

# Mitochondrial Biology

## Insulin vs. Ketones

Benjamin Bikman, Ph.D.

Professor

Cell Biology and Physiology

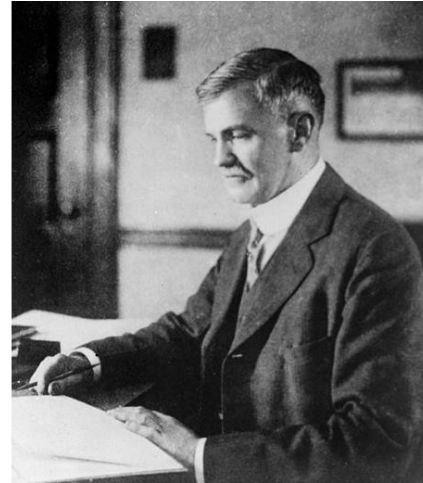
Brigham Young University

# “A study of metabolism in severe diabetes”

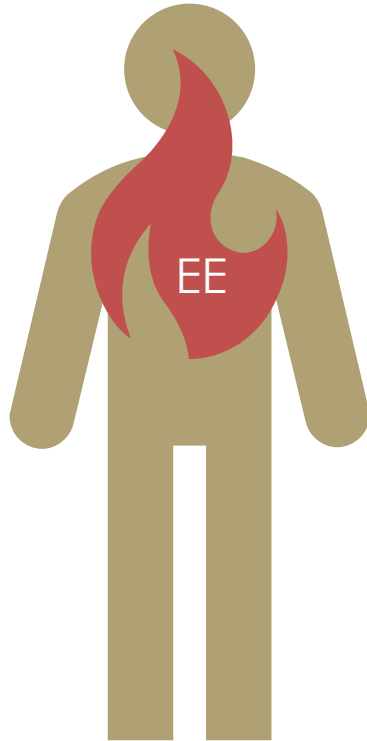
1912



E.P. Joslin



F.G. Benedict

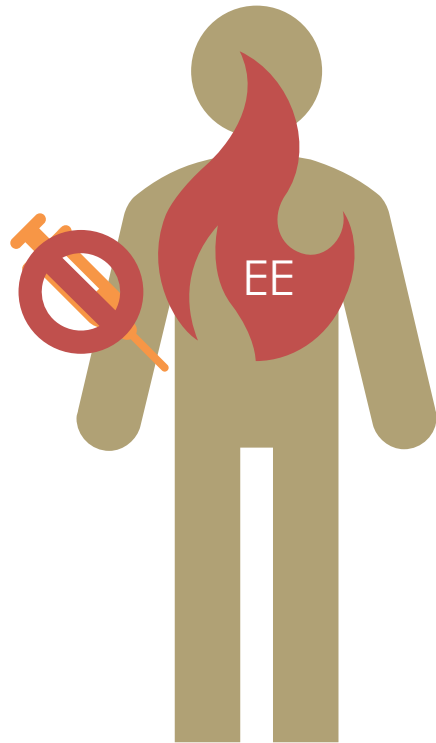


EE 20% higher  
than expected  
in T1DM

Insulin

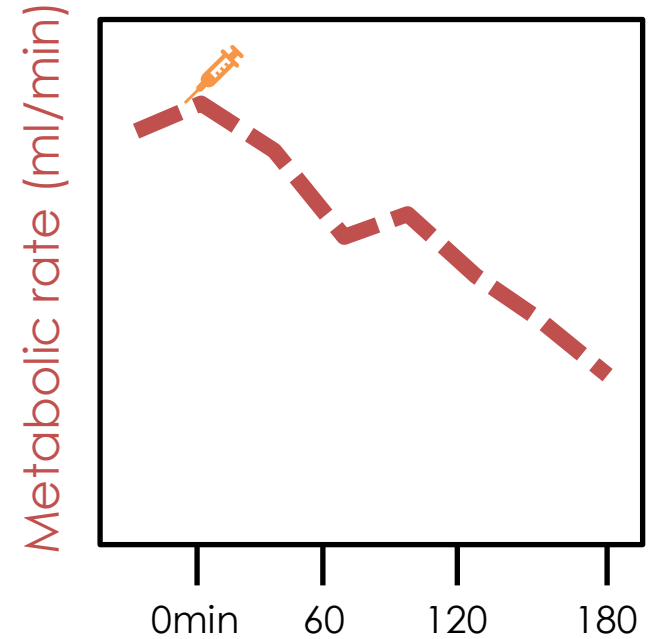
# Increased energy expenditure in poorly controlled type 1 (insulin-dependent) diabetic patients

1984

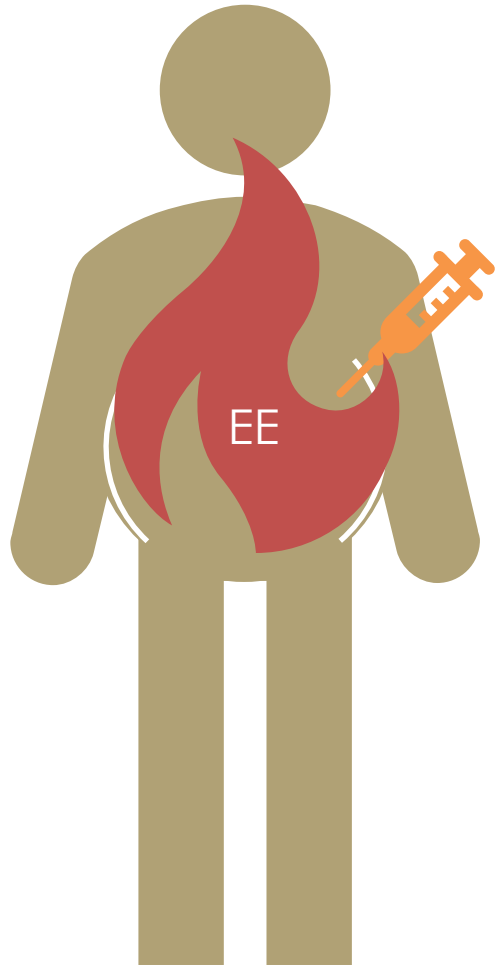


**Insulin**  
reduced EE  
by ~20%

than in M



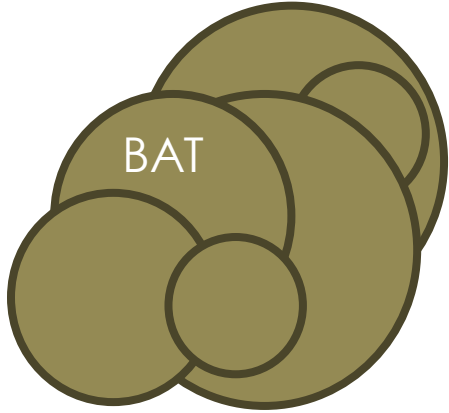
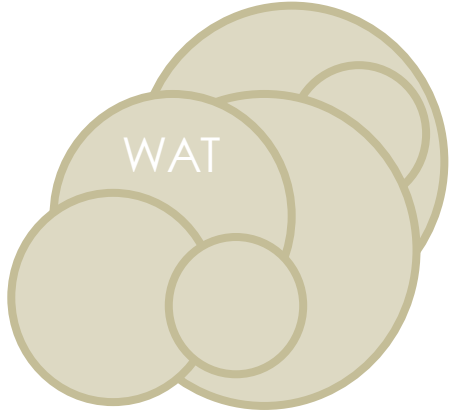
# Factors associated with basal metabolic in patients with type 2 diabetes mellitus

