)
- Treated: 120 ppm Zn: 50% ZnSO\(_4\) & 50% Zn-Amino Acid Complex
Zn and Intestinal Integrity

Lipopolysaccharide (LPS)

LPS-BP

Pearce et al., 2015
Feeding Zn-AA complex improved the intestinal integrity during heat stress (in pigs)
- Sanz-Fernandez et al., 2014;
- Pearce et al., 2015
- Baumgard unpublished (in steers)

Mechanism unknown
- Likely due to up-regulation of HSP prior to heat load?
Seminar Summary

- Heat stress causes leaky gut
- Reduced feed intake causes leaky gut
  - off feed events, weaning etc.
- Increased insulin and decreased adipose tissue breakdown
  - Explains fatter carcasses in late summer
- Leaky gut and endotoxin infiltration
- Potential dietary strategies
- Primary objective is to control environment
Heat Stress: Metabolic and Physiological Summary

Baumgard et al., 2014
Acknowledgments

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• Kemin Industries
• Murphy Brown

• Victoria Sanz-Fernandez
• Sarah Pearce
• Jay Johnson
• Rebecca Boddicker
• Amir Nayeri
• Nathan Upah
• Anna Gabler
• Sam Lei
Questions?

http://www.oildrumpigroasterdesigns.com/
Can “leaky gut” explain suboptimal production frequently observed in animal agriculture?

- Heat Stress
- Inadequate feed intake
  - “off-feed event”
    - The negative effects on growth are bioenergetically unexplainable by reduced feed intake
  - Transition period
    - Cause of ketosis?
  - Weaning
  - Shipping
  - Overcrowding
  - Unpalatable feed
Heat Stress