The Role of Ceramide in the Dairy Cow: an Overview of Current Understanding

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Why the Interest in Ceramides?

OPEN

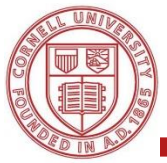
Mechanistic interplay between ceramide and insulin resistance

Federico Reali[1,2,*], Melissa J. Morine[1,*], Ozan Kahramanoğulları[1,2,*], Suryaprakash Raichur[3], Hans-Christoph Schneider[4], Daniel Crowther[4] & Corrado Priami[1,2]

Cell Metabolism
Essay

Could Ceramides Become the New Cholesterol?

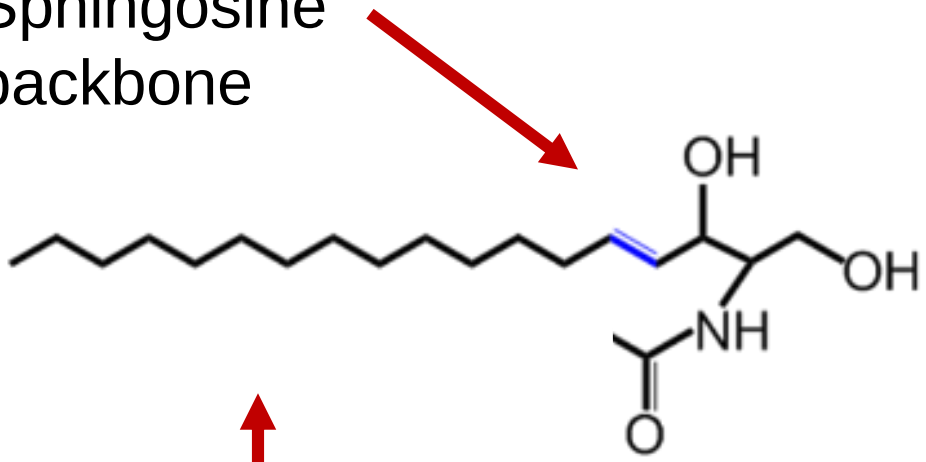
Scott A. Summers[1,*]



What are Ceramides?

- Sphingolipids found in cell membranes
- Serve structural and functional purposes

Sphingosine backbone

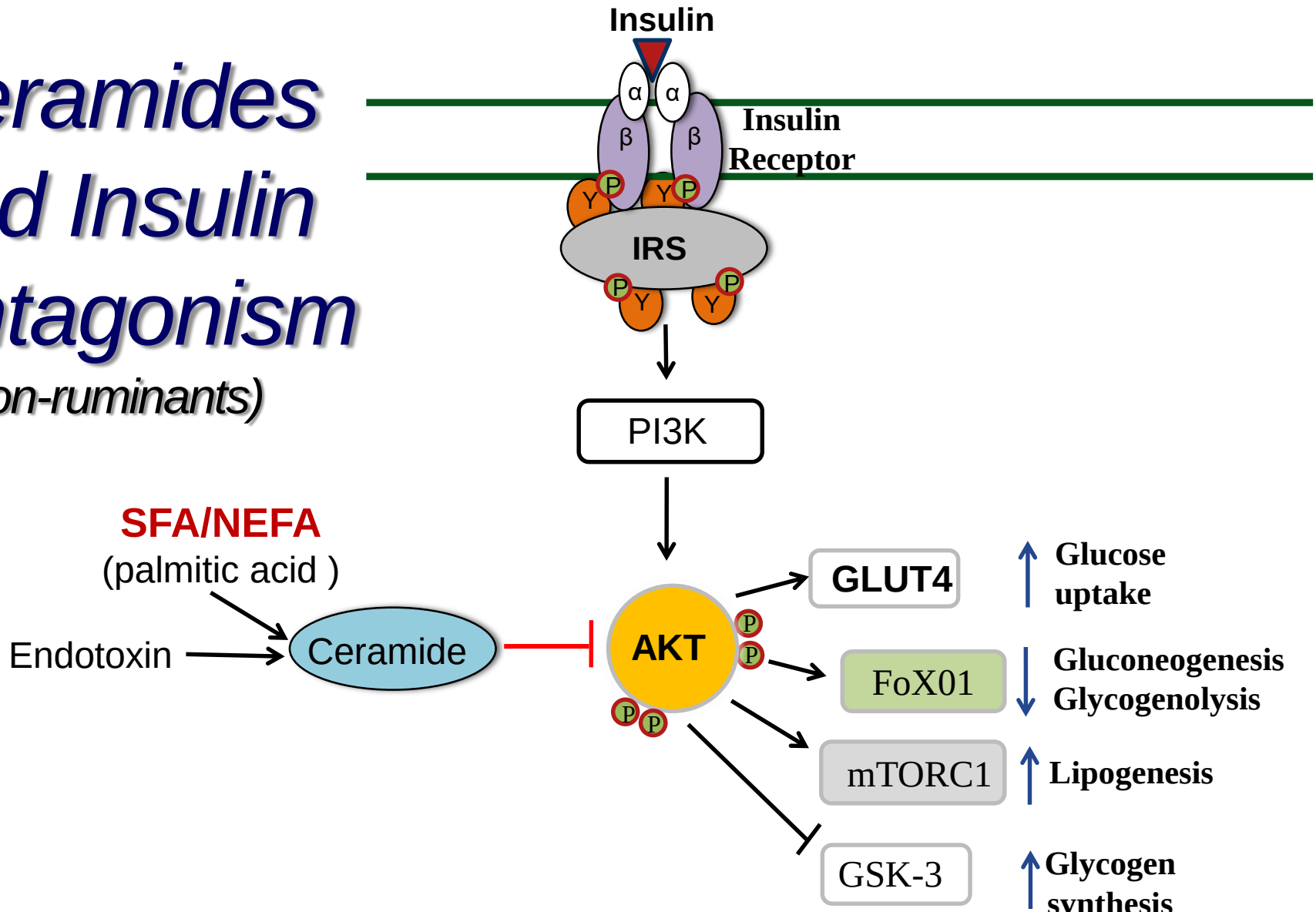


CERAMIDE

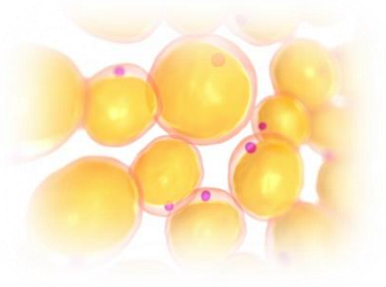
Fatty acid

Ceramides and Insulin Antagonism

(in non-ruminants)



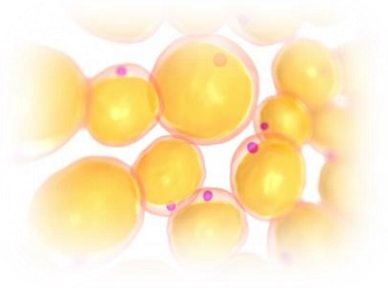
Uncontrolled Lipolysis During Peripartum



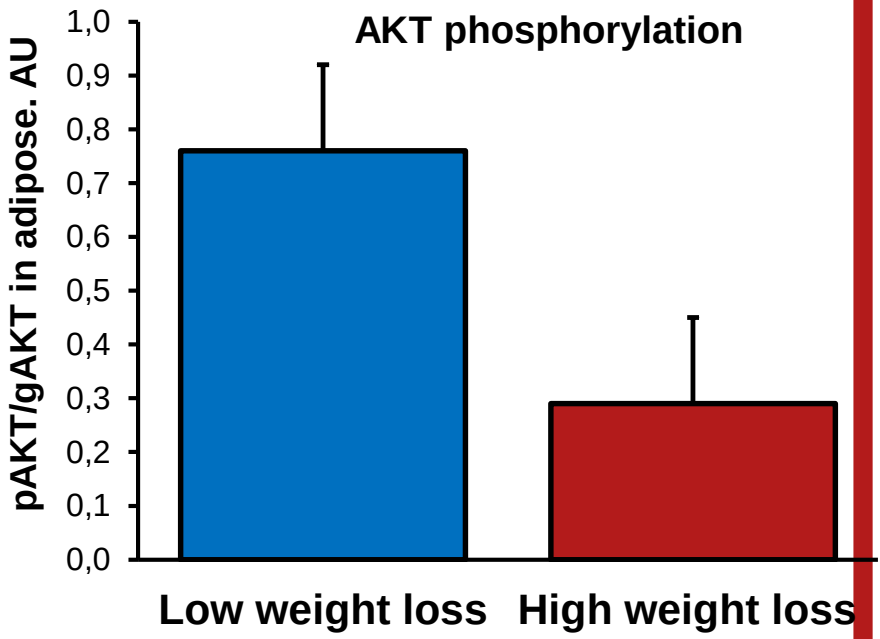
- Excessive lipolysis is associated with increased risk for peripartal diseases.

Le Marchand-Brustel, *et al*., 2003; Holtenius *et al*., 2003; Pires *et al*., 2010; Zachut et al., 2013.

Uncontrolled Lipolysis During Peripartum



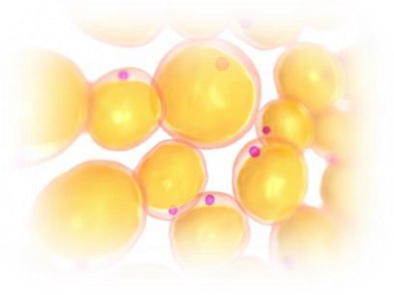
- Excessive lipolysis is associated with increased risk for peripartal diseases.
- Adipose tissue-specific insulin resistance occurs postpartum in cows with accelerated lipolysis.