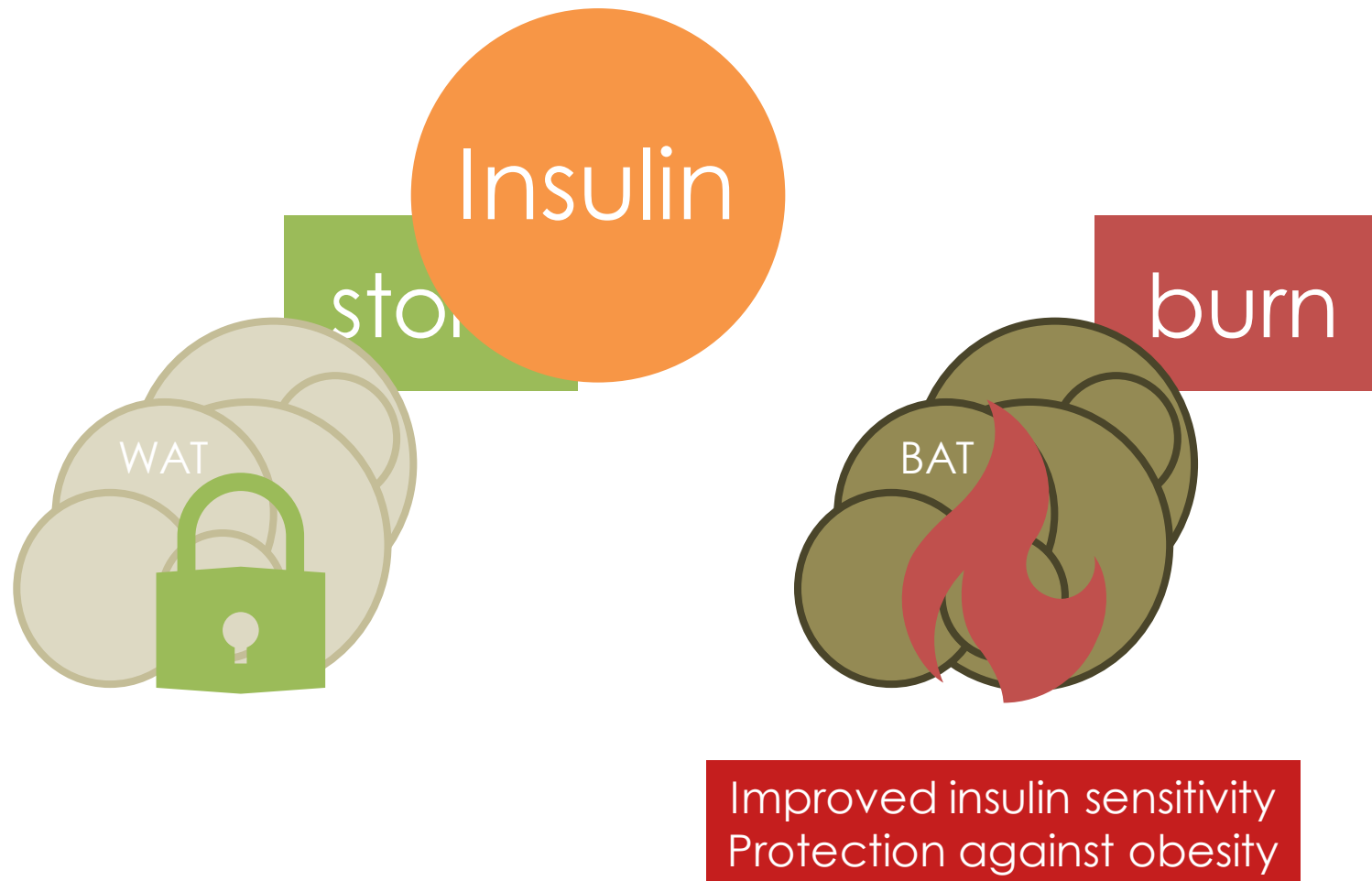


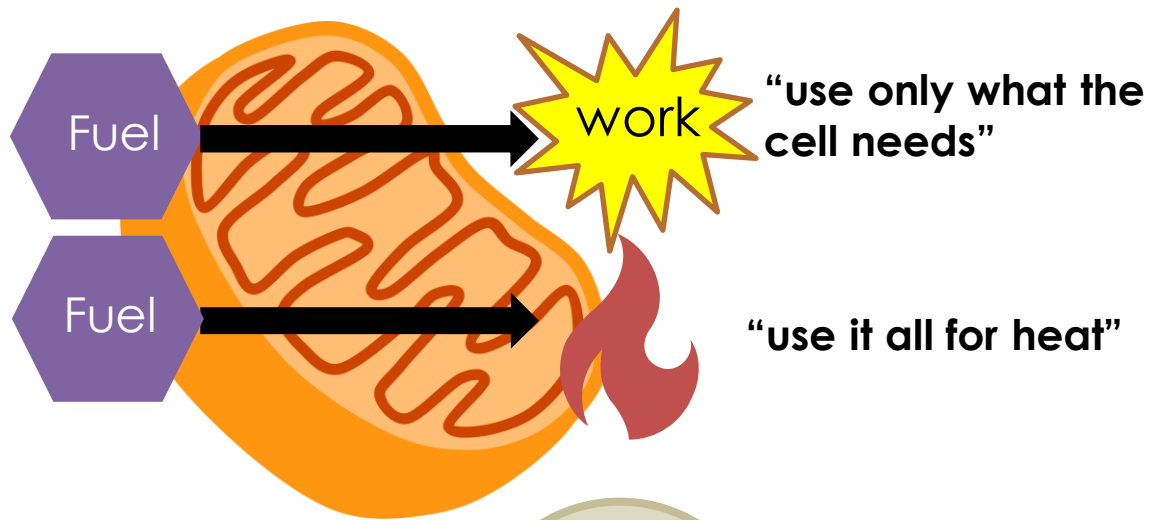
**Insulin**  
reduces EE

*“Basal metabolic rate... decreased significantly with insulin therapy.”*

Insulin

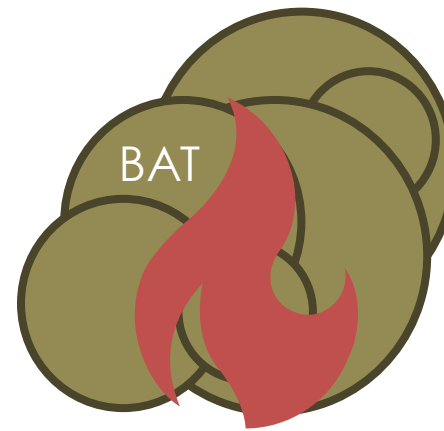


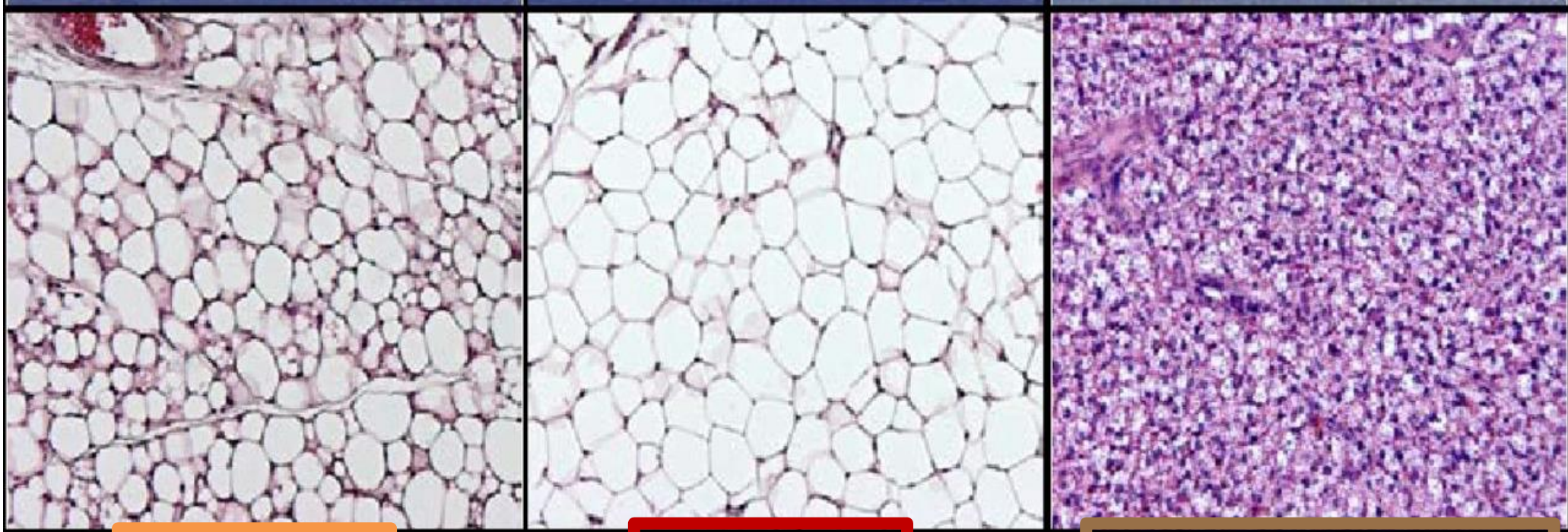




