Interactions of Inflammation and Metabolism in Transition Dairy Cows

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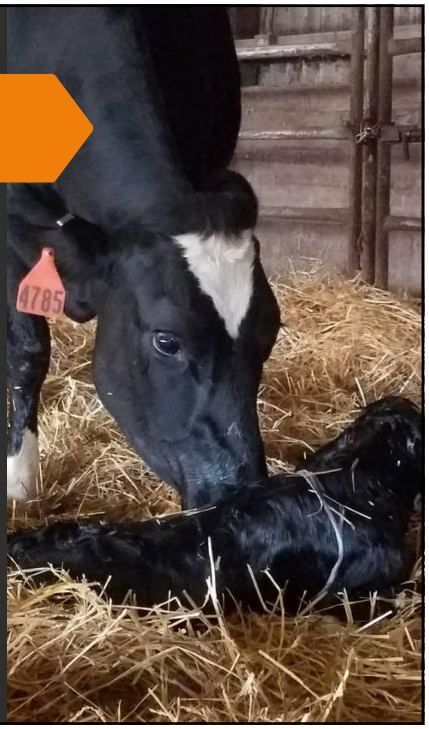
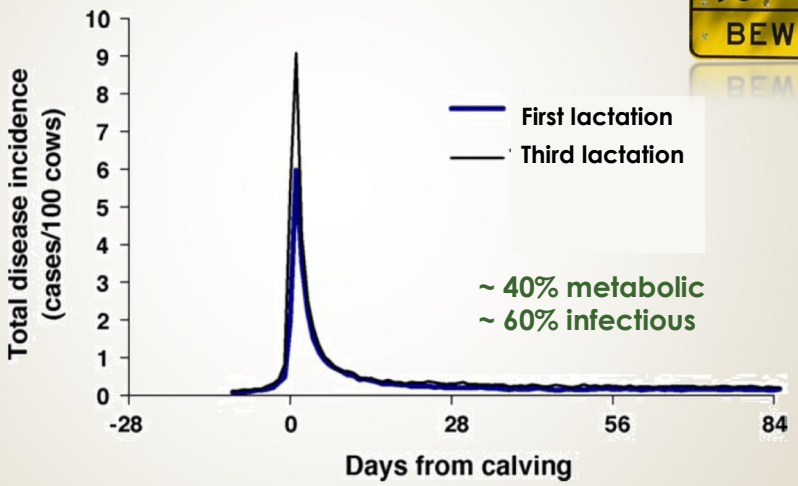
OUTLINE

- Transition inflammation: the evidence
- Physiological roles for inflammation
- Metabolic impacts of inflammatory signaling
- Mammary and lactation responses

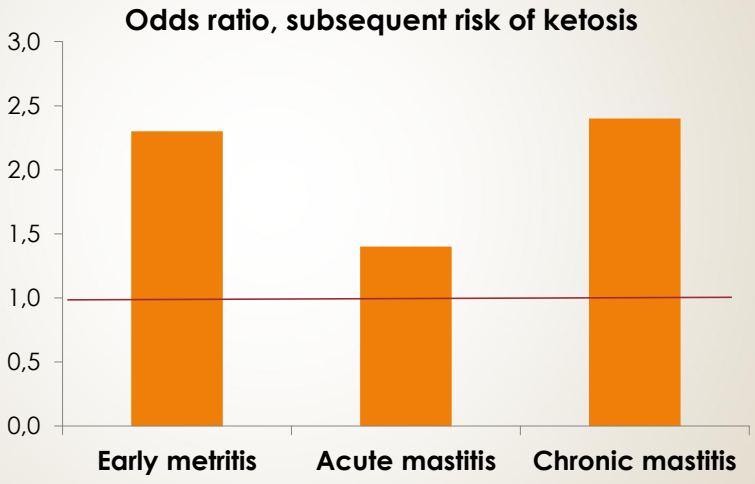


The transition period



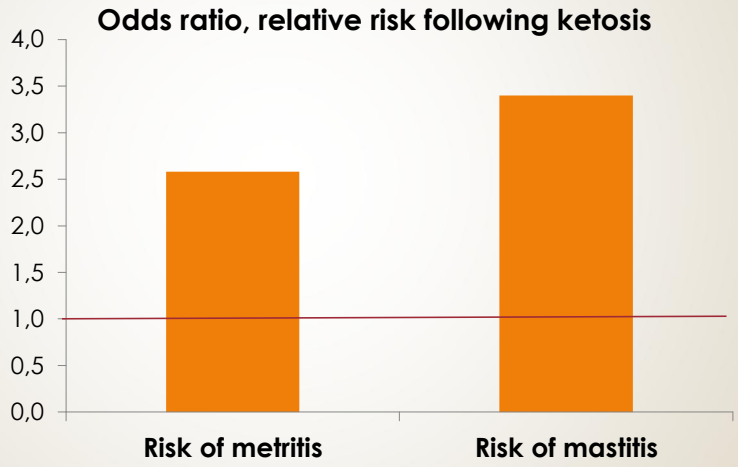
Ingvartsen, 2006

Infections increase ketosis risk



Gröhn et al., 1989

Ketosis increases infection risk



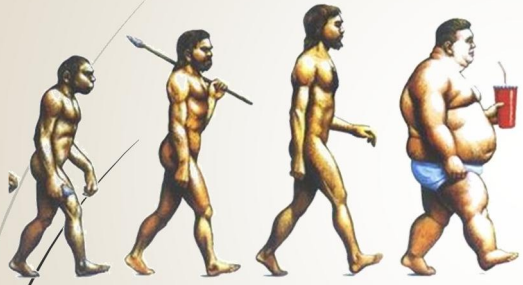
Duffield et al., 2009; Doohoo and Martin, 1984

