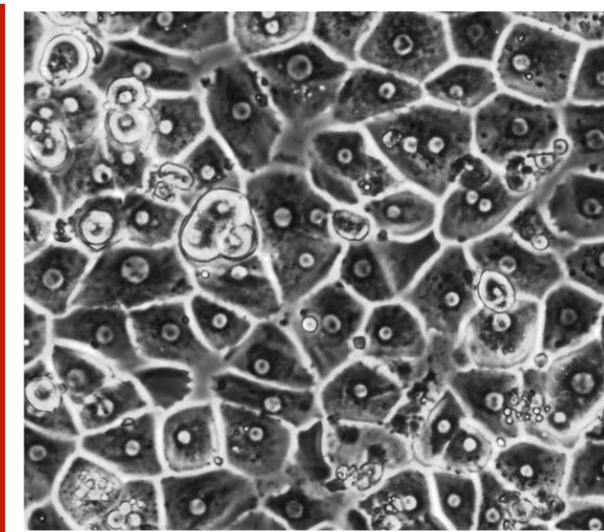




DEPARTMENT OF
DAIRY SCIENCE
University of Wisconsin-Madison

The logo features a black silhouette of a cow standing in a circle. Above the cow is a shield with a white 'W' on a red background, topped with a decorative crest. The text 'DEPARTMENT OF DAIRY SCIENCE' is in a serif font, and 'University of Wisconsin-Madison' is in a sans-serif font below it.

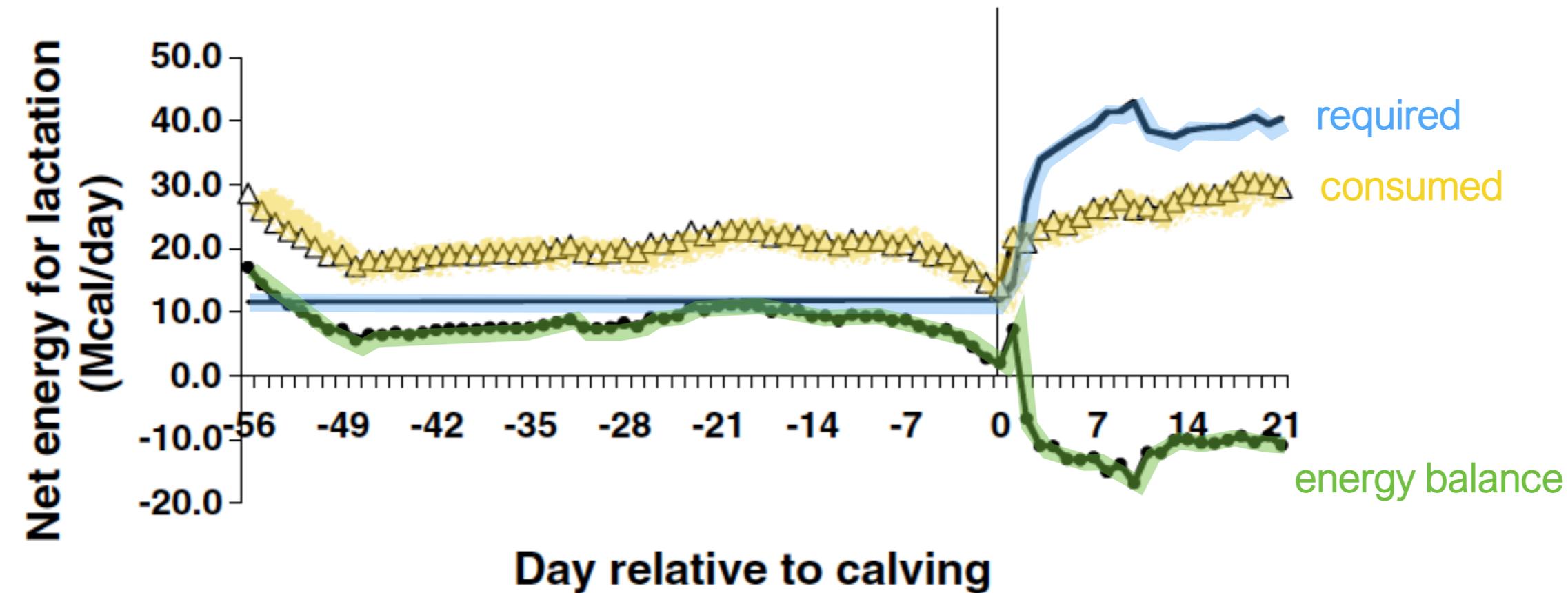
Can we mitigate production limitations by supporting a better transition to lactation in dairy cows?

Dr. Heather White

Associate Professor, Department of Dairy Science

University of Wisconsin-Madison

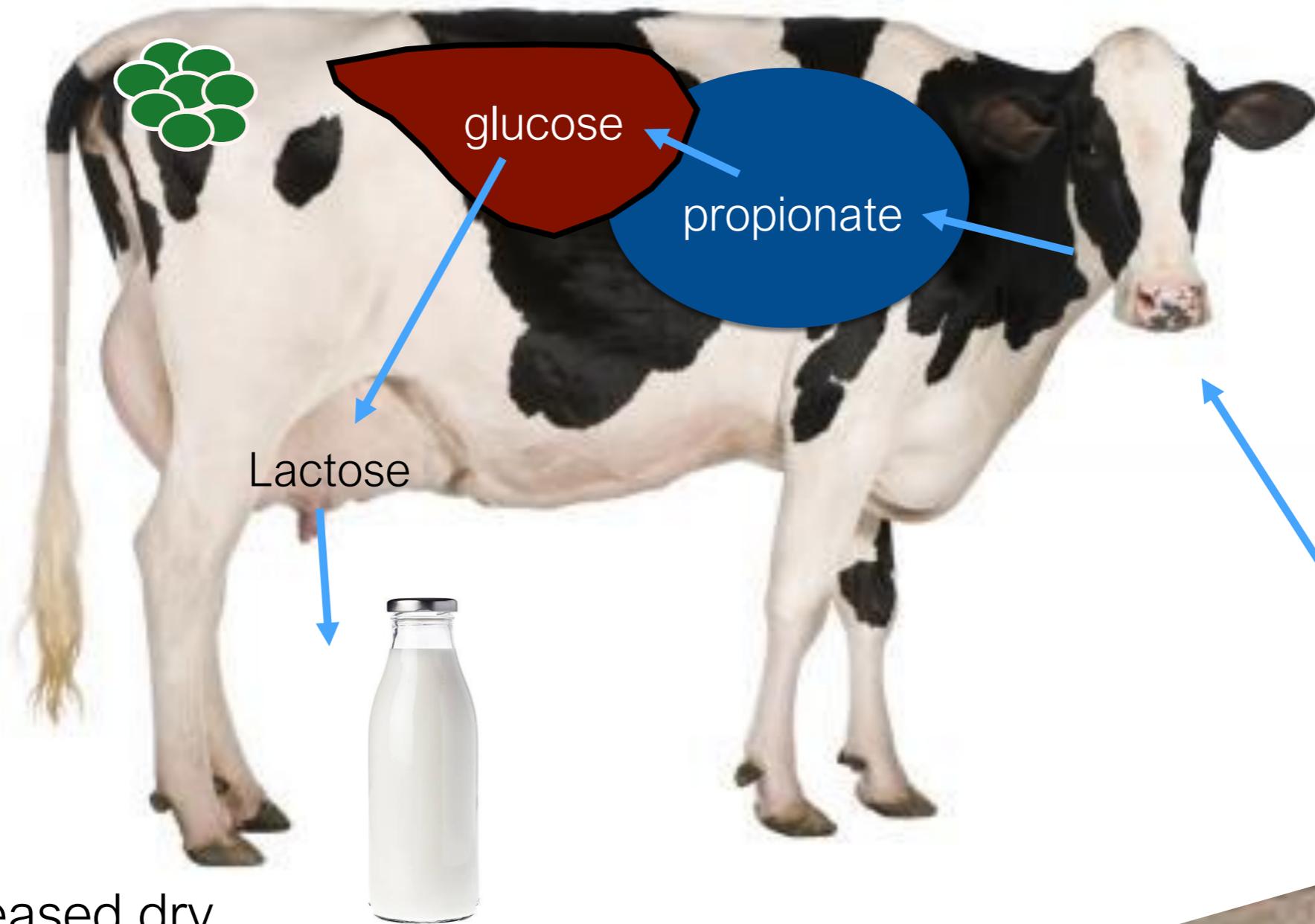
Negative Energy Balance



Negative **Energy** Balance
Negative **Glucose** Balance
Negative **Nutrient** Balance

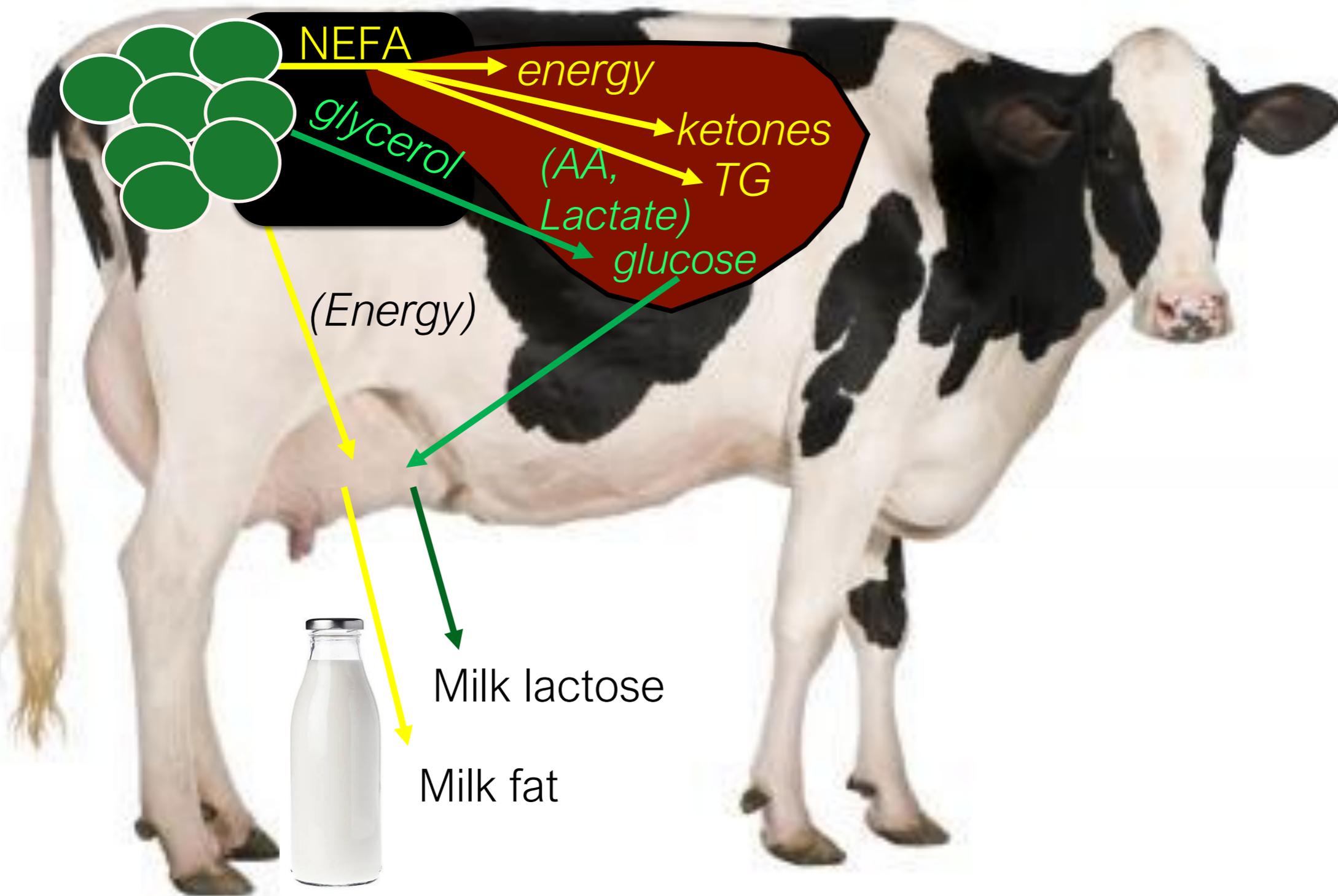


Glucose Production from Feed

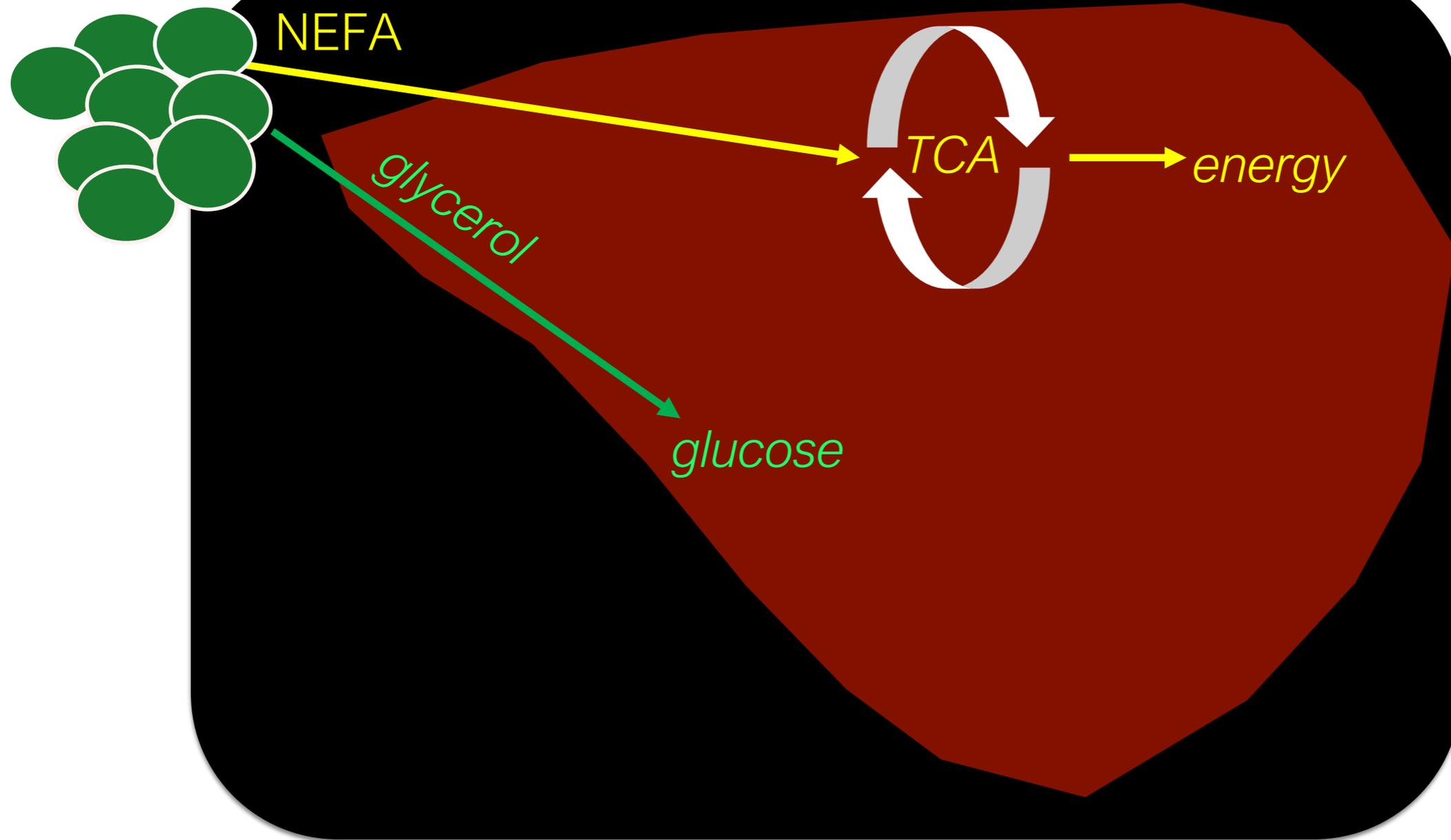


Decreased dry
matter intake =
negative energy balance
negative glucose balance

Mobilization of Fat Stores



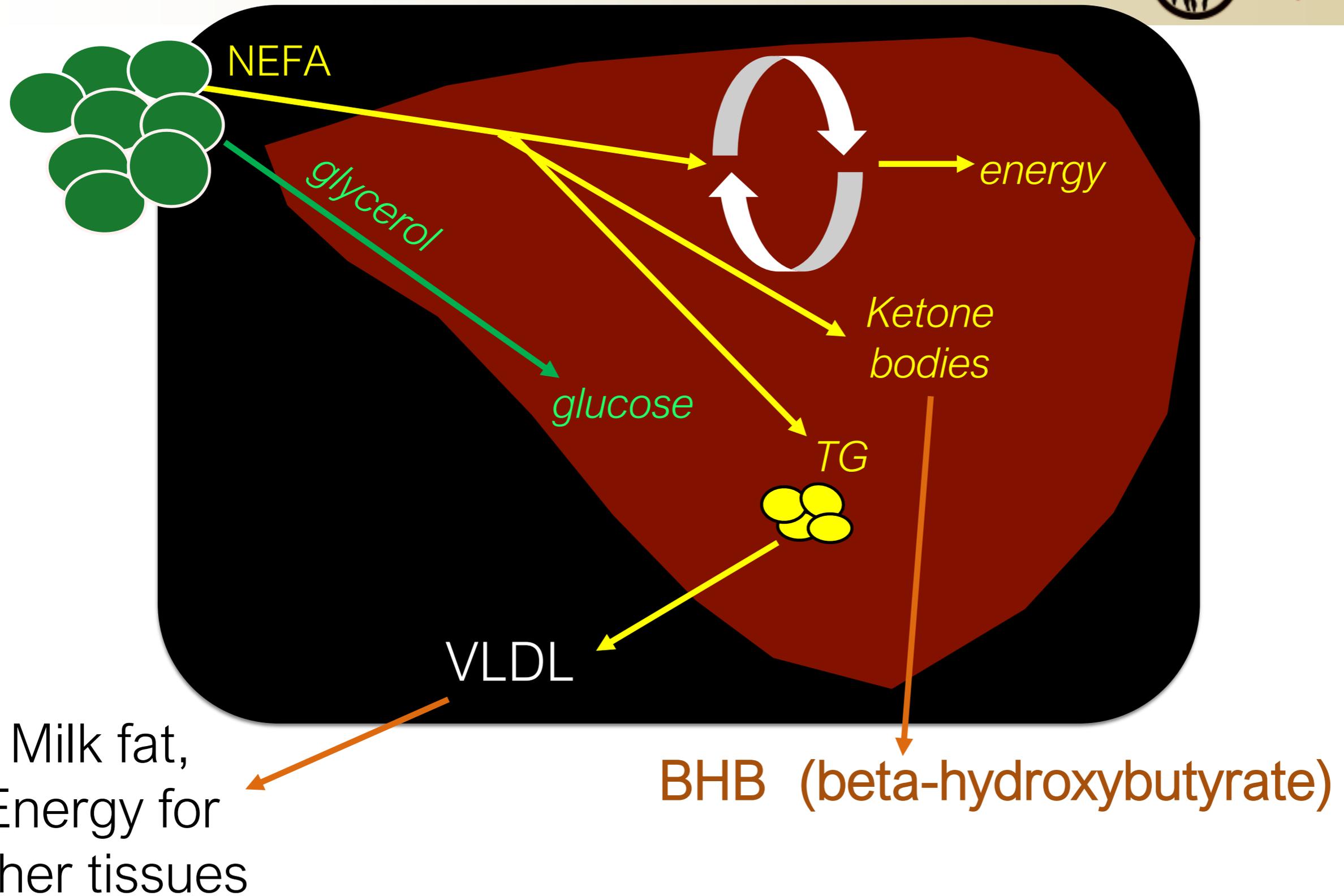
Hepatic Nutrient Partitioning



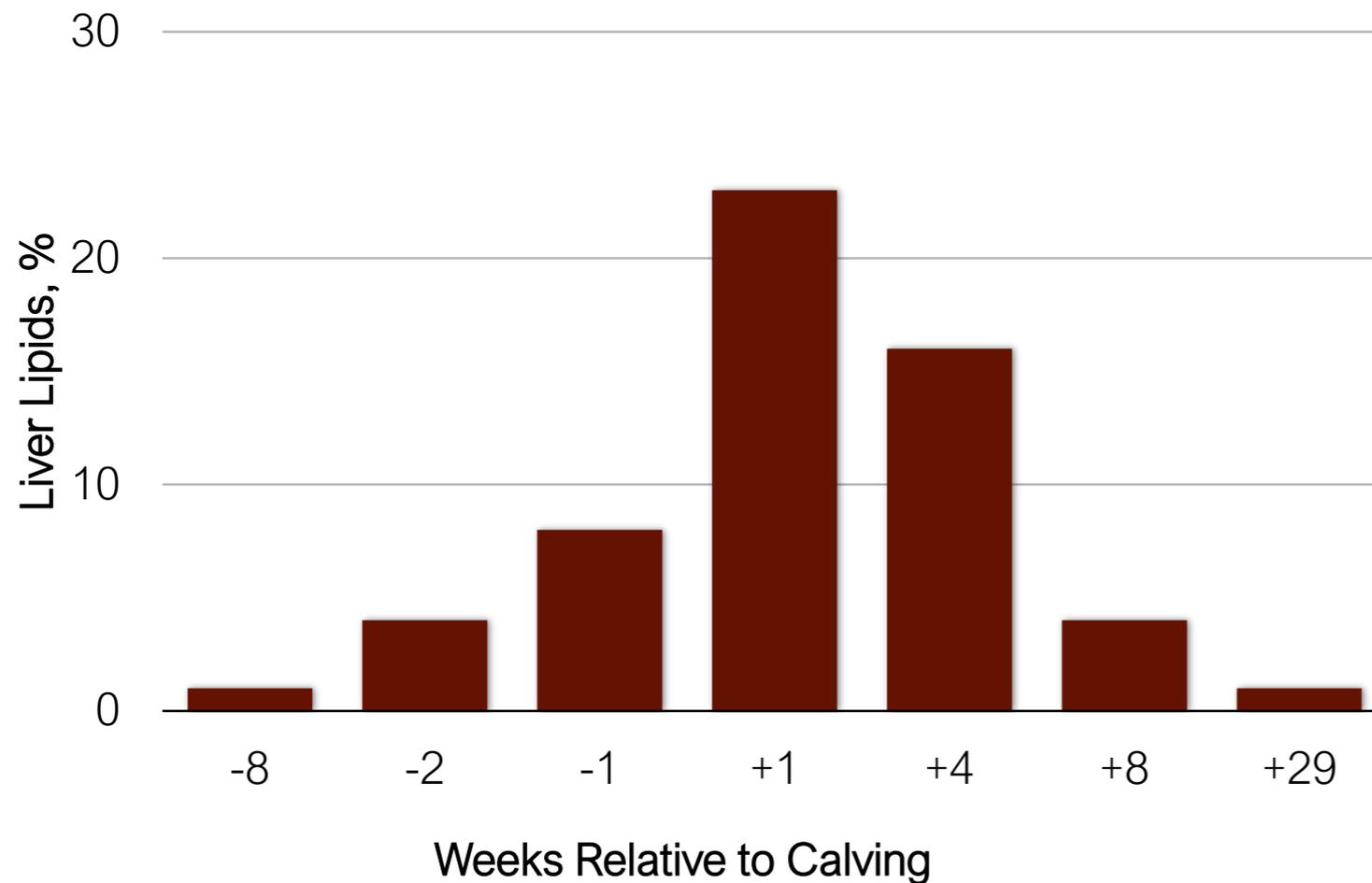
Complete Oxidation is a Carousel!



Hepatic Nutrient Partitioning

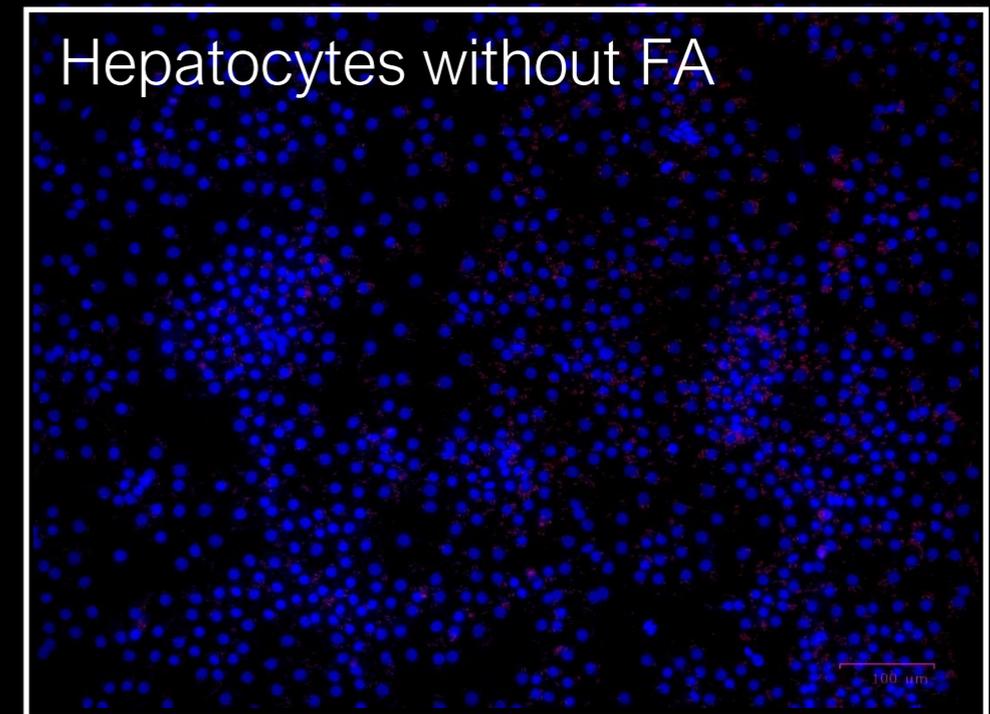


Cellular Lipids



- Hepatic uptake reflects blood flow and [NEFA]
- Accumulation in vivo peripartum is consistent and can be replicated in primary bovine hepatocytes providing an in vitro model for mechanistic objectives