**coupled**

**uncoupled**

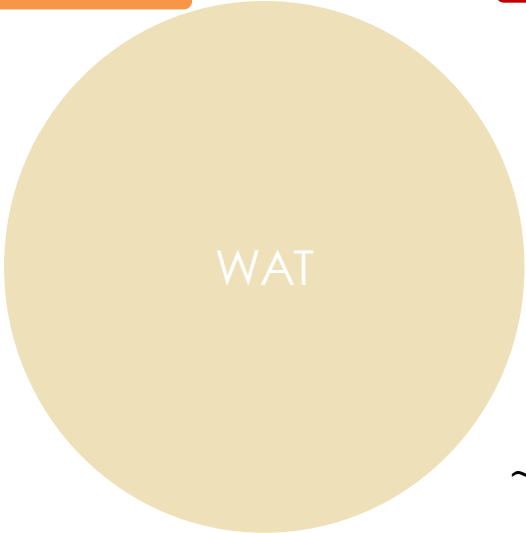




SQ

Visceral

Brown adipose



WAT

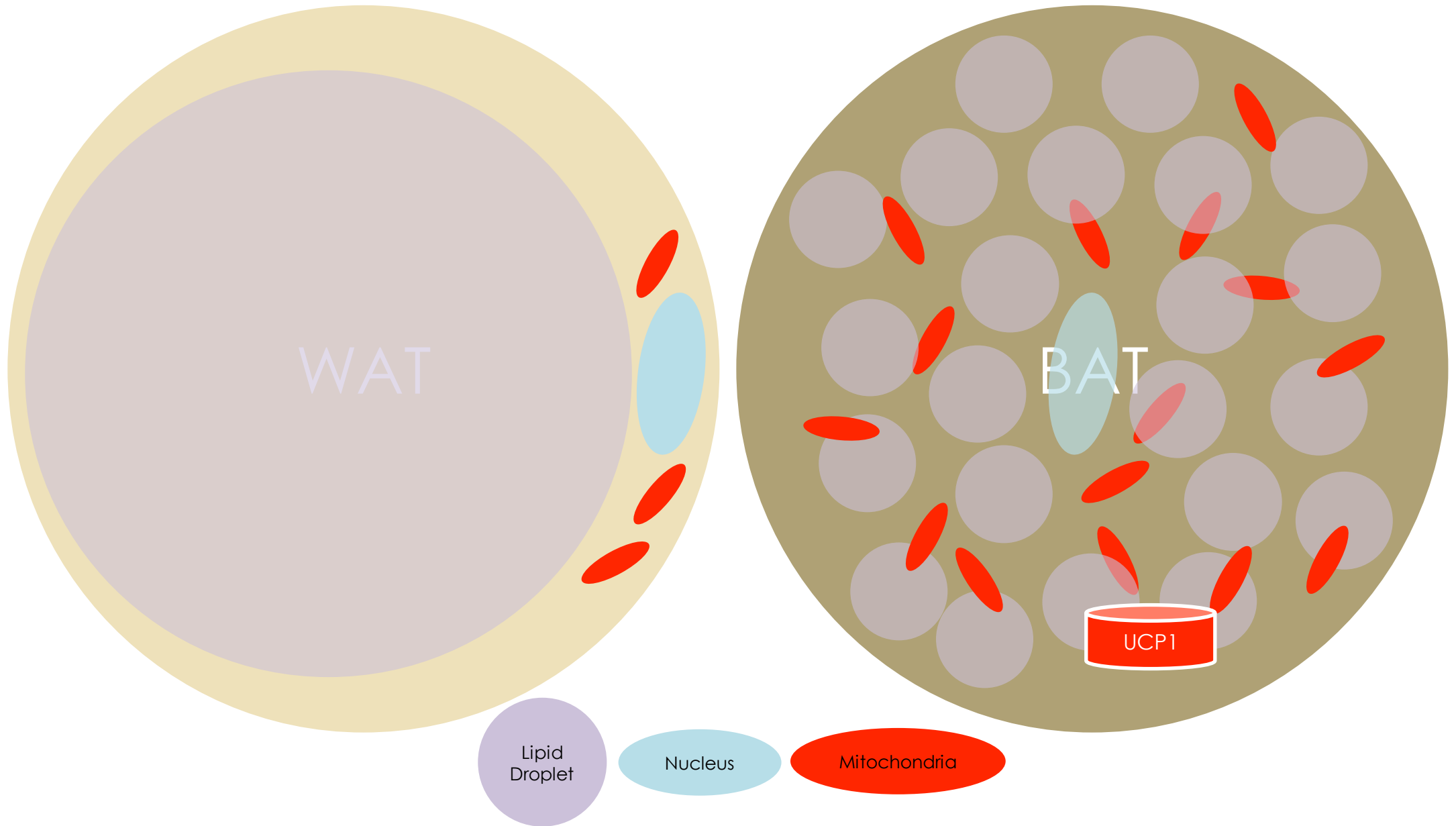
~150 $\mu$ m

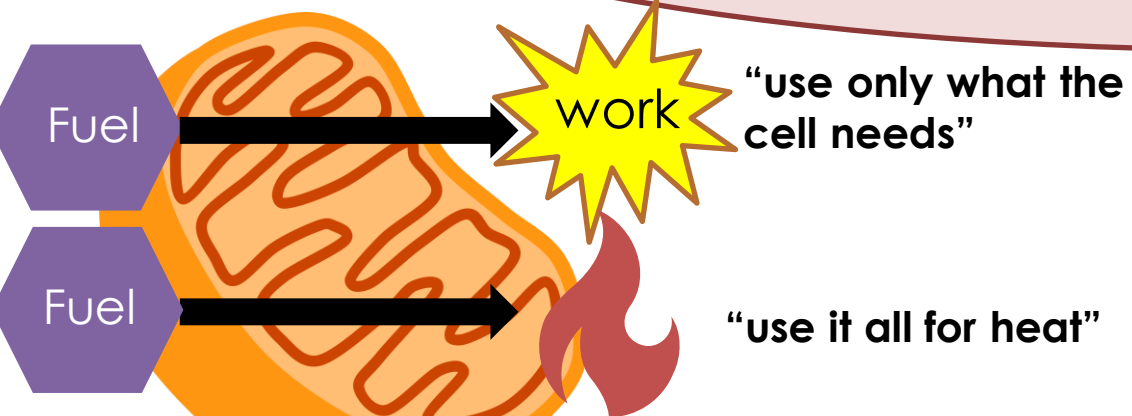
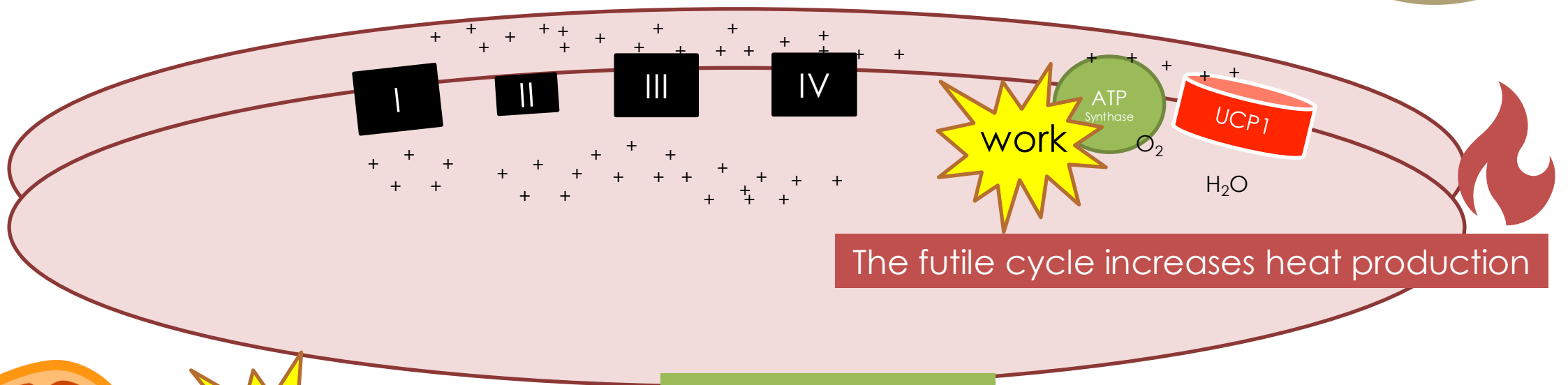
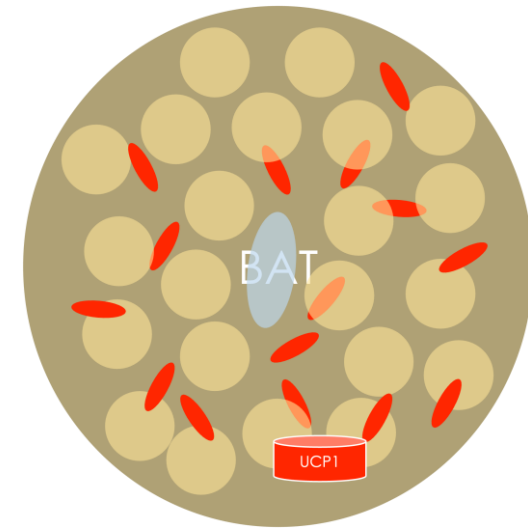


