Nutrients and the Innate Immune Response

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Outline

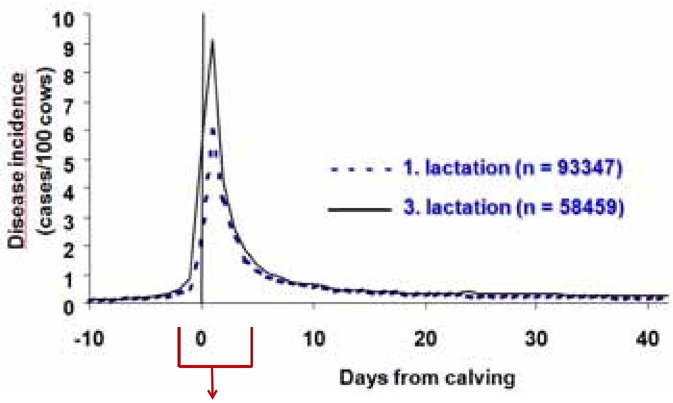
- Overview of immune response
  - Innate and Adaptive
- Impact of stress on immune function
  - Heat
  - Crowding + Transport
  - Malnutrition
  - ***Parturition***
  - Disease
- Nutrient utilization during inflammation
  - ***Glucose***
  - Amino Acids
  - Lipids
- Impact of Vitamin/mineral supply on immune response
  - Vitamin E + Selenium
  - ***Chromium***
- Take-home messages

The immune system

- Leukocyte: White blood cells; cells of the immune system
- Innate
  - Non-specific
  - Neutrophils and macrophages
  - Macrophages:
    - Recruit neutrophils (PMN)
    - Phagocytose (i.e. engulf and kill)
    - Antigen presentation
  - PMN:
    - Chemotaxis
    - Phagocytose
- Adaptive
  - Specific
  - Vaccine development
  - Lymphocytes
    - T and B (antibody [Ig] production)

Stress the Immune System: Parturition

Disease incidence relative to calving



75% of diseases

Adapted from Ingvartsen, 2006 and Ingvartsen and Moyes, 2013

Dysfunctions observed in periparturient dairy cows

(Nielsen, 2002 and Ingvartsen, 2005)

Leukocytes	Dysfunction	Reference
Neutrophils (PMN)	↓ Oxidative metabolism *in vitro*	Detilleux *et al.*, 1995 Kehrli *et al.*, 1989b
	↓ Neutrophil chemotaxis *in vitro*	Nagahata *et al.*, 1988
	↓ Antibody dependent cell-mediated cytotoxic reaction *in vitro*	Cai *et al.*, 1994 Kehrli *et al.*, 1989b
	↓ CD62L and CD18* expression *in vivo*	Lee & Kehrli, 1998
	↓ Phagocytosis	Paape et al., 1981 Saad *et al.*, 1989
Monocytes/ Macrophages	↓ TNF-α production induced by LPS**	Sordillo *et al.*, 1995
	↓ TNF-α production	Røntved, 2000
Lymphocytes	↓ Number in blood *in vivo*	Kehrli *et al.*, 1989a Park *et al.*, 1992 Saad *et al.*, 1989
	↓ Cell division	Kehrli *et al.*, 1989a Saad *et al.*, 1989
	↓ IFN-γ production	Ishikawa *et al.*, 1994

* CD62L and CD18: adhesion molecules involved in the migration from blood into tissue.
** Lipopolysaccharide (LPS) constitutes a part of the cell surface of gram negative bacteria.

What causes periparturient immunosuppression?

- Cumulative effect of a multitude of factors, including endocrine changes?
- Cortisol ⇧ - not a major contributor
- Milk yield?
- Physiological imbalance?
- Nutrition
- Genotype?
- Others?

Adapted from Ingvartsen, 2005

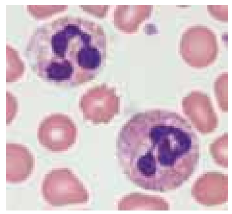
Major Diseases During the Periparturient Period: Mastitis