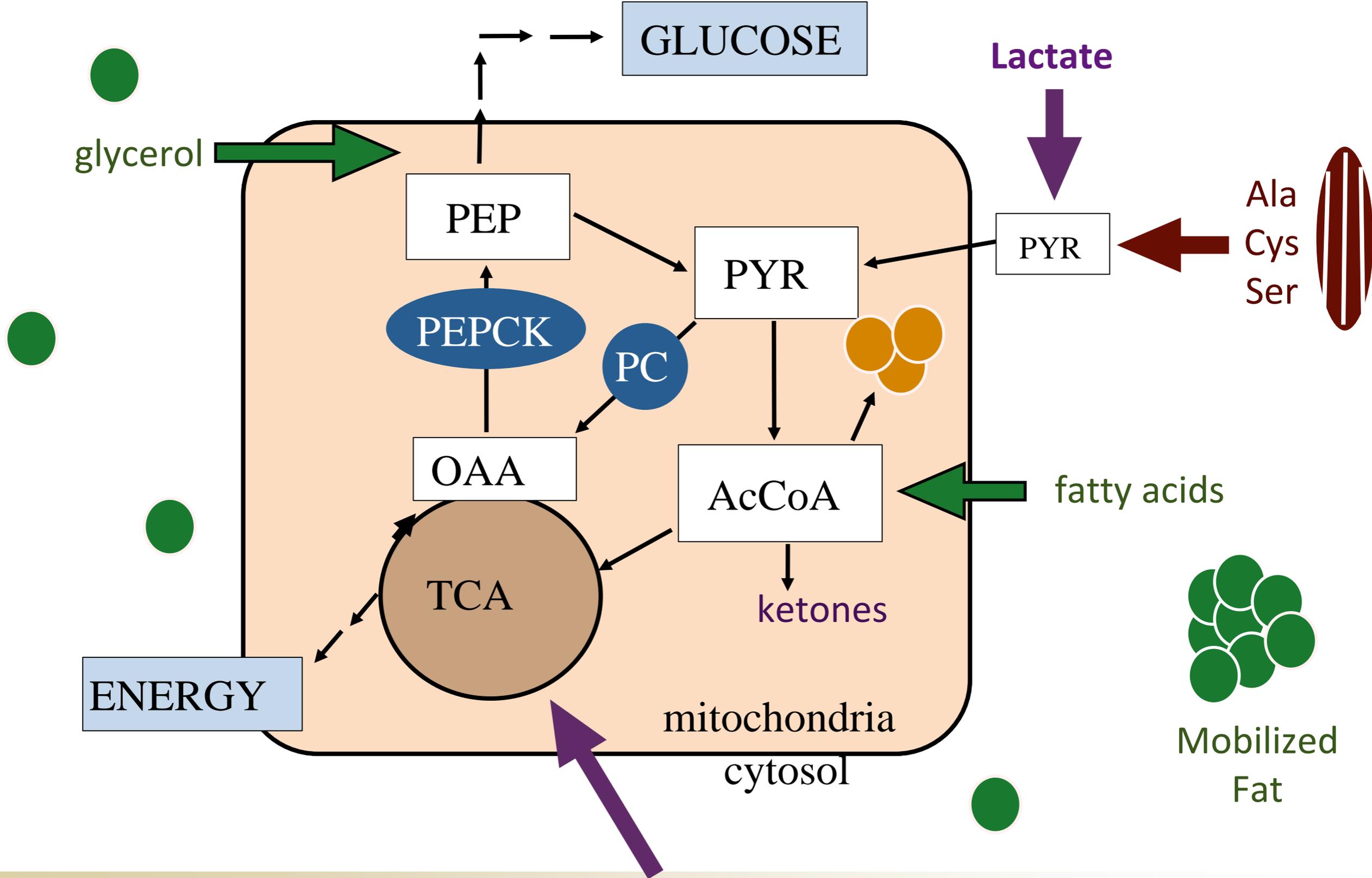
Hepatocytes without FA



Hepatocytes with fatty acids

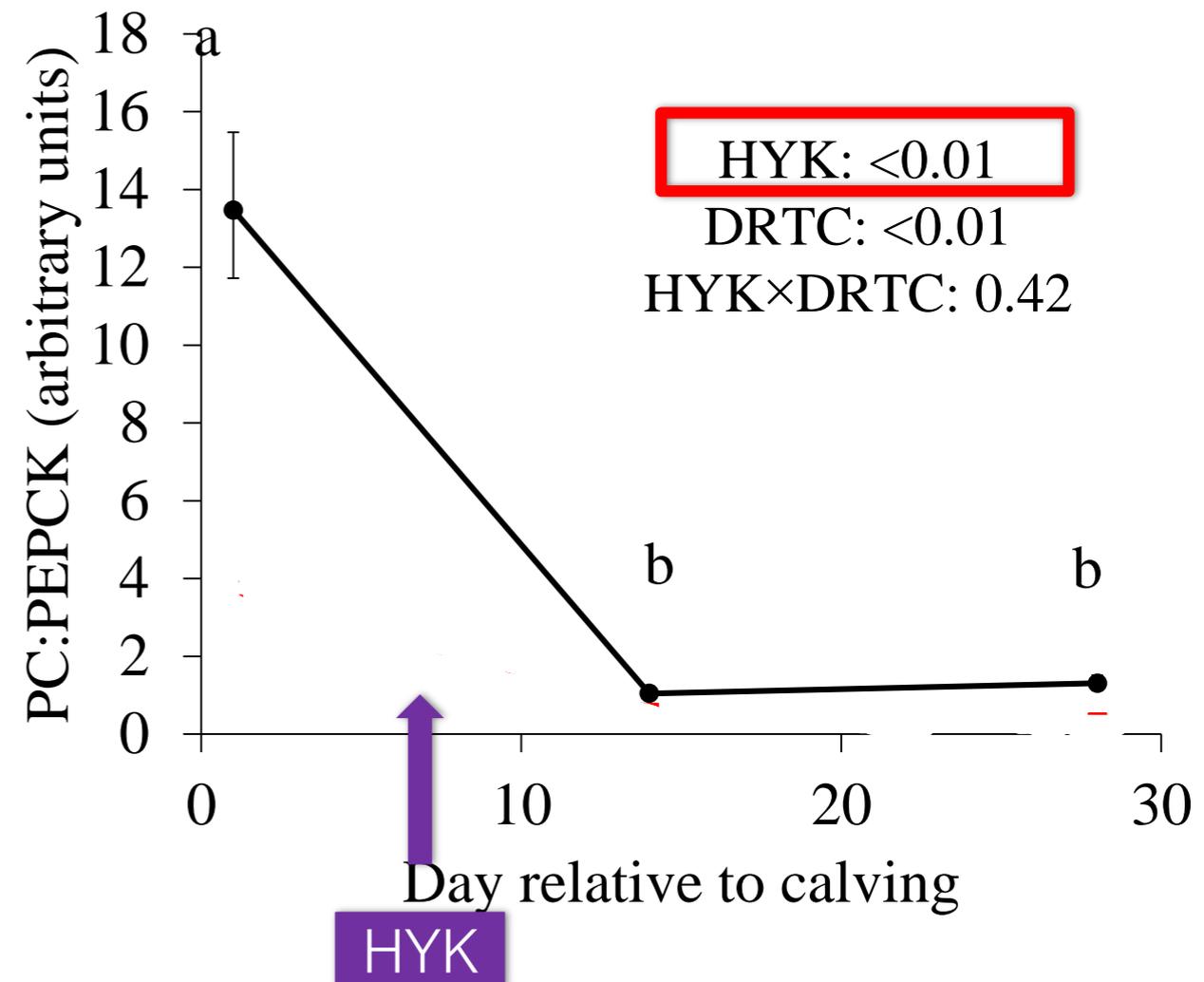
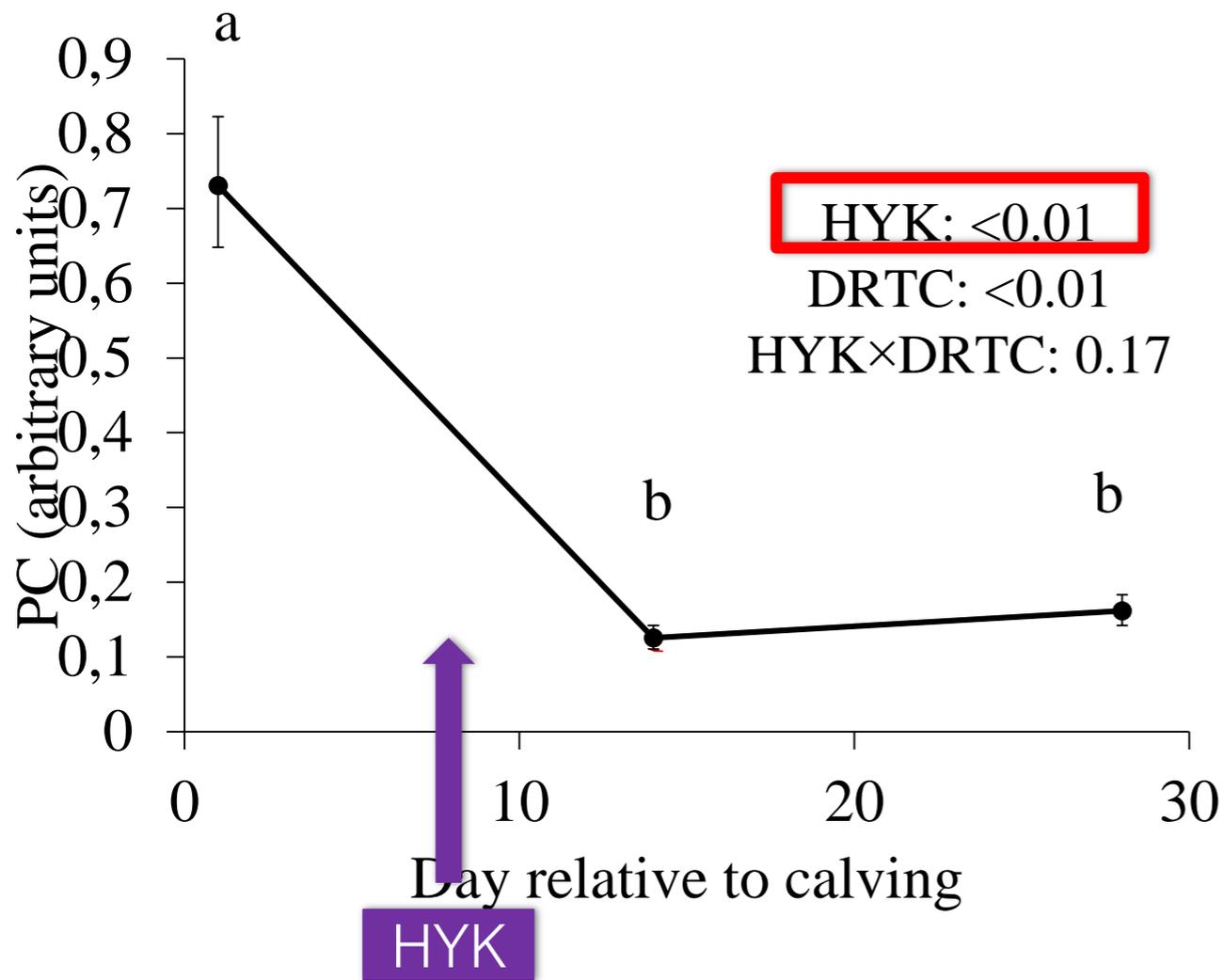


Accumulation of Liver Lipids



Shifting hepatic gene expression likely shifts pathway flux and can contribute to dysregulation.

Capacity for Complete Oxidation



- PC:PEPCKc is suggestive of capacity for complete oxidation
- PC:PEPCKc is decreased at +1 DRTC in cows that subsequently develop HYK

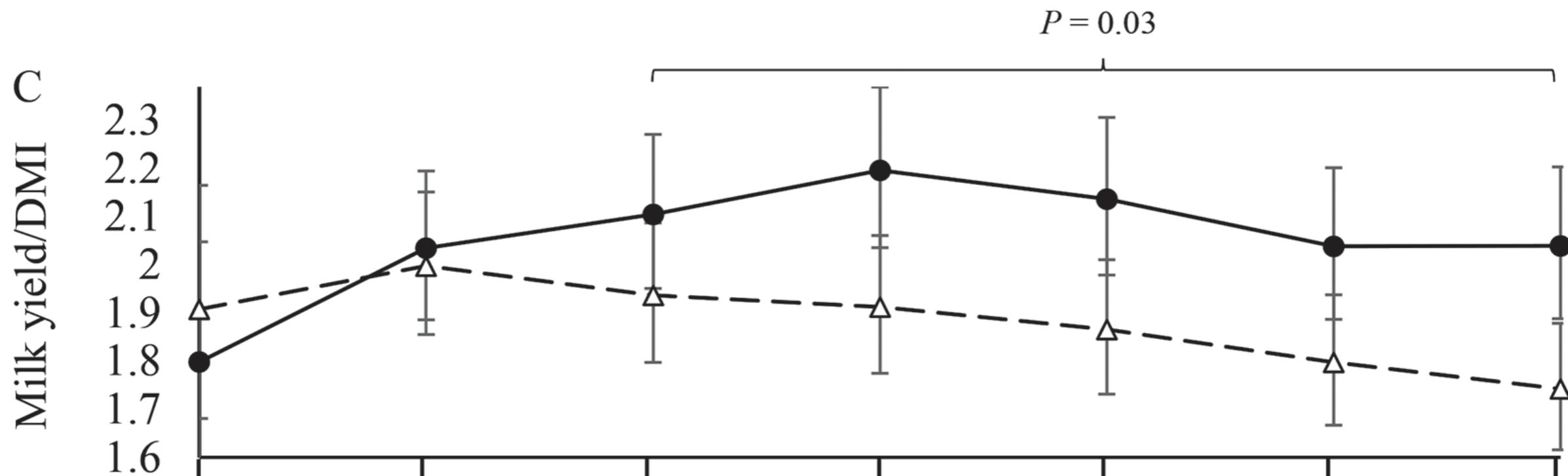
**Hepatic Oxidative Capacity is likely decreased
before HYK onset!**

If insufficient complete oxidative capacity can lead to ketosis and fatty liver, increasing complete oxidative capacity should be beneficial . . .

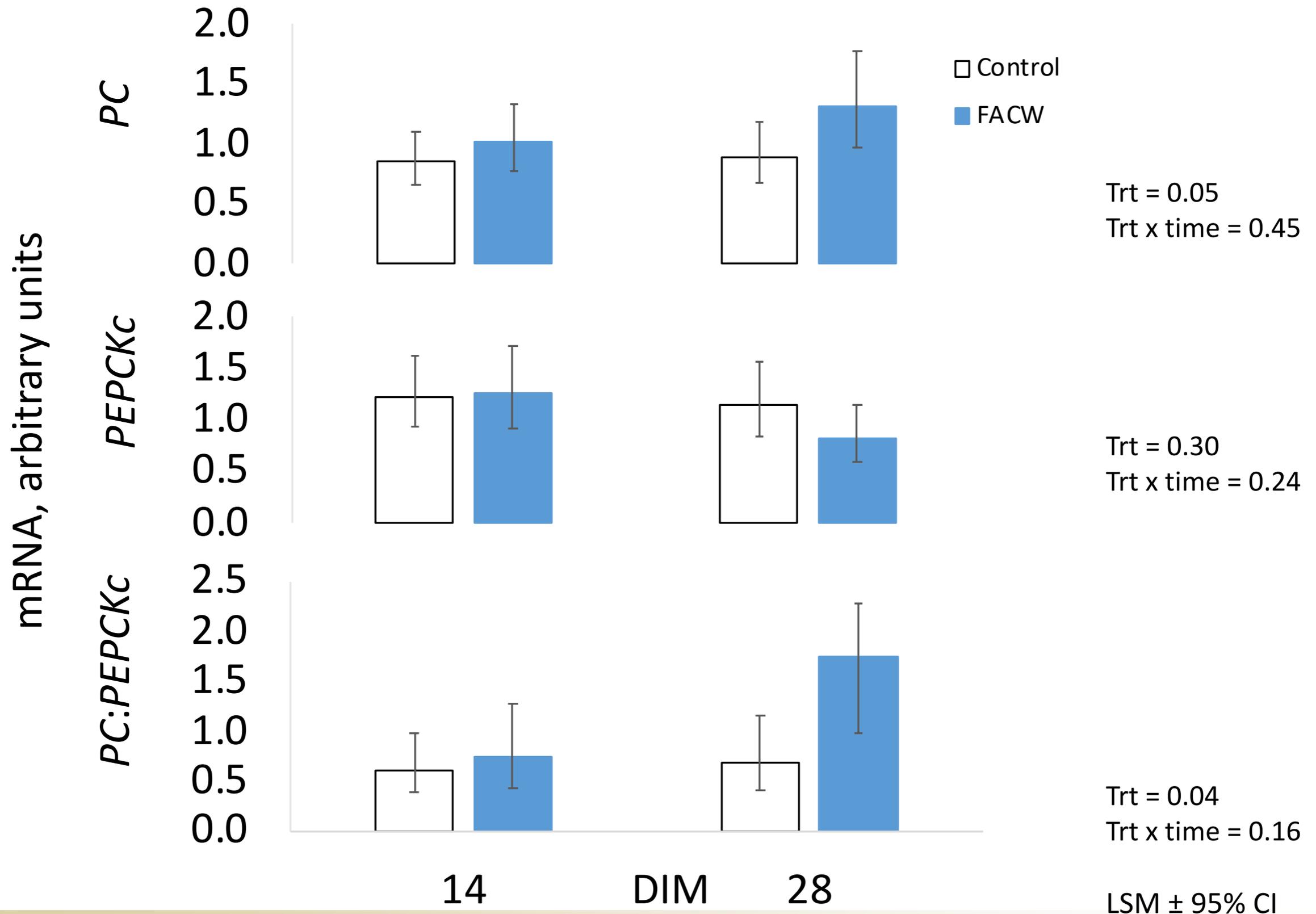
Is improved complete oxidation a result of improved nutrient partitioning or availability?

Postpartum Supplementation of Ammoniated Lactate (FACW)

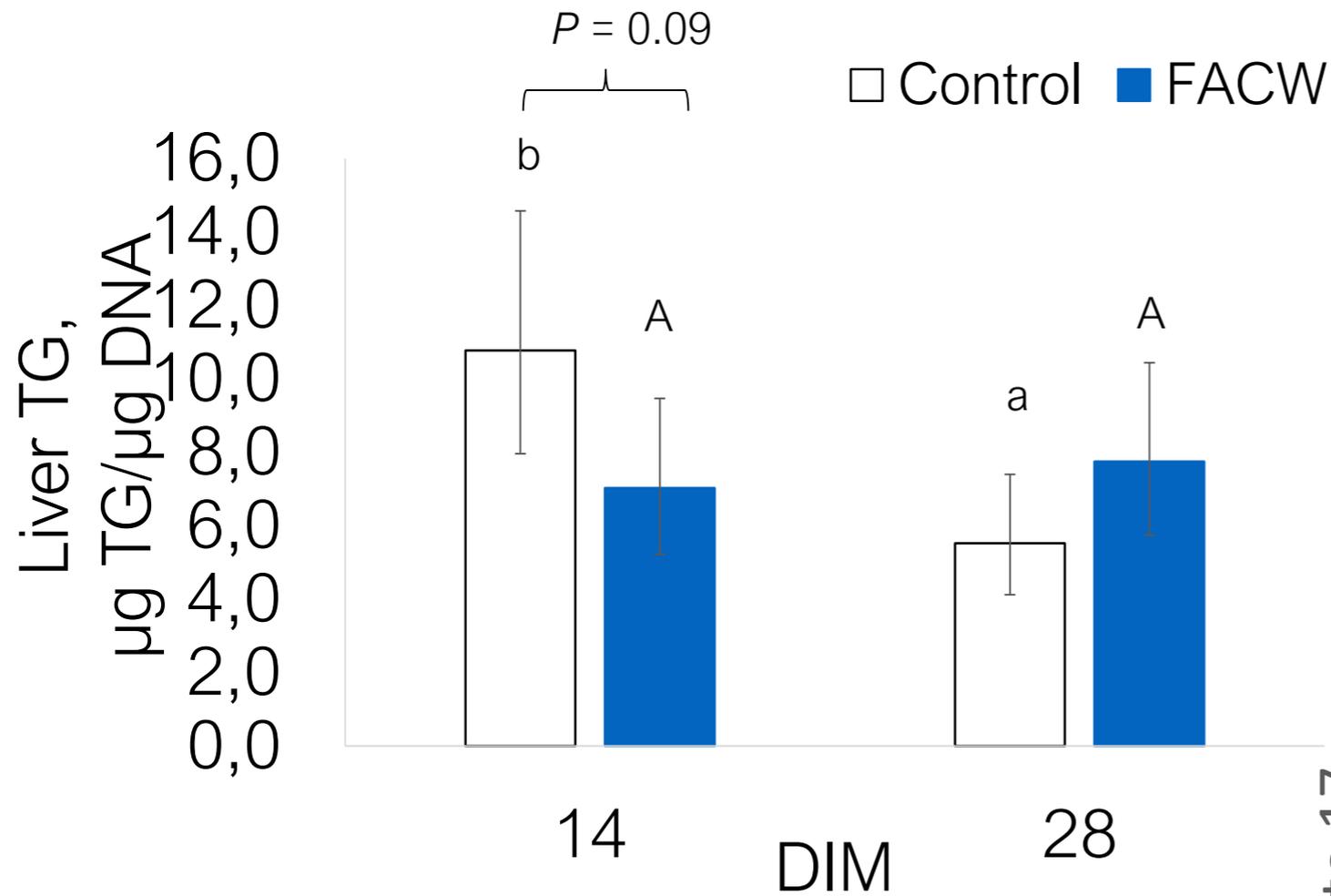
- Improved feed efficiency
- Increased postpartum propionate
- Decreased postpartum NEFA and BHB
- Increased postpartum glucose and insulin



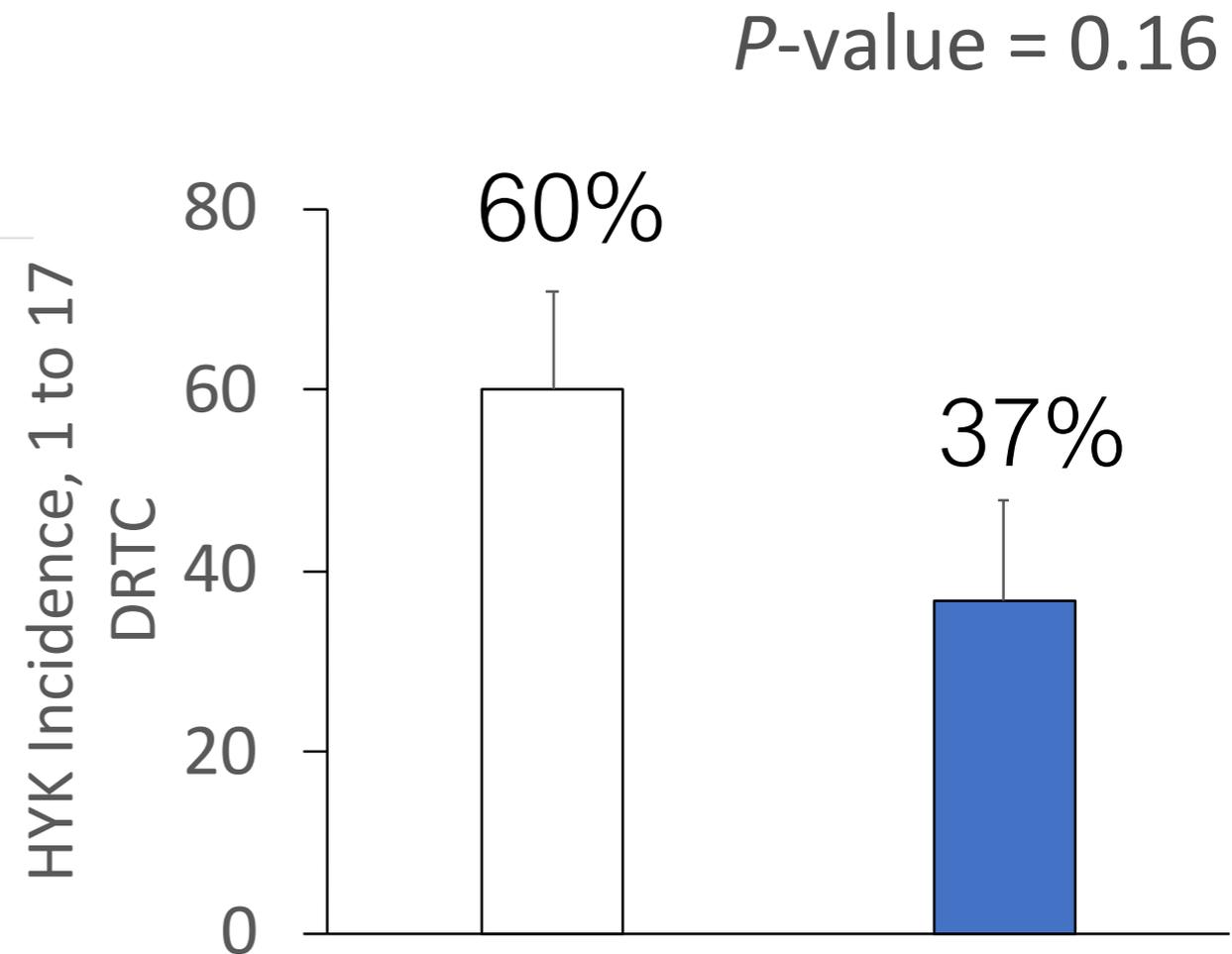
Postpartum Supplementation of Ammoniated Lactate (FACW)



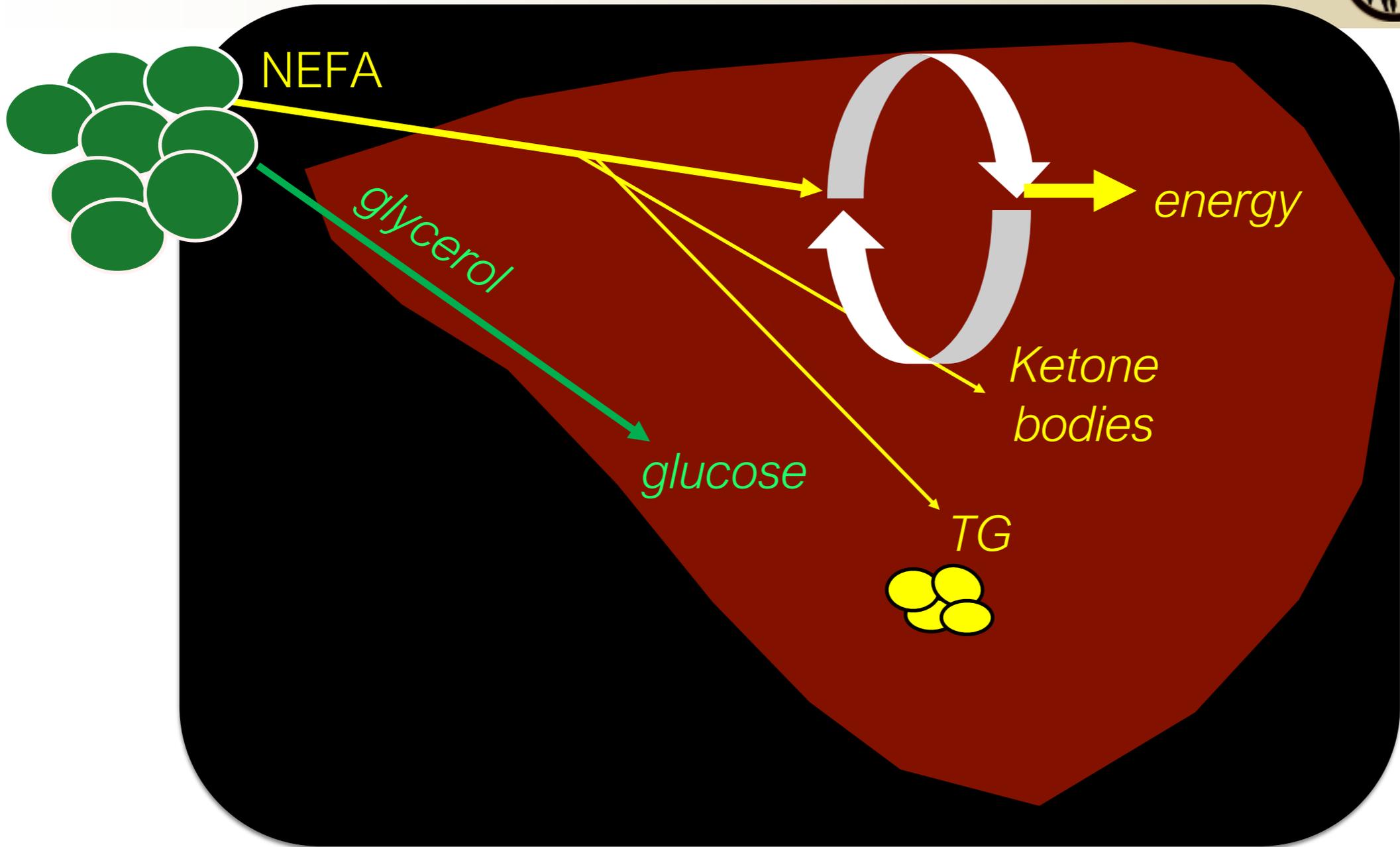
Postpartum Supplementation of Ammoniated Lactate (FACW)



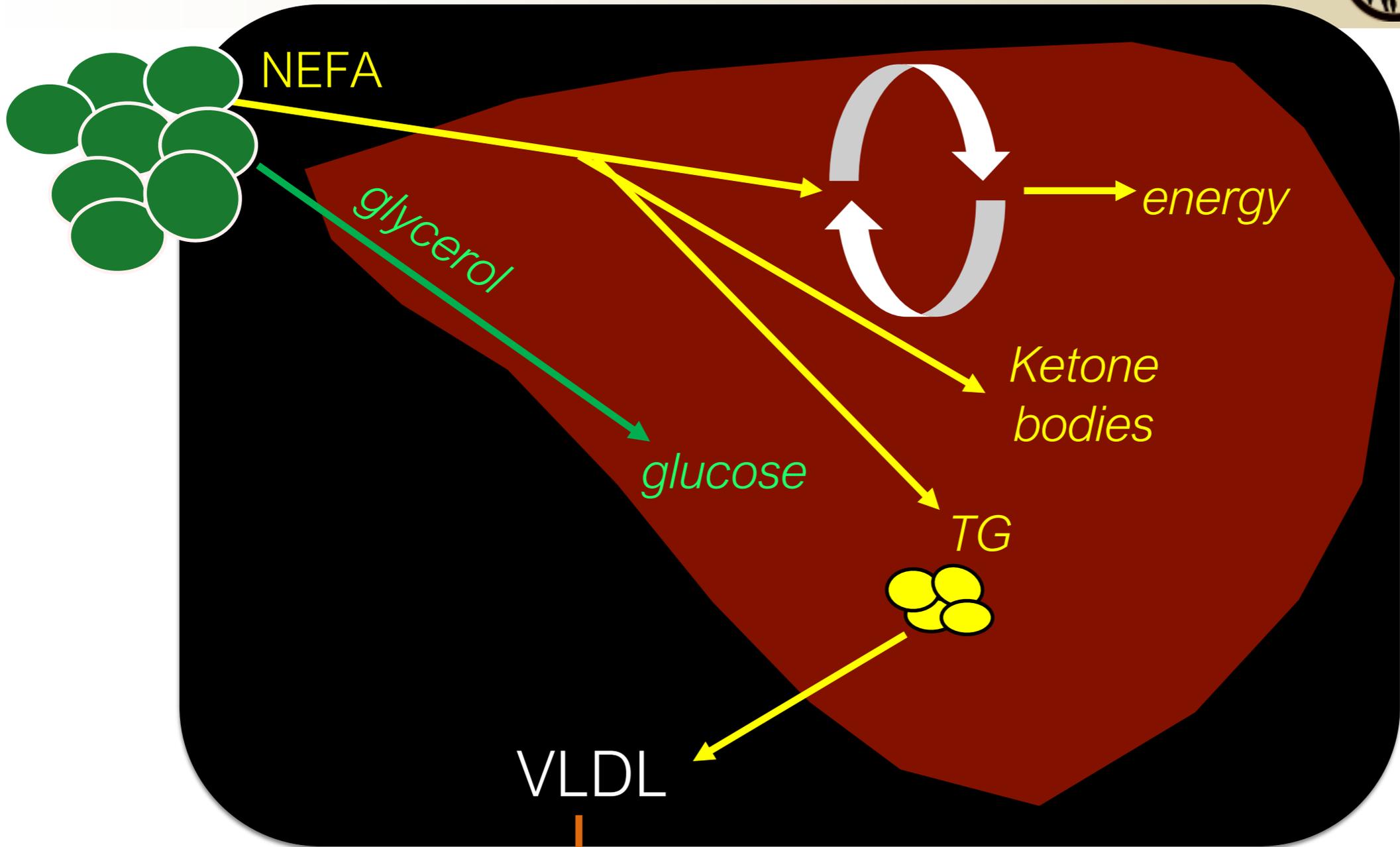
Substrate-driven increase in complete oxidative capacity?