BAT

~10 $\mu$ m



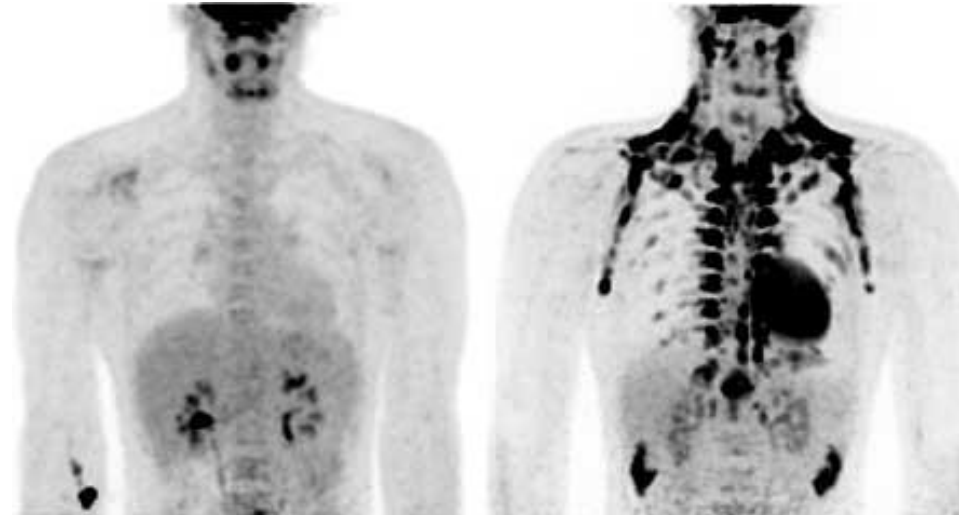




**coupled**

**uncoupled**

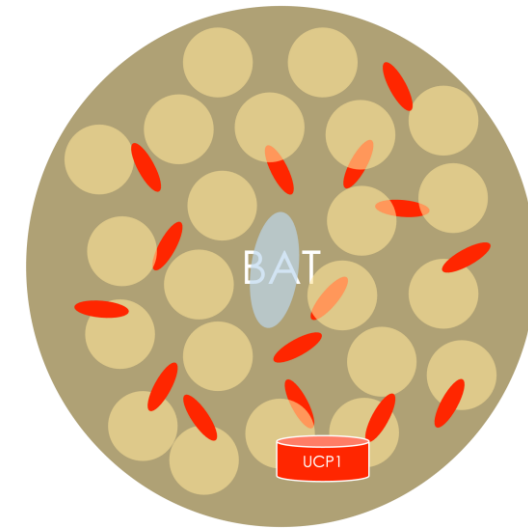
# Brown Adipose



*The NEW ENGLAND JOURNAL of MEDICINE*

ORIGINAL ARTICLE

Identification and Importance  
of Brown Adipose Tissue in Adult Humans



# What are ketones?



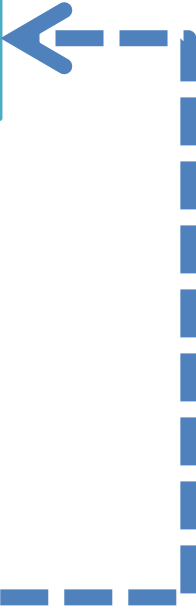
Glucose



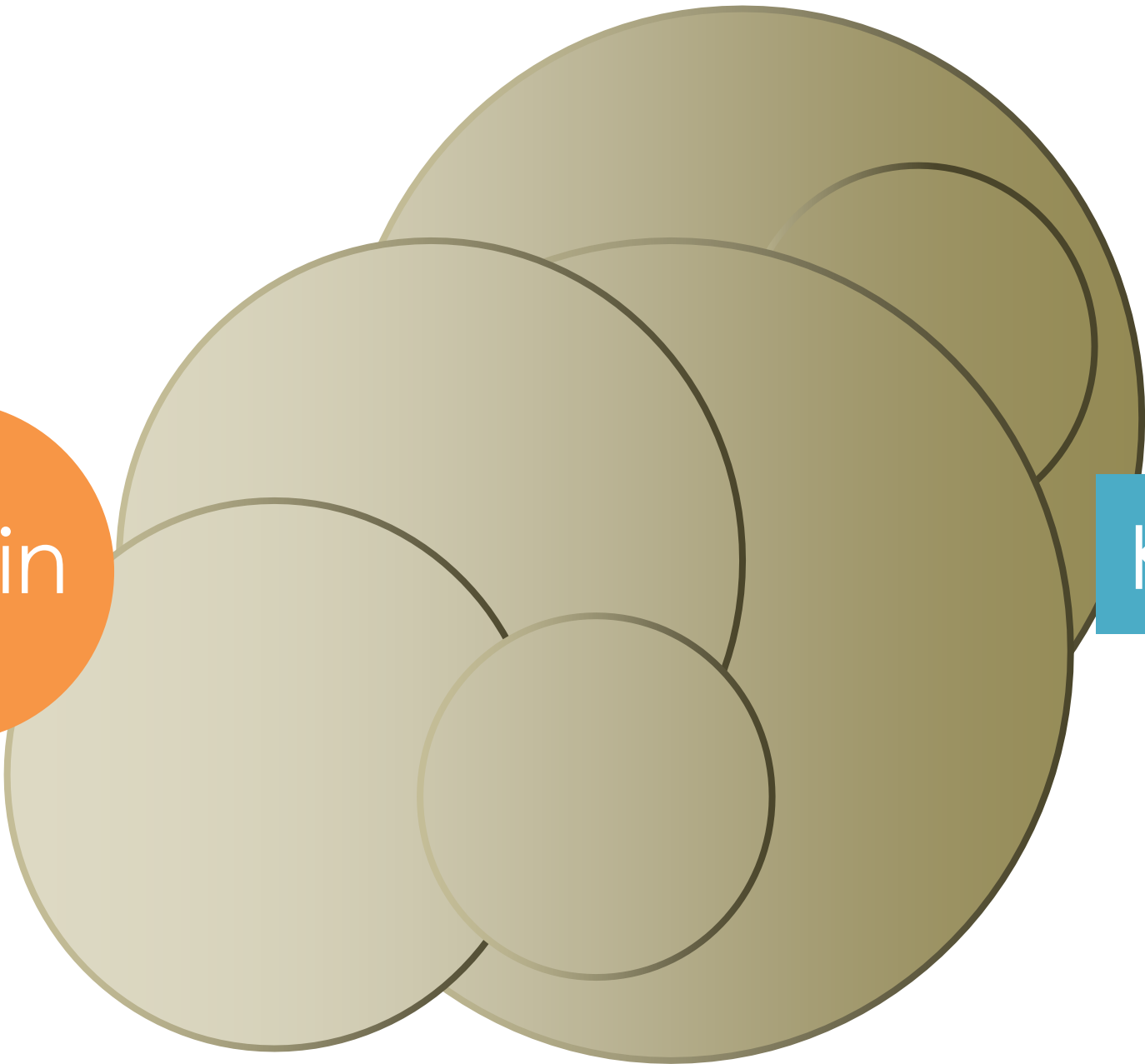
Fat



Ketones



Insulin



Ketone

Insulin

Ketone

What happens if we increase insulin?

study design

Insulin



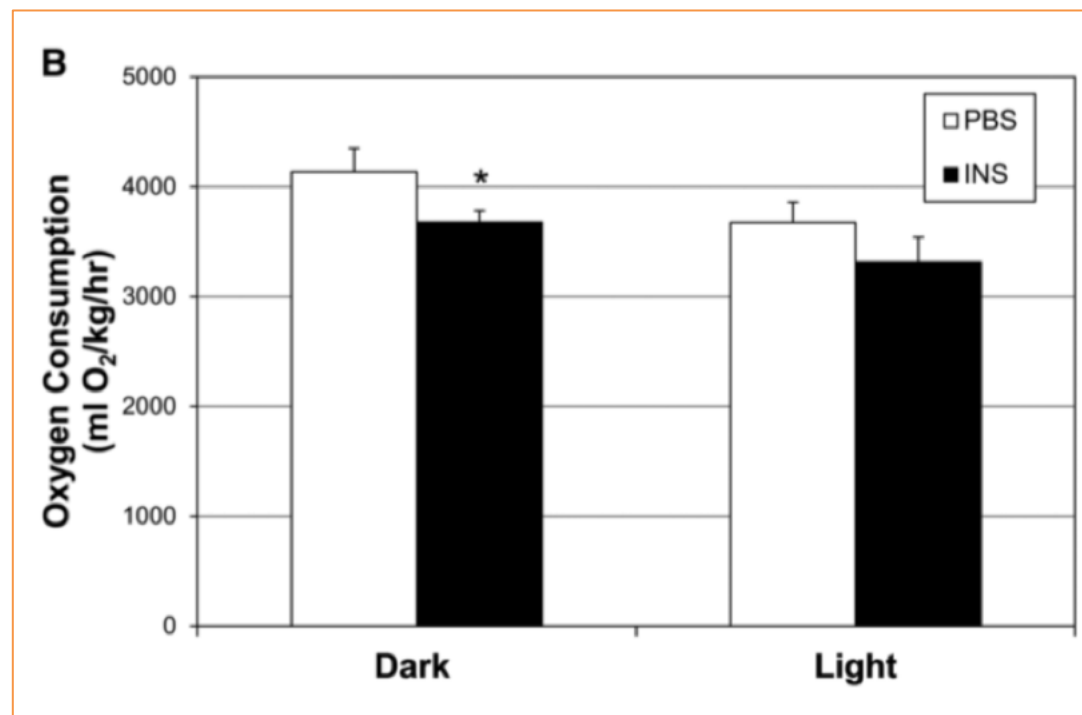
Research Article

# Insulin selectively reduces mitochondrial uncoupling in brown adipose tissue in mice

Blake W. Dallon, Brian A. Parker, Aimee E. Hodson, Trevor S. Tippetts, Mitchell E. Harrison, M. Marissa A. Appiah, Jeffrey E. Witt, Jonathan L. Gibbs, Harrison M. Gray, Thomas M. Sant and Benjamin T. Bikman