Inflammation

Acute inflammation

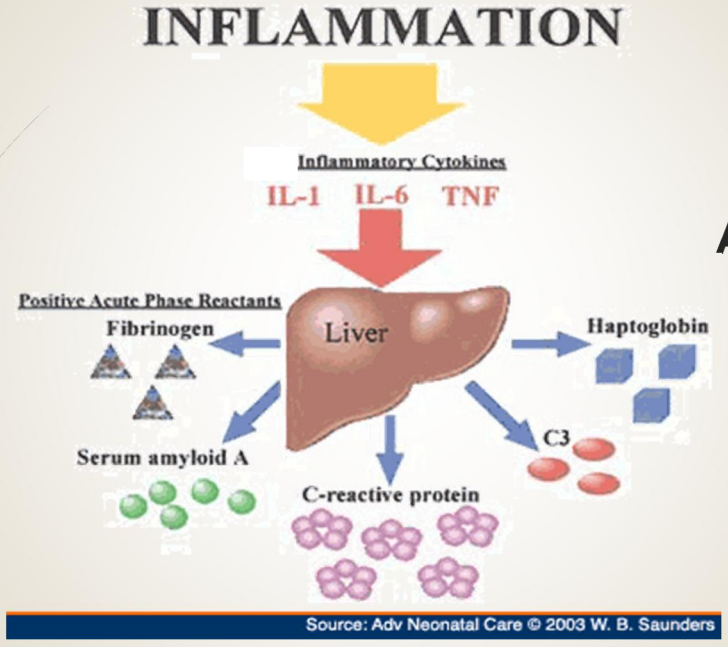
- Associated with immune activation or tissue damage
- Swelling
- Pain
- Fever

Inflammation



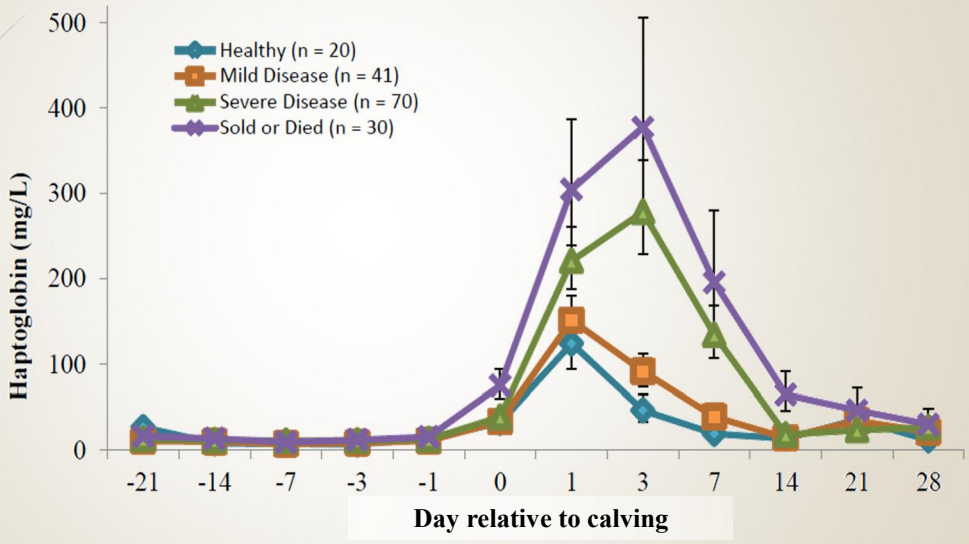
Chronic inflammation

- No outward signs
- Slightly elevated inflammatory mediators
- Alterations in signaling



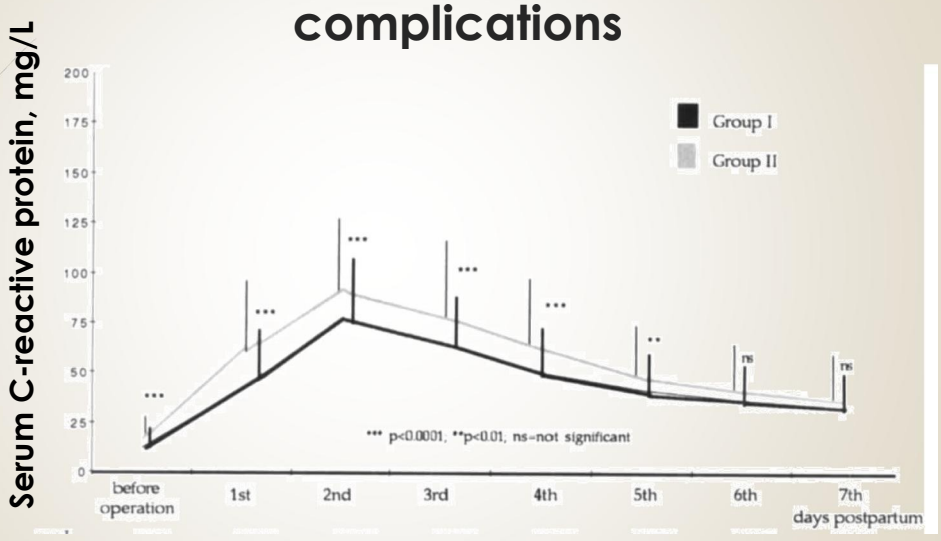
Acute phase proteins

Subacute liver inflammation is common in postpartum cows



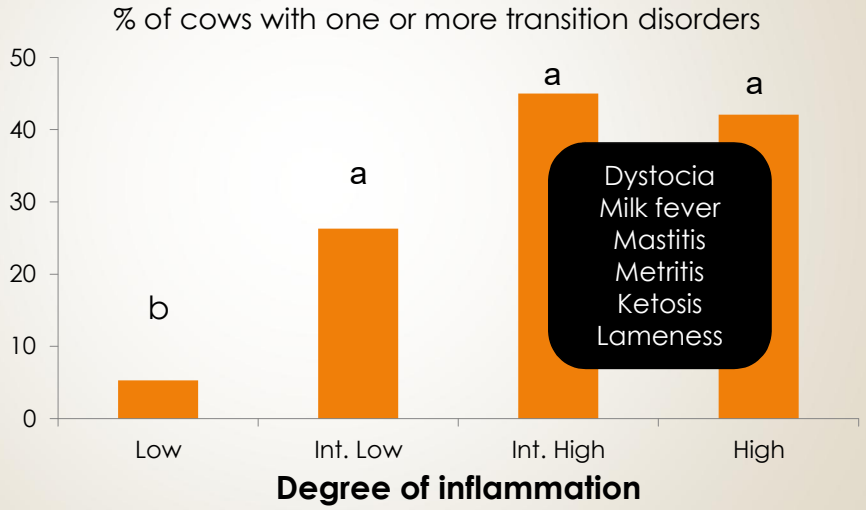
Sabedra, 2012 (thesis)