- An *inflammation* of the mammary gland
- Most costly of all diseases in the dairy industry
  - > $2 Billion annually *(Cha et al., 2011)*

www.valleyveterinarygroup.com

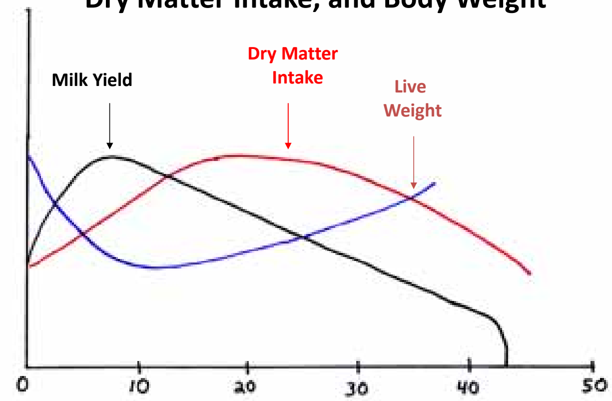
Neutrophils (PMN) and the Immune Response

- Macrophages detect + recruit PMN
- ↑ somatic cells (SCC) indicator of mastitis
- During mastitis, 90% PMN in milk
  - Released from bone marrow
  - Short half-life
  - Few mitochondria
  - Utilize little oxygen
  - 1° phagocytose + kill
- Improving Macrophage + PMN function vital



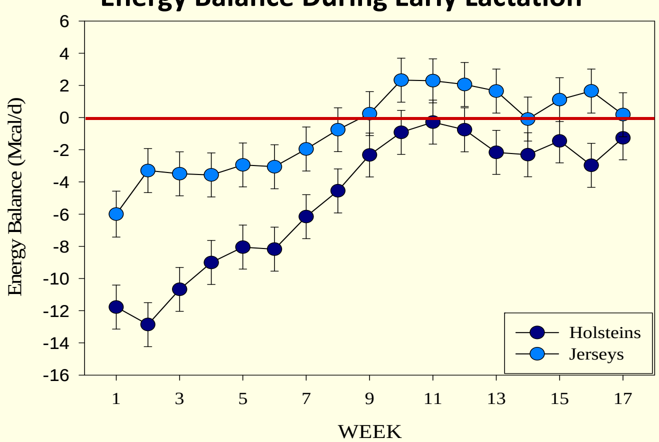
www.39kf.com

Relationships between Milk Yield, Dry Matter Intake, and Body Weight



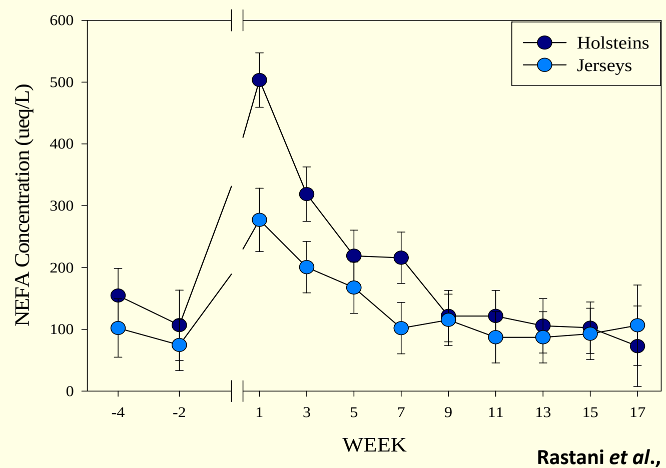
Garnsworthy, 1988

Energy Balance During Early Lactation



Rastani et al., 2001

Non-Esterified Fatty Acid (NEFA) Concentrations During the Transition Period



Rastani *et al.*, 2001

Major Diseases During the Periparturient Period: Ketosis and Fatty Liver

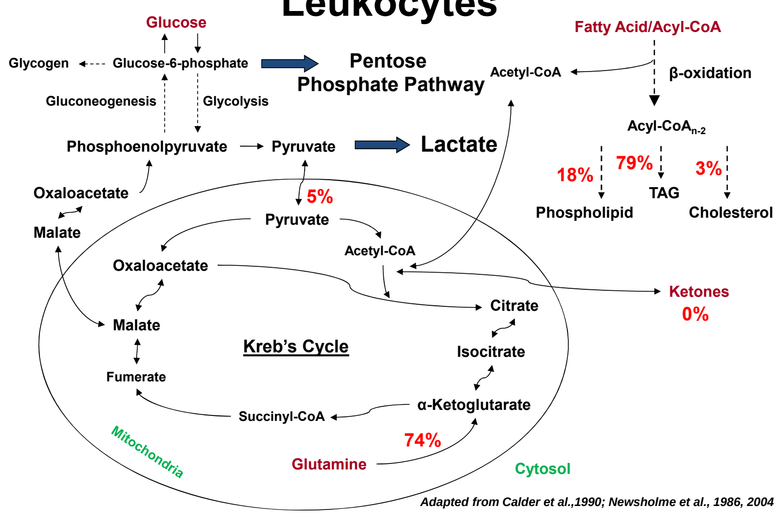
- **Ketosis**
  - ↑ ketones (i.e. BHBA); >1.2 m*M*
- **Fatty liver (i.e. hepatic lipidosis)**
  - NEFA uptake >>> oxidation + export
  - Liver triacylglyceride (TAG)