Insulin

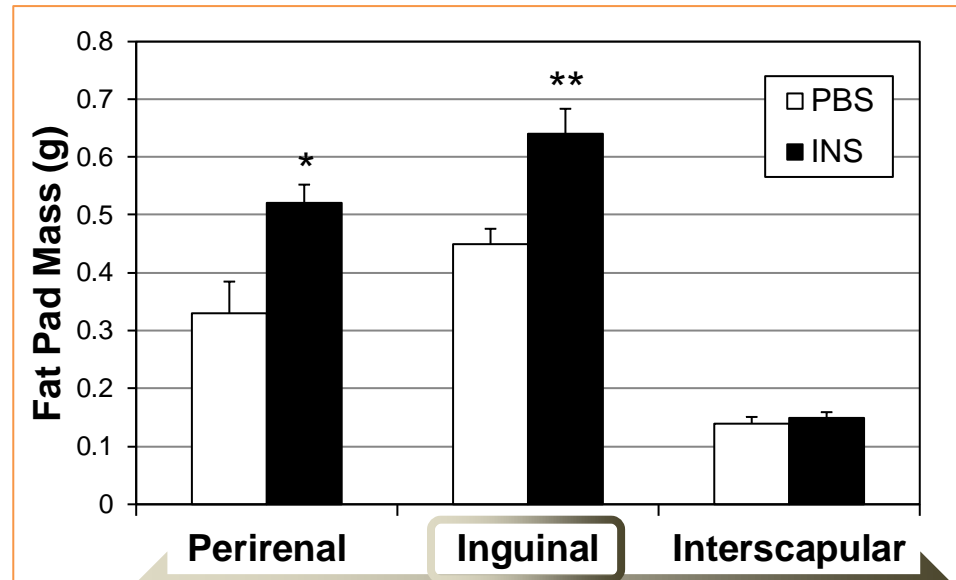
*Insulin lowered  
metabolic rate*



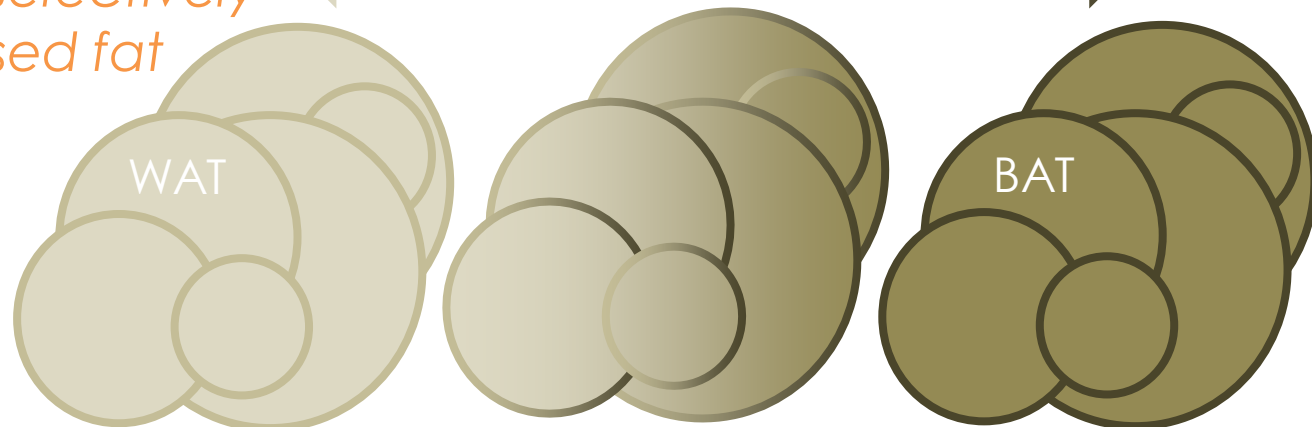


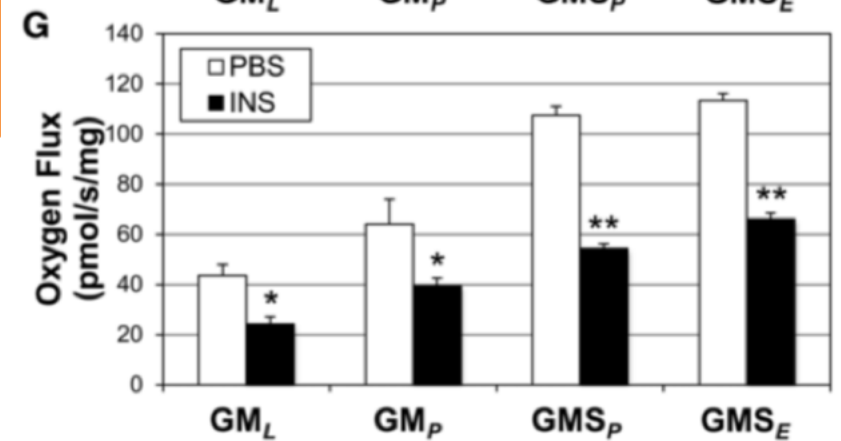
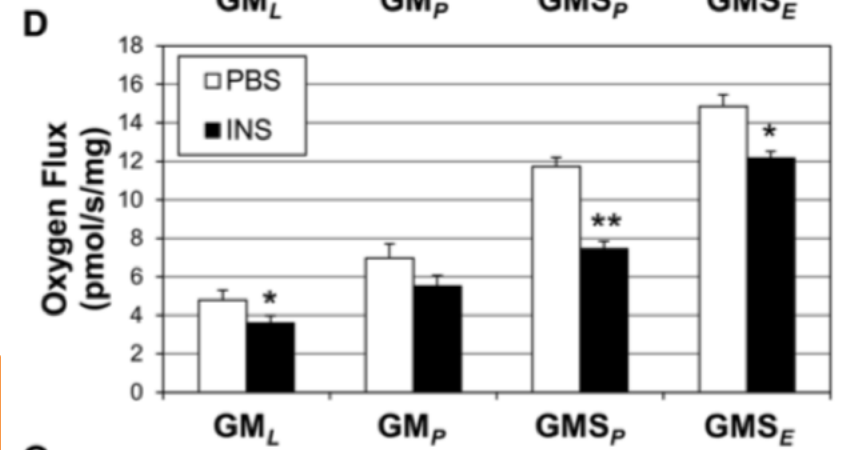
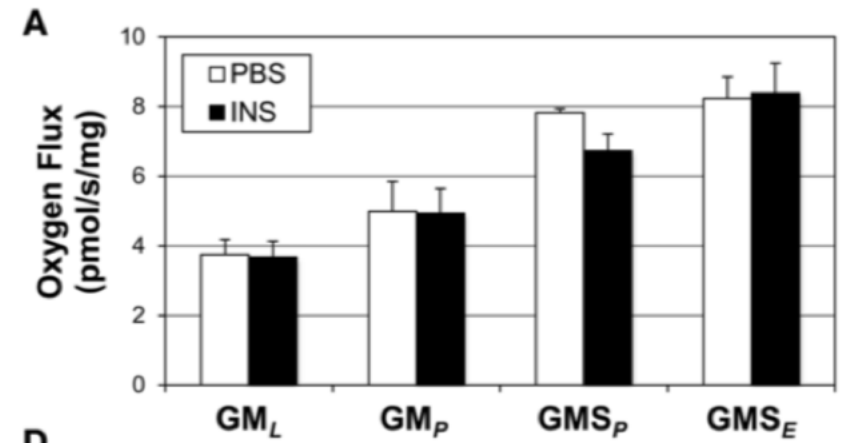
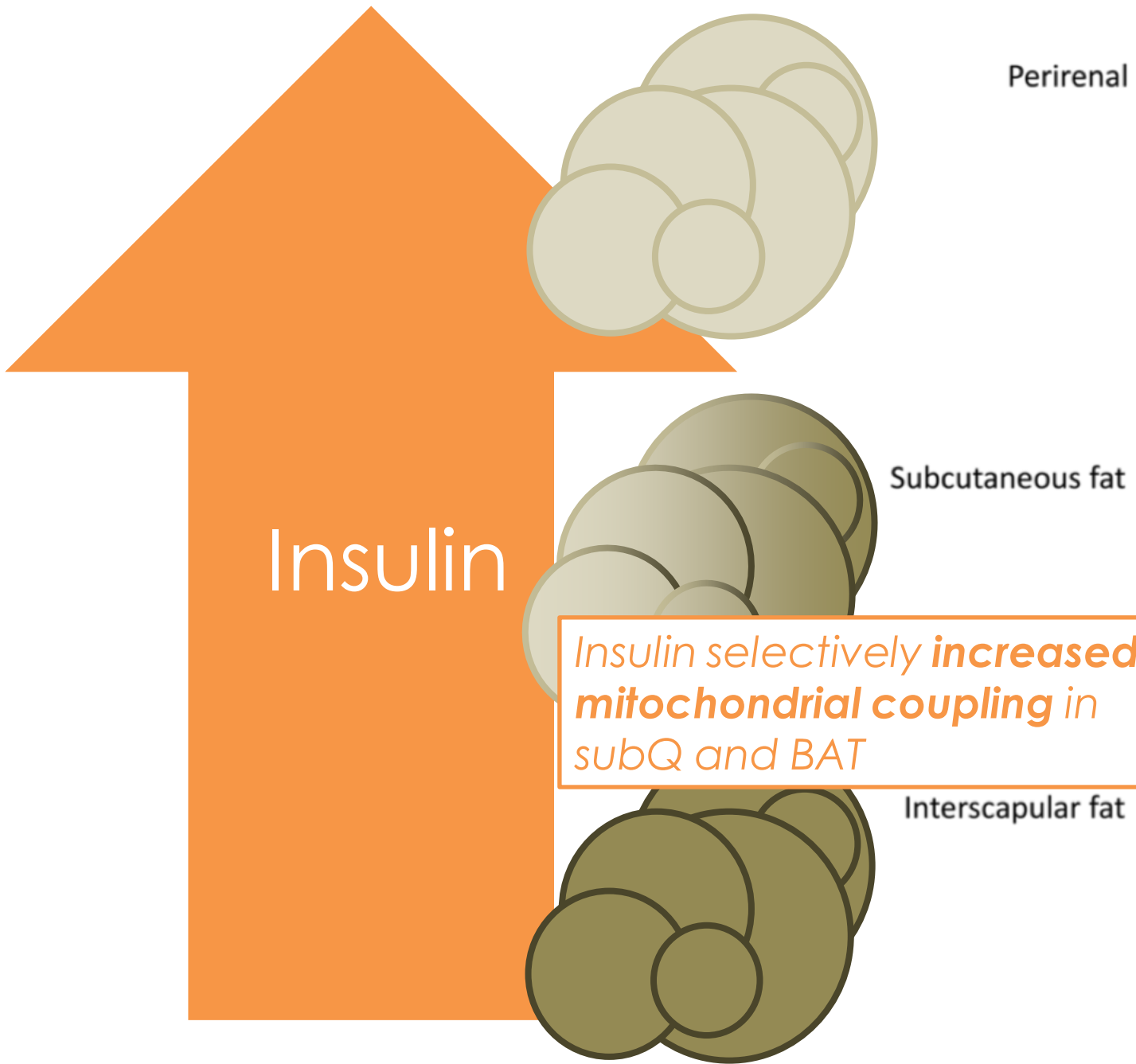


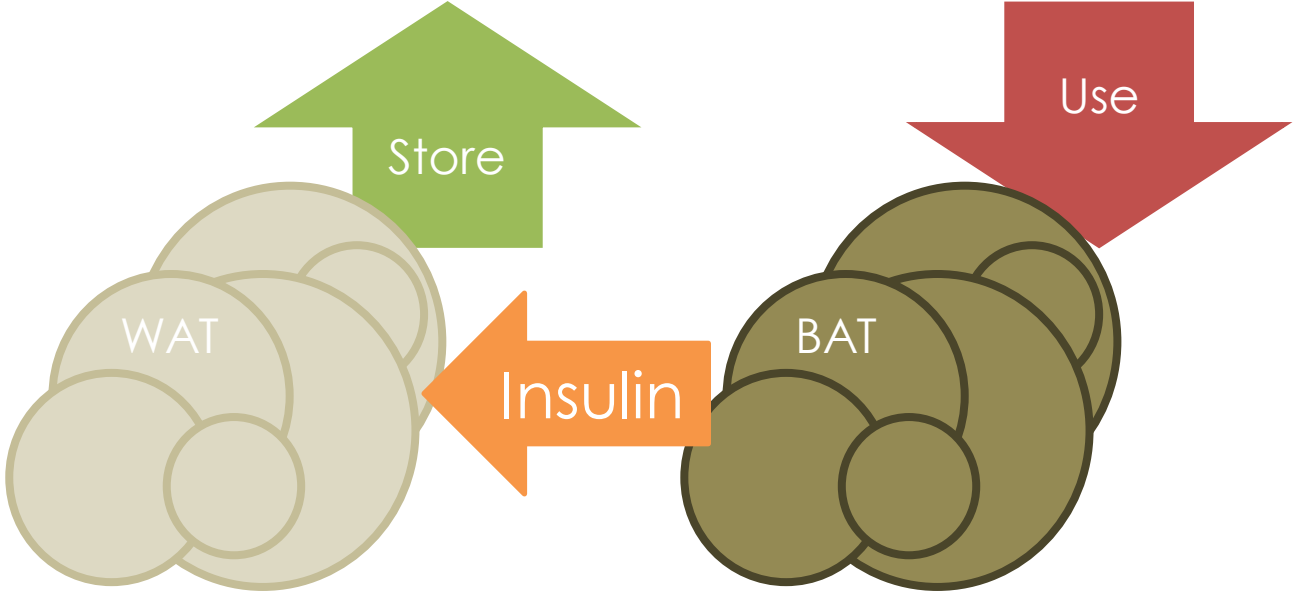
Insulin



*Insulin selectively increased fat mass*







The diagram features a central background of overlapping circles in shades of brown and tan. A large, stylized blue question mark is superimposed over these circles. On the left, an orange arrow points upwards and contains the word 'Insulin' in white. On the right, a blue arrow points upwards and contains the word 'Ketone' in white. At the bottom center, a white rectangular box with a blue border contains the text 'What happens if we increase ketones?' in blue.

Insulin

Ketone

What happens if we increase ketones?

# Study Design




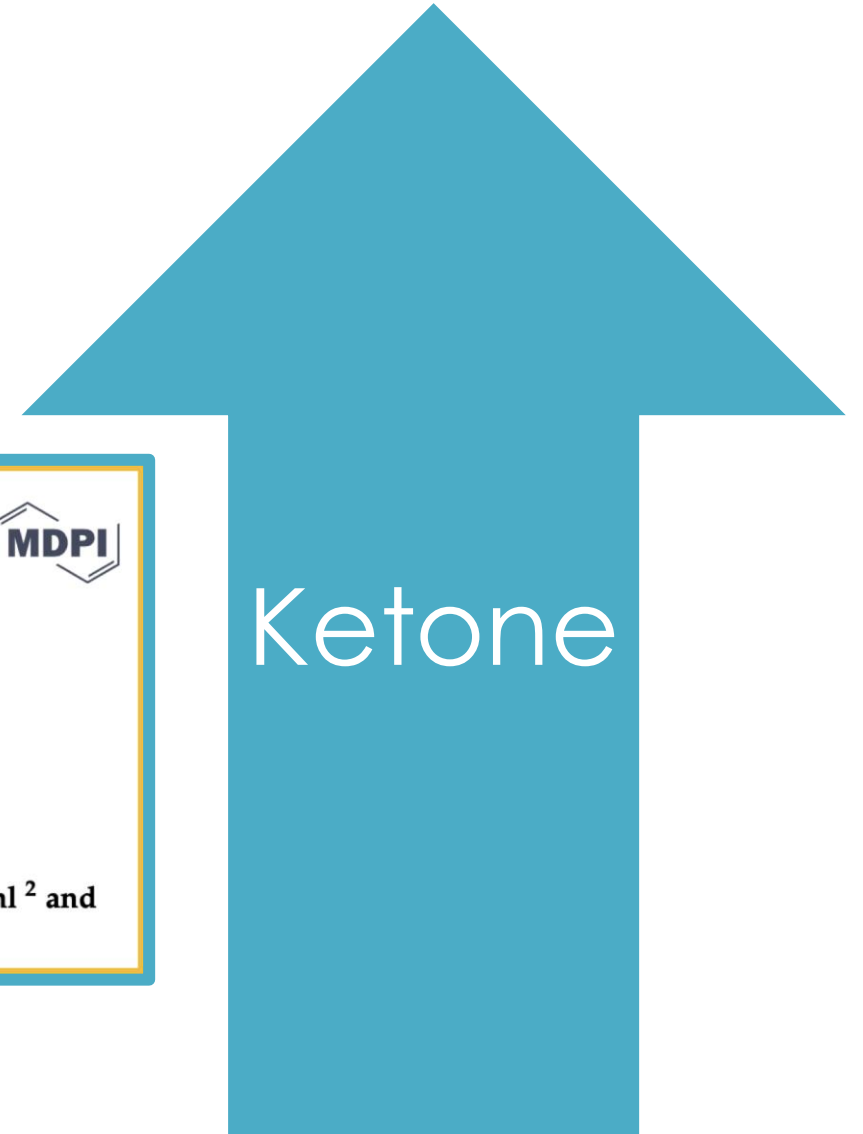
International Journal of  
*Molecular Sciences*