...and in women, even in the absence of complications



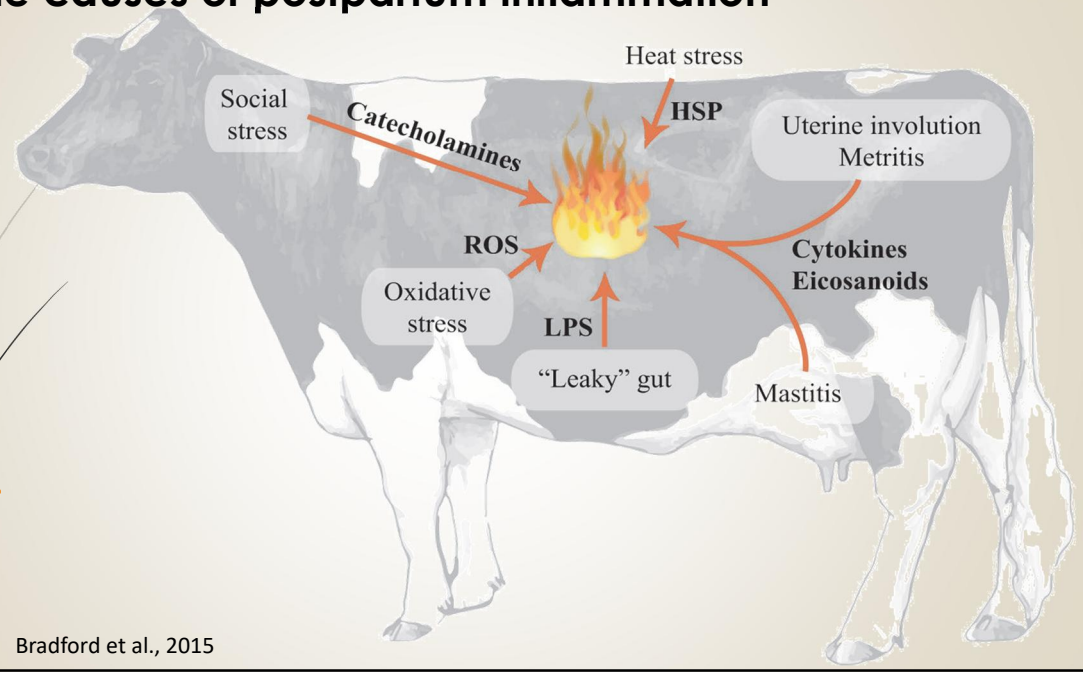
Keski-Nisula et al., 1997

Inflammation is associated with transition disorders



Bertoni et al., 2008

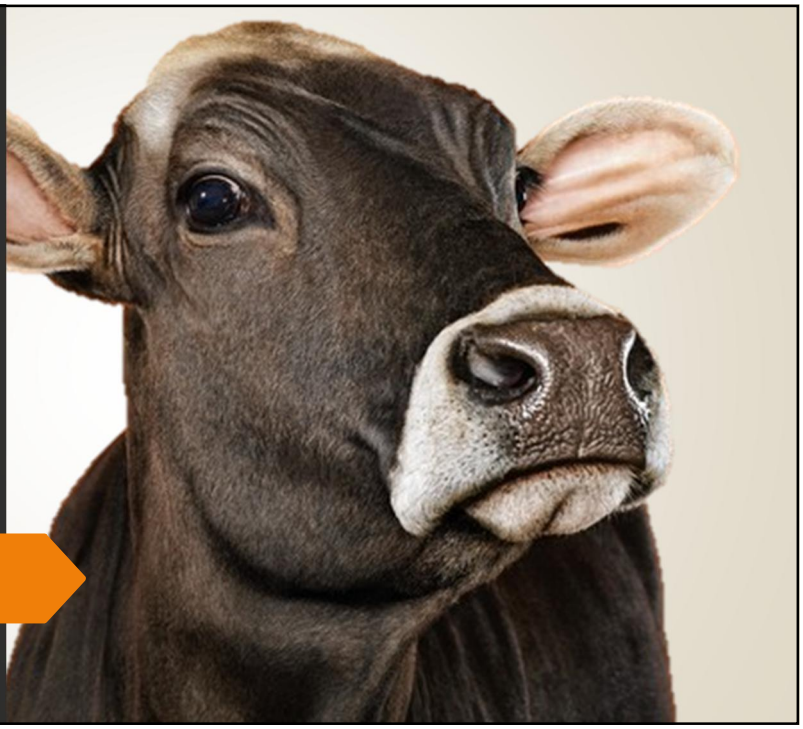
Plausible causes of postpartum inflammation



Bradford et al., 2015

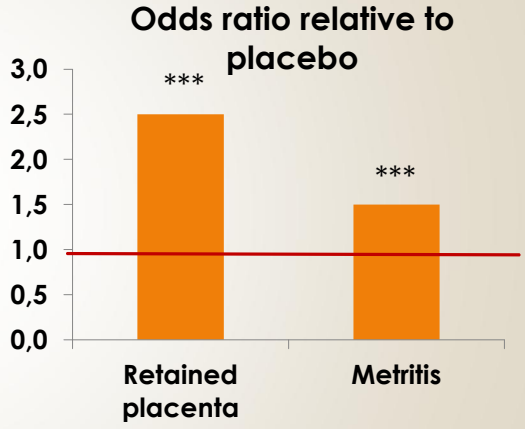
What's the role of "normal" peripartum inflammation?

Parturition



Immediate postpartum anti-inflammatory

- Flunixin meglumine given 2 h and 24 h after calving
- Over 1,300 cows enrolled

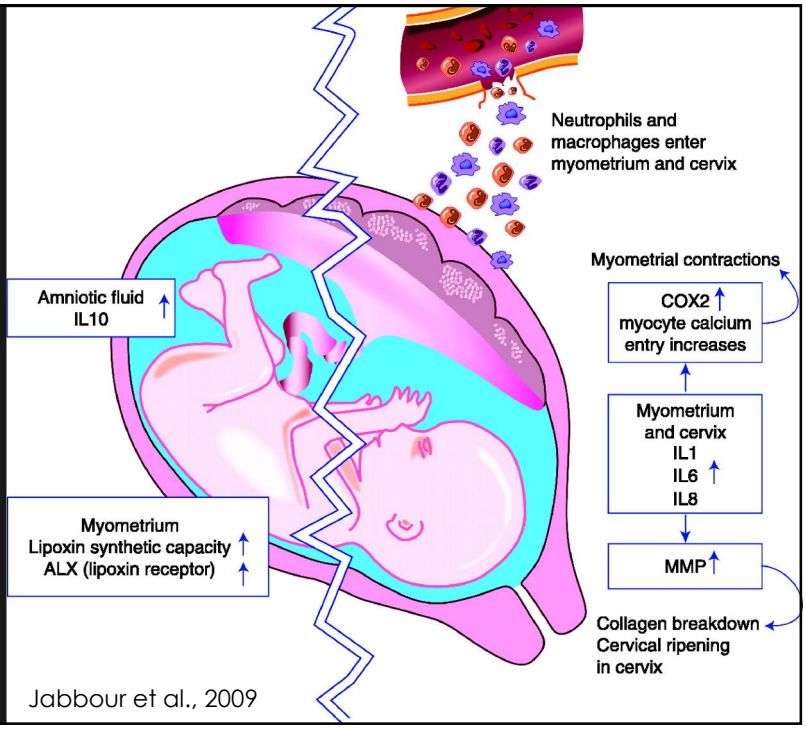


Blocking inflammation on the day of calving can interfere with inflammatory signals needed to expel the placenta

Newby et al., 2017

Inflammatory signals are essential for parturition

1. Stimulate release of proteases
2. Promote contractions
3. Interact with prostaglandin synthesis pathways



Jabbour et al., 2009

Are there metabolic implications of postpartum inflammation?