Liver Category	Liver TAG (% wet wt)
Normal	< 1%
Mild	1-5%
Moderate	5-10%
Severe	>10%

Adapted from Bobe et al., 2004

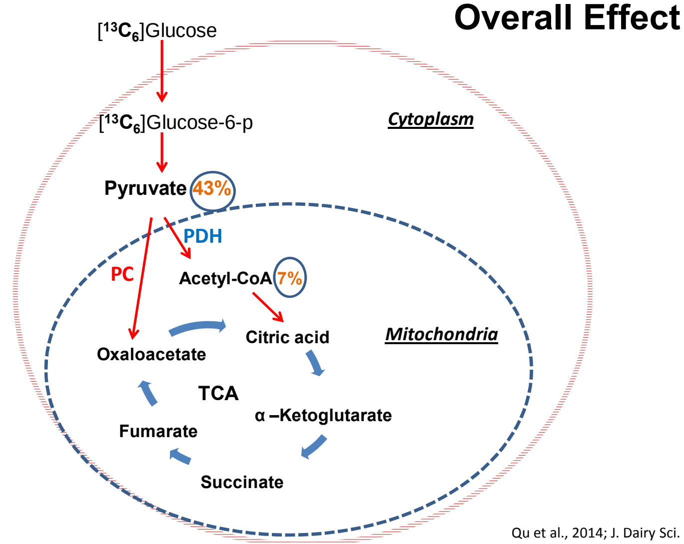
Nutrient Utilization During Inflammation

Fates of Energetic Fuels in Leukocytes



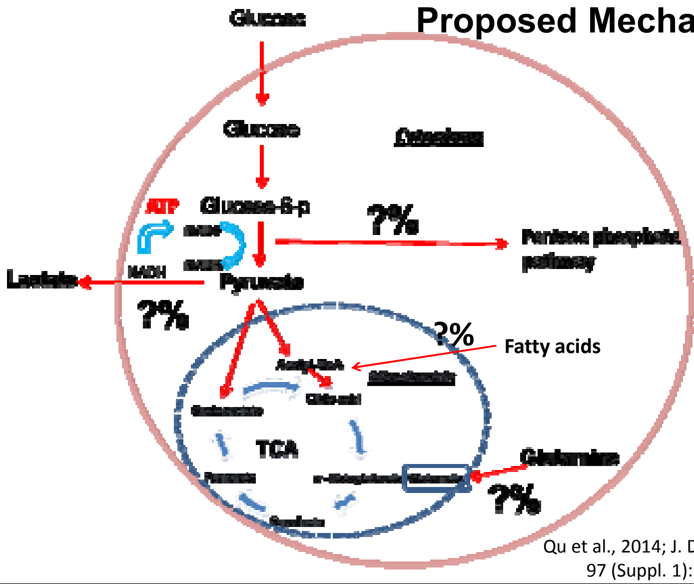
Adapted from Calder et al.,1990; Newsholme et al., 1986, 2004

Overall Effect



Qu et al., 2014; J. Dairy Sci. 97 (Suppl. 1):180.

Proposed Mechanism



Qu et al., 2014; J. Dairy Sci. 97 (Suppl. 1):180.