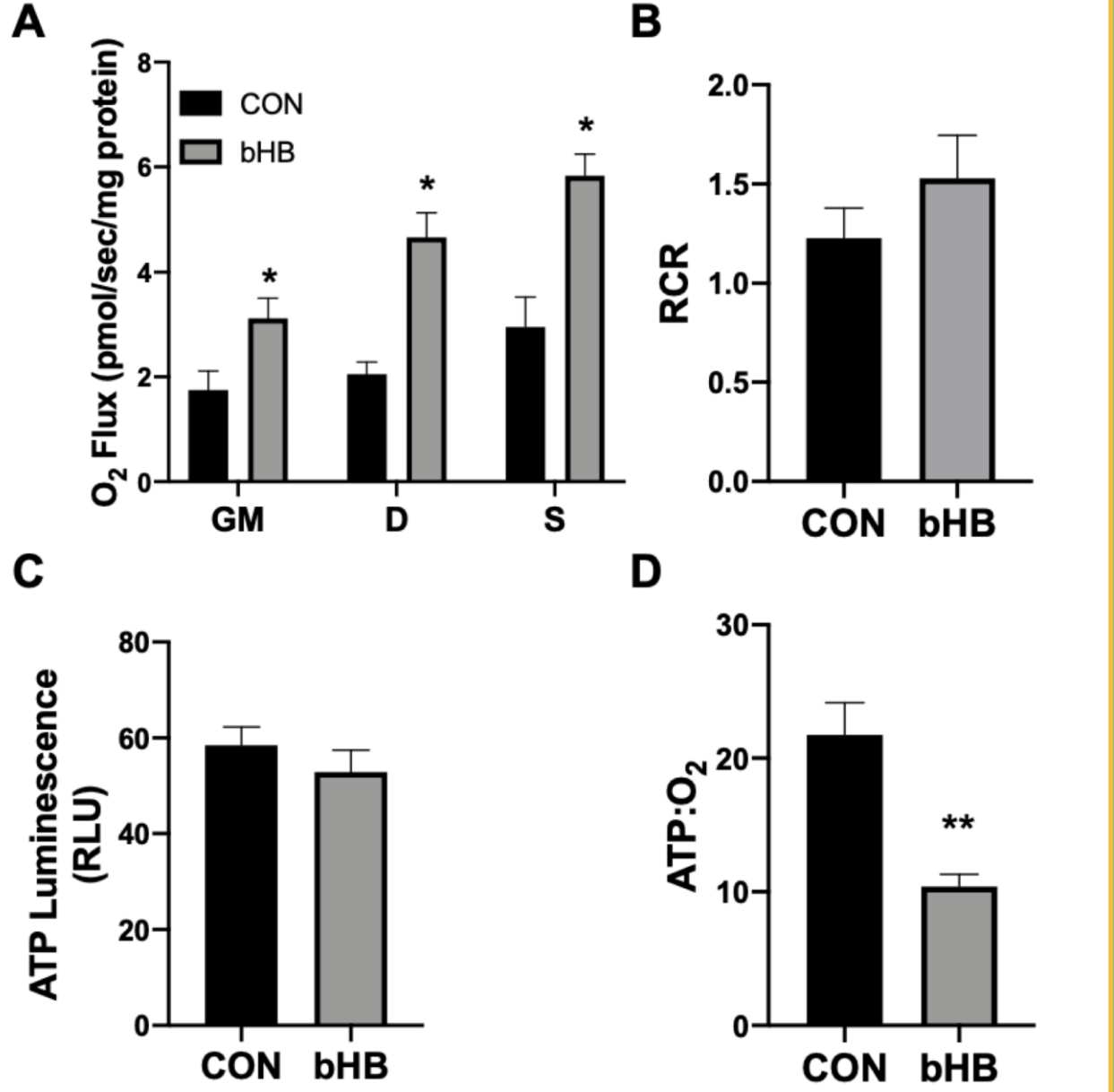


Article

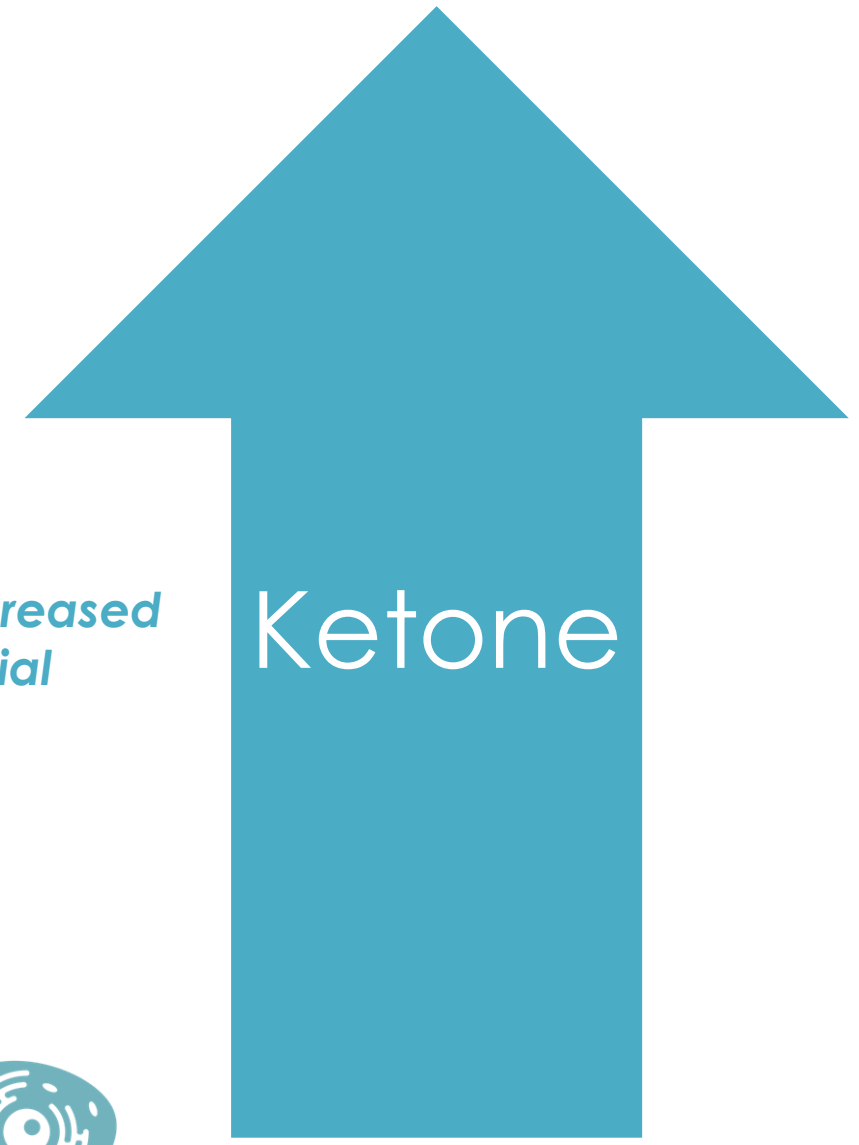
## **Ketones Elicit Distinct Alterations in Adipose Mitochondrial Bioenergetics**

Chase M. Walton <sup>1</sup>, Samuel M. Jacobsen <sup>1</sup>, Blake W. Dallon <sup>1</sup>, Erin R. Saito <sup>1</sup>,  
Shantelle L. H. Bennett <sup>1</sup>, Lance E. Davidson <sup>2</sup> , David M. Thomson <sup>1</sup>, Robert D. Hyldahl <sup>2</sup> and  
Benjamin T. Bikman <sup>1,\*</sup>