Classification of cows according to BW loss postpartum

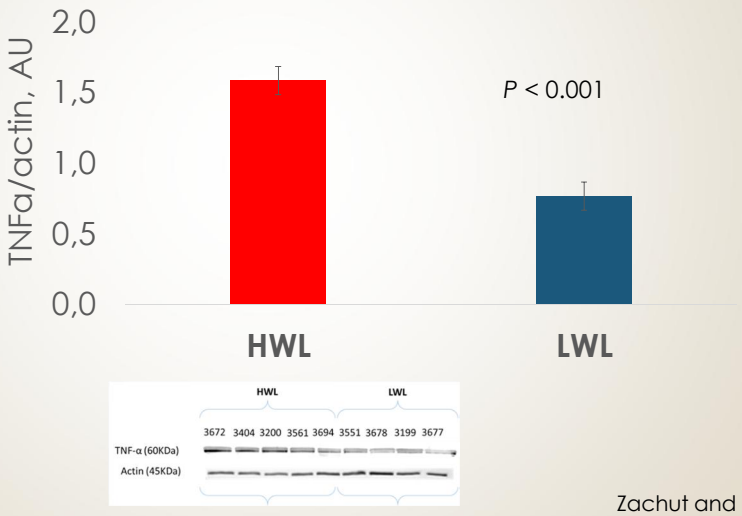
In retrospect, cows were divided according to % of BW loss during the first month postpartum:

1) **HWL** – High weight loss, lost more than the average of %BW loss (> 6%, on average 9%).

2) **LWL** – Low weight loss, lost less than the average of %BW loss (≤ 6%, on average 5%).

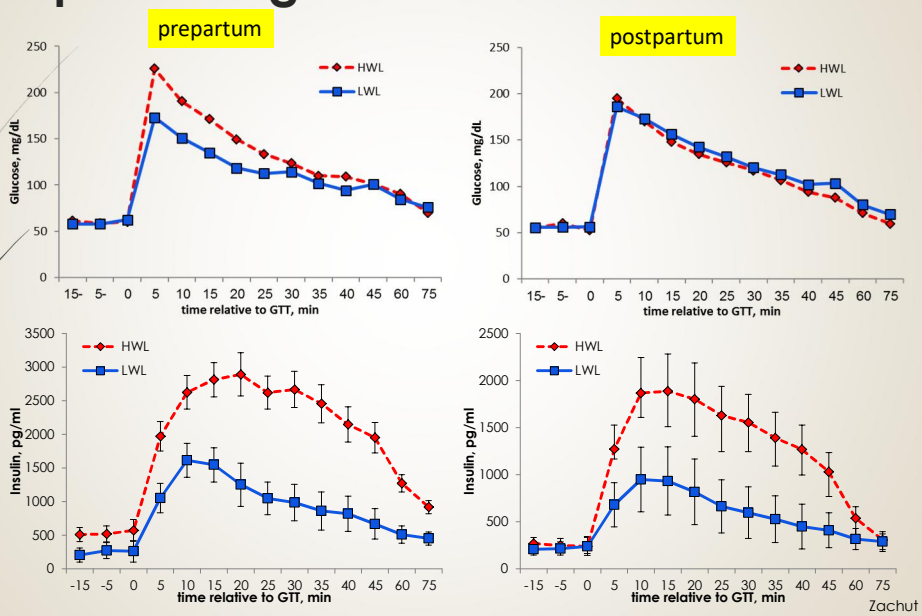
Zachut et al., 2013, 2015, 2017

Increased abundance of TNFα in adipose tissue of HWL cows at 7 d postpartum



Zachut and Moallem, 2017

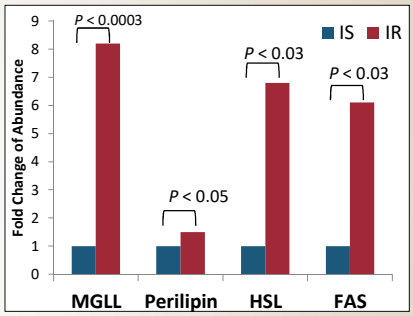
Response to glucose tolerance test



Zachut and Moallem, 2017

Lipolysis and inflammatory proteins higher in IR (HWL) adipose

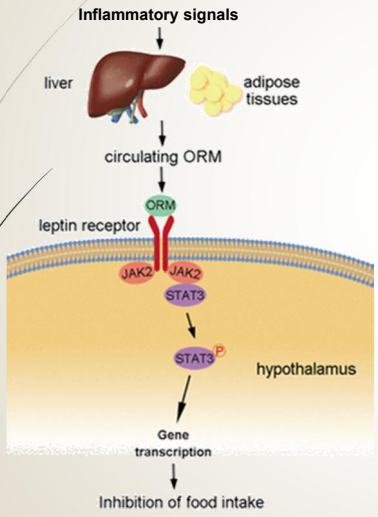
function annotation[a]	*P* value	no. of molecules
inflammatory response	0.0045	10
organization of actin cytoskeleton	0.0000	9
leukocyte migration	0.0040	11
homing of mononuclear leukocytes	0.0021	5
proliferation of T lymphocytes	0.0006	10
reorganization of cytoskeleton	0.0000	7



- Mono-glyceride lipase (**MGLL**)
- Perilipin-1 (**PLIN**)
- Hormone-sensitive lipase (**HSL, LIPE**)
- IR adipose → increased lipolysis