Hepatic Nutrient Partitioning

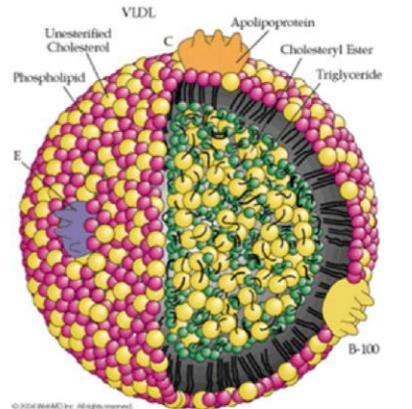
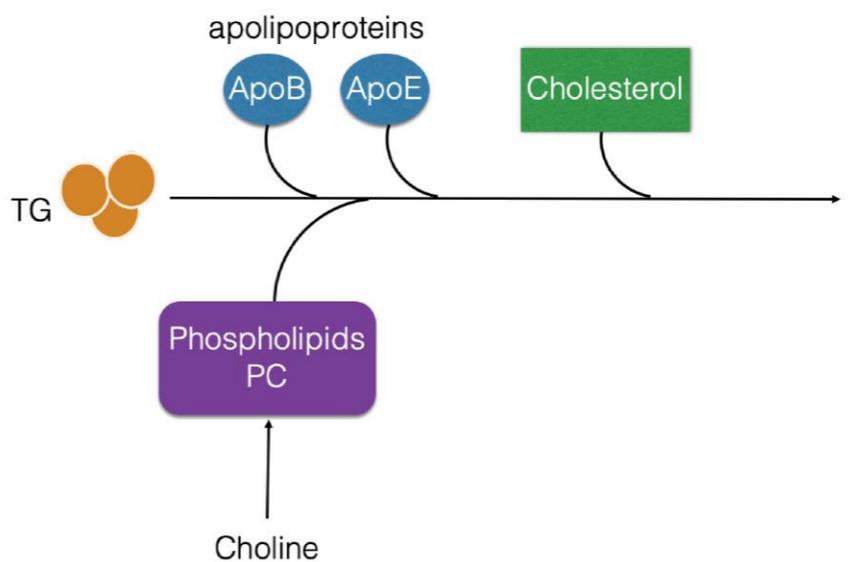


Hepatic Nutrient Partitioning



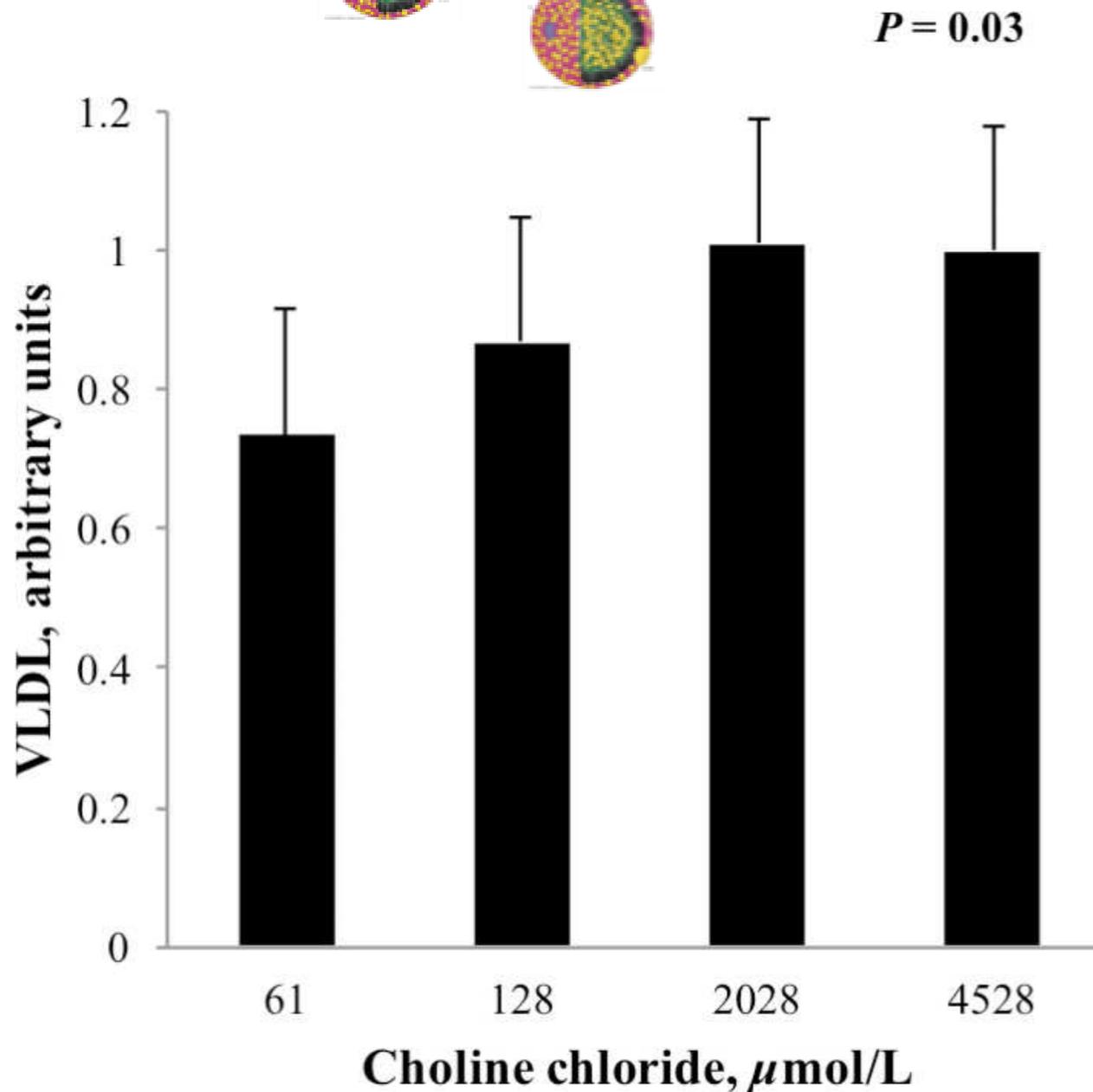
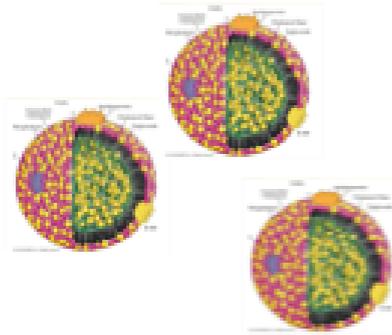
2 possibilities:

- 1. Lipolysis
- 2. Export

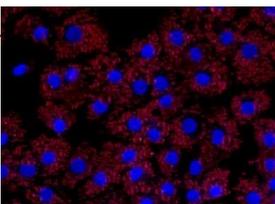
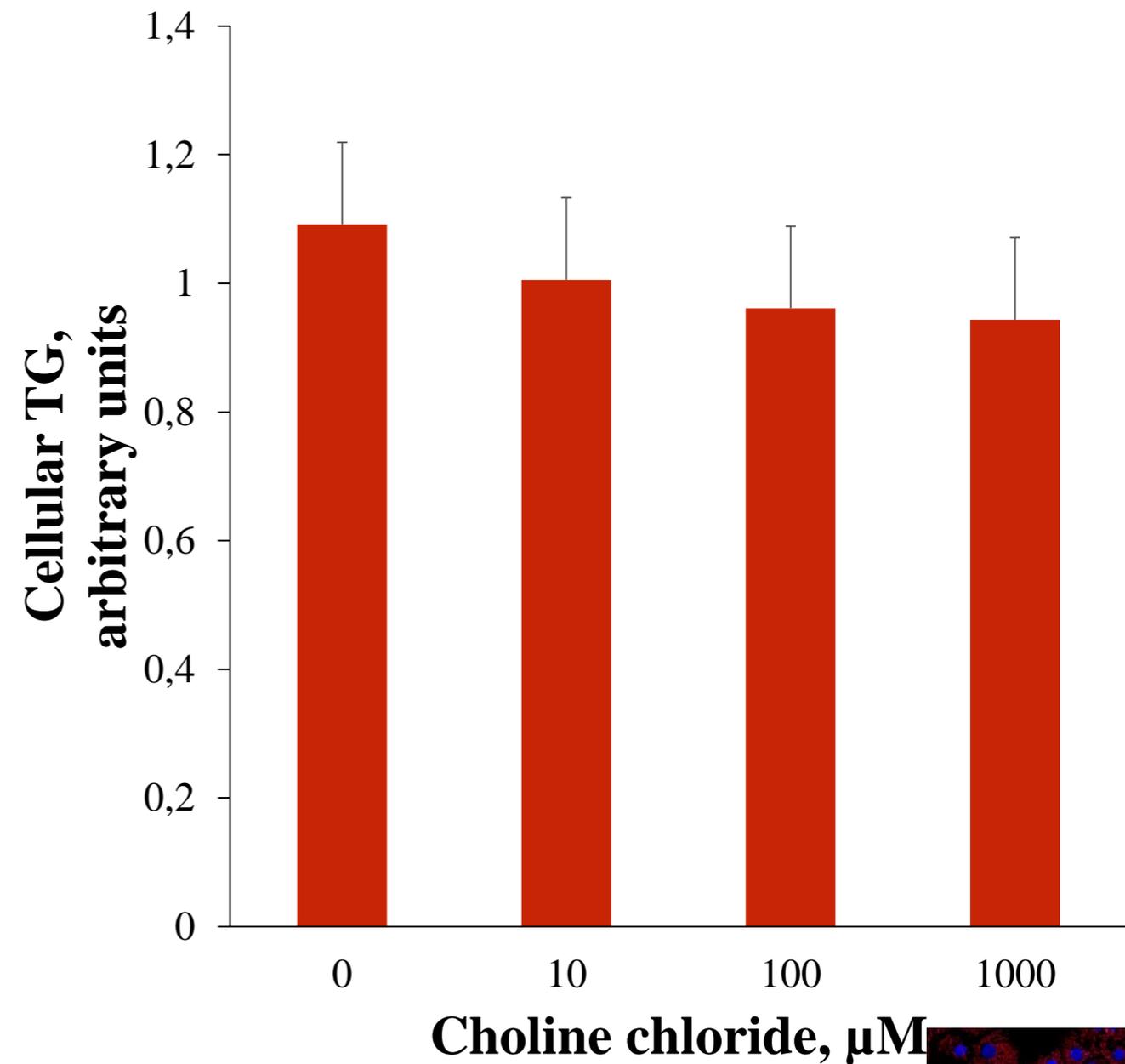


Choline Supplementation Increases

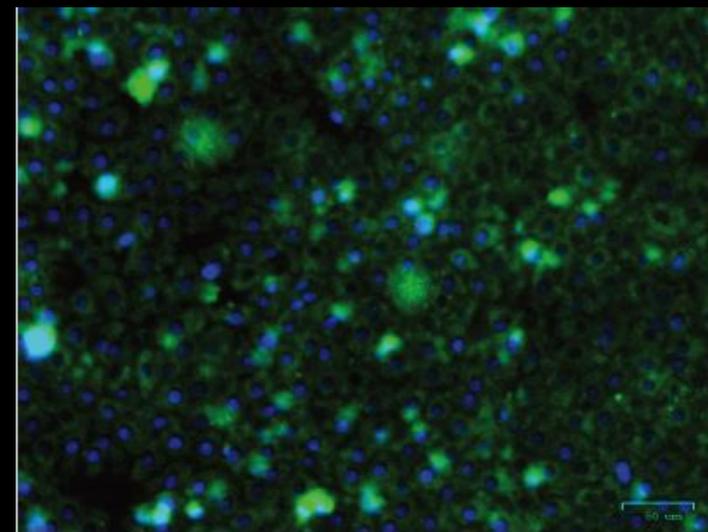
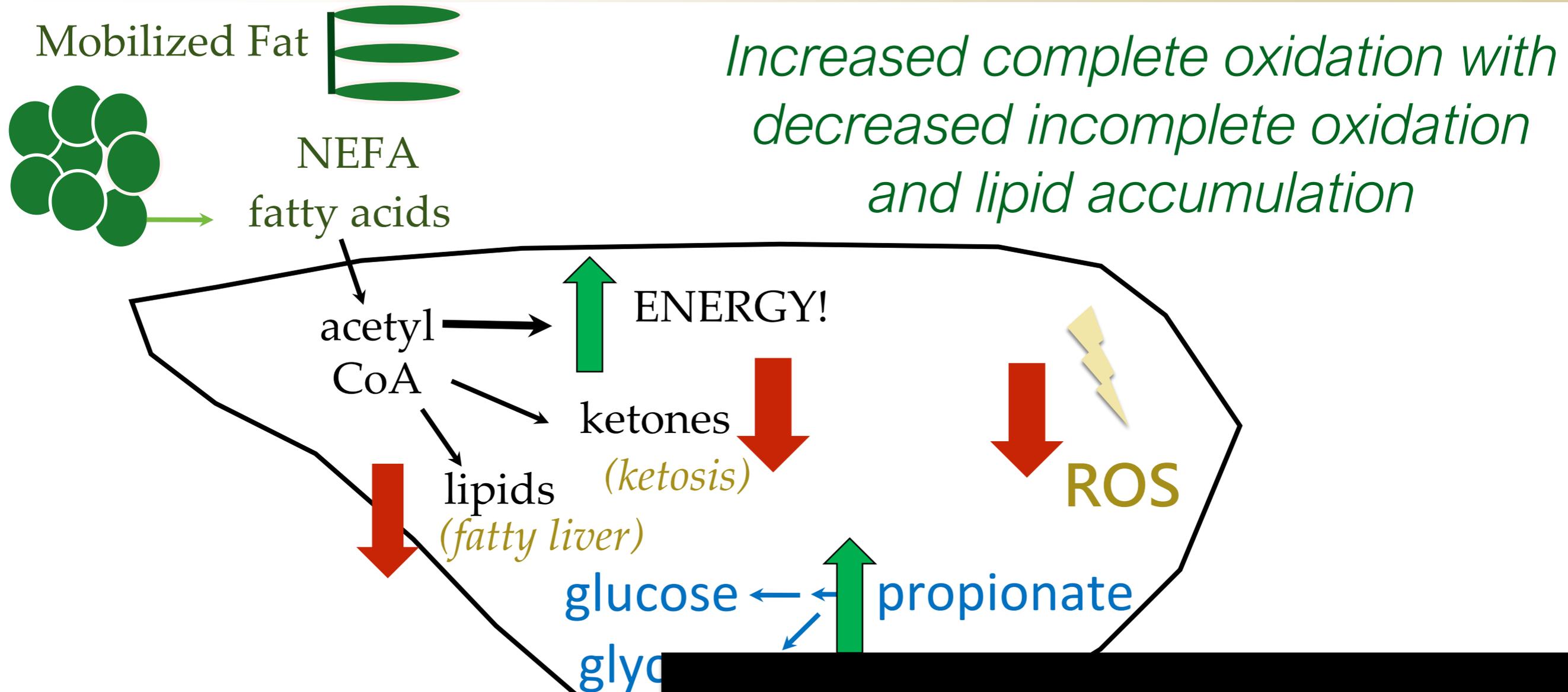
VLDL export



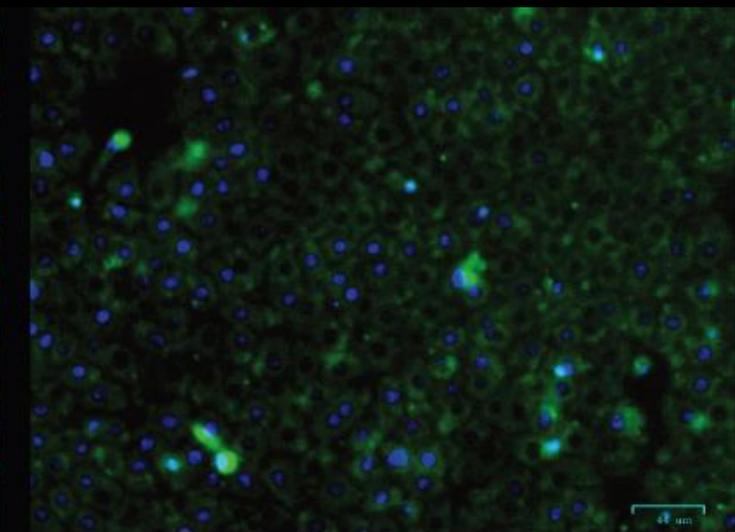
No Choline vs. Choline (10, 100, 1000) μM CC: $P=0.06$



Choline Shifts Pathways in Liver Cells



- Choline



+Choline

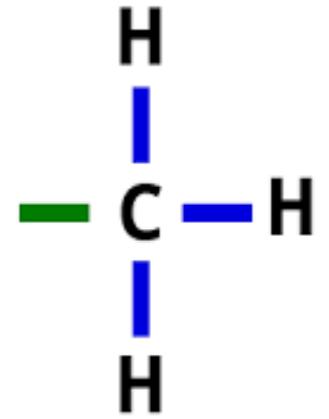
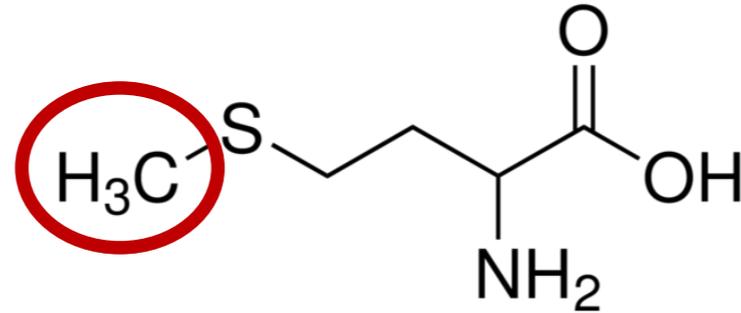
Are the gluconeogenic and lipotropic effects of choline related to inflammatory status of the hepatocyte?

Are they common across methyl donors?

Methyl Group Metabolism

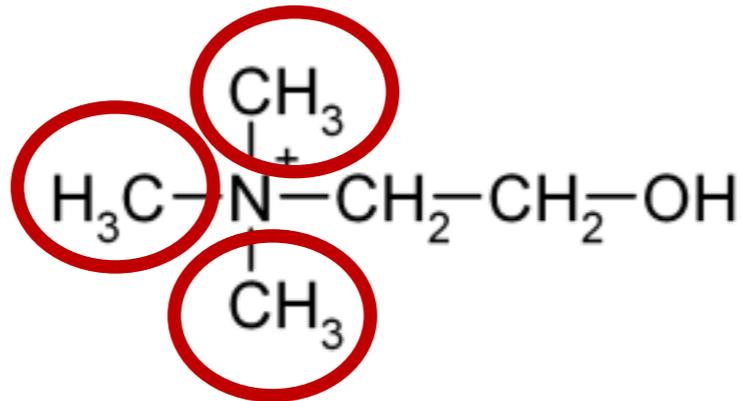
- Methyl groups come from methyl donors

- methionine (1)

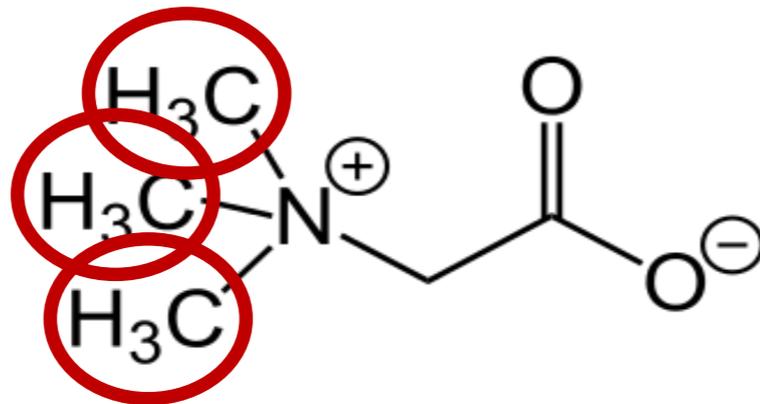


Methyl group

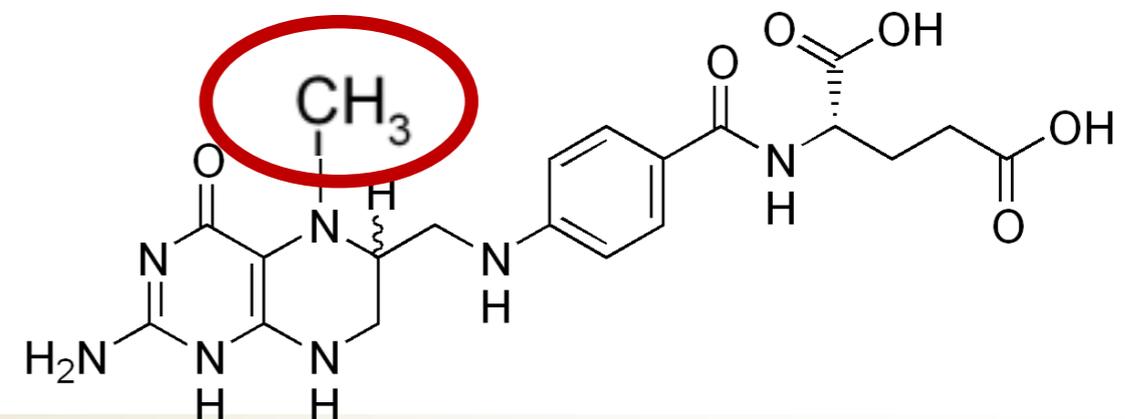
- choline (3)



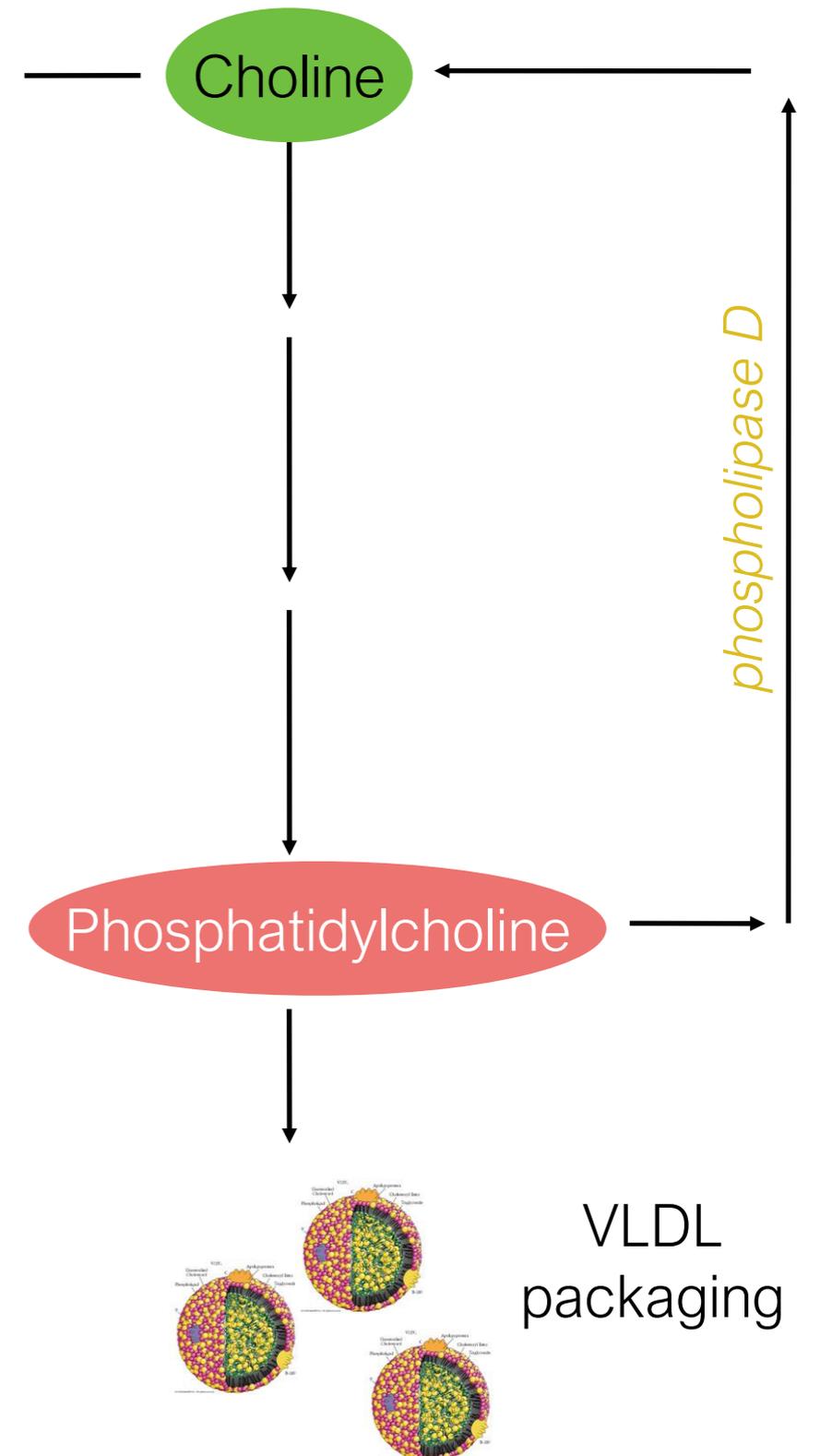
- betaine (3)