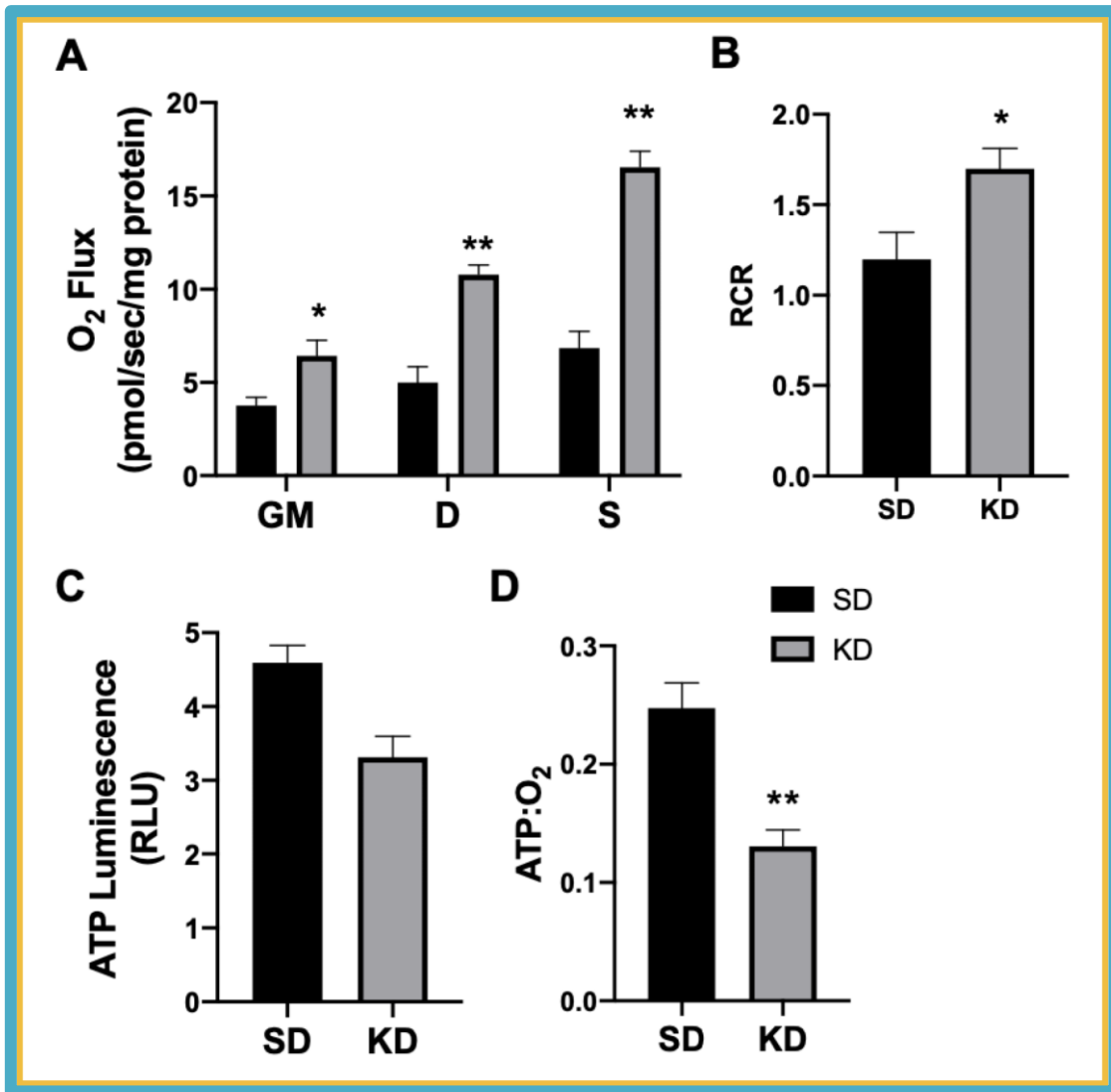




*Ketones increased mitochondrial uncoupling*



3T3-L1 Adipocytes



*Ketogenic diet increased uncoupling*

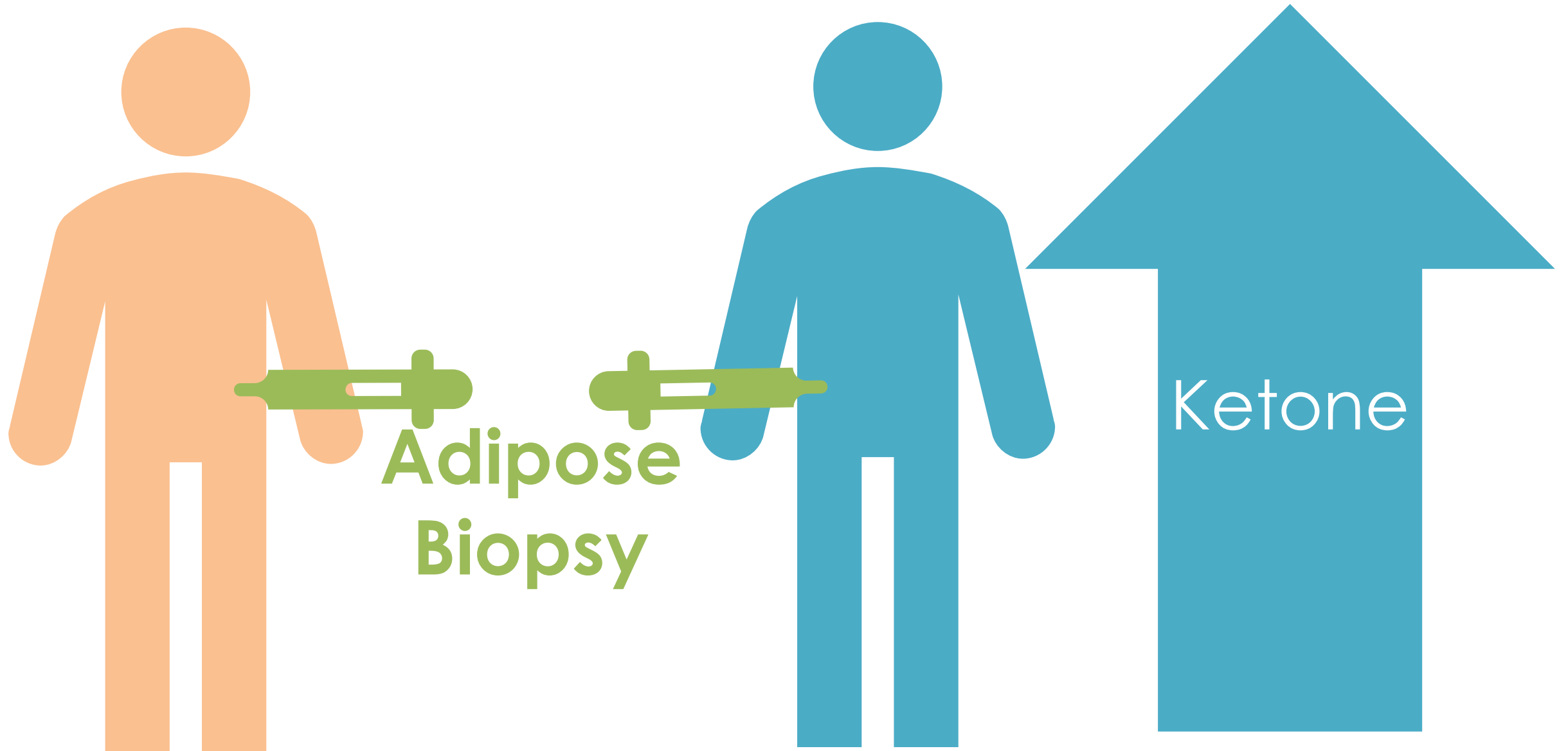
Ketone



Did not happen in visceral adipose!

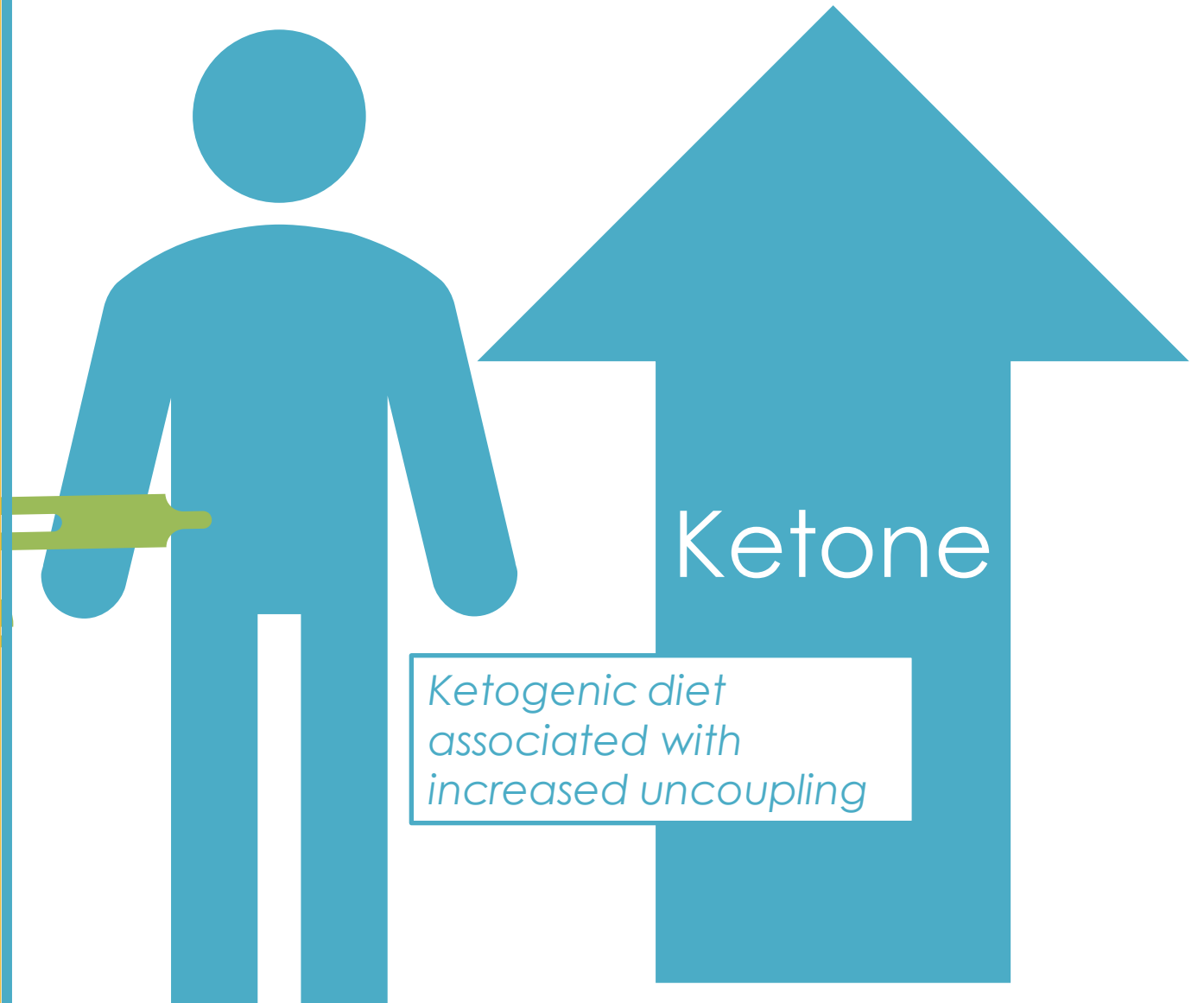
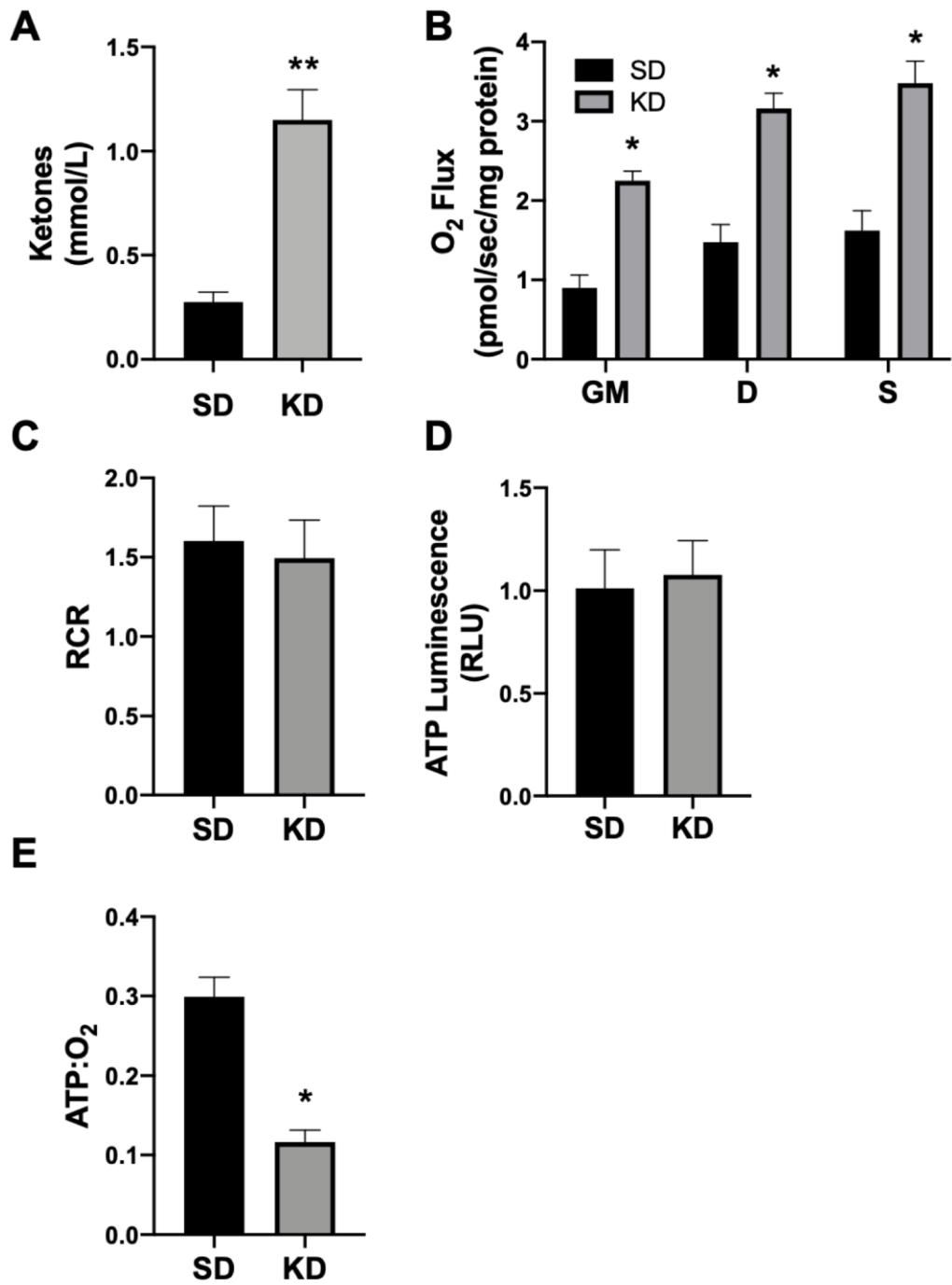