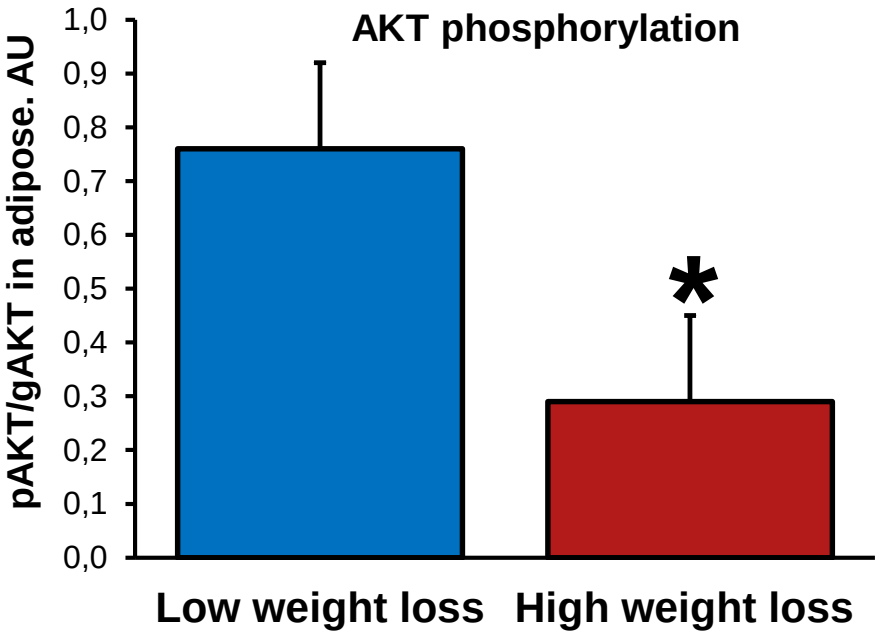
Adapted from Zachut et al., 2013

Le Marchand-Brustel, *et al*., 2003; Holtenius *et al*., 2003; Pires *et al*., 2010; Zachut et al., 2013.

Uncontrolled Lipolysis During Peripartum



- Excessive lipolysis is associated with increased risk for peripartal diseases.
- Adipose tissue-specific insulin resistance occurs postpartum in cows with accelerated lipolysis.
- High NEFA is associated with insulin resistance via incompletely understood mechanisms.



Adapted from Zachut et al., 2013

Le Marchand-Brustel, *et al*., 2003; Holtenius *et al*., 2003; Pires *et al*., 2010; Zachut et al., 2013.

Metabolomics has Transformed our Understanding

Biological Question

?

Experimental Design

- *In vivo* or *in vitro* model
- Expected variation
- Population parameters

Sampling

- Plasma/Serum
- Tissues
- Urine
- Cell lysate
- Saliva
- Food

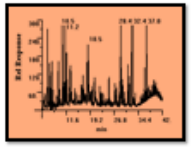
Sample Preparation

- Extraction
- Dry-down
- Derivatization
- Internal standards
- Reconstitution

Data Acquisition

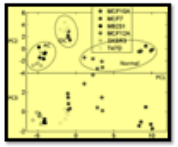
- Analytical platform
- Instrumentation method
- External standards

Data Processing



- Normalization
- Peak alignment
- Peak validation

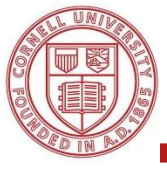
Statistical Analysis



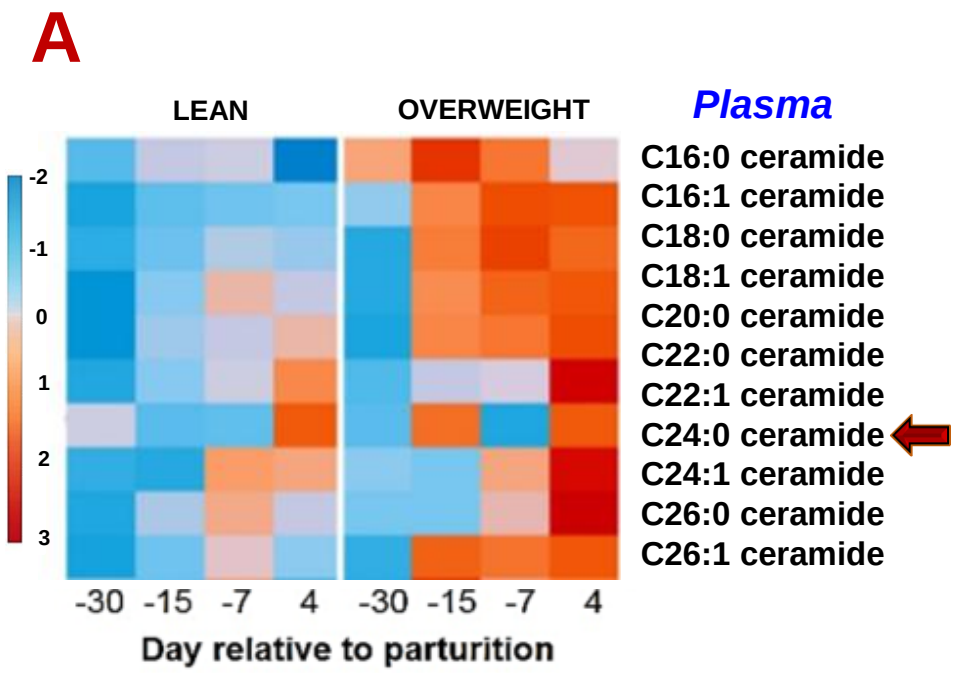
- ANOVA
- Principal component analysis
- PLS cluster analysis

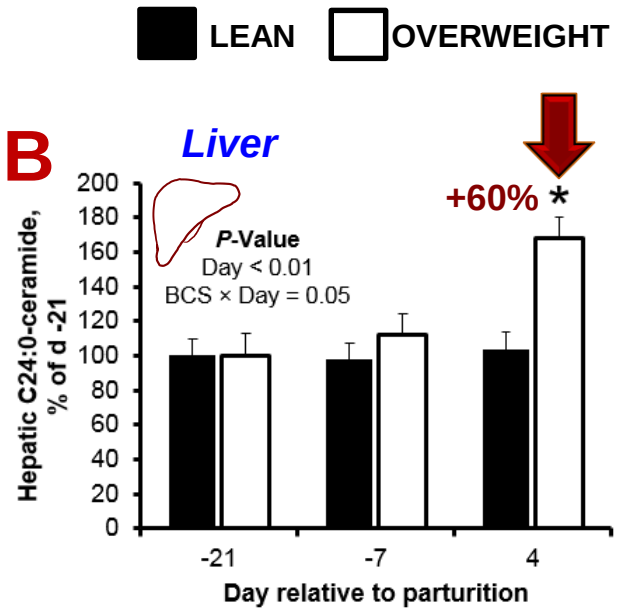
Interpretation

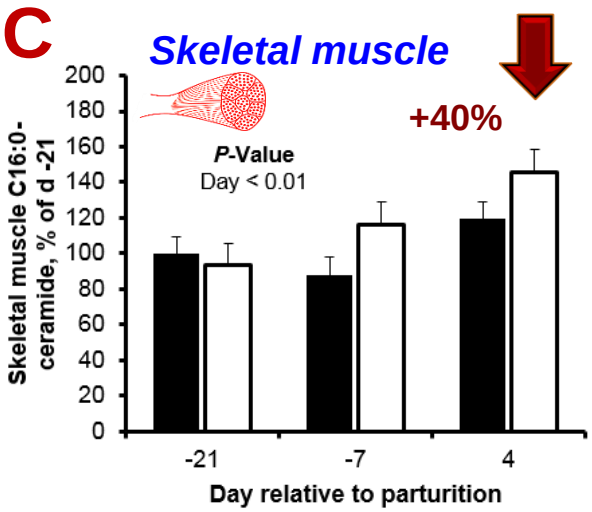
!