- folate (5-methyltetrahydrofolate; 1)



Methyl Group Metabolism



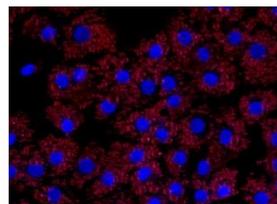
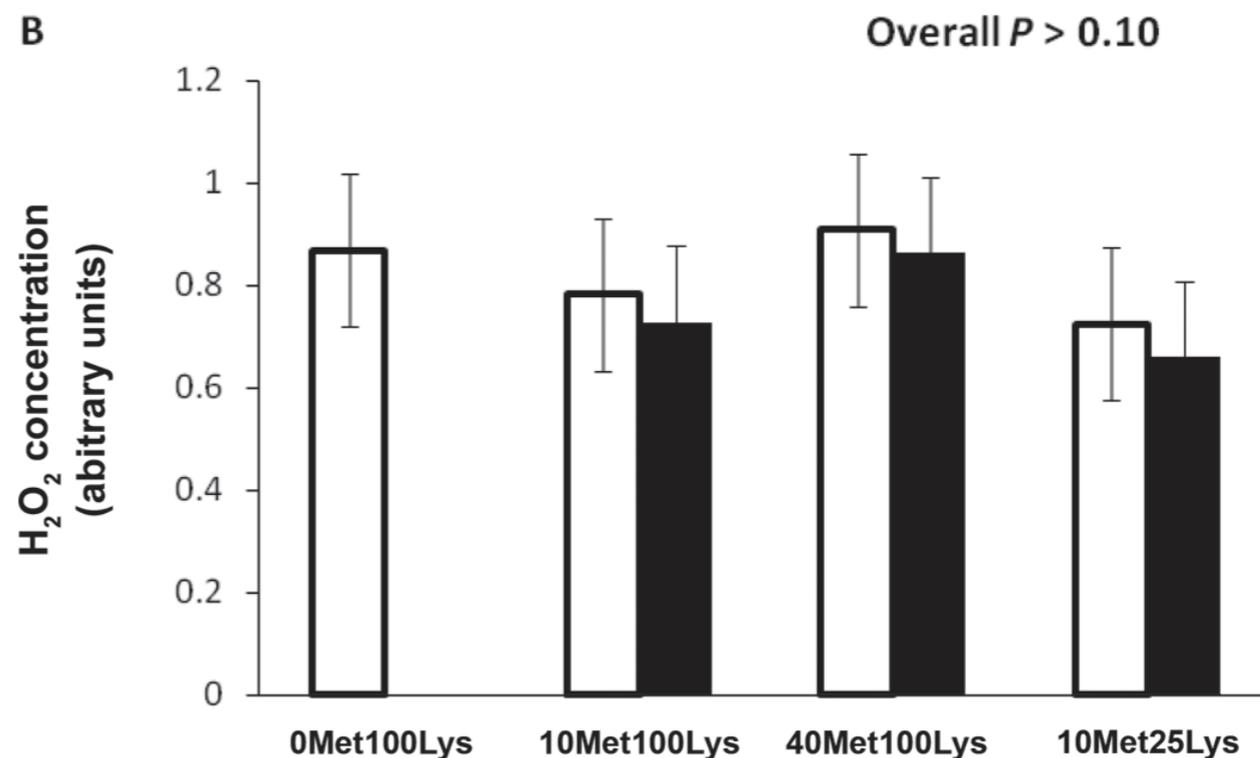
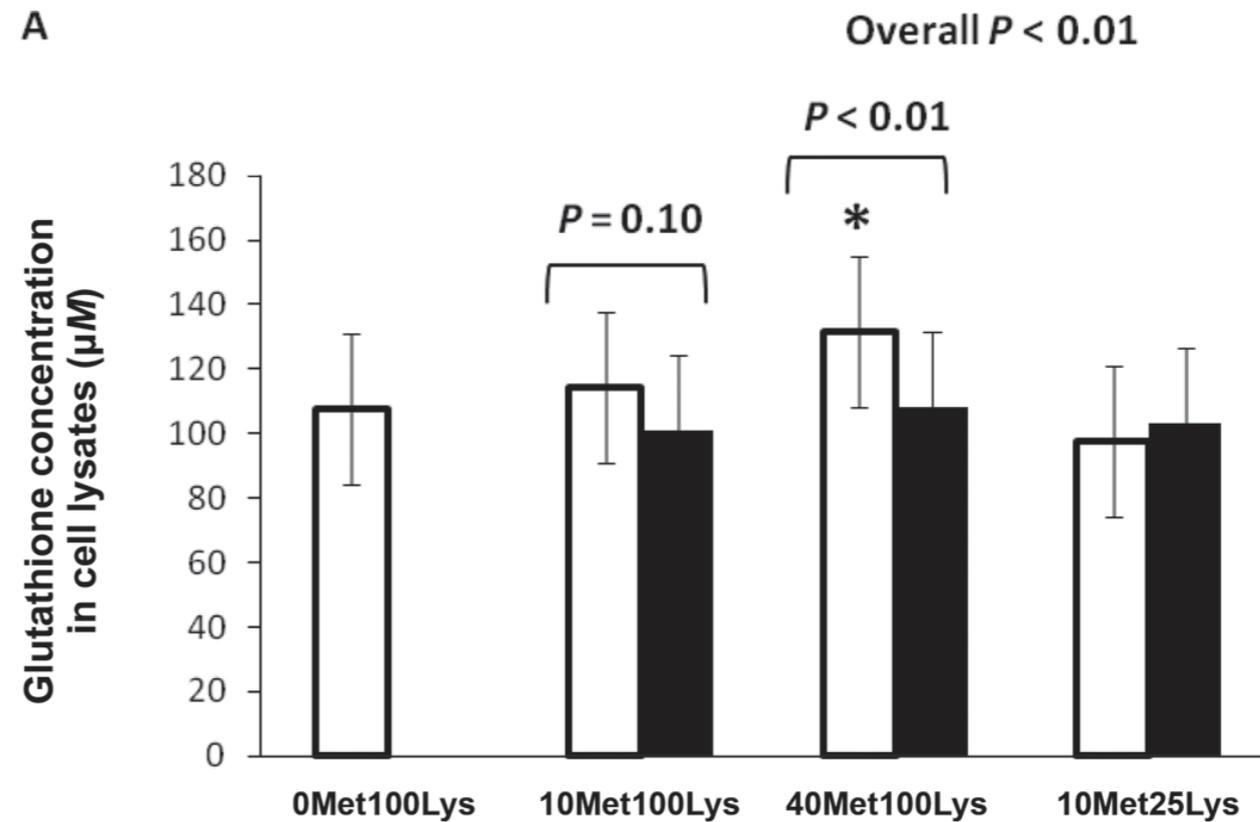
Consistent effects on Hepatocytes

Pathway	Choline Chloride	Methionine
Lipid Export		
VLDL	↑	↔
TG	↓ ✓	↔
Oxidation		
Complete oxidation (TCA cycle)	↑	↔
BHB production (incomplete oxidation)	↓ ✓	↔
ROS secretion	↓	↔
Glucose Metabolism		
glycogen	↑ ✓	↔
Inflammatory Response		
Glutathione production	↔	↑ ✓
Methionine Regeneration (aka methyl donation)	↑ ✓	Supplied!

Methionine Ameliorates LPS Challenge

- ROS and Glutathione may be independent
- What is the optimal amount or balance of glutathione, ROS, and other markers?

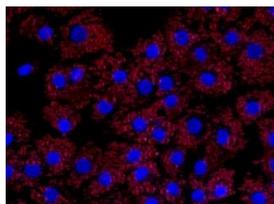
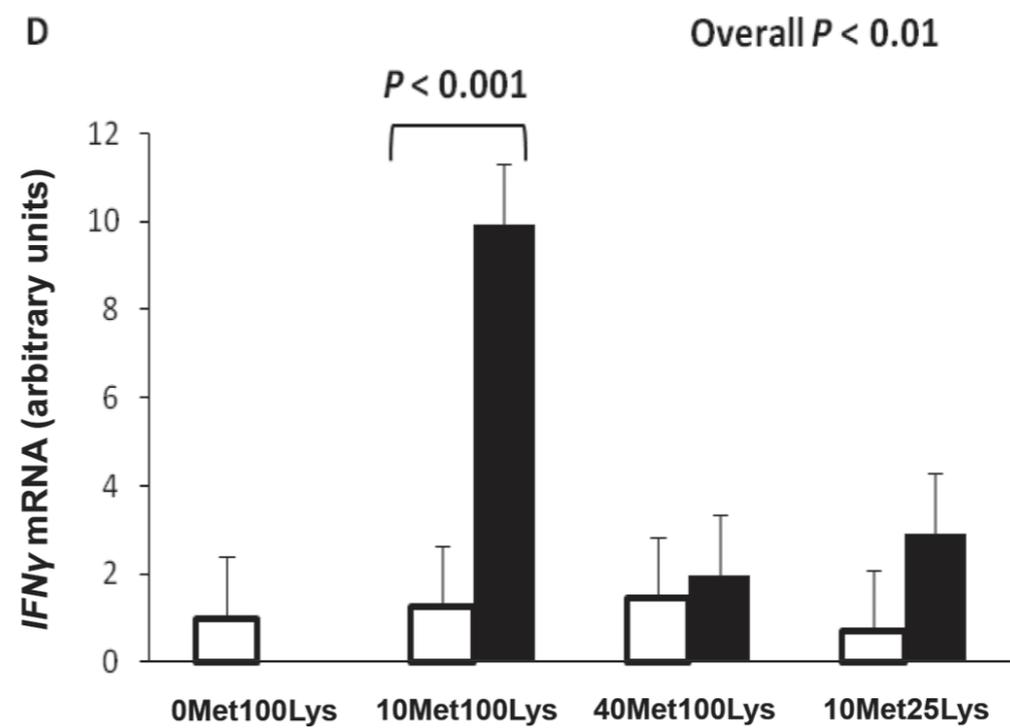
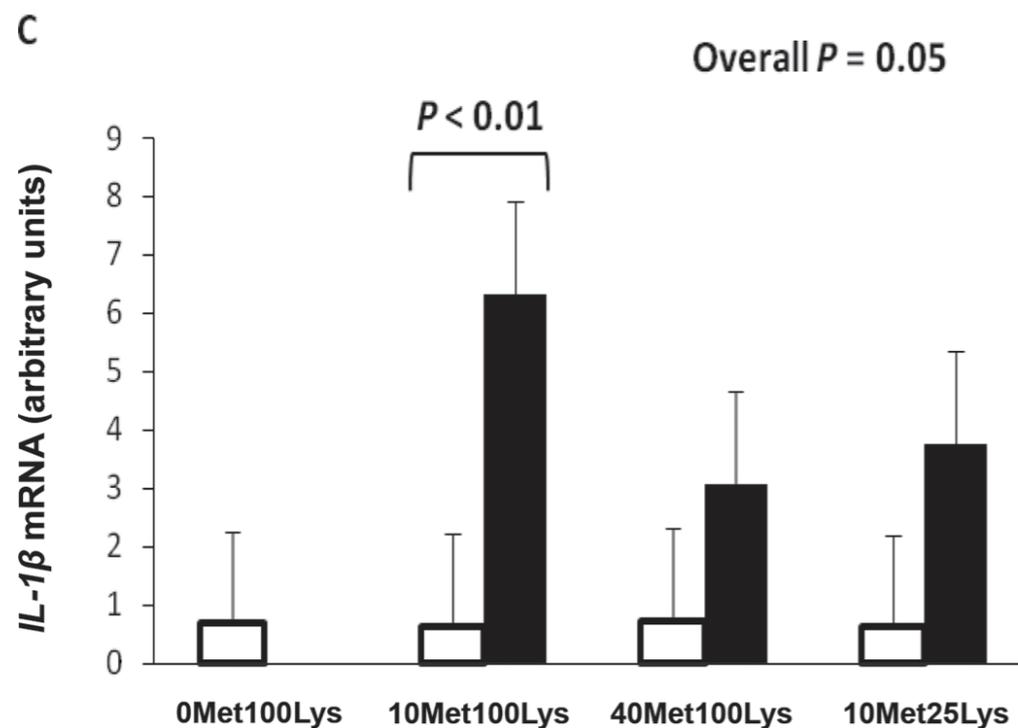
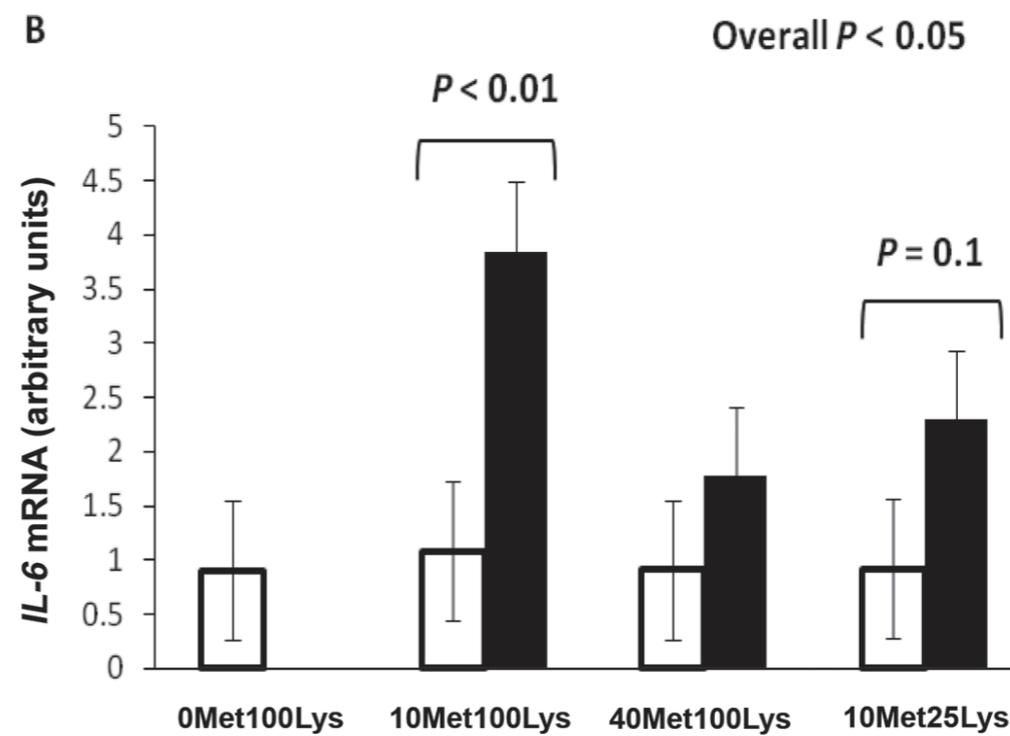
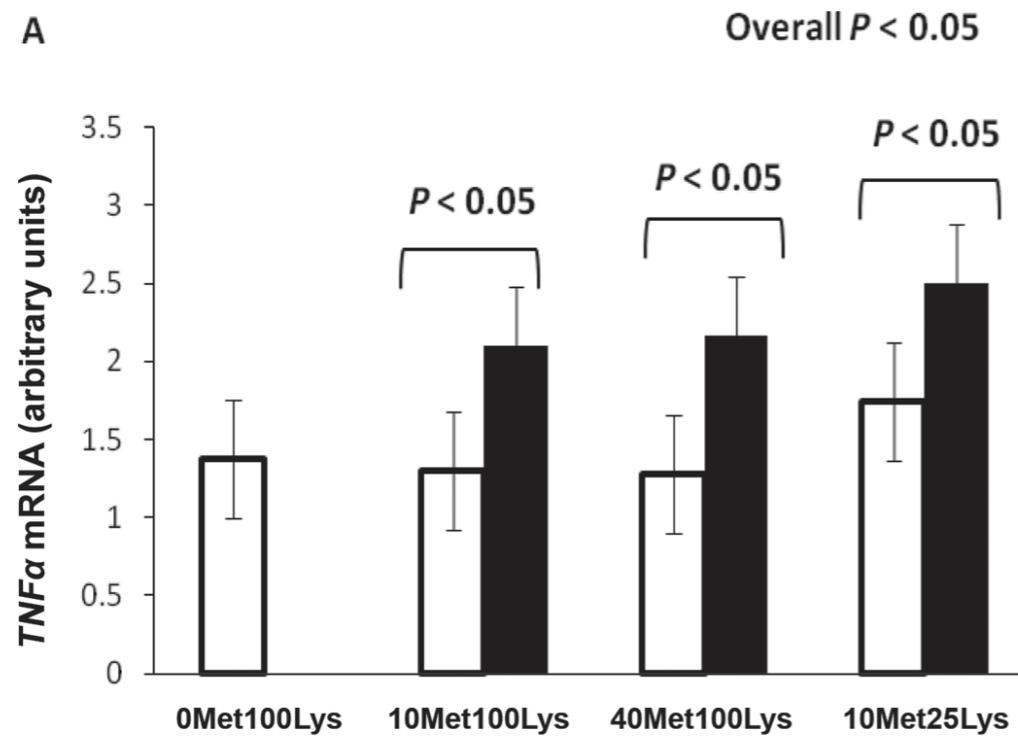
□ No LPS challenge
■ LPS challenge



Methionine Ameliorates LPS Challenge

□ No LPS challenge

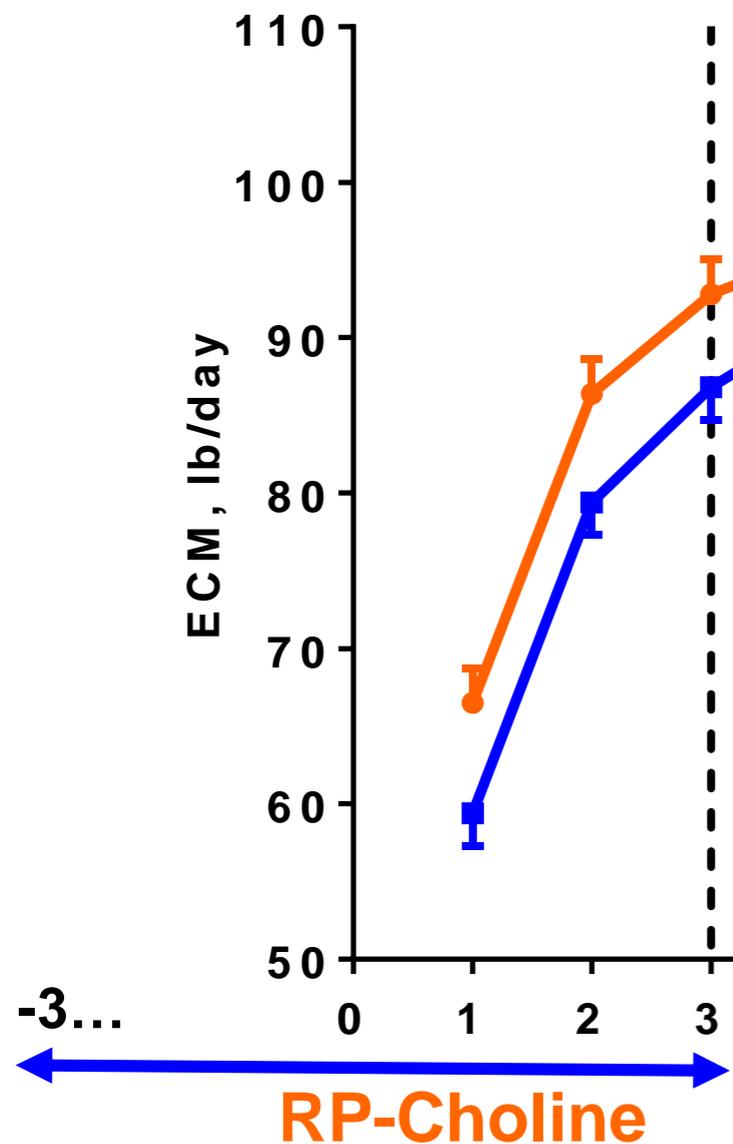
■ LPS challenge



Lack of methyl donors =
increased liver inflammation,
decreased liver oxidation,
and
decreased methyl donation

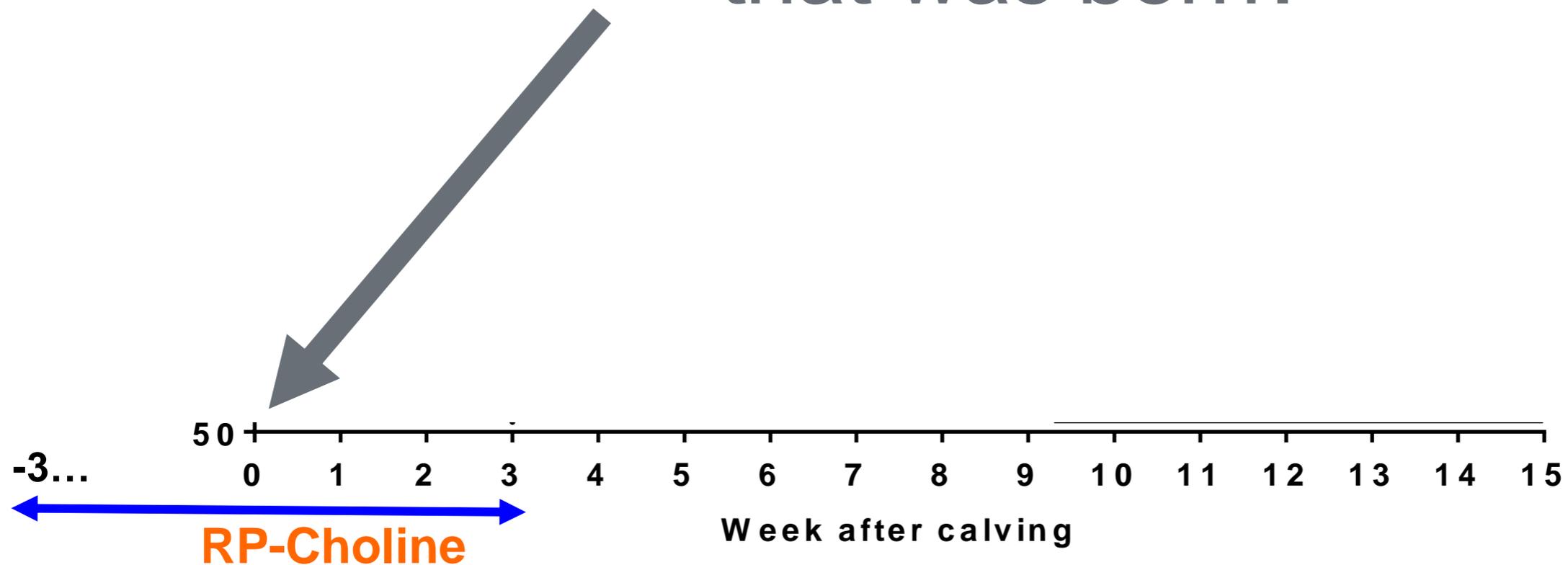
Does an improvement in the transition to
lactation period carry over for the remainder
of the lactation?

Positive Benefits of RP Choline on Milk Production

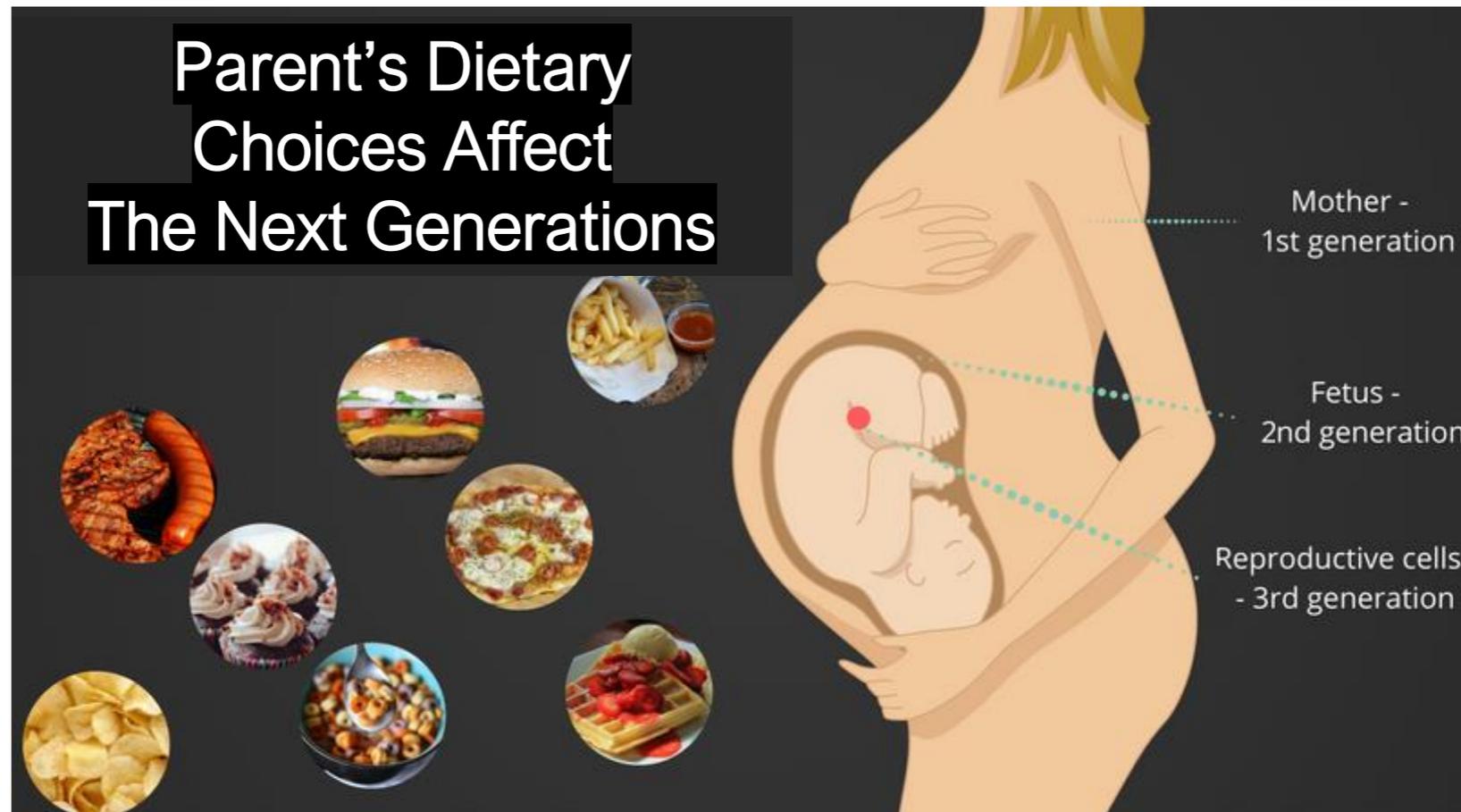


Positive Benefits of RP Choline on Milk Production

What about the calf that was born?