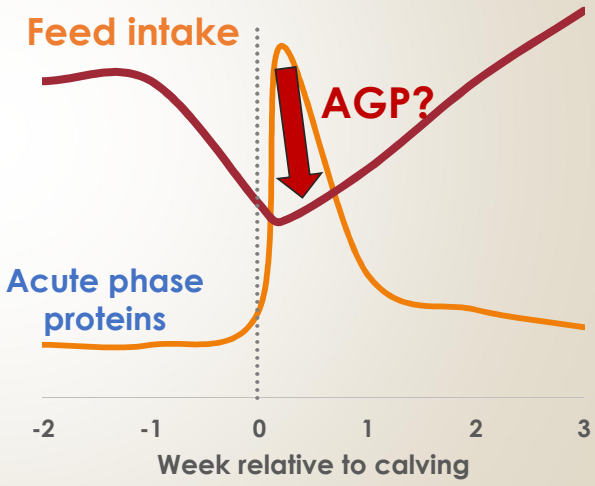
Zachut, J Proteome Research, 2015

Alpha-1 acid glycoprotein (AGP)

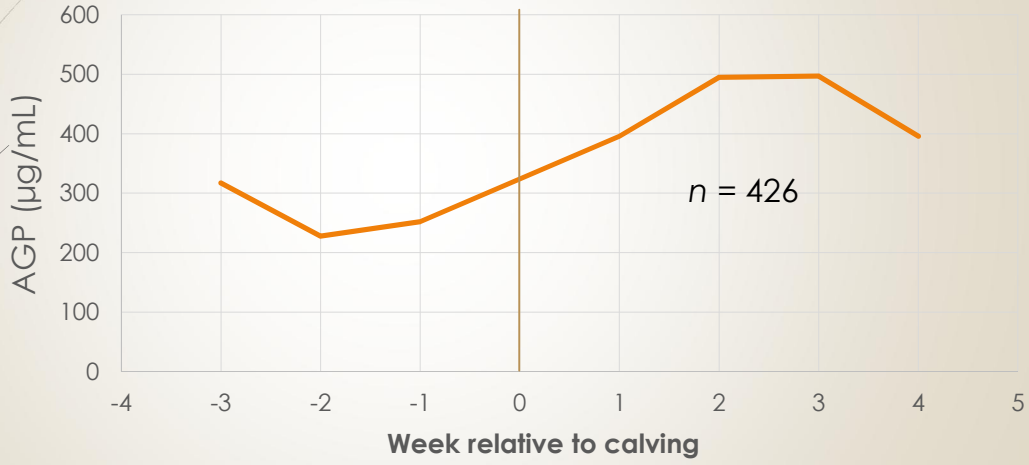


Sun et al., 2016

TRANSITION DAIRY COWS:

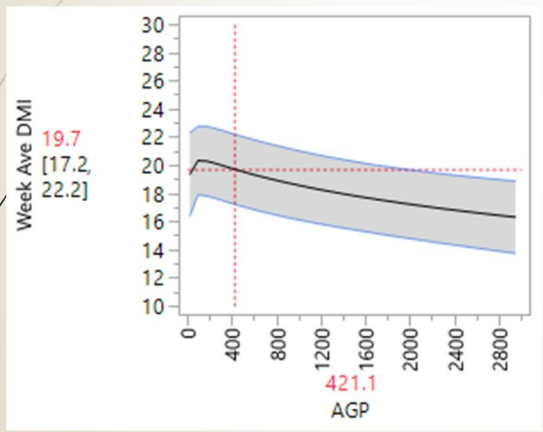


AGP in transition cows



Unpublished data, Bradford et al.

AGP associated with reduced intake

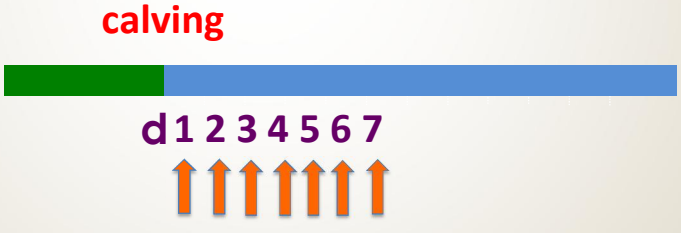


- AGP explained 20% of variation in within-farm DMI during weeks 1-4 postpartum ($P < 0.001$)
- Rising from the 25th percentile to the 75th is associated with a 1 kg/d drop in DMI

Unpublished data, Bradford et al.

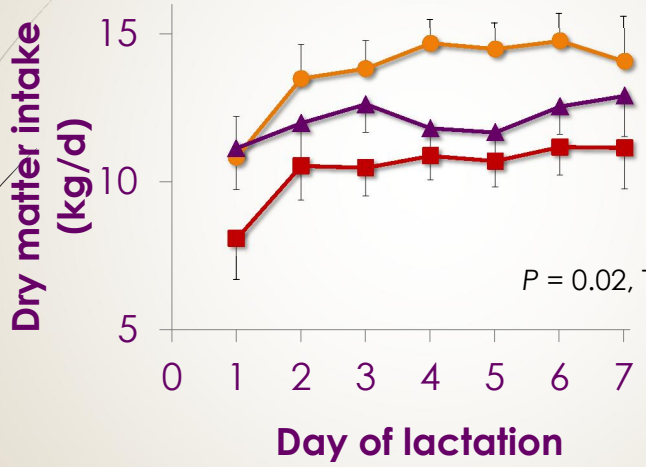
Do repeated inflammatory signals alter metabolism?

- 33 Holstein cows were assigned to 1 of 3 treatments (n = 11) at calving.
- 3 treatments: 0, 1.5, or 3.0 µg TNFα/kg BW.



Yuan et al., 2013

Inflammation suppresses intake



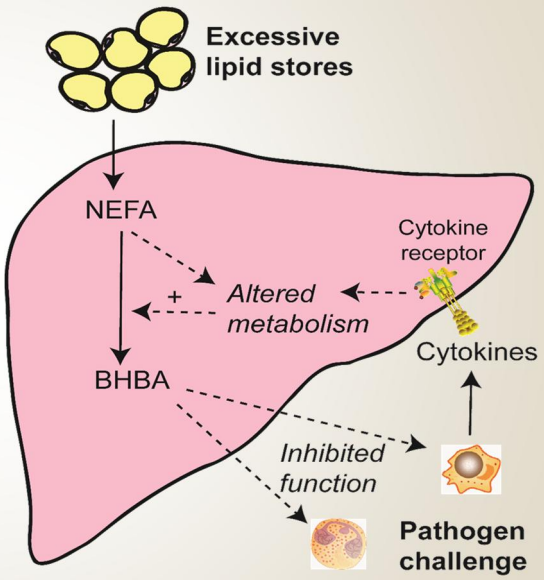
Subclinical Ketosis	
Control	9%
1.5 µg/kg TNF	27%
3.0 µg/kg TNF	27%

P = 0.02, TNFa vs. control (18% decrease)

Yuan et al., 2013

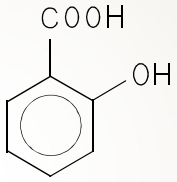
A vicious cycle?