Ceramide Accrual Develops During Peripartum





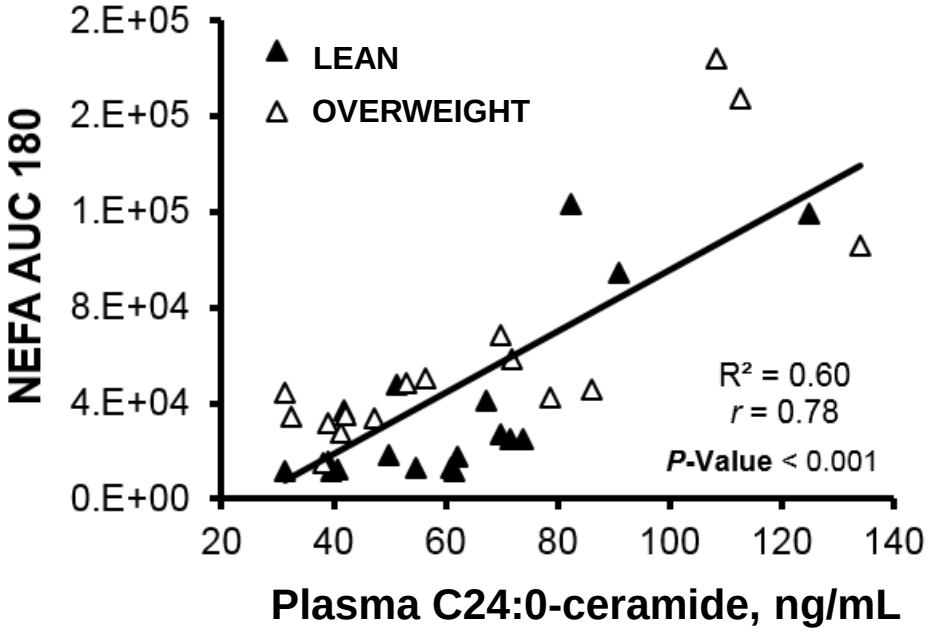


*, $P < 0.05$

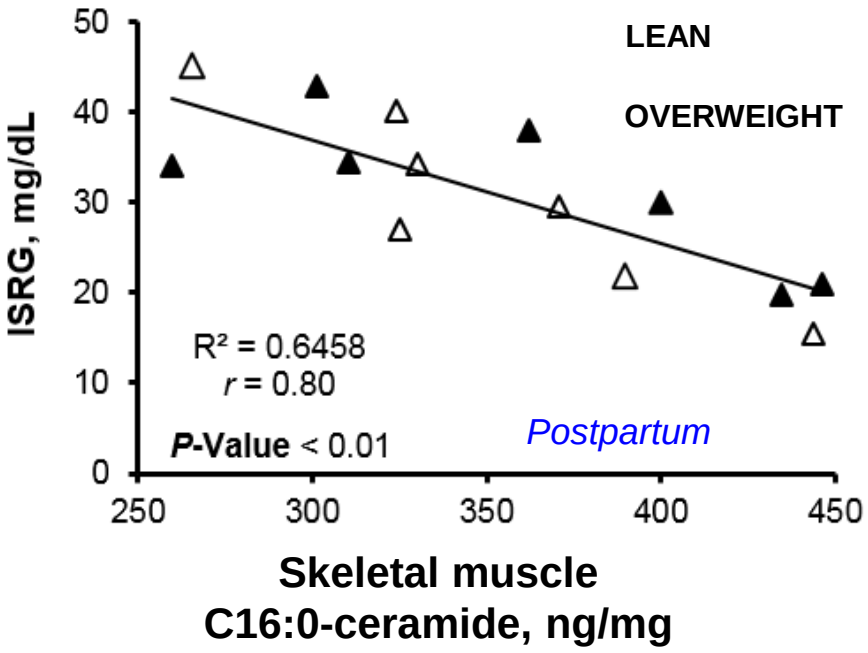
Rico et al., 2015, 2017

Ceramide is Inversely Related to Insulin Sensitivity

A *GTT; measure of lipolysis*



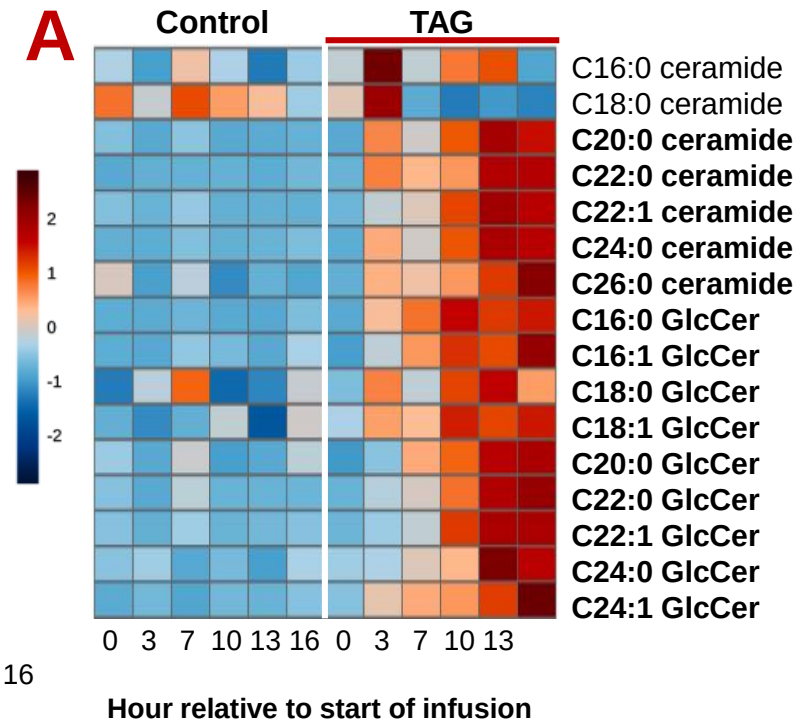
B *ITT; Systemic insulin sensitivity*

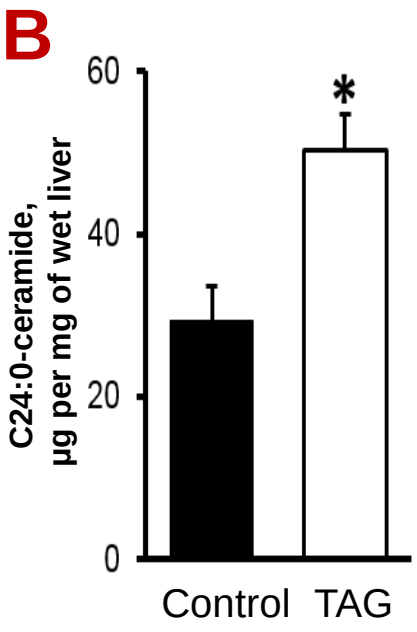


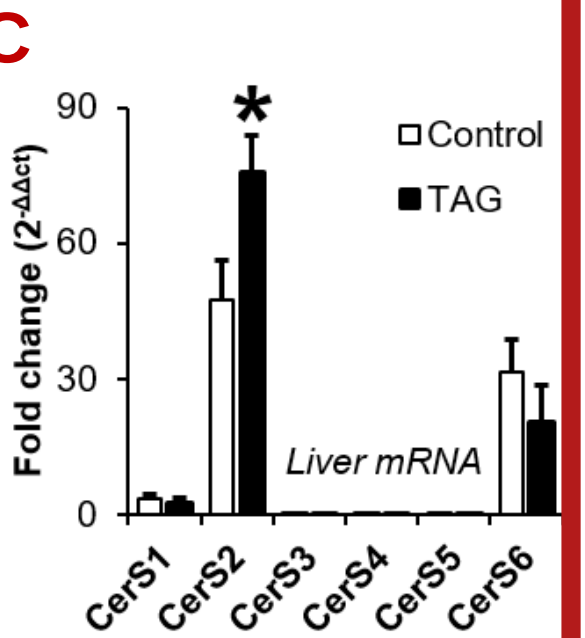
ISRG: Insulin-stimulated reductions in glucose

Rico et al., 2017

Inducing Hyperlipidemia Increases ceramide Synthesis







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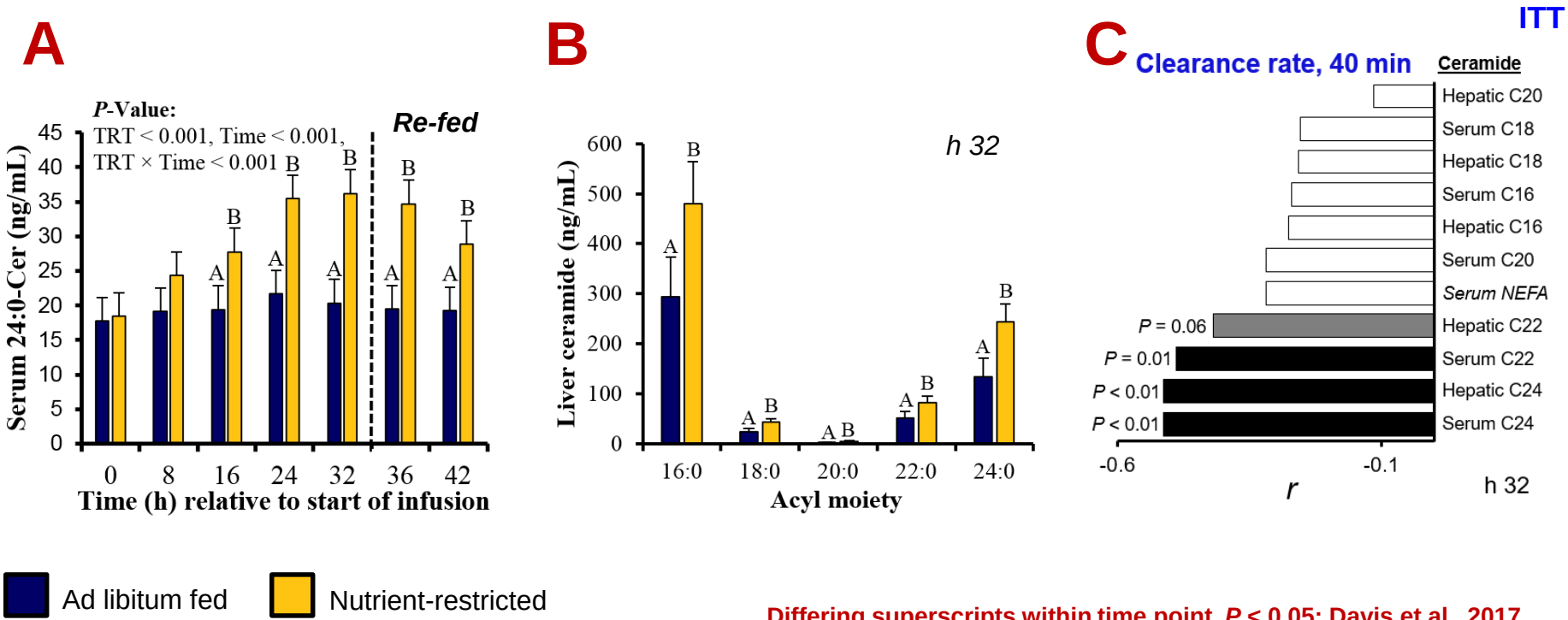
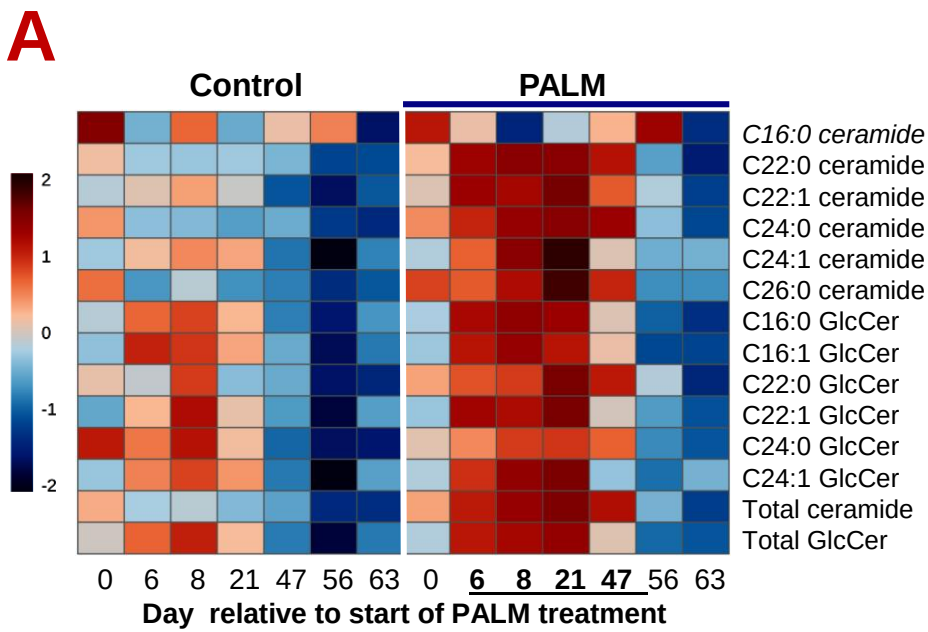
i.v. TAG infusion; GlcCer = Monohexosylceramide; bold or *, *P* < 0.05; Rico et al., 2018