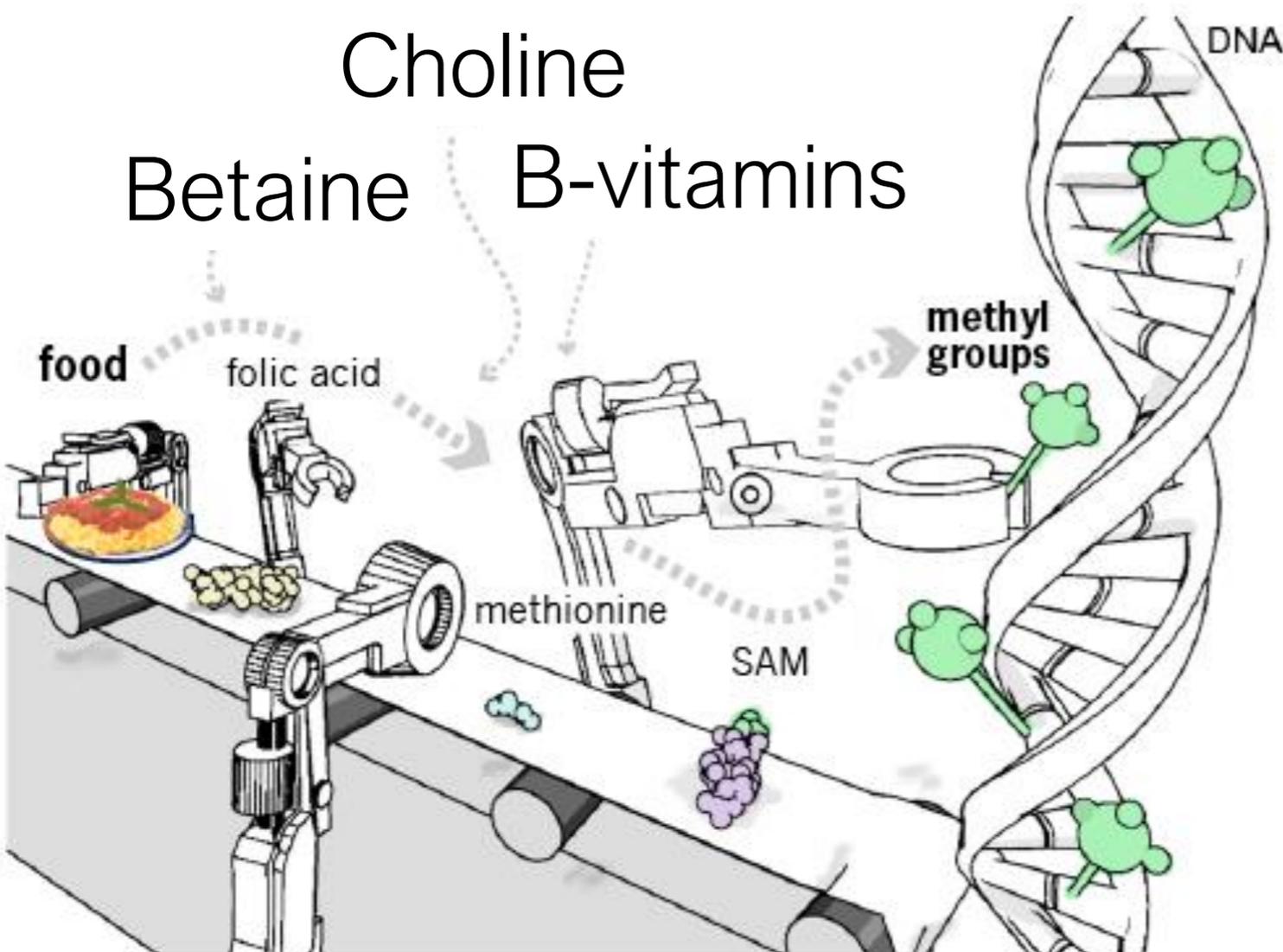


Feeding particular nutrients to the mother during a critical period of fetal development can have immediate and long-term effects on the offspring.



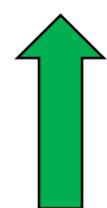
<https://www.diet-health.info/en/100122/papers/6267/principles/nutritional-programming>

Nutrigenomic Responses



Animal studies have shown that a diet with too little methyl-donating choline or folate before or just after birth causes certain regions of the genome to be under-methylated for life.

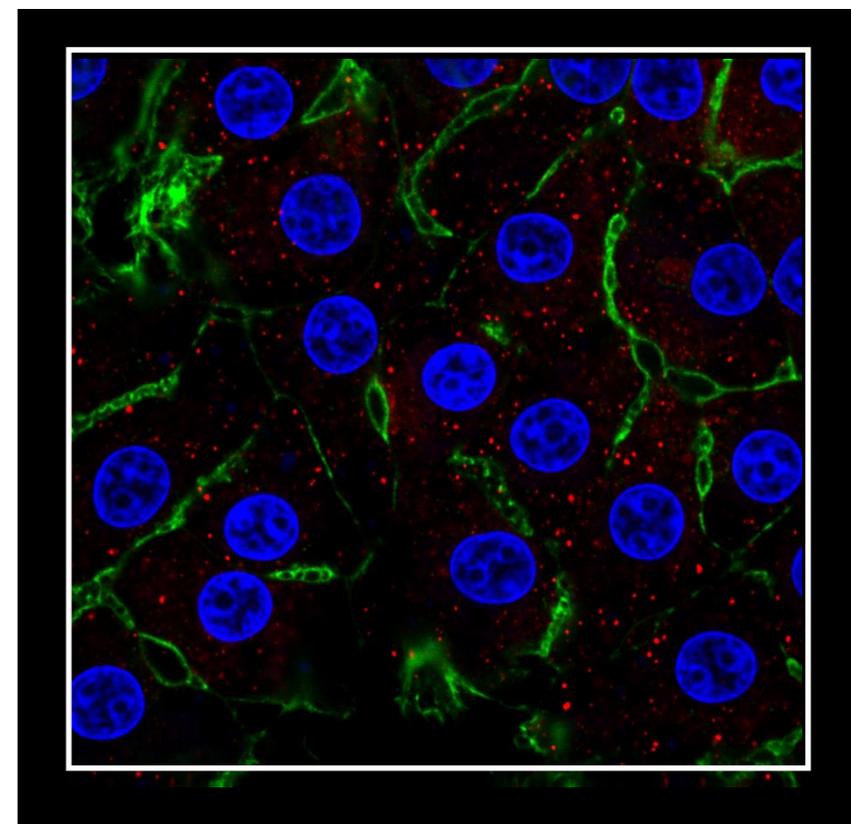
Choline supplementation of Liver Cells



Increased methyl group donation



Methionine regeneration



What does this mean to the calf?

Calves born to Cows fed RP Choline

have increased average daily gain (ADG)

Birth to ~50 weeks of age
by heifers

2015

1.77 vs.

1.86 lb/d;

$P = 0.06$

$n = 35$

2017

1.70 vs. **1.80**

lb/day

$P = 0.09$

$n = 46$

Birth to 5 weeks of
age by bulls
(given LPS)

2017

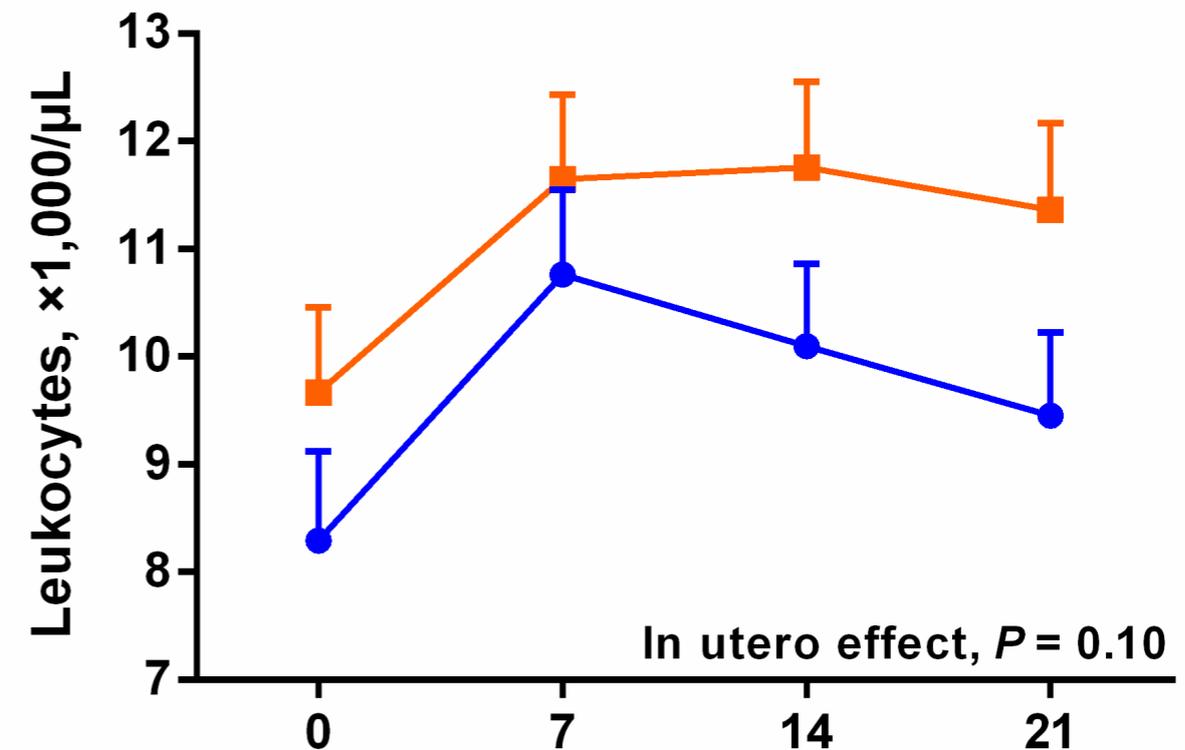
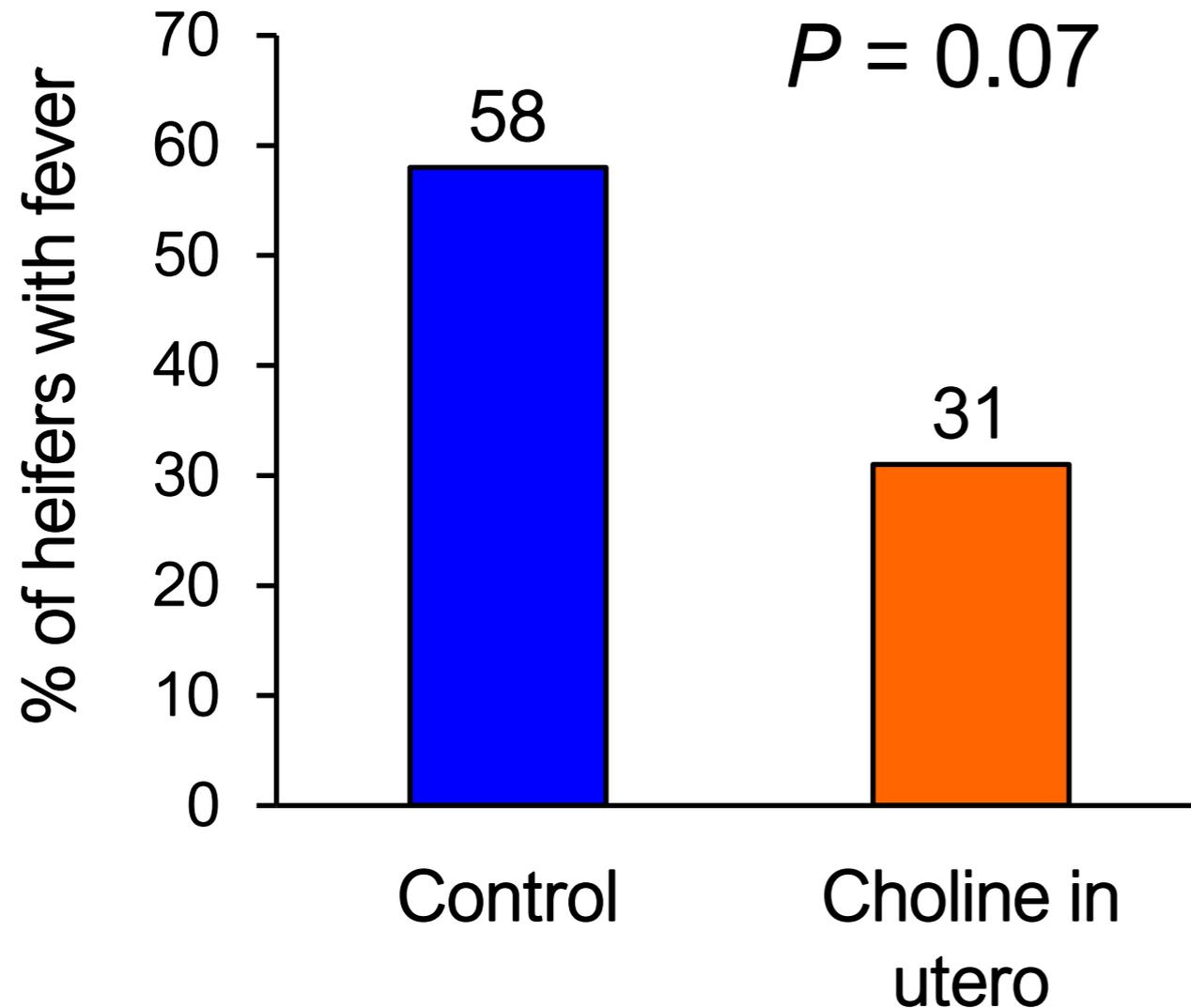
0.96 vs. **1.23**

lb/day

$P = 0.06$

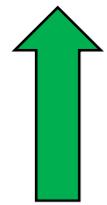
$n = 38$

Calves born to Cows fed RP Choline Had Improved Immune Response



Rectal temperatures measured daily.
Fever: $>103.1^{\circ}\text{F}$.

Choline supplementation at the end of gestation impacts the fetus:



Average Daily Gain



Immune Maturation/Function



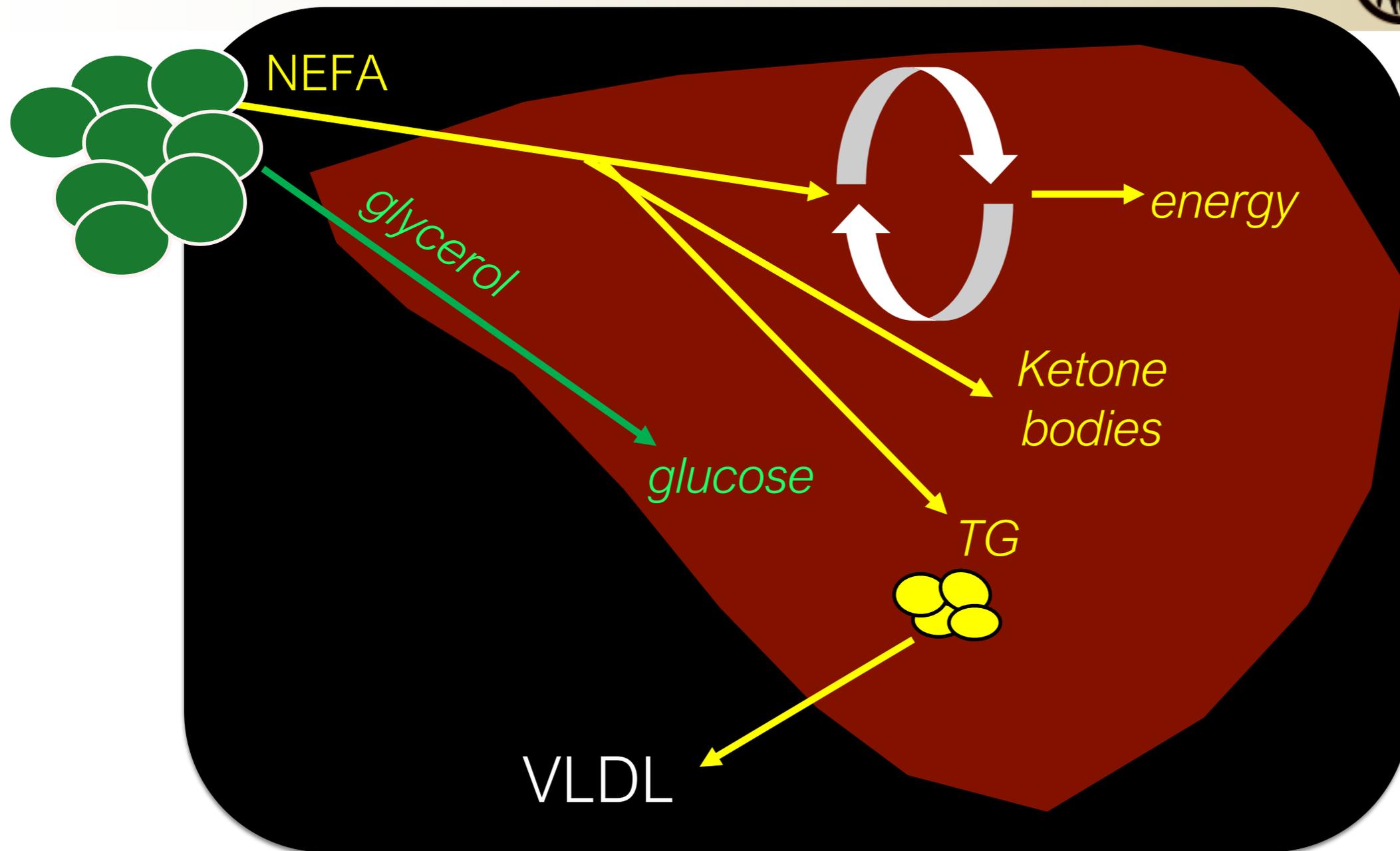
Lung Development and Maturation

What happens when these heifer calves
enter the milking herd?

Piecing It All Together

- **Manipulating the capacity for complete oxidation likely has a metabolic impact**
 - Decreased PC:PEPCKc at calving in cows that subsequently develop HYK
 - Increased availability of substrate (propionate and lactate) or key coenzymes (ex. Choline) may lead to improved metabolic health, production, and feed efficiency
- **Supplementation of methyl donors may improve hepatic efficiency to positively impact cow and calf production in a donor-specific manner**
 - Export of hepatic lipids and glycogen production and calf growth and health are increased with choline supplementation
 - Methionine supports milk protein synthesis and ameliorates inflammatory response during LPS challenge
 - Biological priority for methyl donors (choline and methionine) is apparently different within hepatocytes

Taken Together

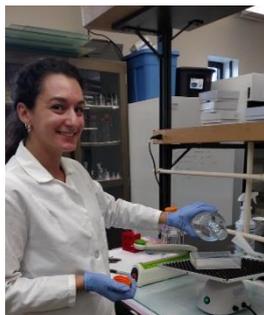


Optimizing hepatic nutrient partitioning can reduce metabolic disorders, support hepatic output, and improve feed efficiency. . .

. . . and we likely have much more room for progress!

Acknowledgments

Current White Lab Group



Sophia Erb,
Research Specialist



Rafael Oliveira



Ryan
Pralle



Henry Holdorf



Malia Martin

Recent Contributors



Tawny Chandler



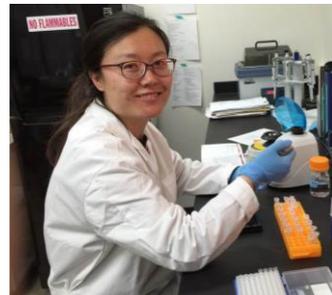
Claira Seely



Kristina Weld



Frankie Rathbun



Qian Zhang



Valentina Caprarulo

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Ric Grummer

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Mentors and Colleagues

Research Farm Staff

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USDA NSF EAGER 2017-67007-25947

USDA HATCH

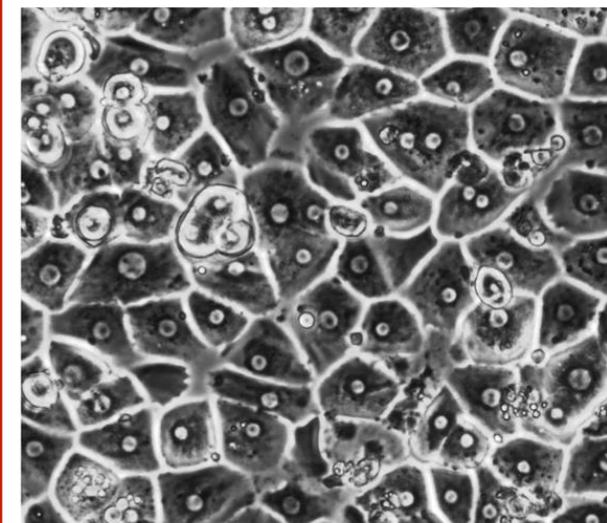
UW Foundation

Adisseo, Agsource, Balchem, BASF, and
Fermented Nutrition

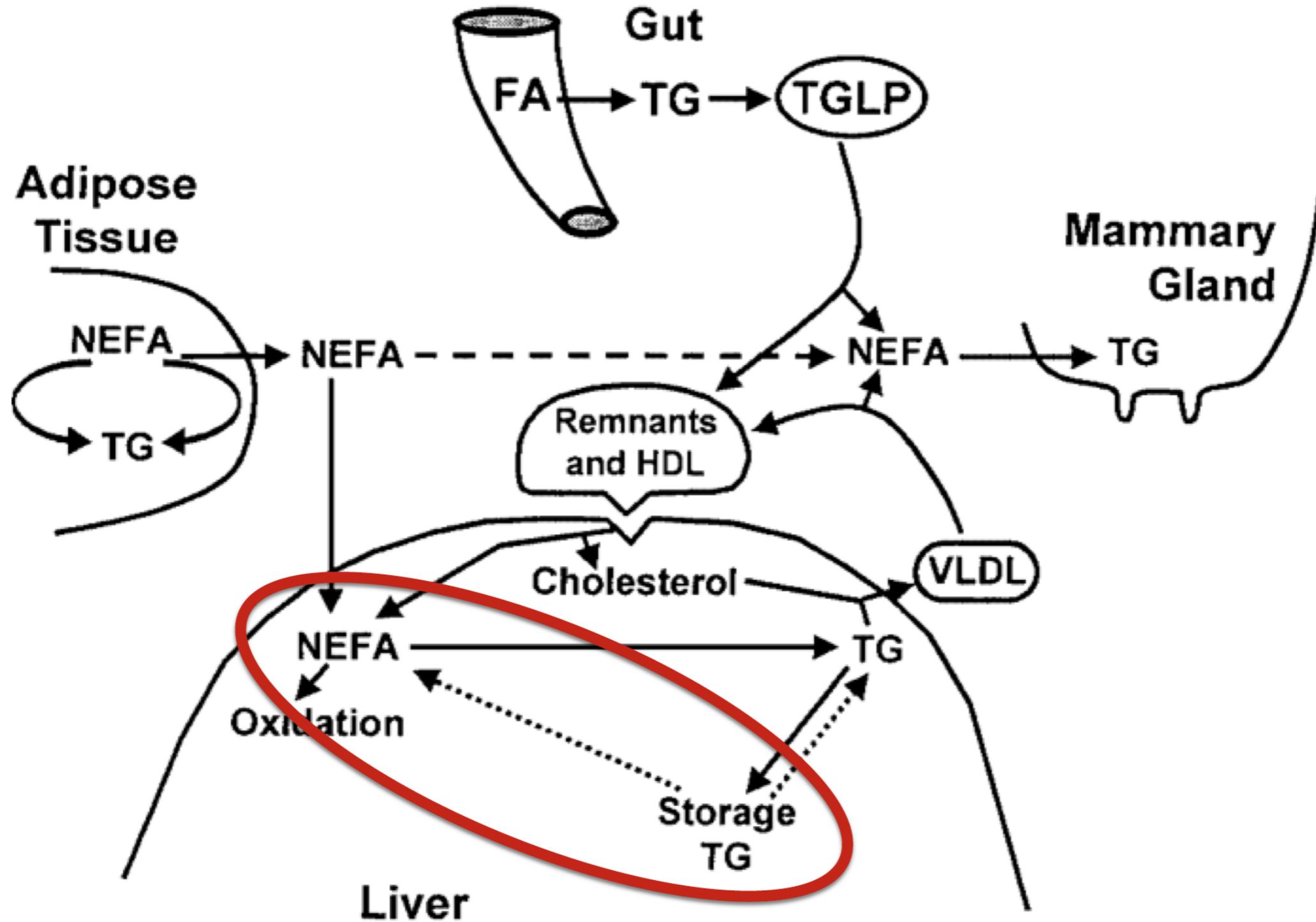
Student support from Purina and VitaPlus



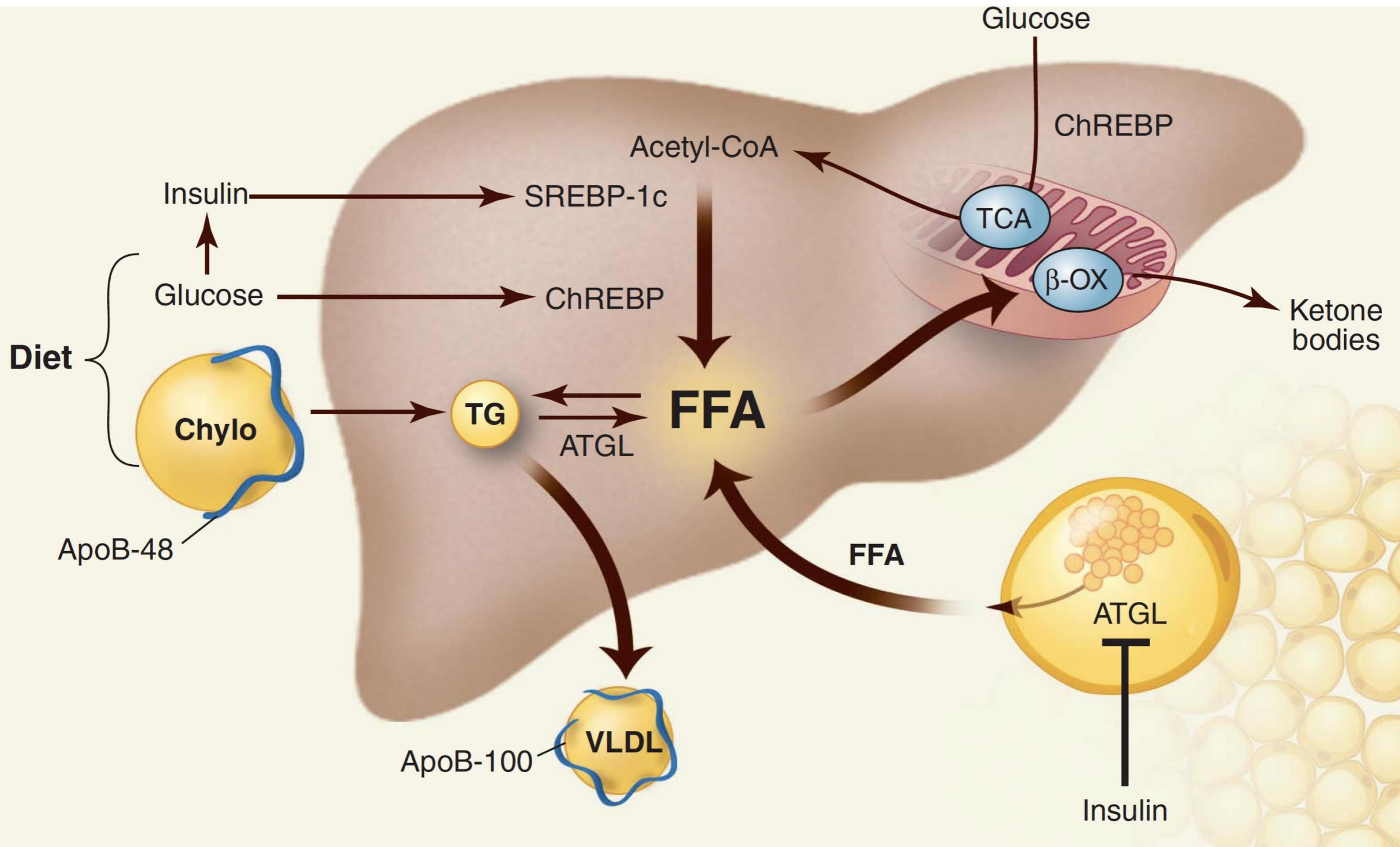
Questions?