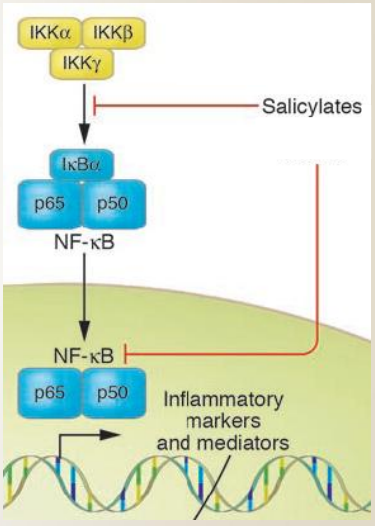
Metabolic disorders
promote
Infections
promote
Metabolic disorders



Anti-inflammatory drug salicylic acid

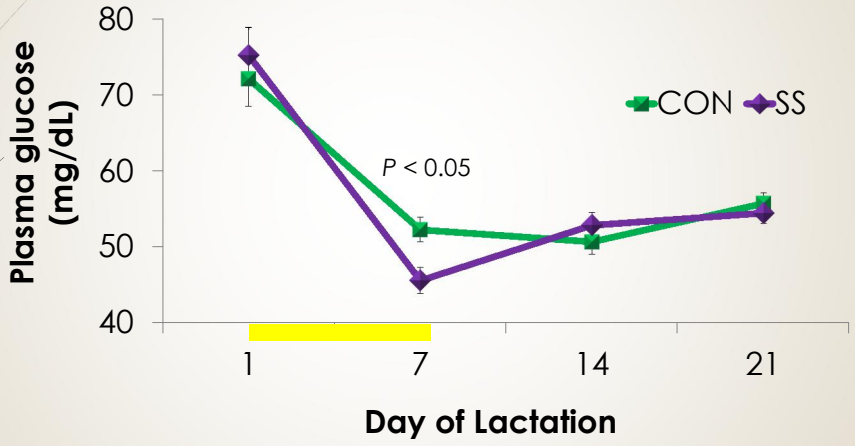
- The parent compound for aspirin
- Interrupts central inflammatory pathways found in most cells