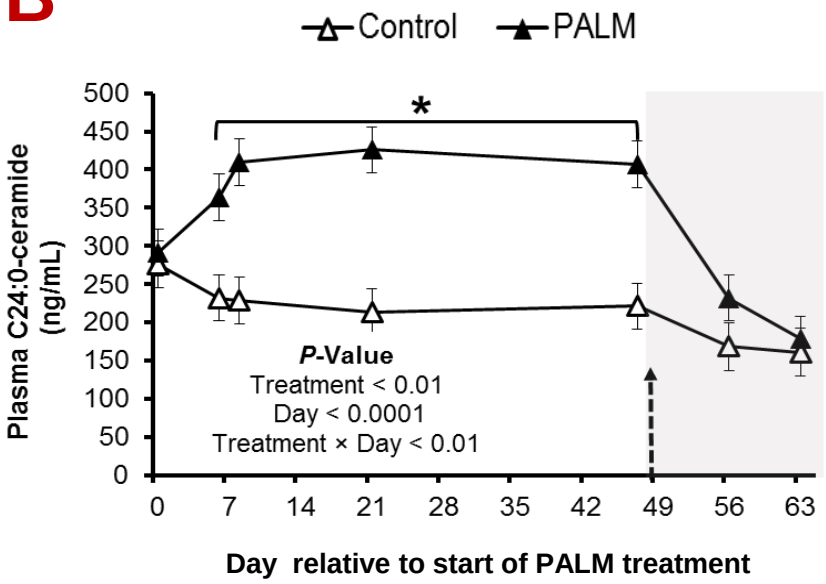
Nutrient Restriction Increases Ceramide in Cows Experiencing Insulin Intolerance



Differing superscripts within time point, $P < 0.05$; Davis et al., 2017

Palmitic Acid Feeding Increases Plasma Ceramide

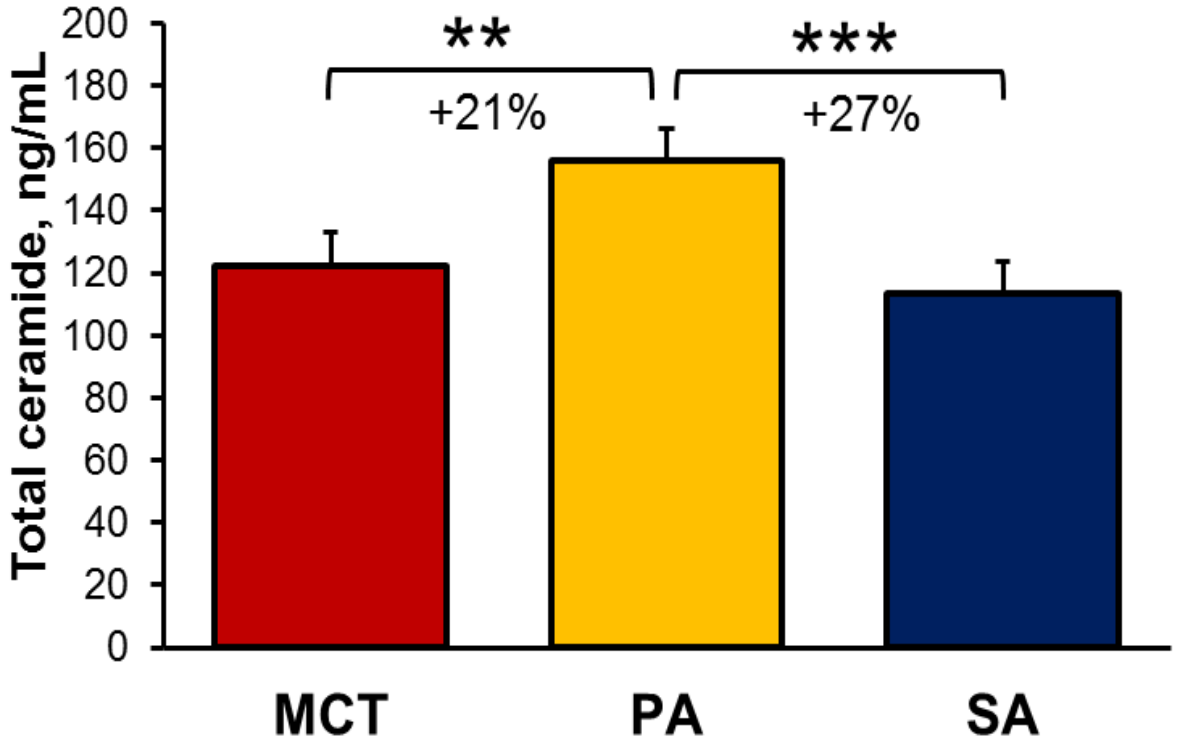




Palmitic acid feeding increased hepatic ceramide (wk 7).

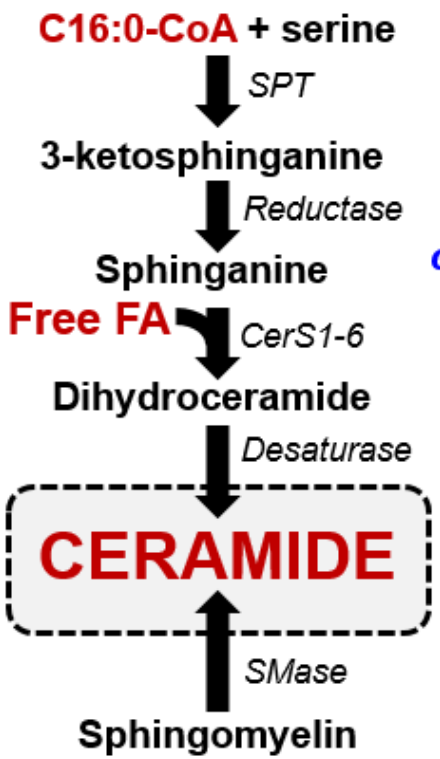
Mid-lactation cows (N = 20); *, *P* < 0.05; Rico et al., 2016

Palmitic Acid Increases Plasma Ceramide Relative to Other Saturated Fatty Acids



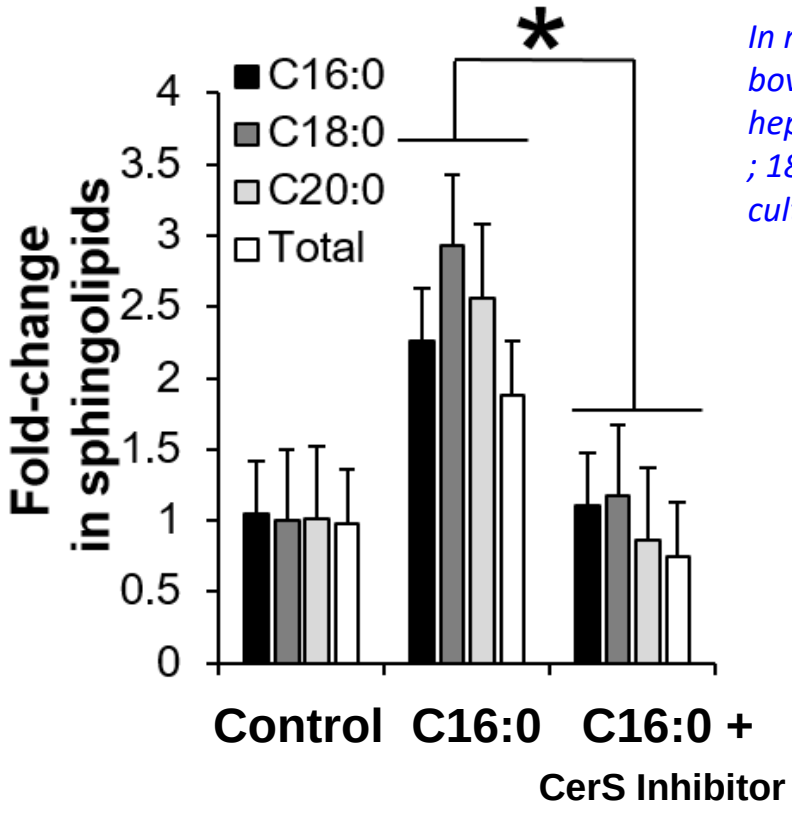
Plasma; **, *P* < 0.01; ***, *P* < 0.001; Rico et al., 2017, 2018 (ADSA Abstracts)