Nutrients and Leukocyte Function

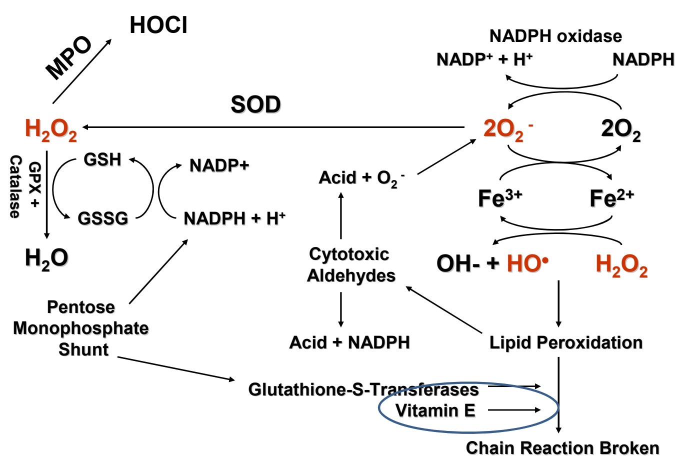
	Effect on Immunity	
Nutrient	Inhibitory (-)	Stimulatory (+)
Glutamine		Cytokine and ROM production; phagocytosis; CD4 T cell adherence
Glucose		Proliferation, survival, differeniation; chemotaxis/ phagocytosis
Free fatty acids (NEFA) (Saturated vs. unsaturated)	Phagocytosis; IgM secretion; cytokine production; cell viability; diapedesis; antigen presentation	Phagocytosis; oxidative burst; cytokine and ROM production; TLR activation
Ketones (BHBA)	Chemotaxis; phagocytosis; PMN trap formation; oxidative burst; ROM production; IgM secretion	
Energy Balance	Chemotaxis; phagocytosis; diapedesis; antigen presentation; acute phase response; oxidative burst; cytokine production	Diapedesis; antigen presentaton; acute phase response; cytokine production; TLR signaling

Adapted from Ingvartsen and Moyes, 2013

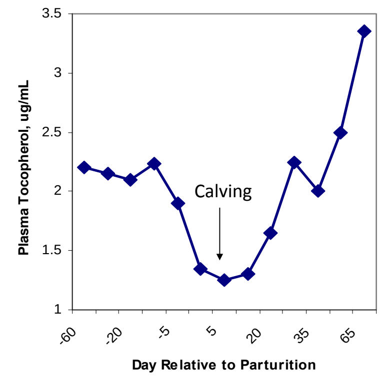
Vitamin/Mineral Supply and the Immune Response

Vitamin E (alpha-tocopherol)

- **General Aspects:**
  - **Most important fat-soluble antioxidant**
  - **Protects membrane lipids from oxidative damage**



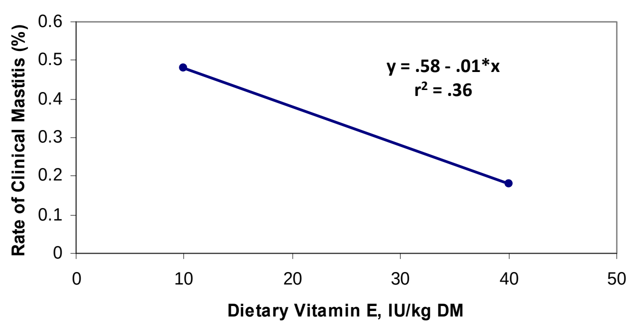
The Effect of Vitamin E on Mammary Gland Health During the Transition Period



- Plasma Vitamin E suppression coincides with ↑ incidence of disease around calving
- Reducing the suppression of plasma vitamin E may help ↓ incidence of disease during transition period

Adapted from Weiss et al., 1990

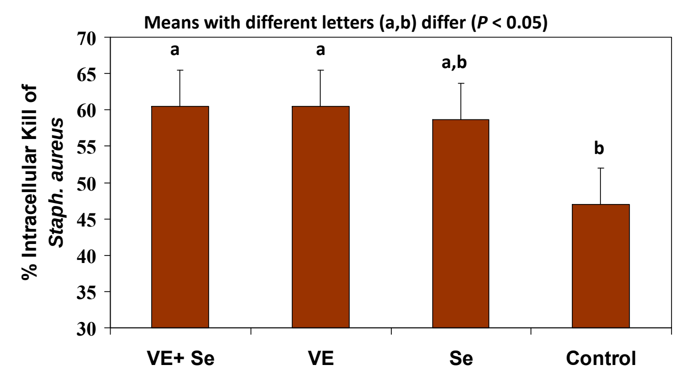
Dietary vitamin E ↓ the rate of clinical mastitis[1] (*P* < .09).



[1]Rate of clinical mastitis = [(# cases/305) + .001]

Adapted from Weiss et al., 1990

Percent intracellular kill of *Staph. aureus* in blood PMN ↑ with vitamin E (VE), Selenium (Se) or both.