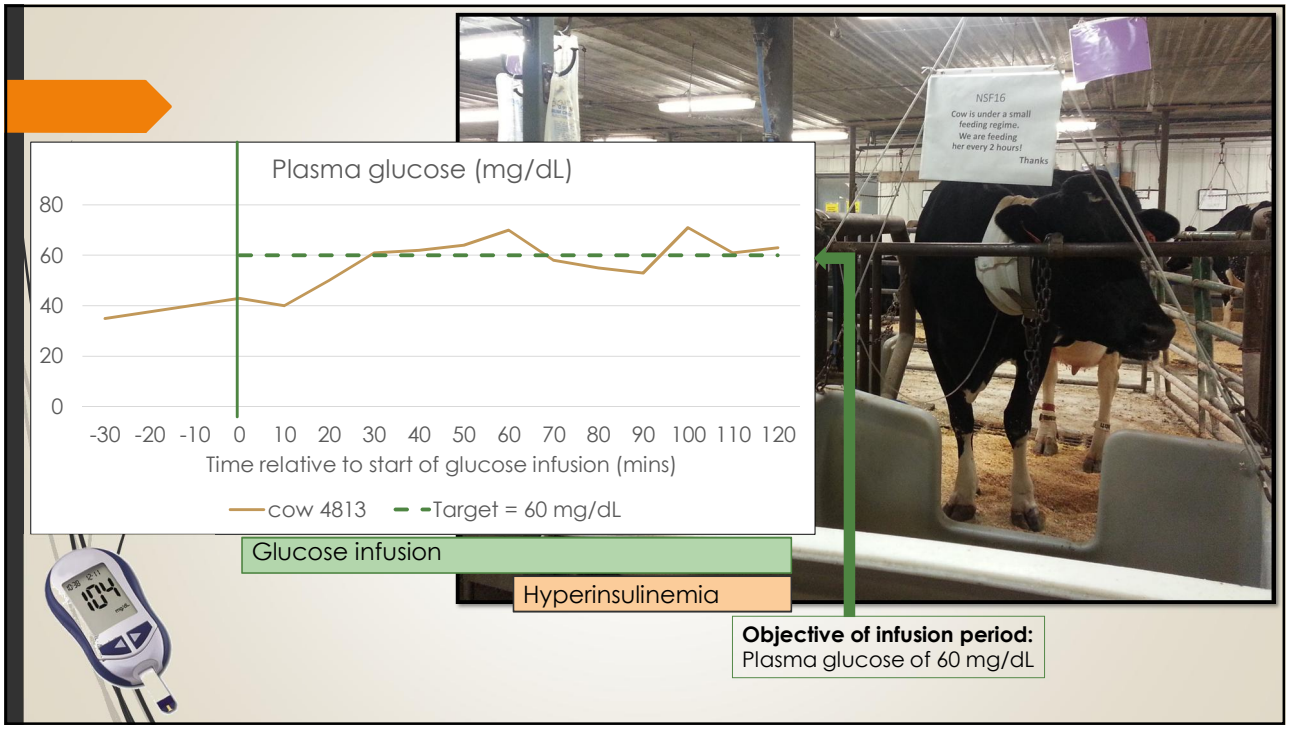


Shoelson et al., 2006

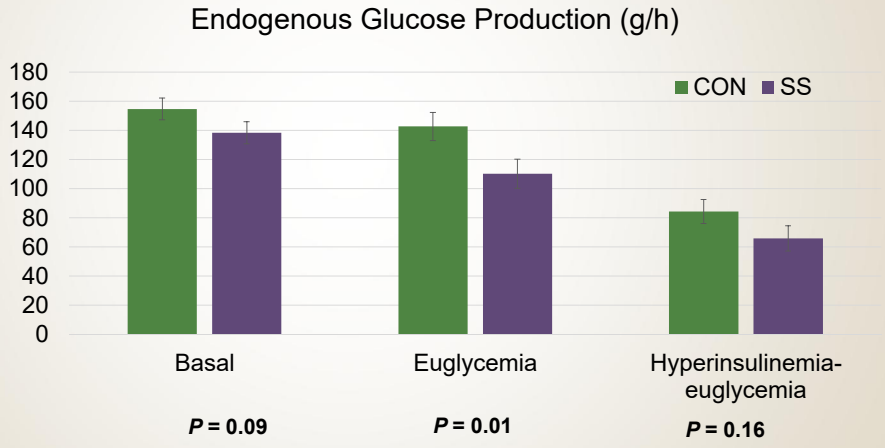
Salicylate induces mild hypoglycemia



Farney et al., 2013



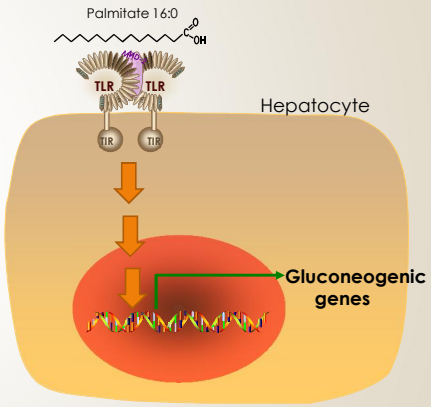
Is salicylate-induced hypoglycemia driven by enhanced insulin sensitivity?



Garcia, Ylioja, et al., 2018 (abstract)

Inflammatory pathways can promote gluconeogenesis

The saturated fatty acid palmitate promotes transcription of gluconeogenic genes by activating TLR4 (the LPS receptor)



Mamedova et al., 2013

Transition metabolism is a balancing act

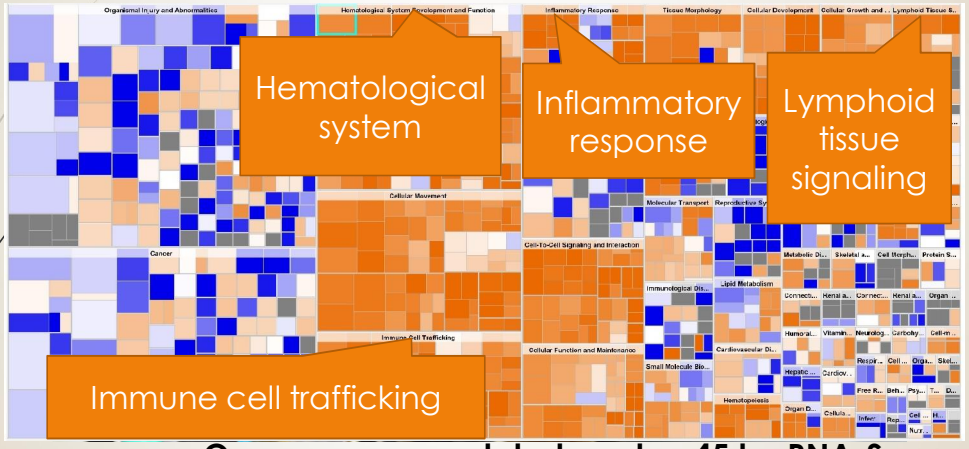
- Inflammation may help promote homeorhetic mechanisms to promote glucose synthesis and conservation
- Excessive inflammation impairs feed intake, drives lipolysis

Mammary responses

Inflammatory biomarkers predict lost milk

- Plasma concentrations of haptoglobin >1.1 g/L were associated with a 947 kg decrease in 305-day mature equivalent milk yield (Huzzey et al., 2015)
- Cows with haptoglobin concentrations greater than 0.1 g/L a week after calving produced 11% less milk in the first 2 months of lactation than those below that threshold (Shin et al., 2018)

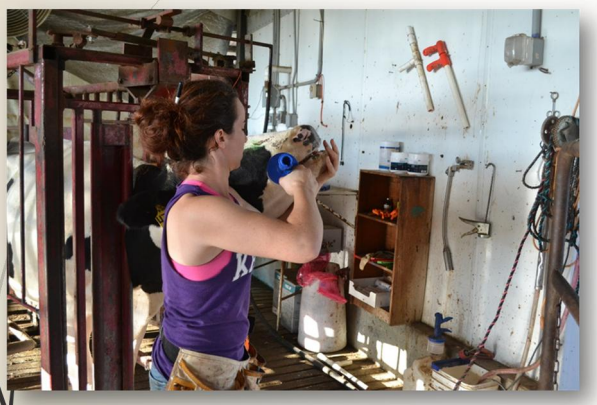
Processes activated on day 1 of lactation



Orange = up-regulated vs. day 45 by RNA-Seq

Ylioja et al., 2017 (Abstr.)

Postpartum NSAID study

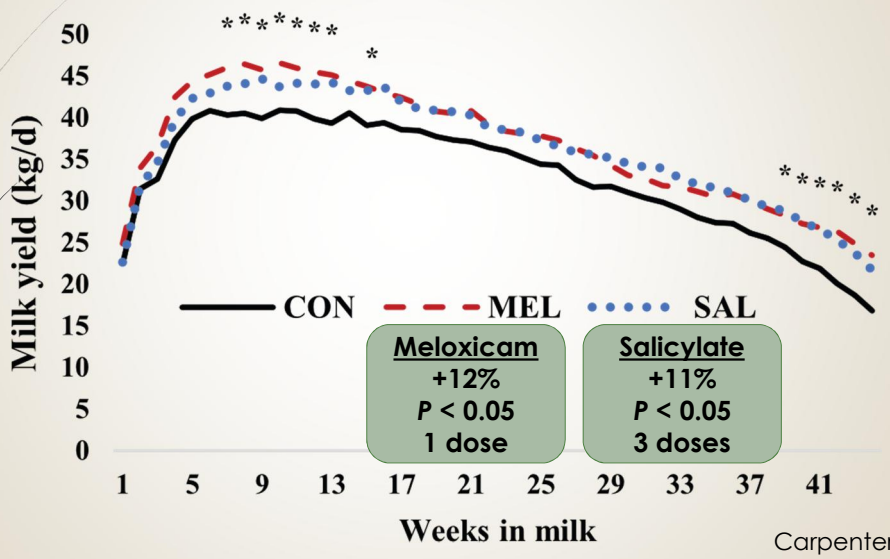


1. **Na salicylate**
2. **Meloxicam**
3. **Placebo**

- Administered orally starting 24 h postpartum
- 51 multiparous cows per treatment