Palmitate Increases Hepatocyte Ceramide Synthesis



De novo ceramide synthesis

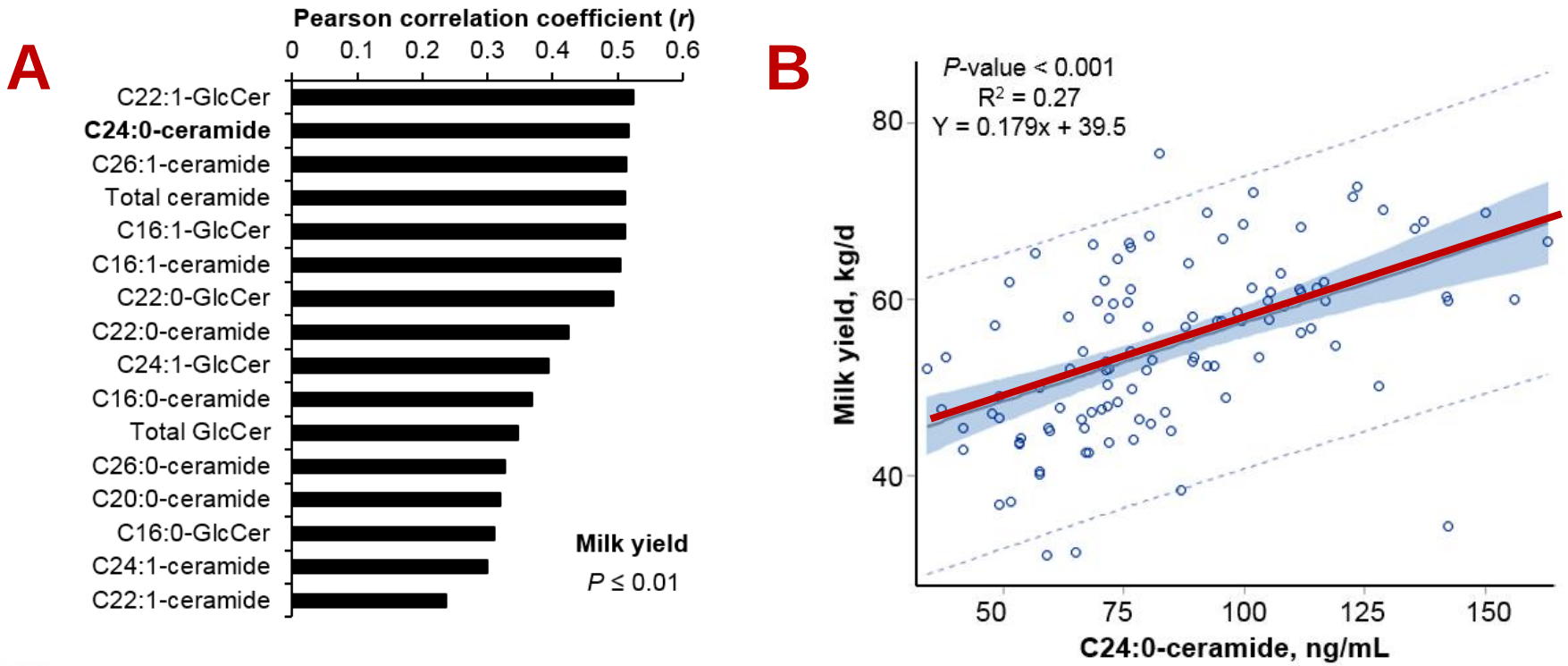
Sphingomyelin hydrolysis



In neonatal bovine hepatocytes ; 18 h culture

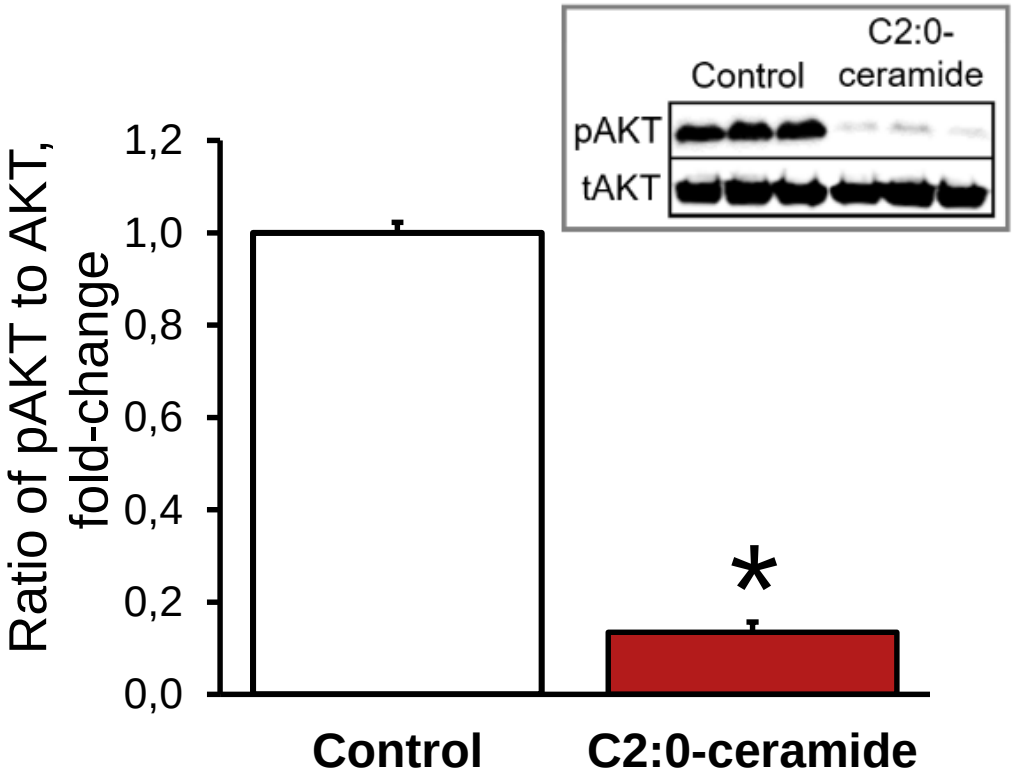
*, $P < 0.05$; McFadden et al., 2018 (ADSA Abstract); 4 calves for hepatocyte cultures, 3 reps/calf

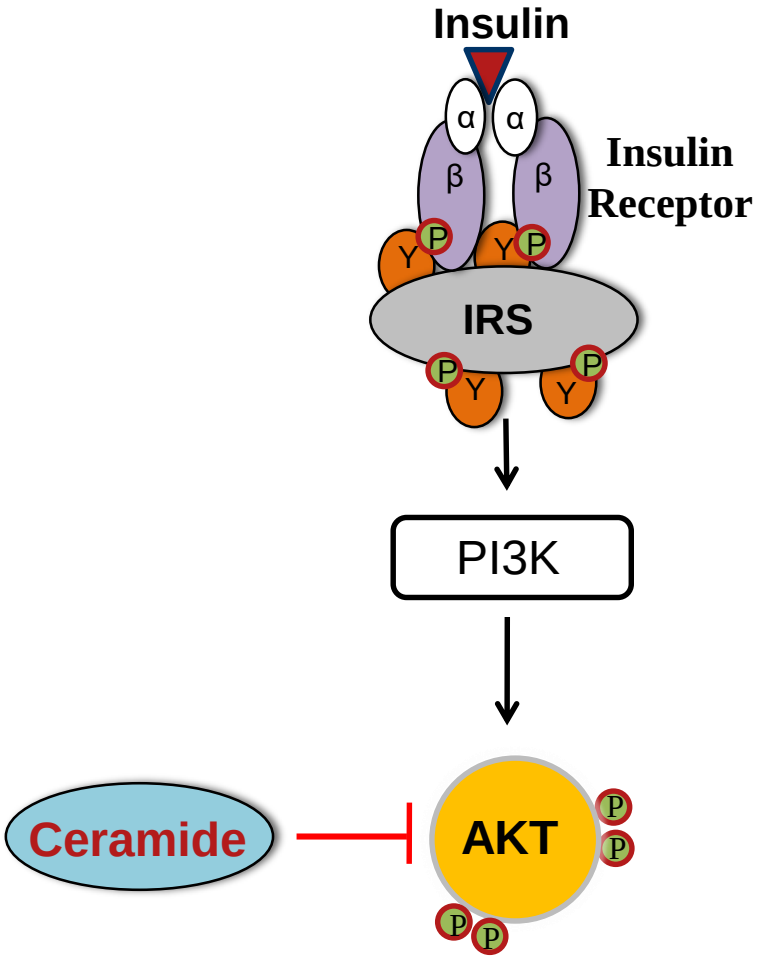
Circulating Ceramide is Consistently Positively Related to Milk Yield



Early lactation; Plasma; N = 37; Rico et al., 2016, 2017 (ADSA abstract); Davis et al., 2017 (ADSA abstract)

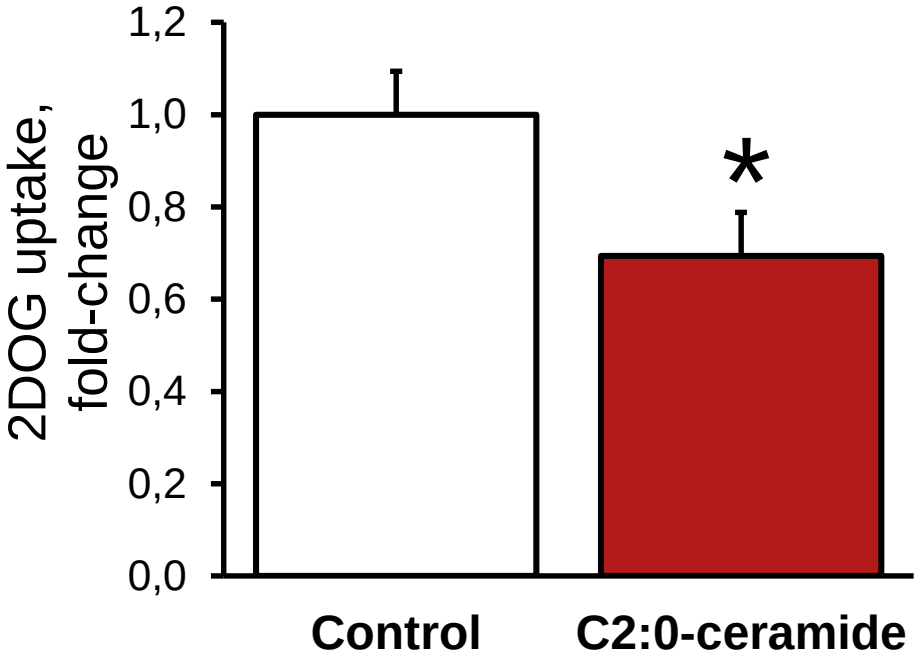
Exogenous Ceramide Inhibits Insulin Sensitivity via AKT