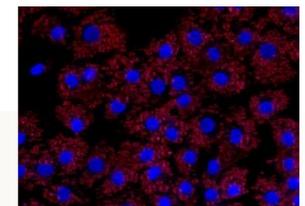
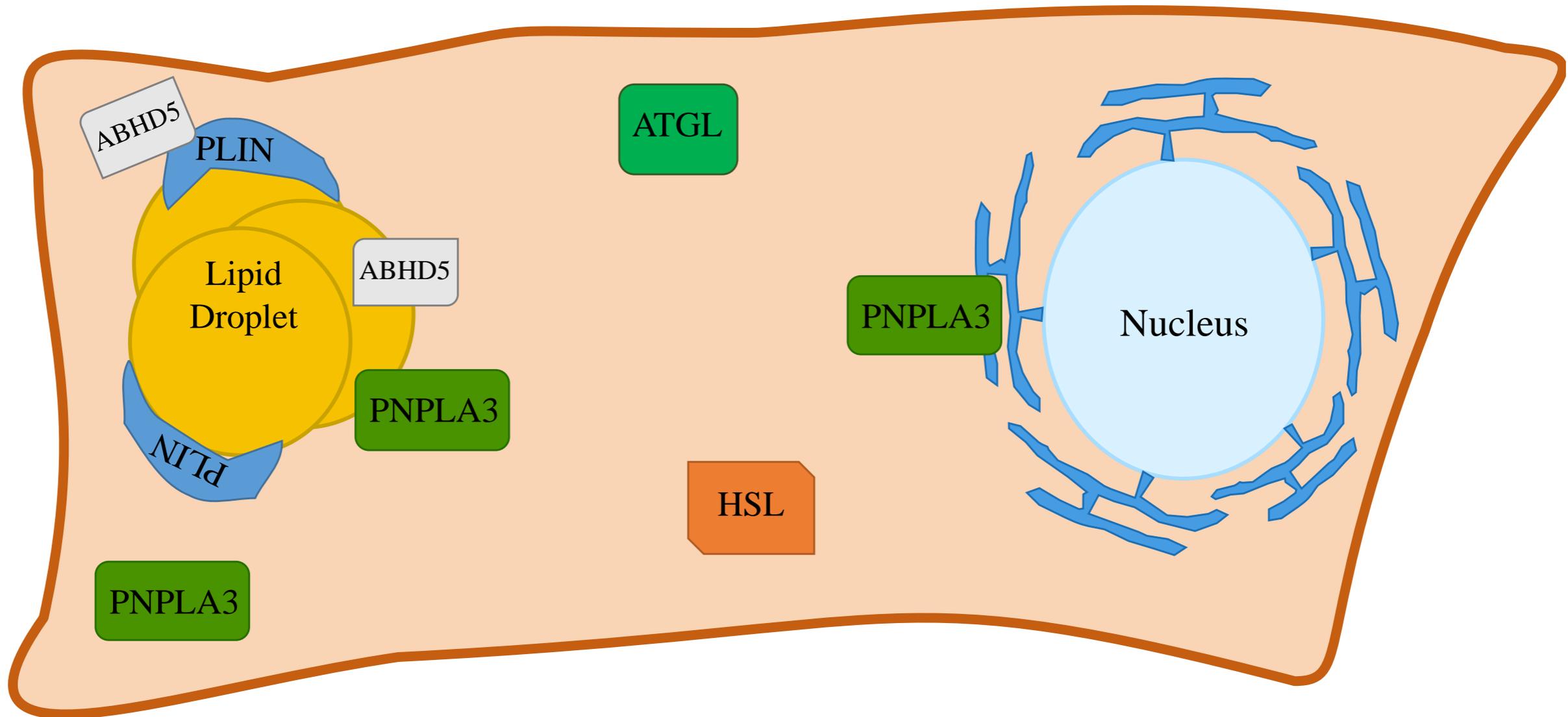
Remobilization of Liver Lipids



Remobilization of Liver Lipids

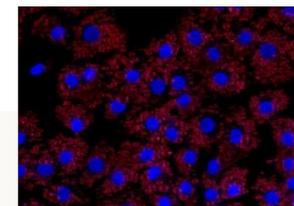
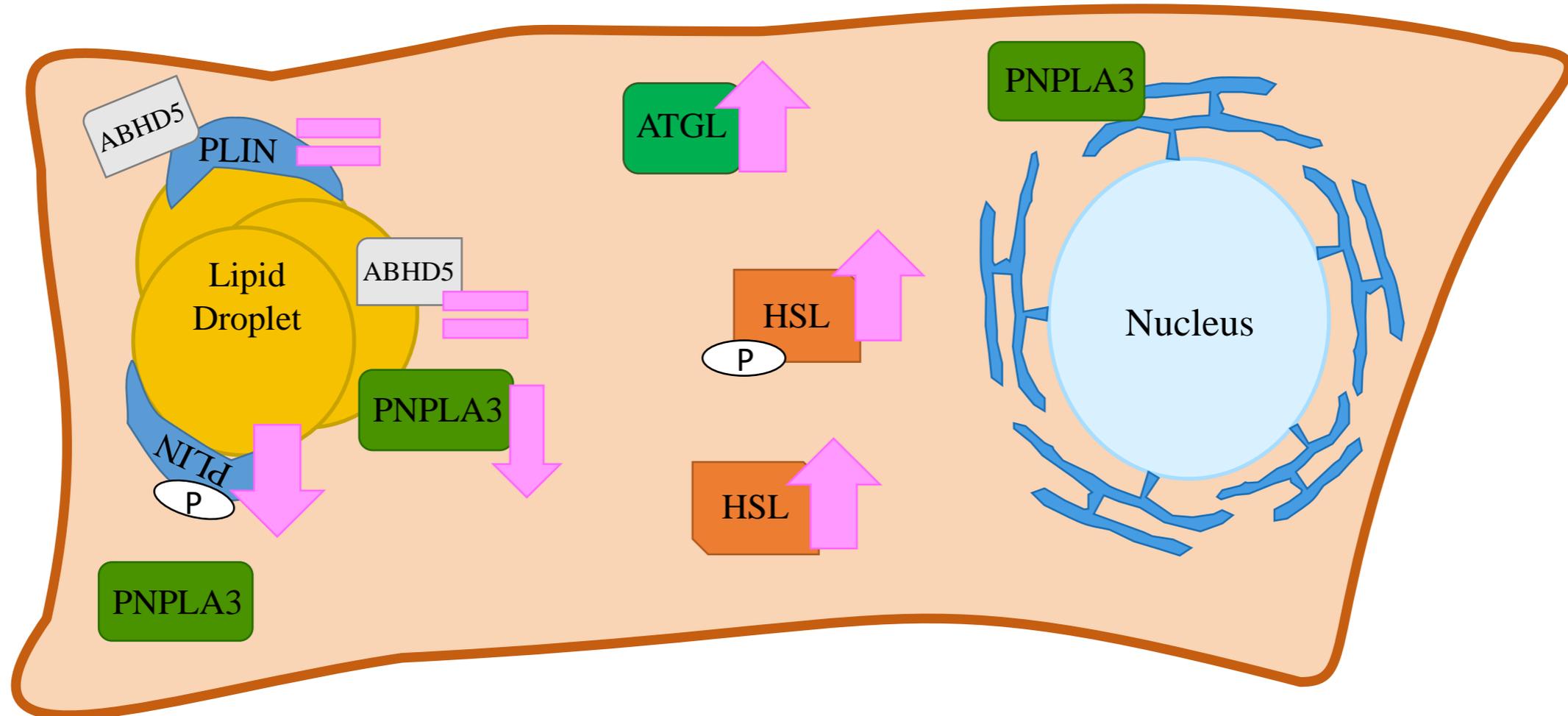


Filling in the Details on Hepatic Lipolysis



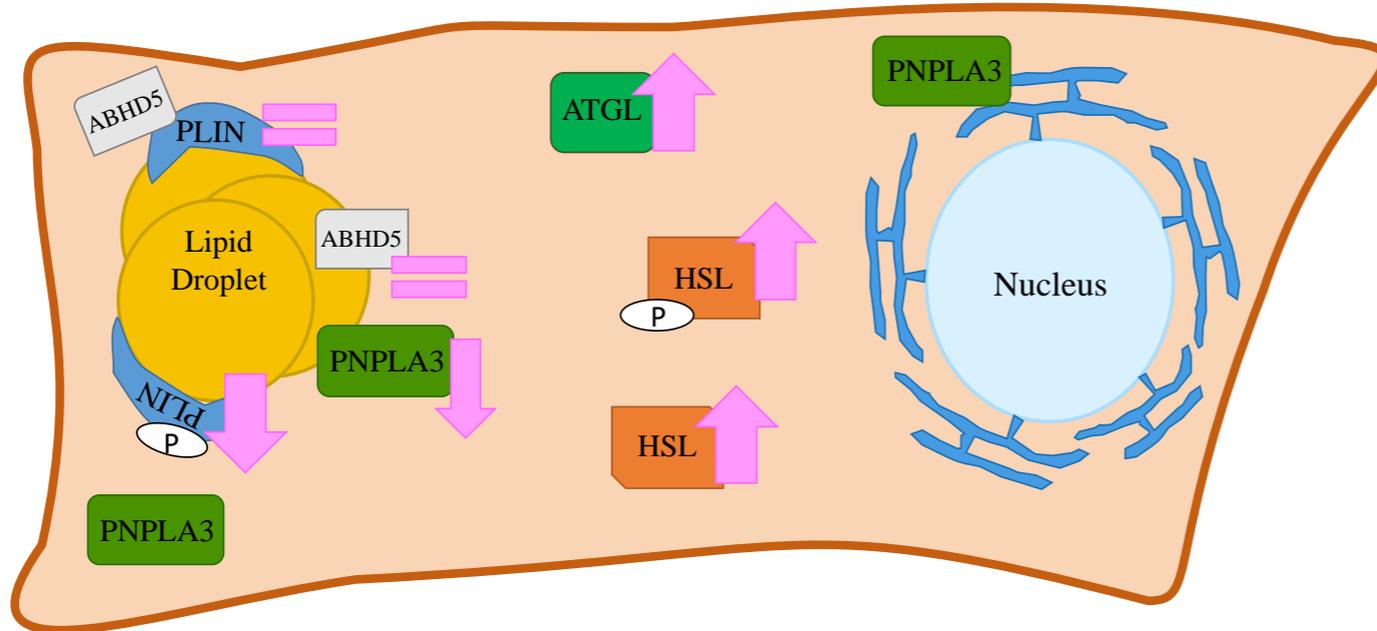
Hepatic Lipid-Associated Proteins

At Calving, when liver lipids are accumulating:

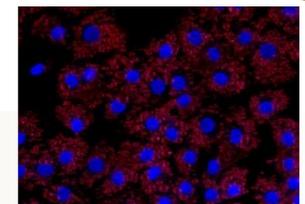
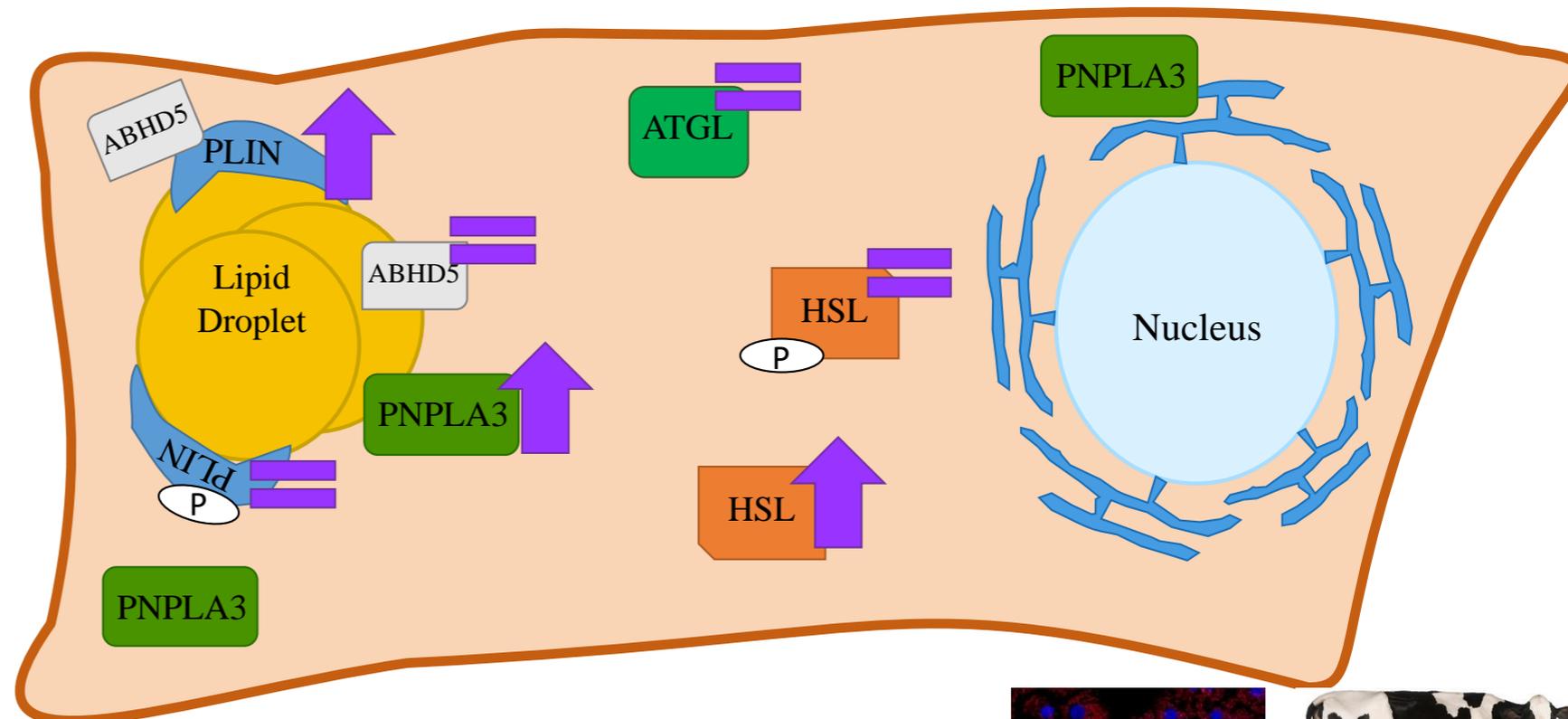


Hepatic Lipid-Associated Proteins

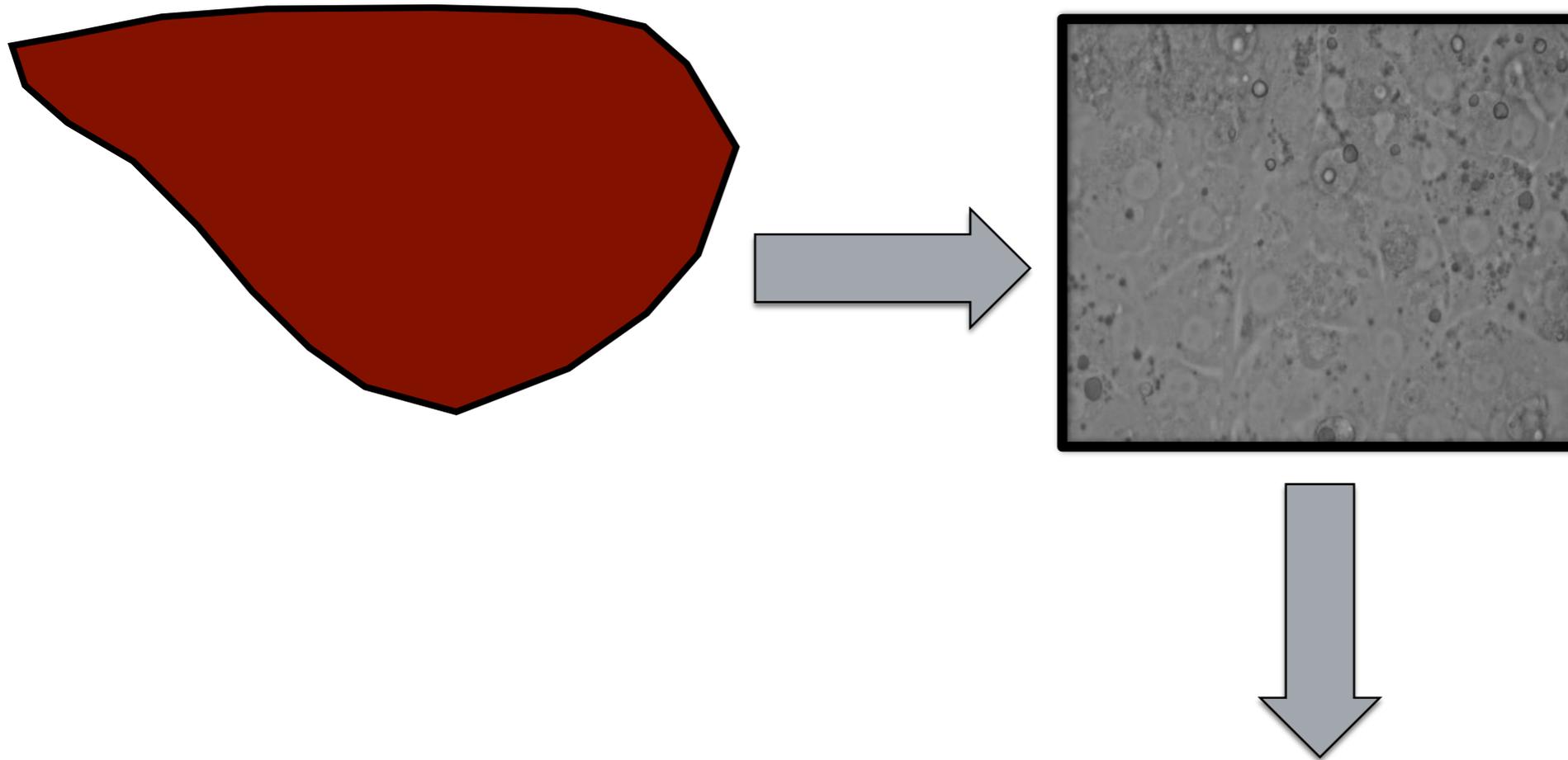
At Calving, when liver lipids are accumulating:



Postpartum, when liver lipids are decreasing:



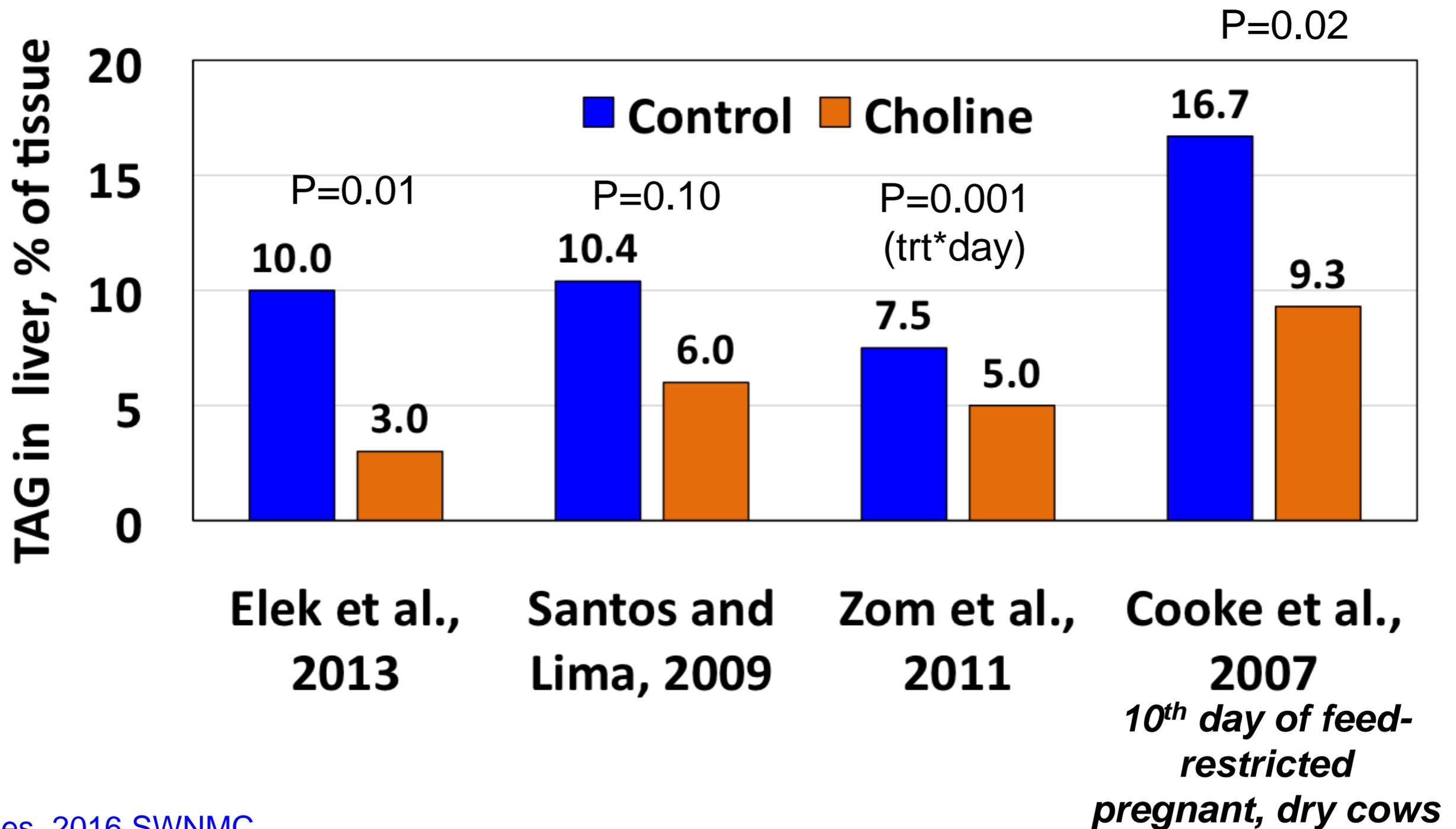
Cell Culture Models



		Choline, mM			
		0.033	0.1	2	4.5
dL Met, mM	0.016				
	0.030				
	0.100				
	0.300				

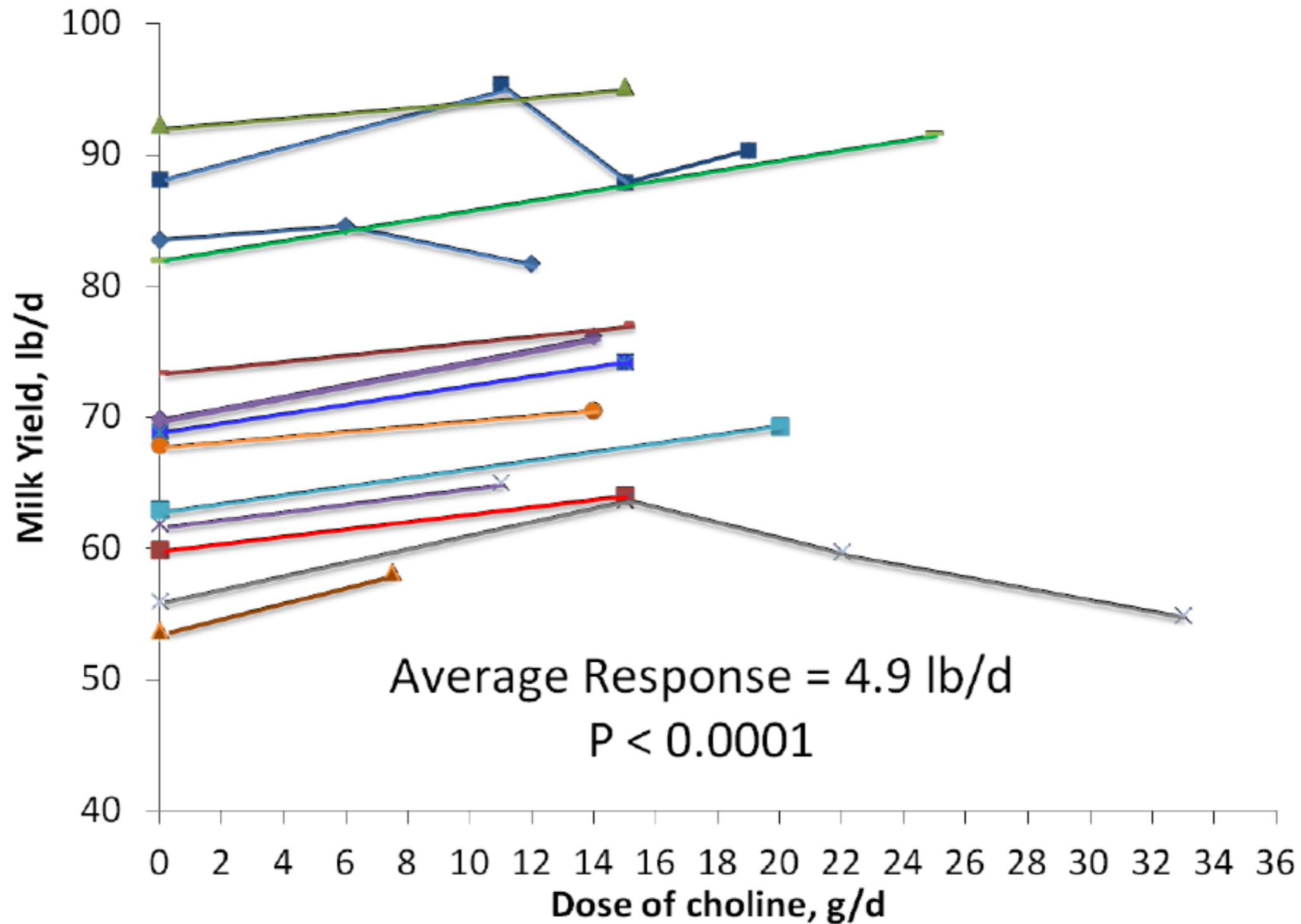
		Choline, mM			
		0.033	0.1	2	4.5
dL Met, mM	0.016	1 mM Fatty Acid Cocktail			
	0.030				
	0.100				
	0.300				