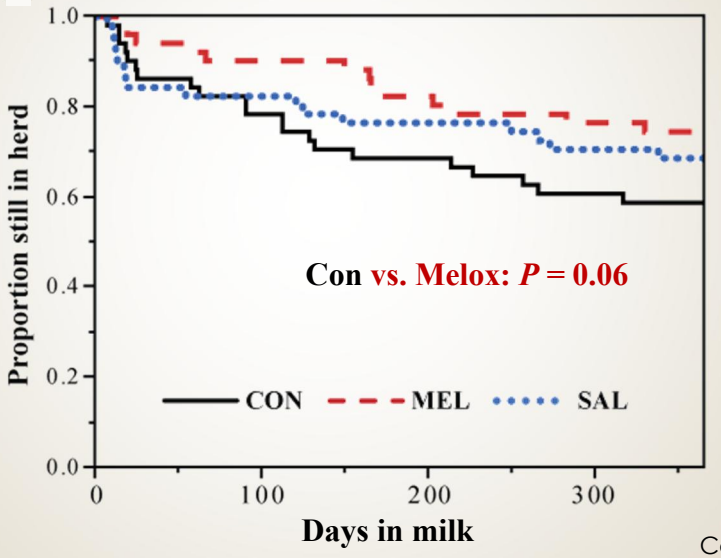
Carpenter et al., 2016

Anti-inflammatories in early lactation



Carpenter et al., 2016

Herd survival analysis

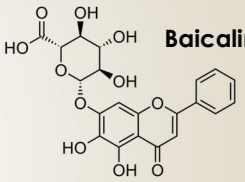


Carpenter et al., 2016

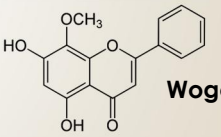
Chinese skullcap (*Scutellaria baicalensis*)

- Used in traditional Chinese medicine
- Liver-protective effects
- In vitro anti-tumoral effects
- Anti-inflammatory effects

→ Effects in dairy cows?



Baicalin

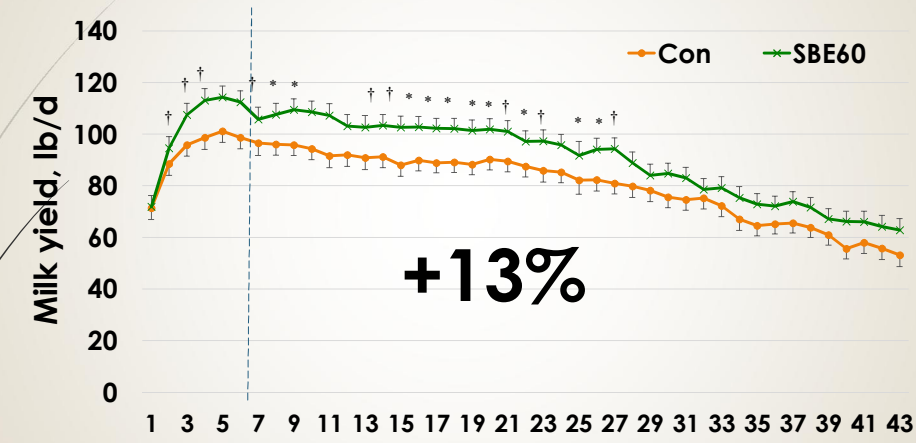


Wogonin

Scutellaria baicalensis extract experiment

- 40 multiparous cows per treatment
- Randomized block design
- Commercial dairy farm with an Automatic Milking system (AMS)
- Treatment pre-mixed in concentrate pellet

Whole-lactation response

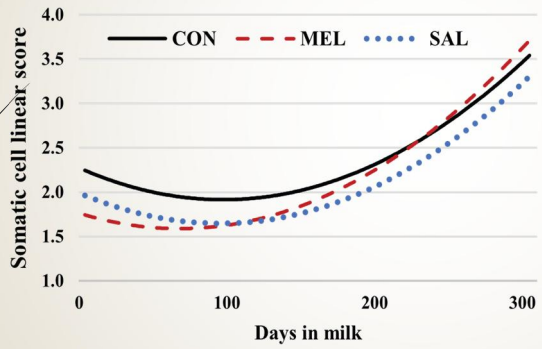


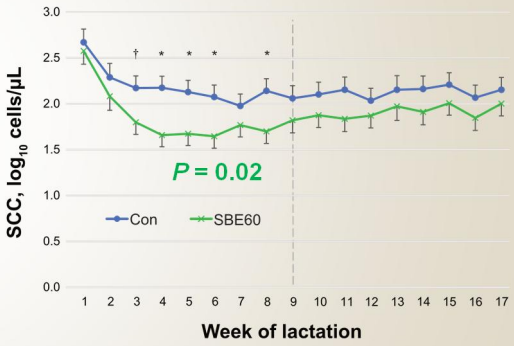
Con v. SBE60: *P* = 0.07

Con v. SBE60: *P* = 0.04

Olagaray et al., 2019

Decreased somatic cells point to reduced mammary inflammation

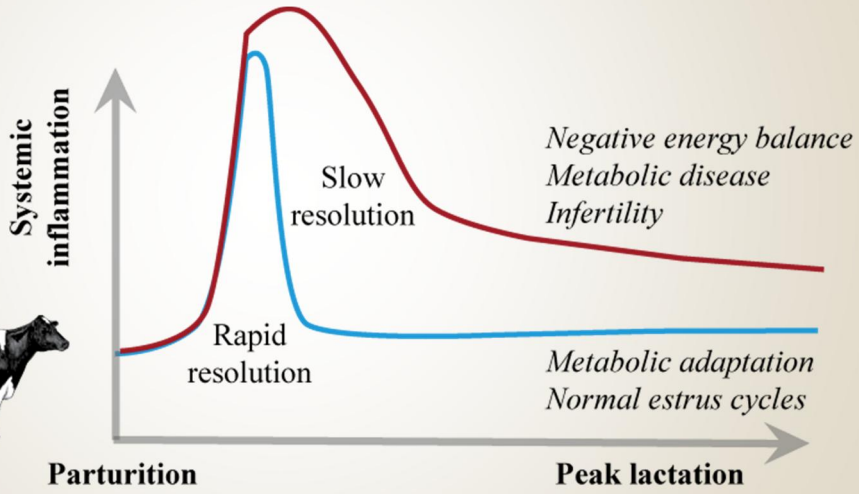




Carpenter et al., 2016

Olagaray et al., 2019

Hypothetical impacts of *unresolved* inflammation



Bradford et al., 2015

Acknowledgements

Dairy Metabolism Group

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Thank you!

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Any questions?