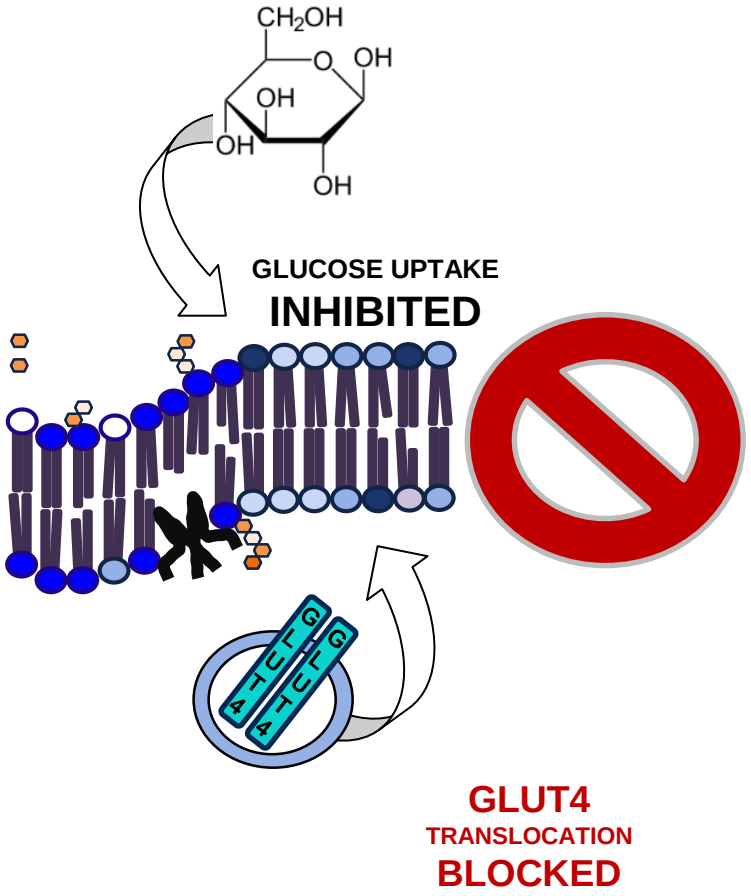




Primary bovine adipocytes; *, $P < 0.05$; Rico et al. 2018

Exogenous Ceramide Inhibits Glucose uptake

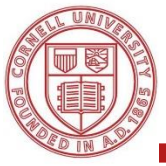




Primary bovine adipocytes; *, *P* < 0.05; Rico et al. 2018

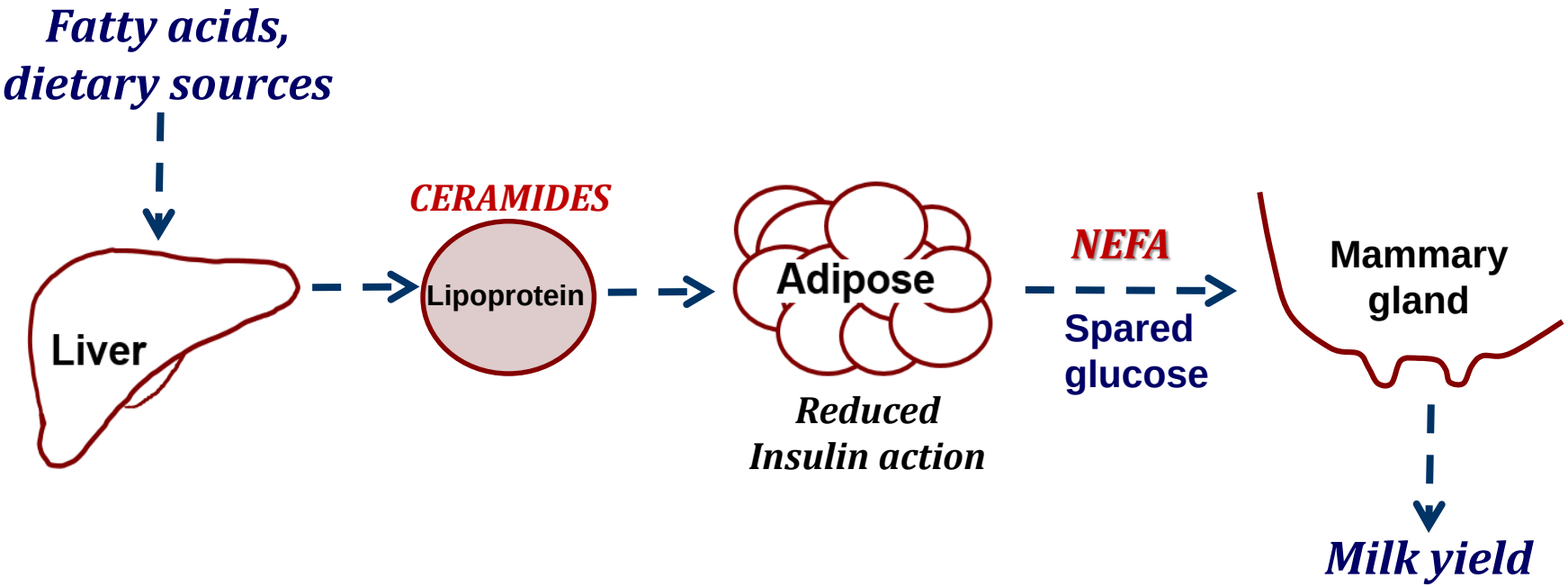
Summary of Findings

- Ceramide increases during the transition from gestation to lactation and is associated with lipolysis and reduced insulin sensitivity
- Ceramide is produced by hepatic cells and can impair insulin sensitivity of adipose cells



Current Model & Future work:

The Adipose-Liver-Mammary Gland Axis



- *in vivo* effects of ceramides?
- Evaluate as biomarkers: <u>disease/productive life</u>

Acknowledgements

- **Trainees**
  - **Amanda Davis**
  - **William Myers**
  - **Ananda Fontoura**
  - Dr. Sina Saed Samii
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  - Mary Coleman
  - Hannah Bailey
  - Dr. Qi Zeng

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  - Dr. Heather White, University of Wisconsin
  - Dr. Susan Duckett, Clemson University

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Berg+Schmidt Functional Lipids

NSF

USDA NIFA United States Department of Agriculture National Institute of Food and Agriculture


Thank You!

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Questions?

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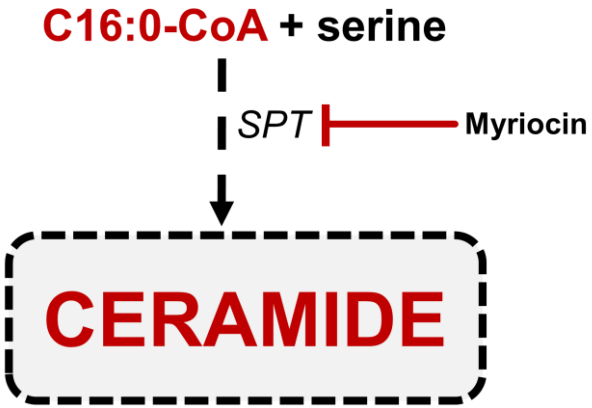
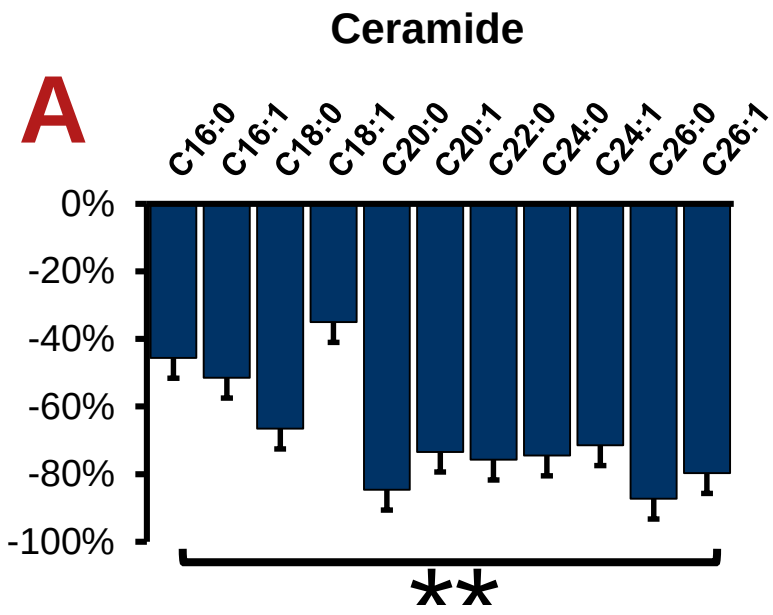
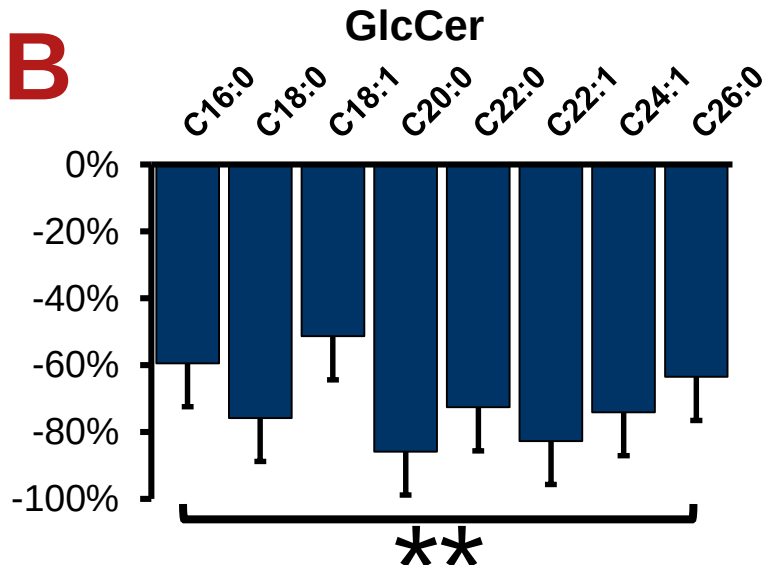
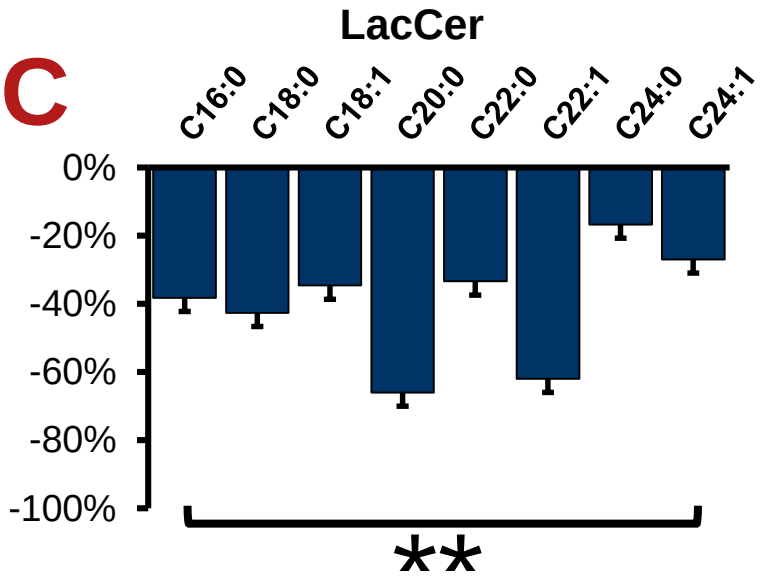
Cornell CALS College of Agriculture and Life Sciences