Reduced Fatty Liver with Rumen Protected Choline Supplementation

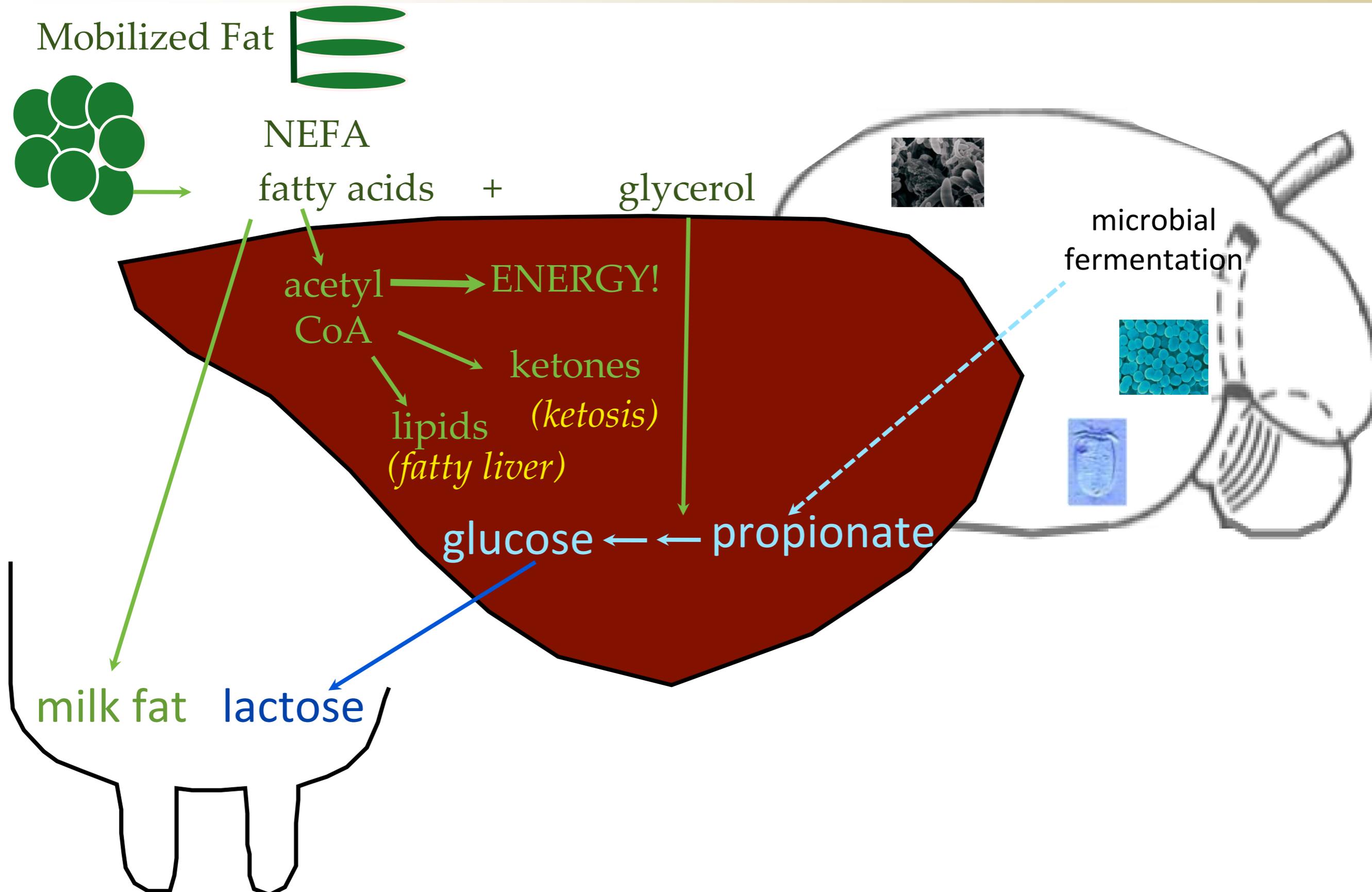


Staples, 2016 SWNMC

Increased Milk Production with RP Choline Supplementation



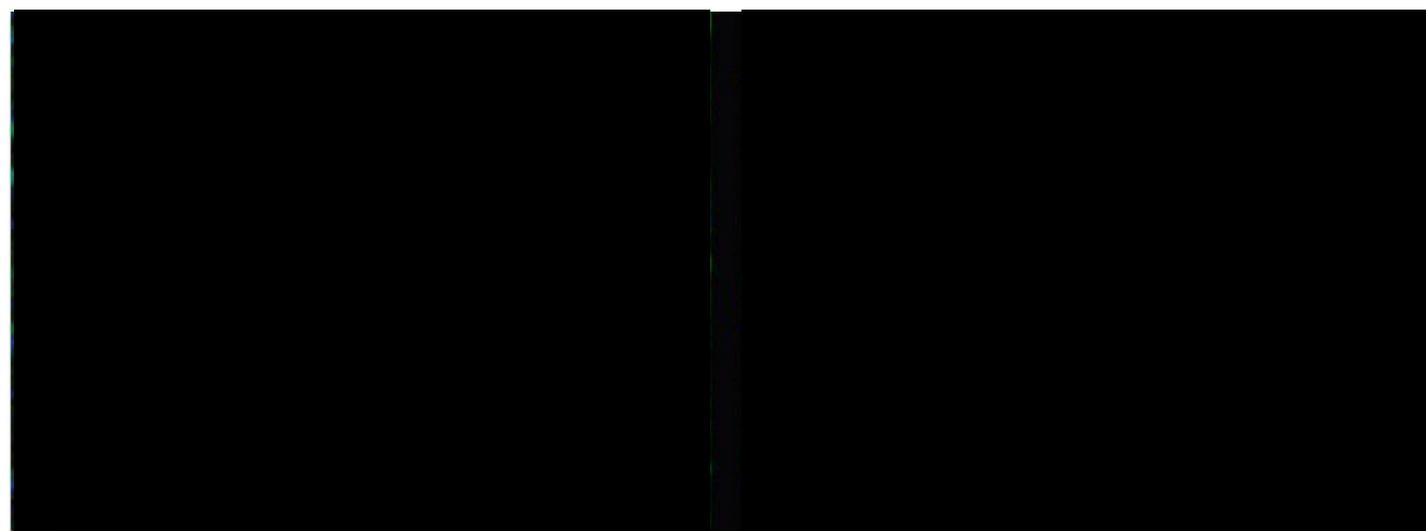
Transition Cow Liver Metabolism



Rumen-Protected Choline

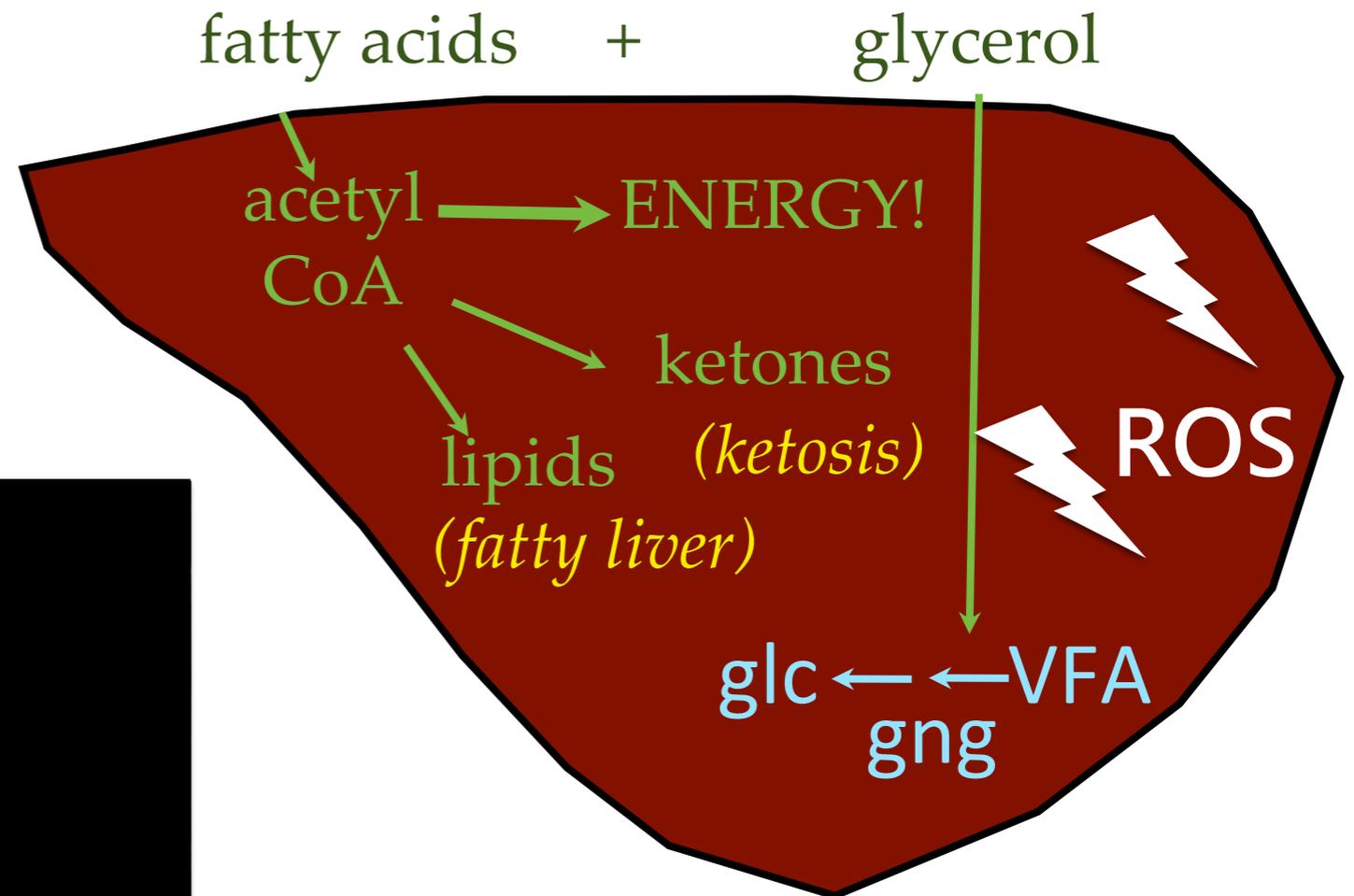
- Oxidizing fatty acids causes oxidative stress
 - Generation of reactive oxidative species (ROS)
 - Decrease cell health and function

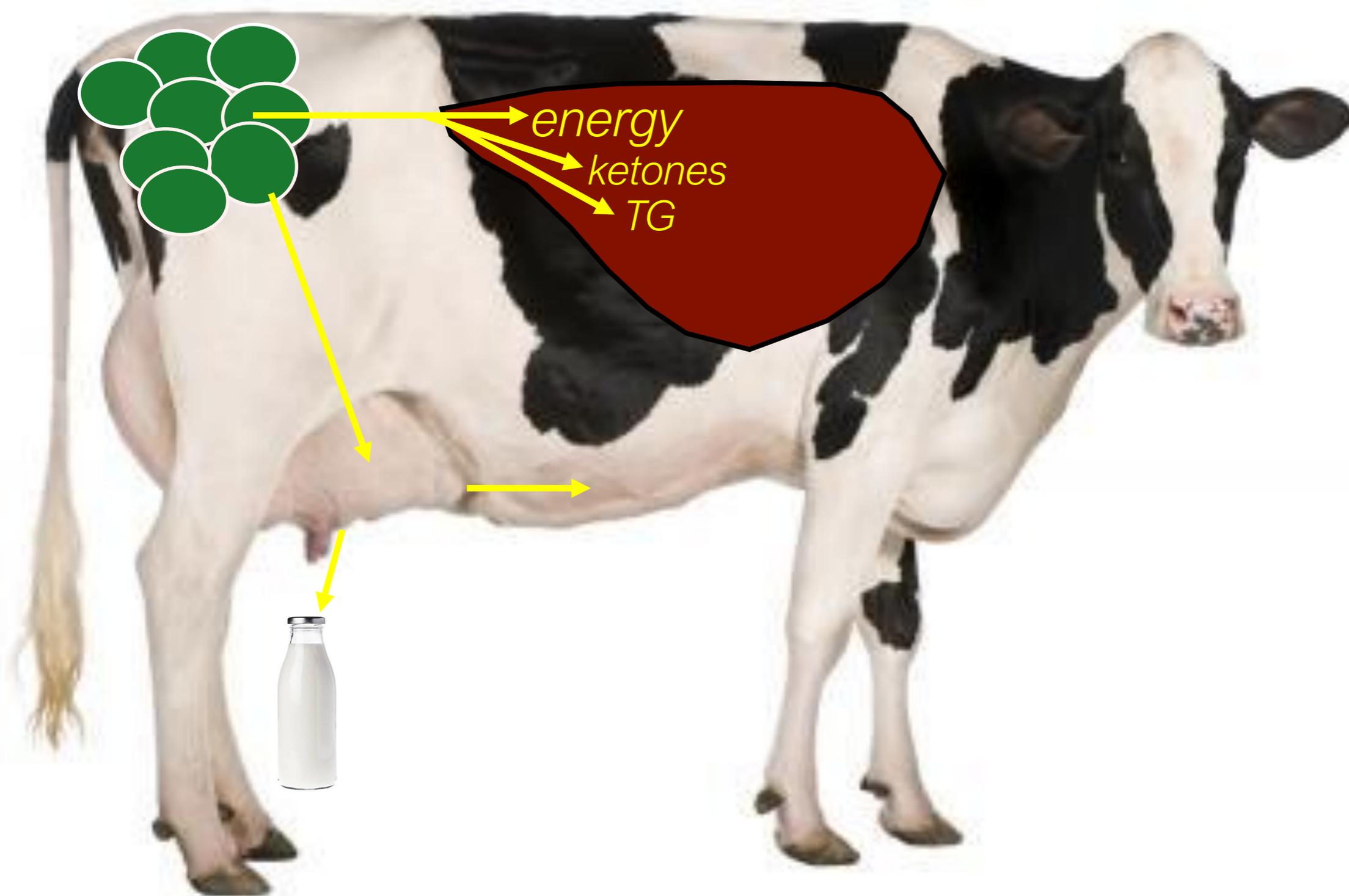
Choline also reduced ROS
(2 mM choline had the lowest ROS)

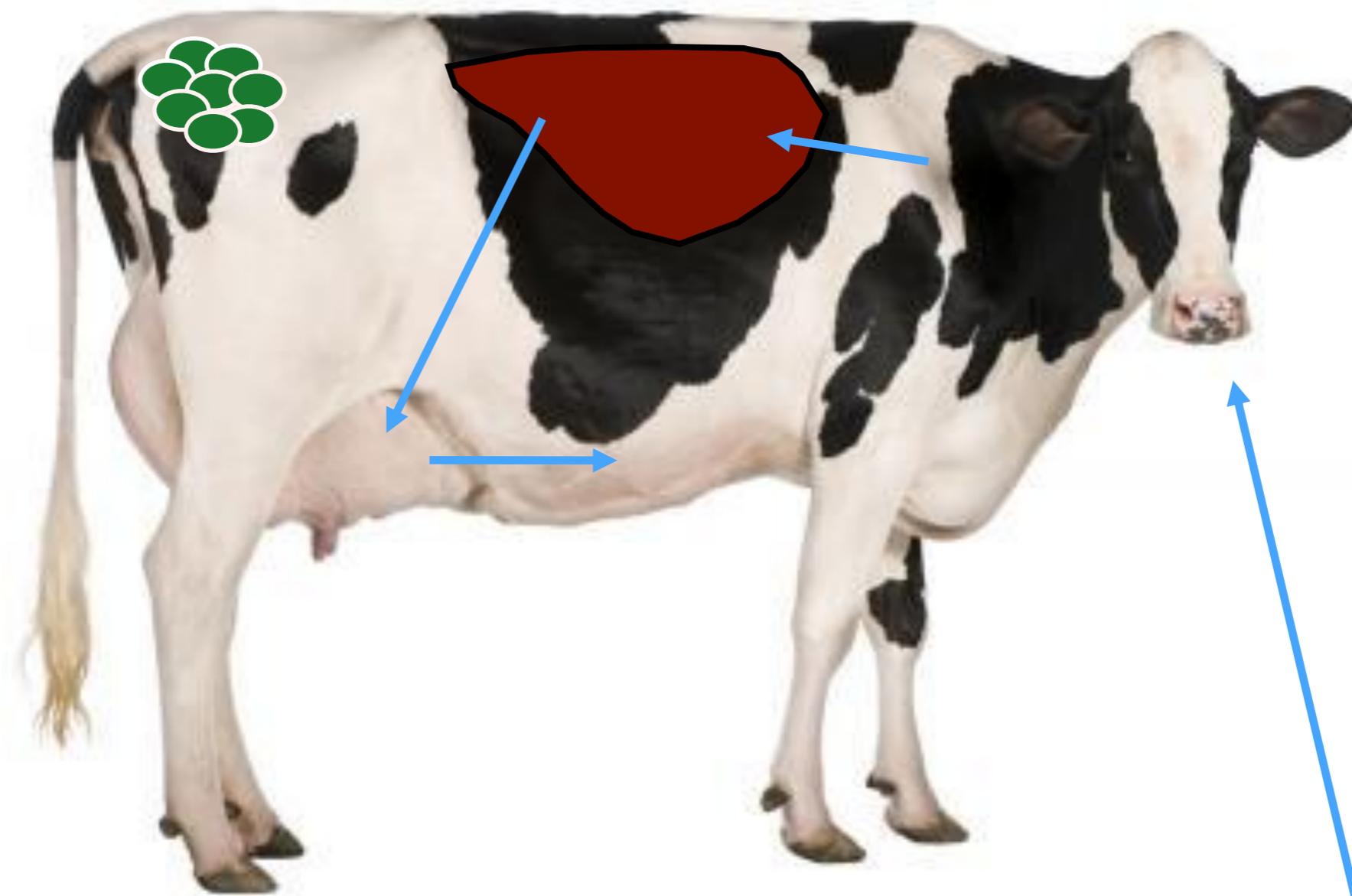


- Choline

+Choline







choline

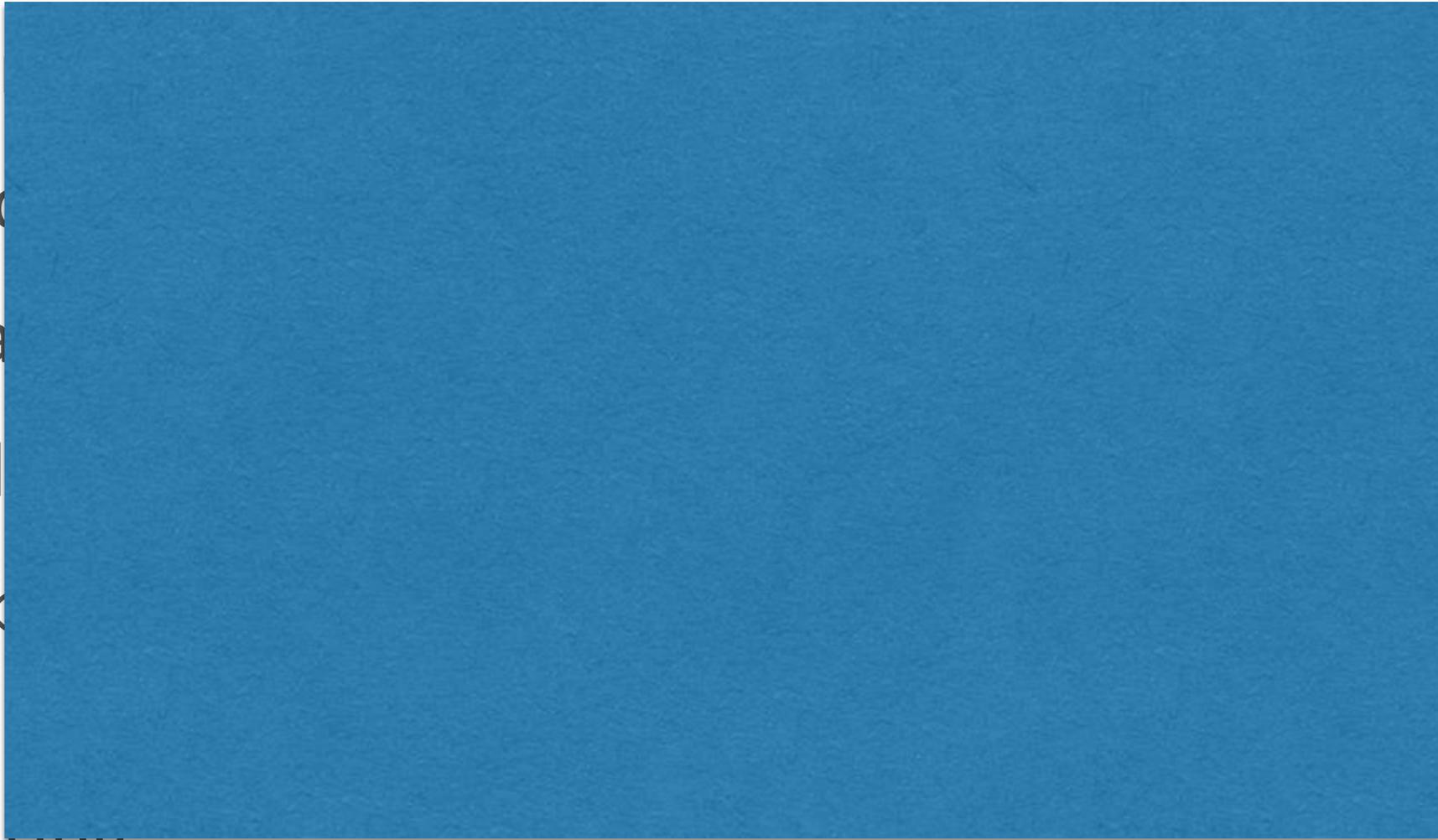
fatty acids

amino acids

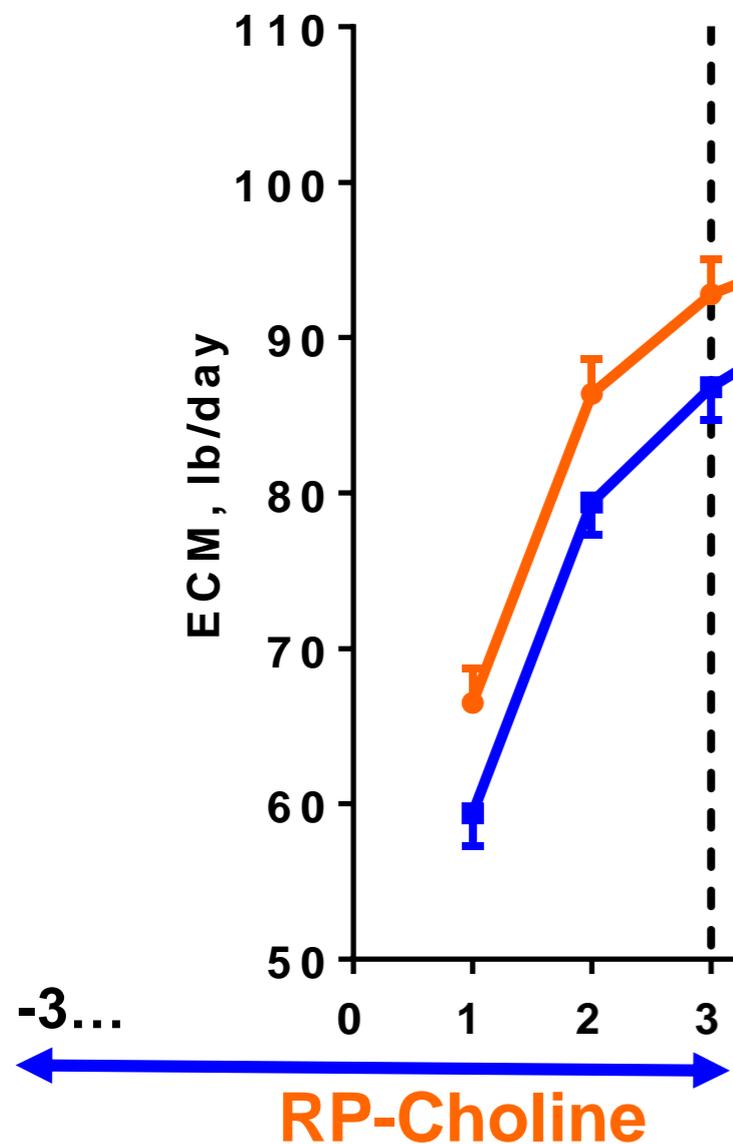
CLA

lactate

Nutrition Can Propagate our Impact

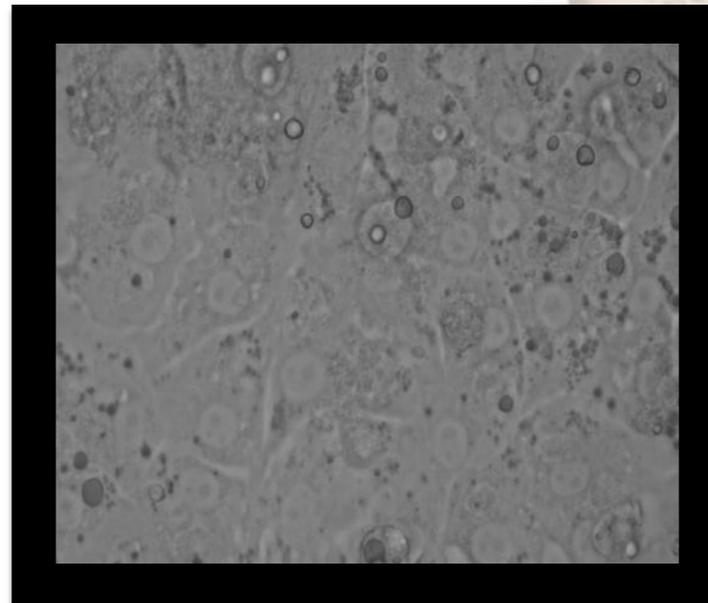
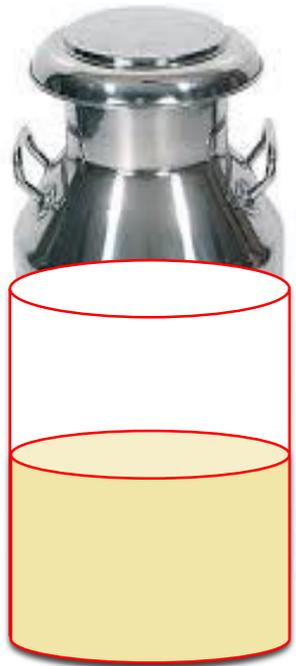
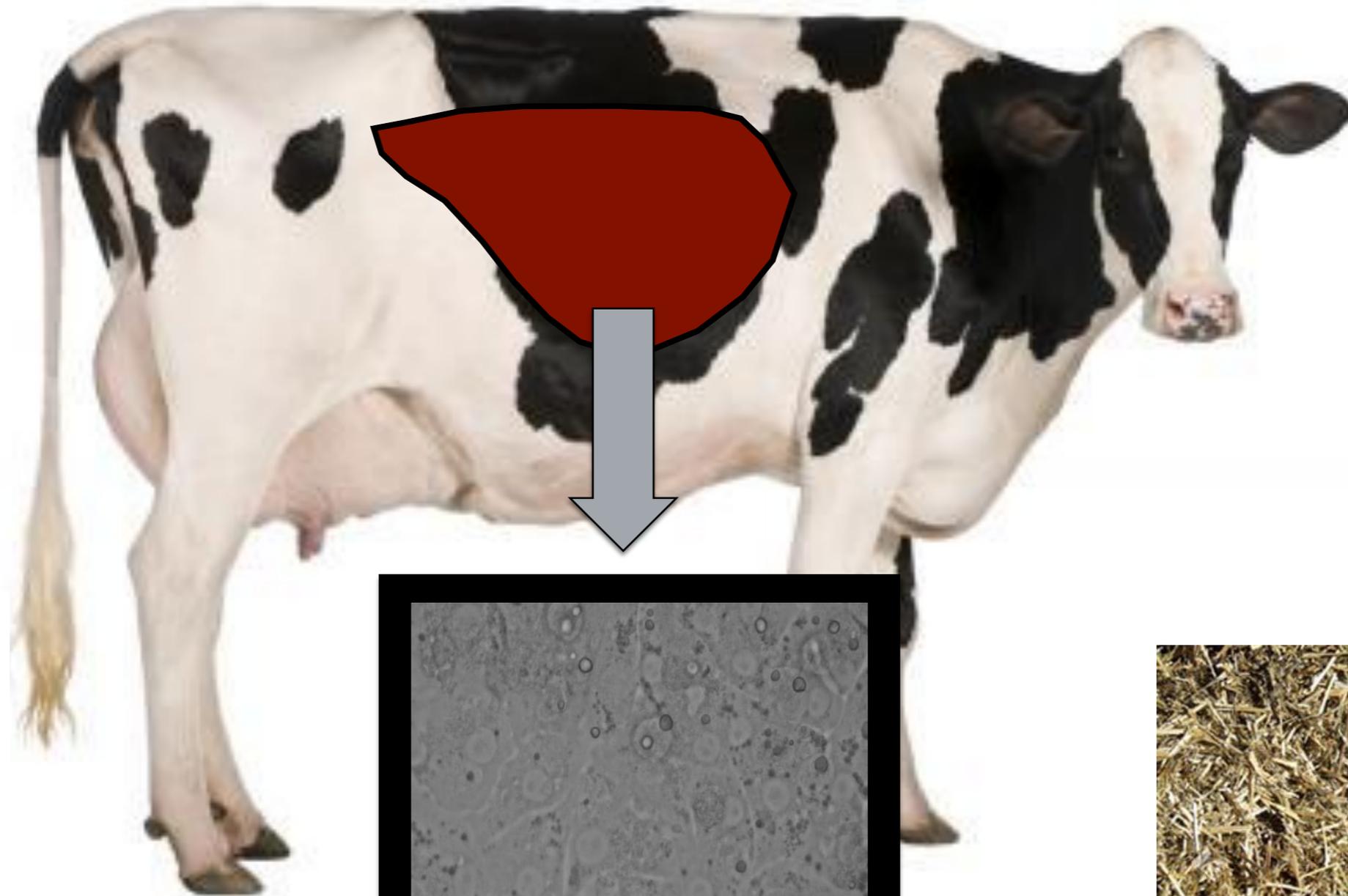
- Impact during RP Choline supplementation is well documented
 - Inc  (Grummer, 2012, CNC)
 - Dec
- Susta on
 - Ind
 - Imp
- Impa offspring
 - In utero programming
 - Colostrum