Note: VE = 90 mg/kg concentrate DM; Se = 0.45 mg/kg concentrate DM

Adapted from Hogan et al., 1990

Mechanistic Action of Chromium (Cr)

- Cr and glucose metabolism
  - Modulates tissue response to insulin (Vincent, 2004)
- Cr and stressors
  - Stress reduces Cr excretion + Cr status (Yasui et al., 2014)
    - Gestation
    - Lactation
    - Infection
- Unclear role Cr supplementation for periparturient cows

Cr supplementation in lactating dairy cows

- ↑ Improves insulin sensitivity during periparturient period (Subiyatno et al., 1996) and glucose tolerance (Hayirli et al., 2001)
- ↑ DMI (Smith et al., 2005; Hayirli et al., 2001)
- ↑ Milk yield + components (Hayirli et al., 2001; Smith et al., 2005; Vargas-Rodriguez et al., 2014)
- Improves energy metabolism during early lactation
  - ↓ NEFA (Bryan et al., 2004; Soltan, 2010; Yasui et al., 2014)
  - ↓ Loss in body condition (Hayirli et al., 2001; Soltan, 2010)
  - ↑ Energy balance (Soltan, 2010)
  - ↓ Cytological endometritis (Yasui et al., 2014)
  - Improves reproductive performance (Bryan et al., 2004; Soltan, 2010)
- Role of Cr on mammary epithelial cells in vitro (Garcia et al., unpublished)

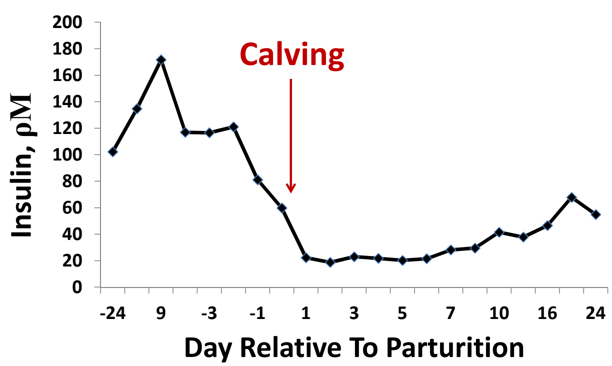
Chromium Modulates Innate Immune Response

- Circulating monocytes
  - ↑ Antibody response around calving (Burton et al., 1993)
  - ↓ TNF-α and IL-2 production during peak lactation (Burton et al., 1996)
  - ↑ monocytes, glucose, *IGF1* and *SLC2A3*; ↓ TNF-α production; Primi- > multi-parous cows mid-lactation (Garcia et al., 2016 under review)
- Circulating PMN
  - ↑ *TNFA* during peak lactation (Yuan et al., 2014)
  - ↑ % PMN in early lactation (Yasui et al., 2014)
- Cr improves anti-inflammatory response for heat-stressed cows in mid-lactation
  - ↑ IL-10 and IκBα (Zhang et al., 2014)

Mechanistic Action of Chromium (Cr)

- Cr and glucose metabolism
  - Modulates tissue response to insulin (Vincent, 2004)

Serum concentration of insulin around calving
(Adapted From Ingvartsen et al., 1995)



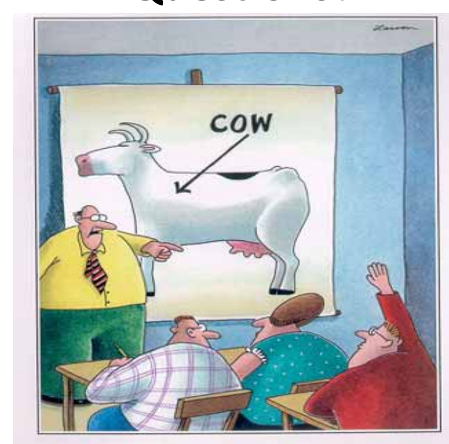
Insulin receptors on leukocytes in cows

- Leukocytes use insulin-independent receptors (GLUT-1 and GLUT-3) for glucose uptake
- Insulin receptors are present on bovine monocytes with low expression on PMN (Nielsen et al., 2003)
  - Insulin receptors stimulate leukocyte functions (Spagnoli et al., 1995)
  - Suggests insulin plays a role in PMN recruitment???
- Cr supplementation improve bovine monocyte insulin response?

Take-Home Messages

- Most cows immunosuppressed around calving
- Major nutrients that change around calving alter immune response
  - Glucose + glutamine = 
  - Ketones = 
  - Fatty acids = ???
- Vitamins/Minerals alter immune response
  - VE + Se = 
  - Chromium =  ??
    - Altered by age, physiological state, stage of lactation, other stressors

Questions?



"Yes…I believe there is a question in the back"