Ceramide Synthesis is Reduced by Myriocin

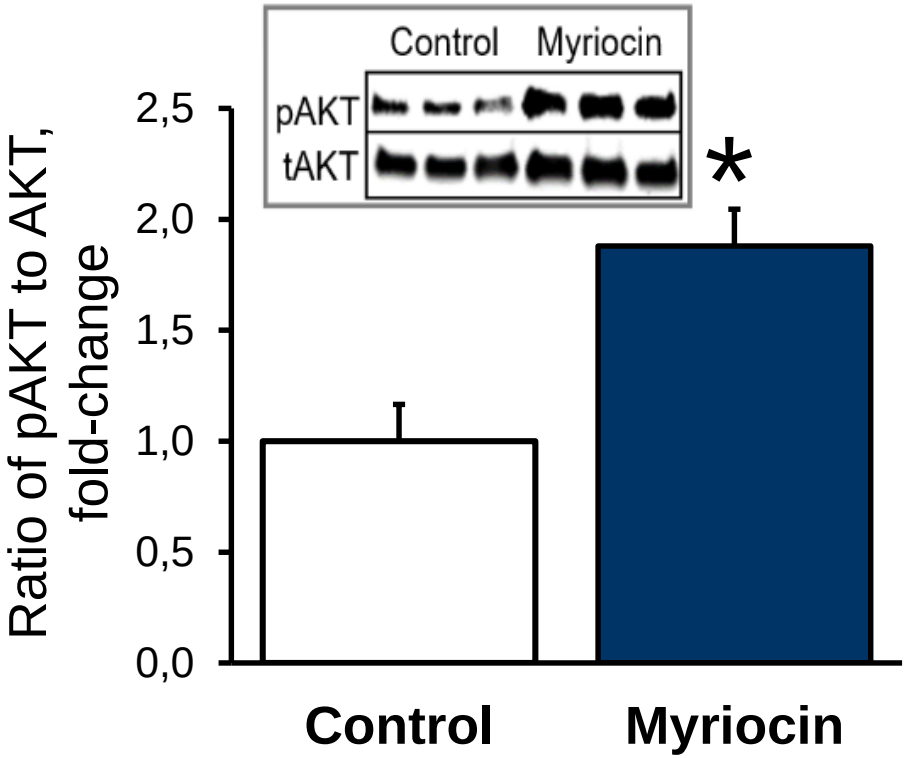


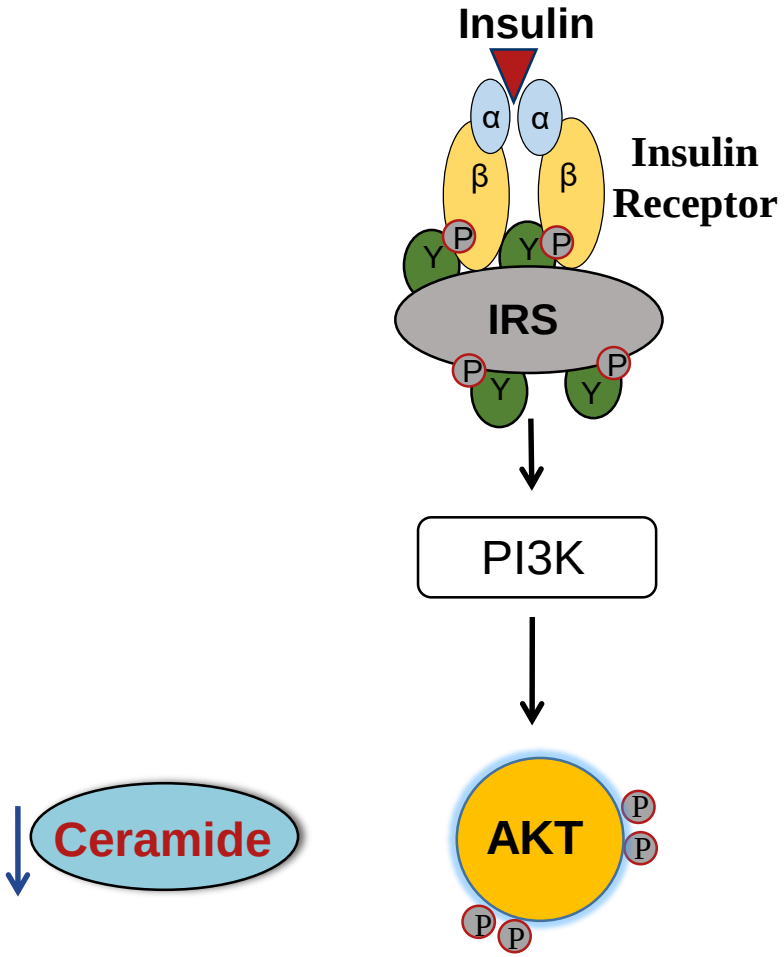






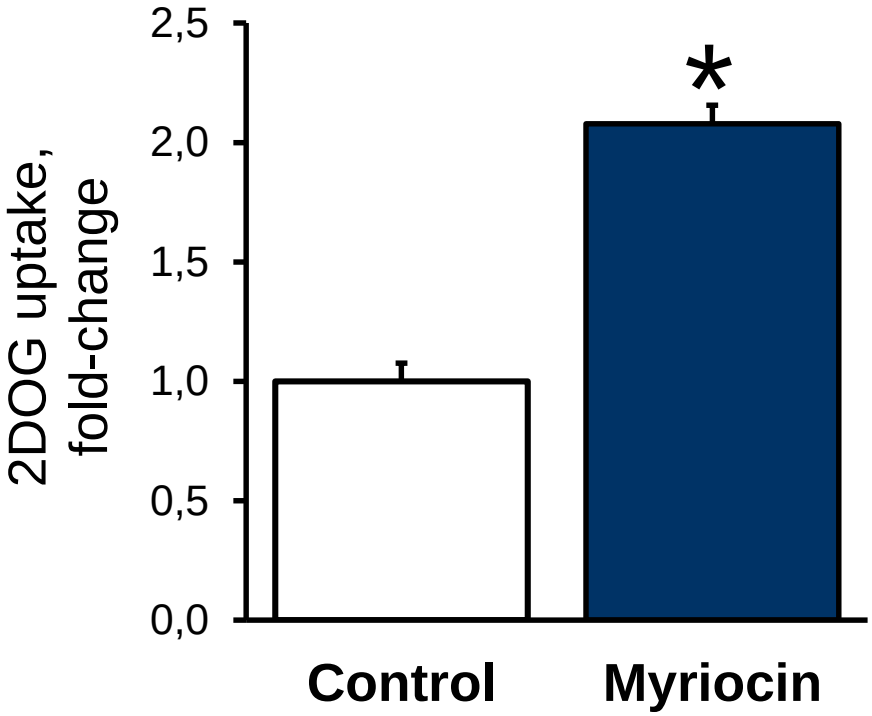
Inhibition of Ceramide Synthesis Increases Insulin Sensitivity