Positive Benefits of RP Choline on Milk Production

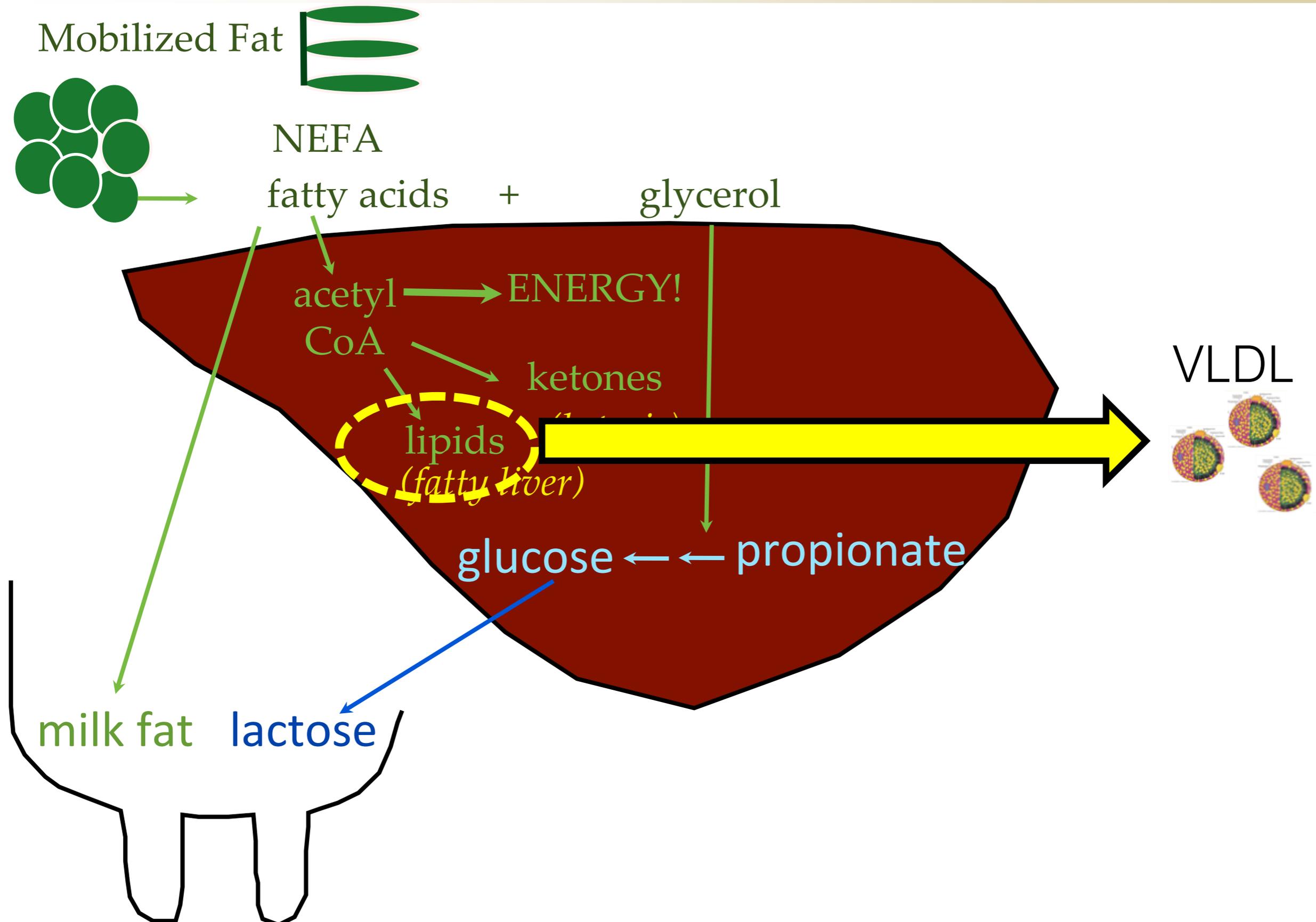


*How is milk production increased during,
and AFTER,
supplementation of RP choline??*

Black Box Nutrition

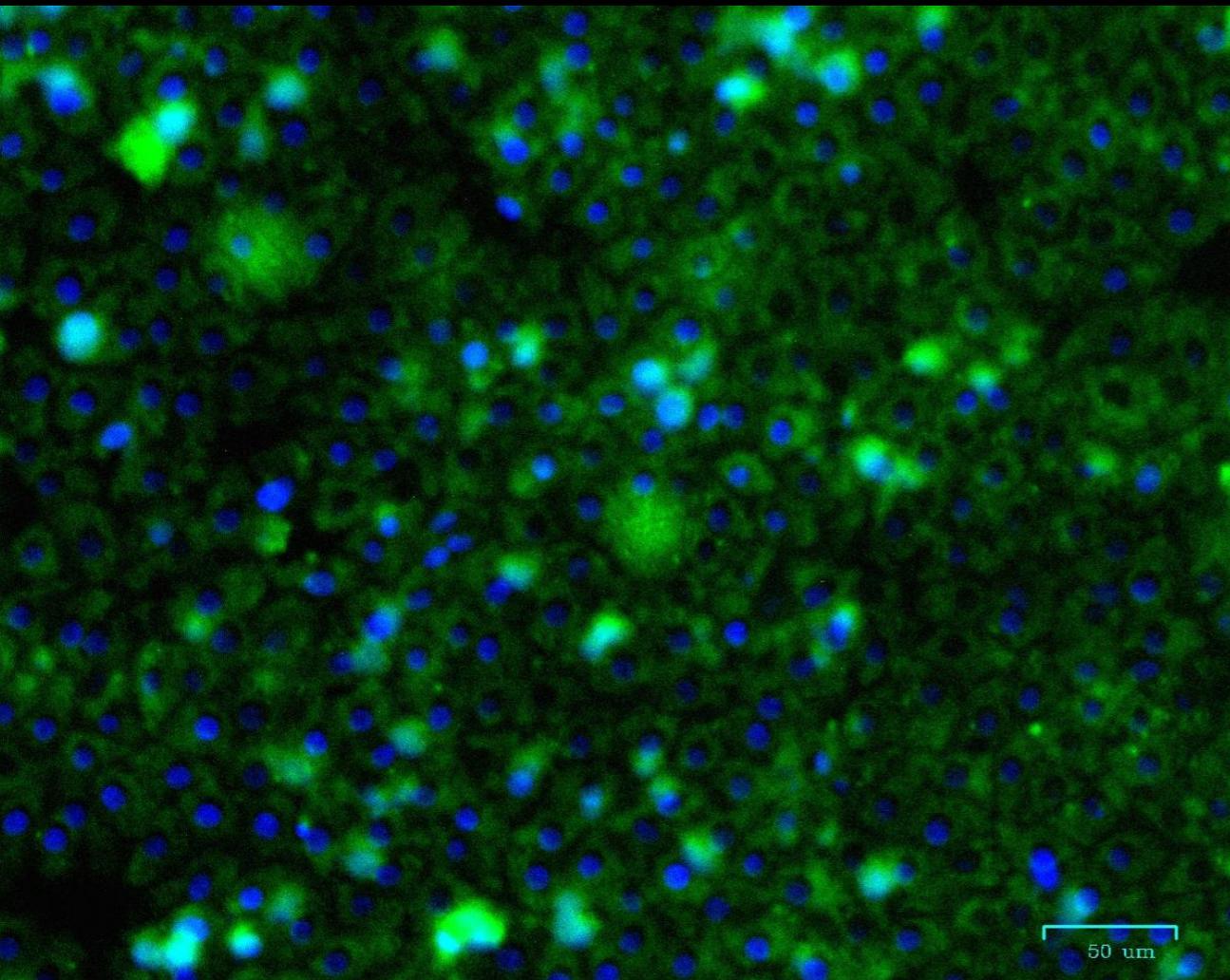


Transition Cow Liver Metabolism

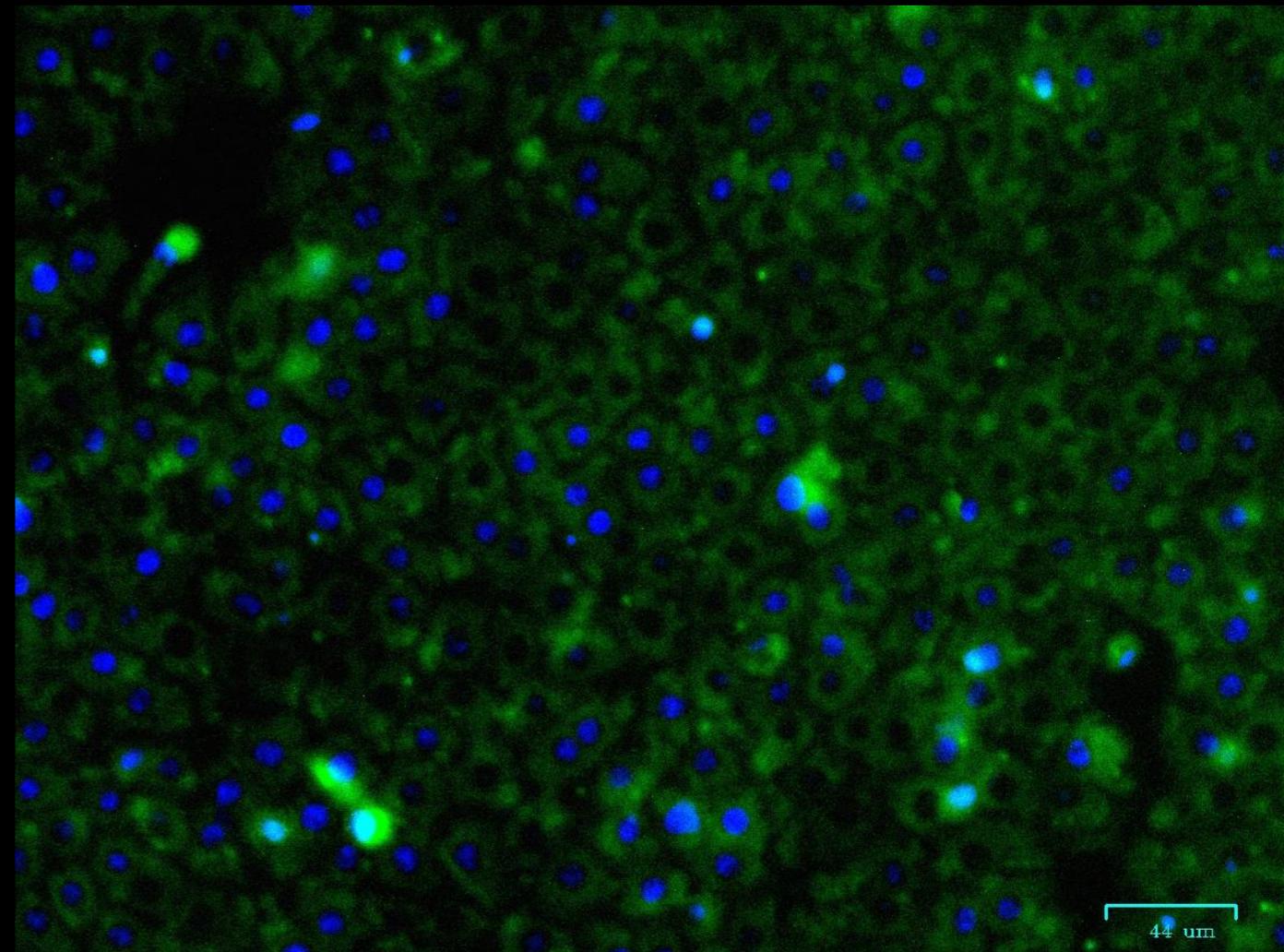


Oxidative Stress

Fatty acid oxidation can lead to reactive oxidative species production

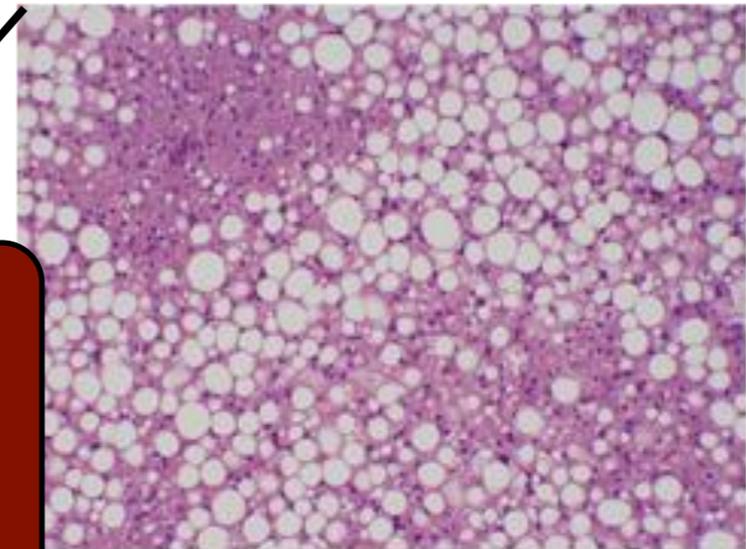
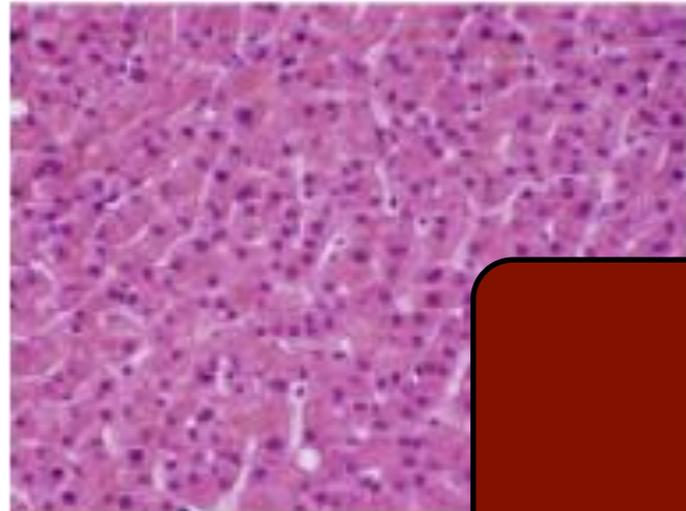


- Choline

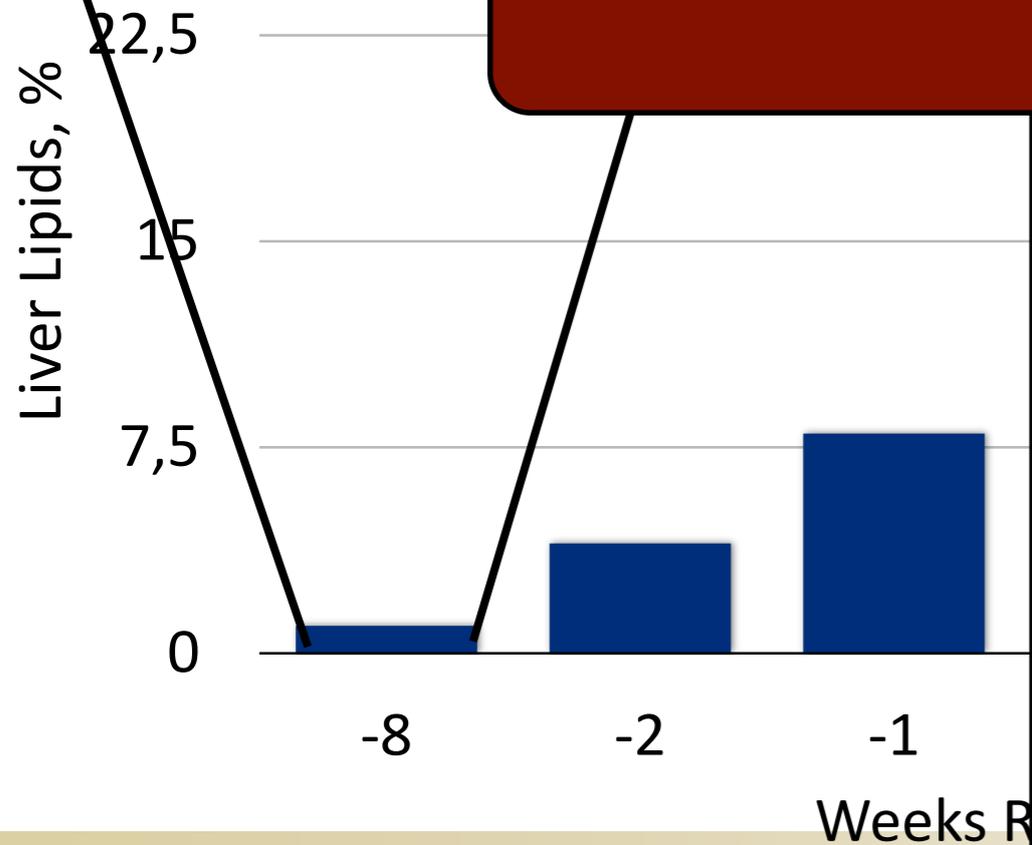


+ Choline

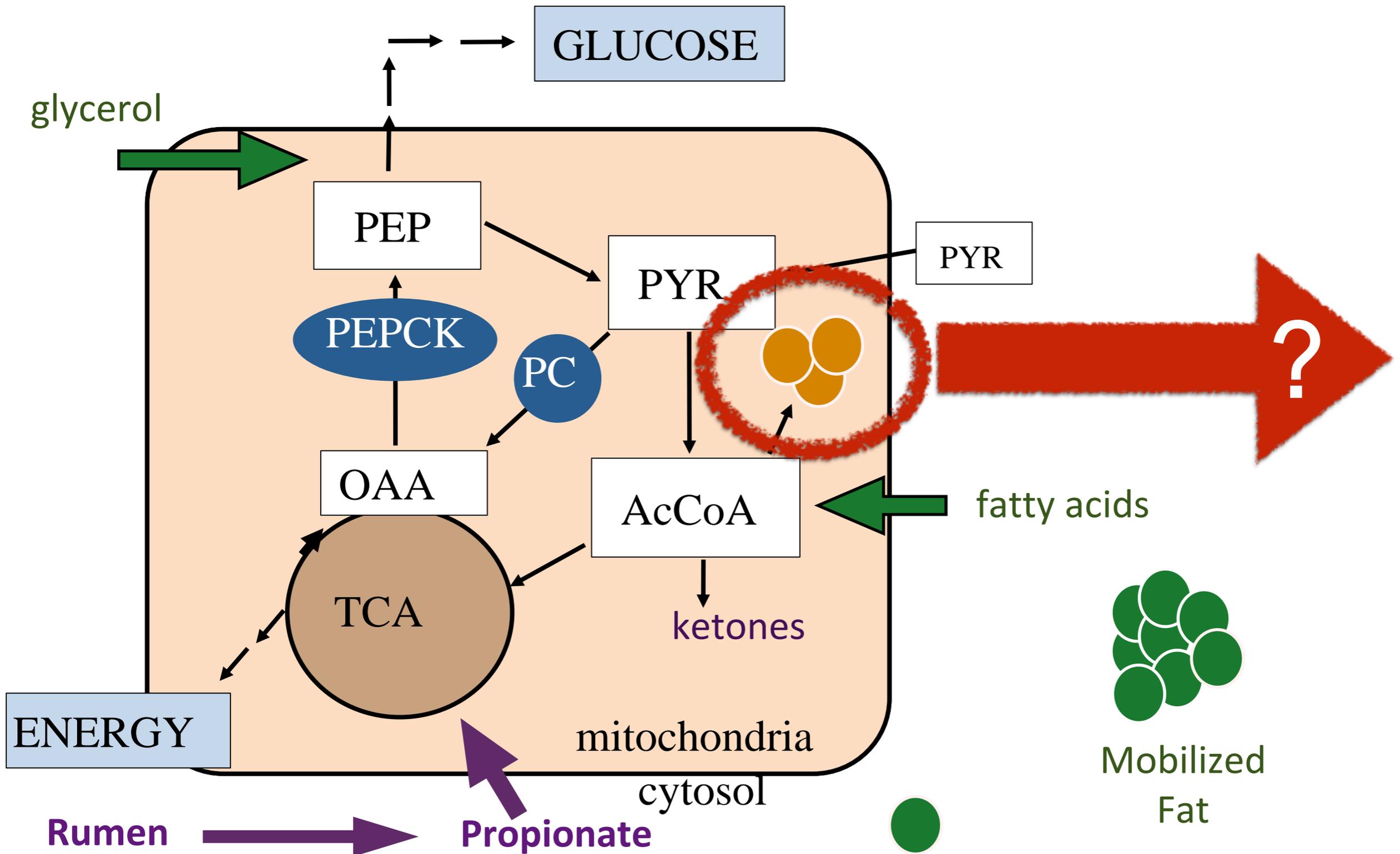
Impact of Dysregulation



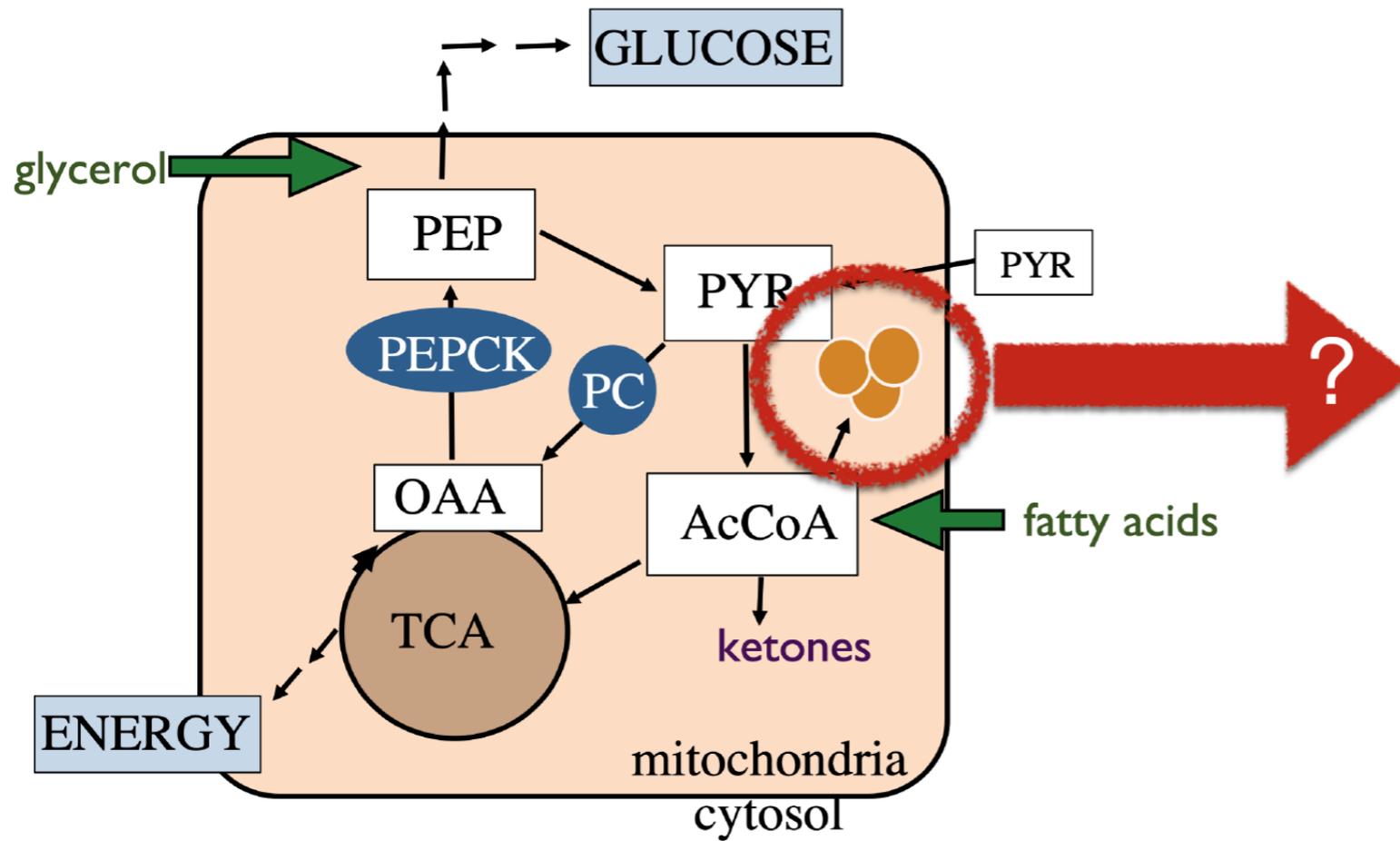
**\$60 to 70 million
nationwide per year**



Energy and Glucose Precursors

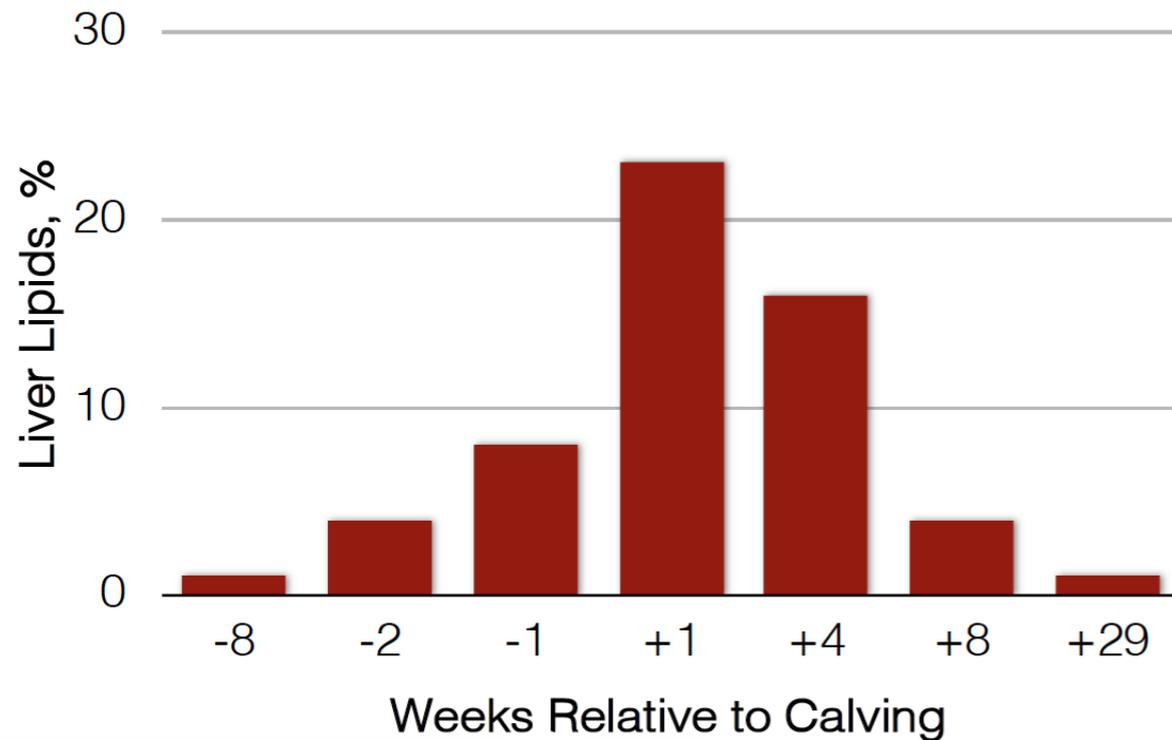


Remobilization of Liver Lipids



2 steps:

1. Lipolysis
2. Packaging and export



- Are fatty acids equally oxidized (completely or incompletely) or stored?
 - FAP
 - Is this influenced by metabolic health status? (PC:PEPCK at +1)
- What lipolytic proteins control the release of TG from the liver during the characteristic recovery period?
- Can we nutritionally alter the oxidative capacity?
 - Less fat, less oxidation, choline direct impact, prec
- Does ketosis influence fatty acid uptake by the mammary gland?
- Do milk FA reflect metabolic status
 - ursors like lactate?