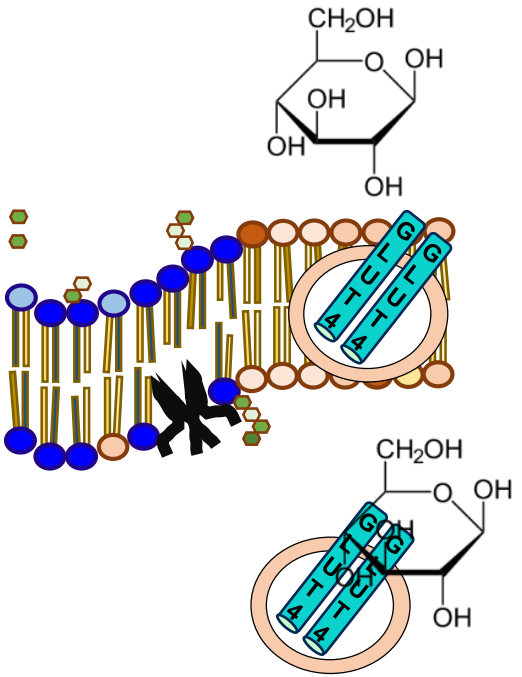




Primary bovine adipocytes; *, $P < 0.05$; Rico et al. 2018

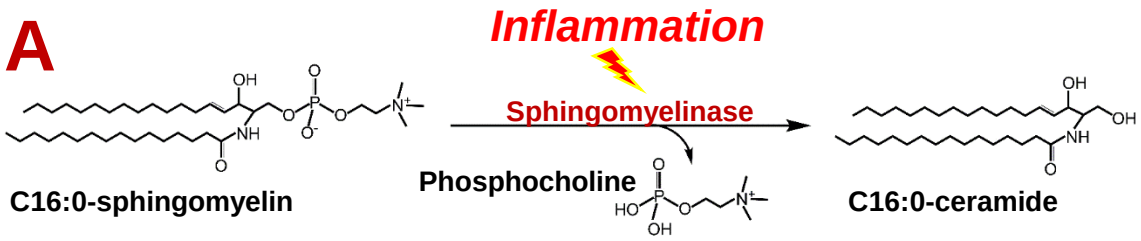
Inhibition of Ceramide Synthesis Increases Glucose Uptake

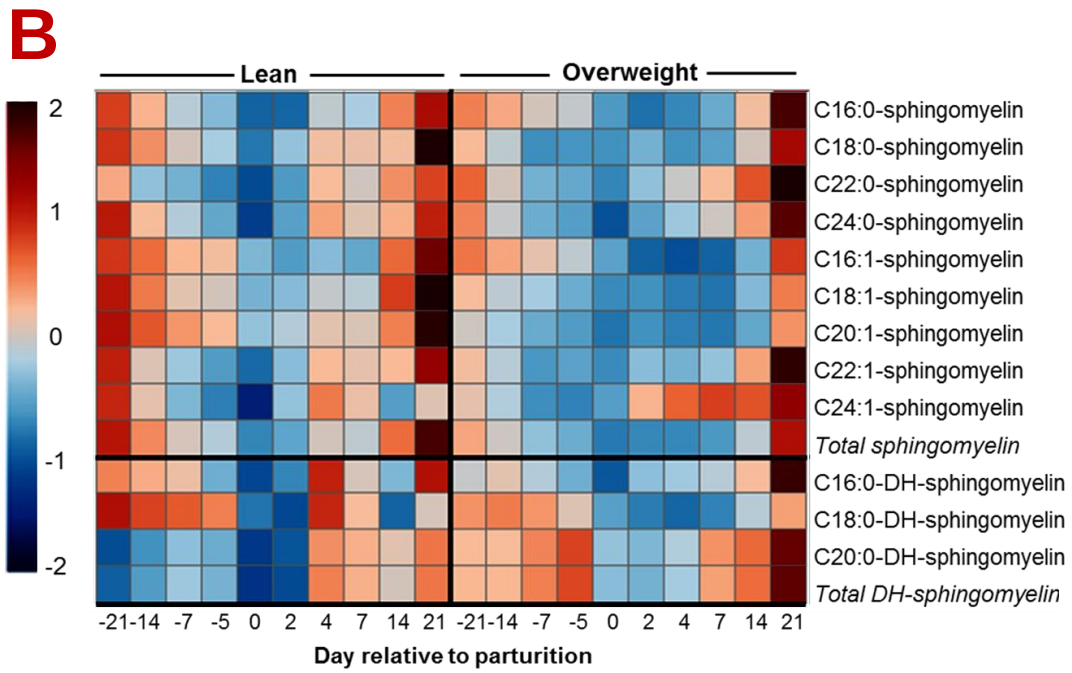


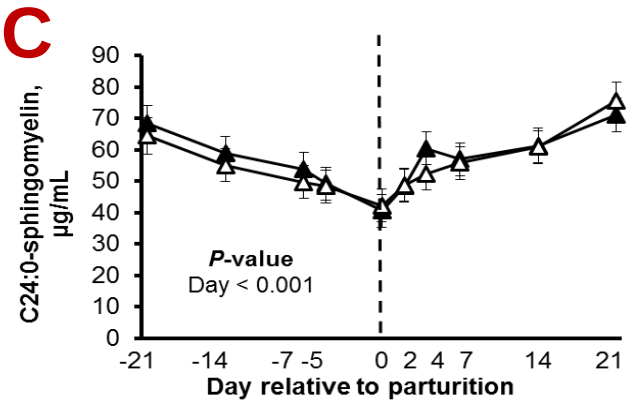


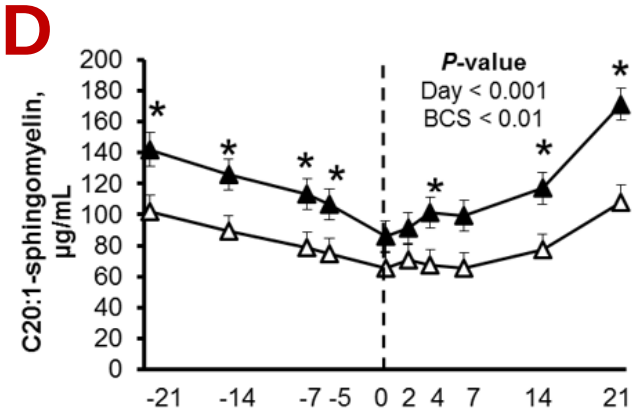
Primary bovine adipocytes; *, $P < 0.05$; Rico et al. 2018

Inflammation may Increase Ceramide Synthesis









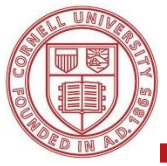
*, $P < 0.05$; Rico et al., 2017; 2018.

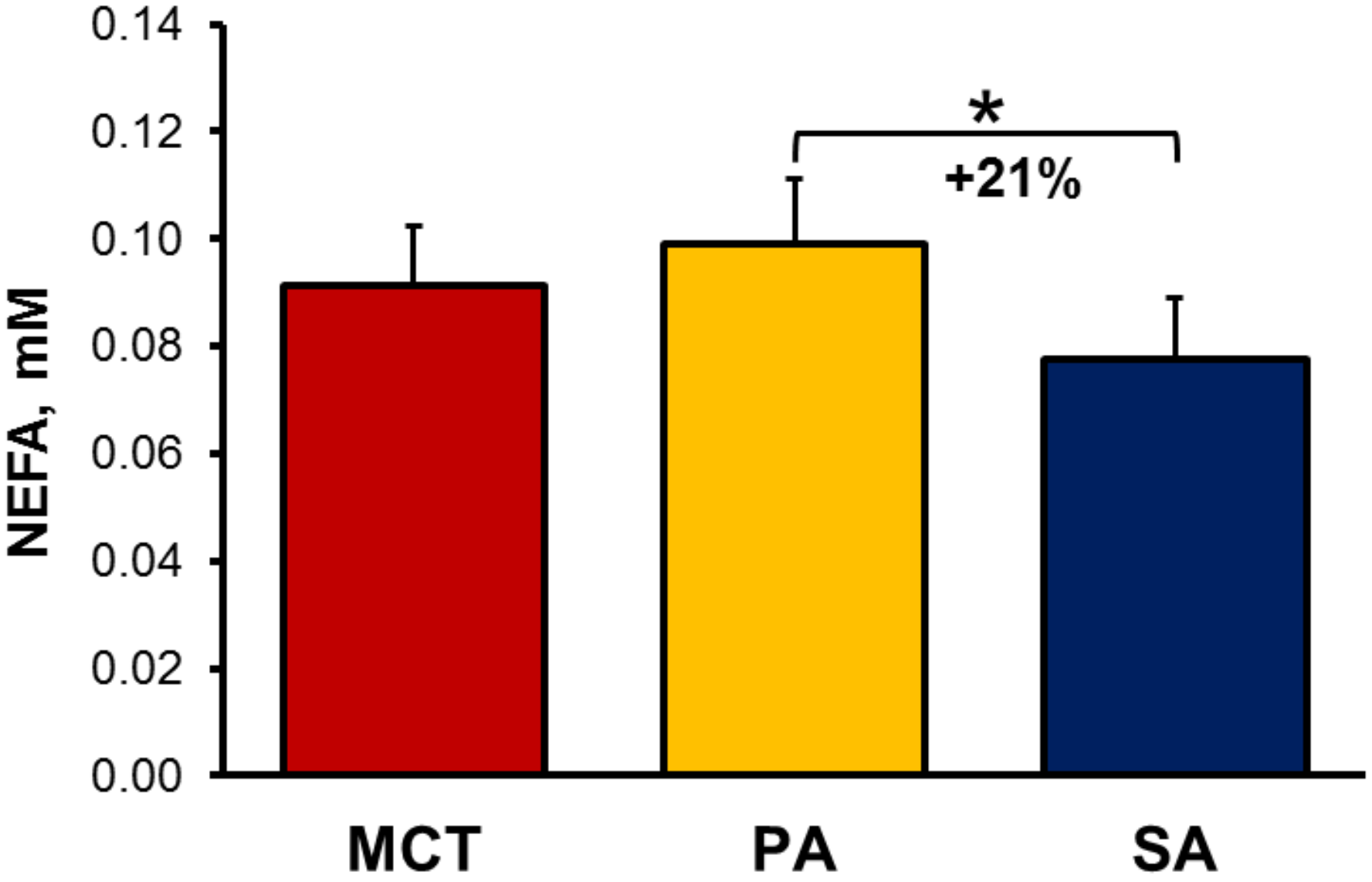
Conclusion and Importance

- Ceramide inhibits insulin stimulated glucose uptake by downregulating AKT activation in primary bovine adipocytes.
- The potential exists to modulate ceramide synthesis and insulin resistance in ruminants.
- Novel strategies to improve metabolic health and productive performance.

Future Research

- The *in vivo* assessment of the direct effects of ceramides on insulin action is required.

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