SubQ adipose from rodents fed a ketogenic diet



SubQ adipose from humans following a standard or a ketogenic diet





## BRIEF COMMUNICATION OPEN



# A high-carbohydrate diet lowers the rate of adipose tissue mitochondrial respiration

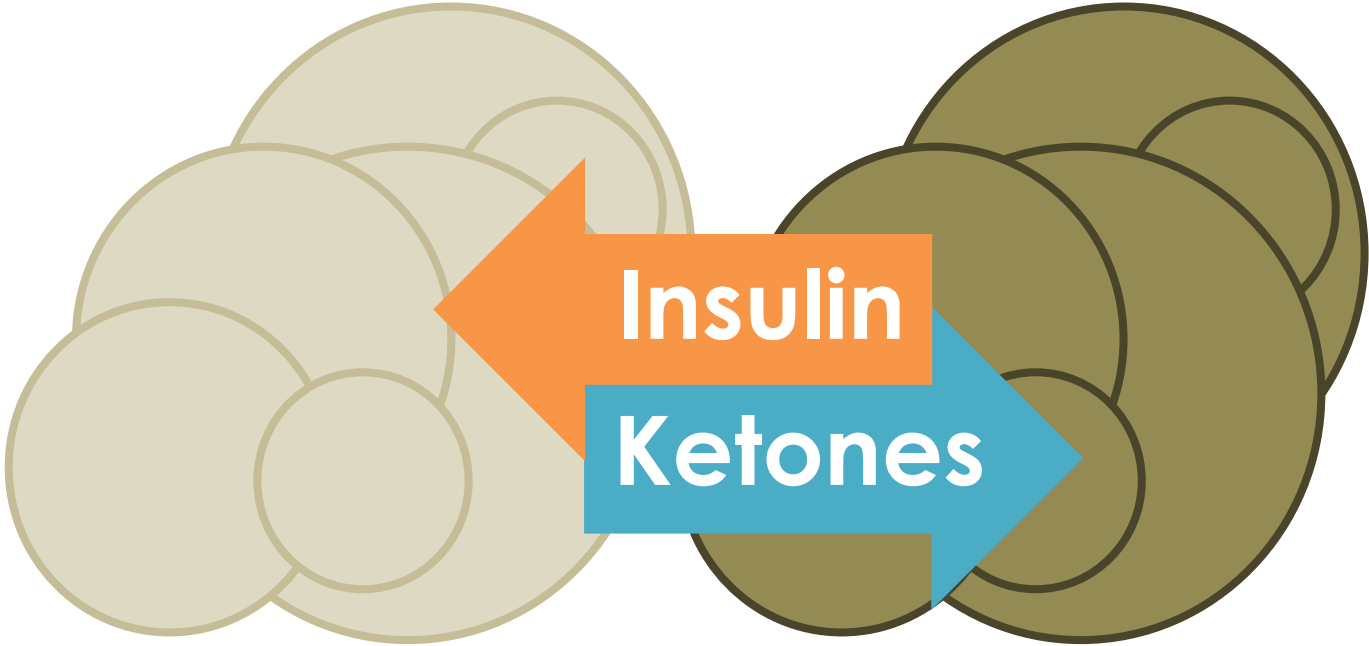
Benjamin T. Bikman <sup>1</sup>✉, Kim J. Shimy <sup>2,3</sup>, Caroline M. Apovian<sup>4</sup>, S. Yu<sup>2</sup>, Erin R. Saito<sup>1</sup>, Chase M. Walton<sup>1</sup>, Cara B. Ebbeling<sup>2</sup> and David S. Ludwig <sup>2</sup>

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Adipocyte mitochondrial respiration may influence metabolic fuel partitioning into oxidation versus storage, with implications for whole-body energy expenditure. Although insulin has been shown to influence mitochondrial respiration, the effects of dietary macronutrient composition have not been well characterized. The aim of this exploratory study was to test the hypothesis that a high-carbohydrate diet lowers the oxygen flux of adipocyte mitochondria ex vivo. Among participants in a randomized-controlled weight-loss maintenance feeding trial, those consuming a high-carbohydrate diet (60% carbohydrate as a proportion of total energy,  $n = 10$ ) had lower rates of maximal adipose tissue mitochondrial respiration than those consuming a moderate-carbohydrate diet (40%,  $n = 8$ ,  $p = 0.039$ ) or a low-carbohydrate diet (20%,  $n = 9$ ,  $p = 0.005$ ) after 10 to 15 weeks. This preliminary finding may provide a mechanism for postulated calorie-independent effects of dietary composition on energy expenditure and fat deposition, potentially through the actions of insulin on fuel partitioning.

*European Journal of Clinical Nutrition* (2022) 76:1339–1342; <https://doi.org/10.1038/s41430-022-01097-3>

Diet highest in carbohydrates had lowest adipose metabolic rate

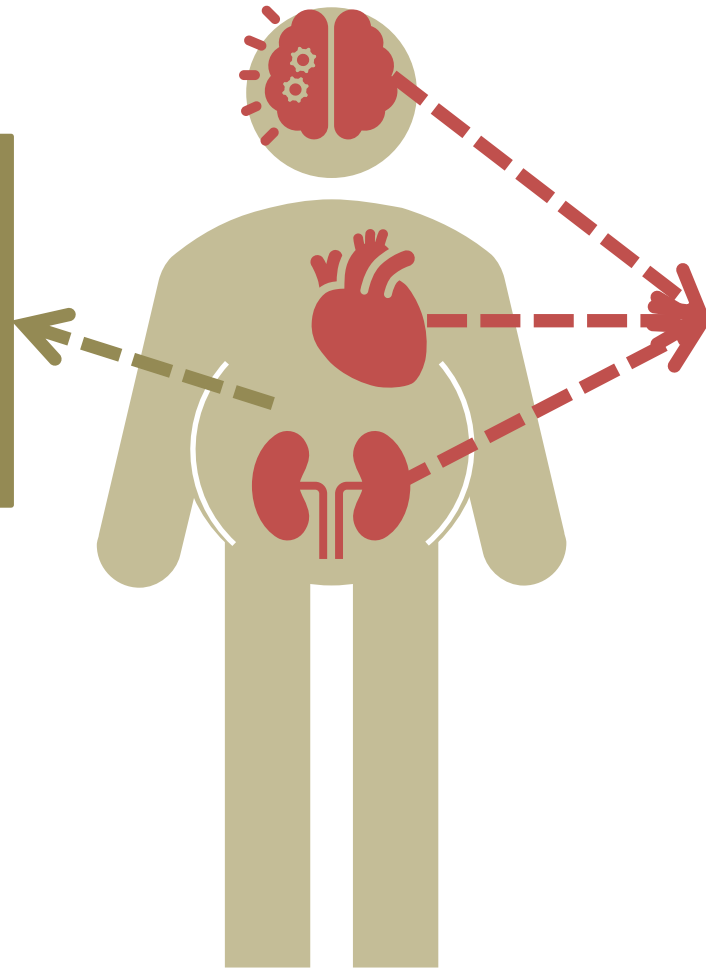




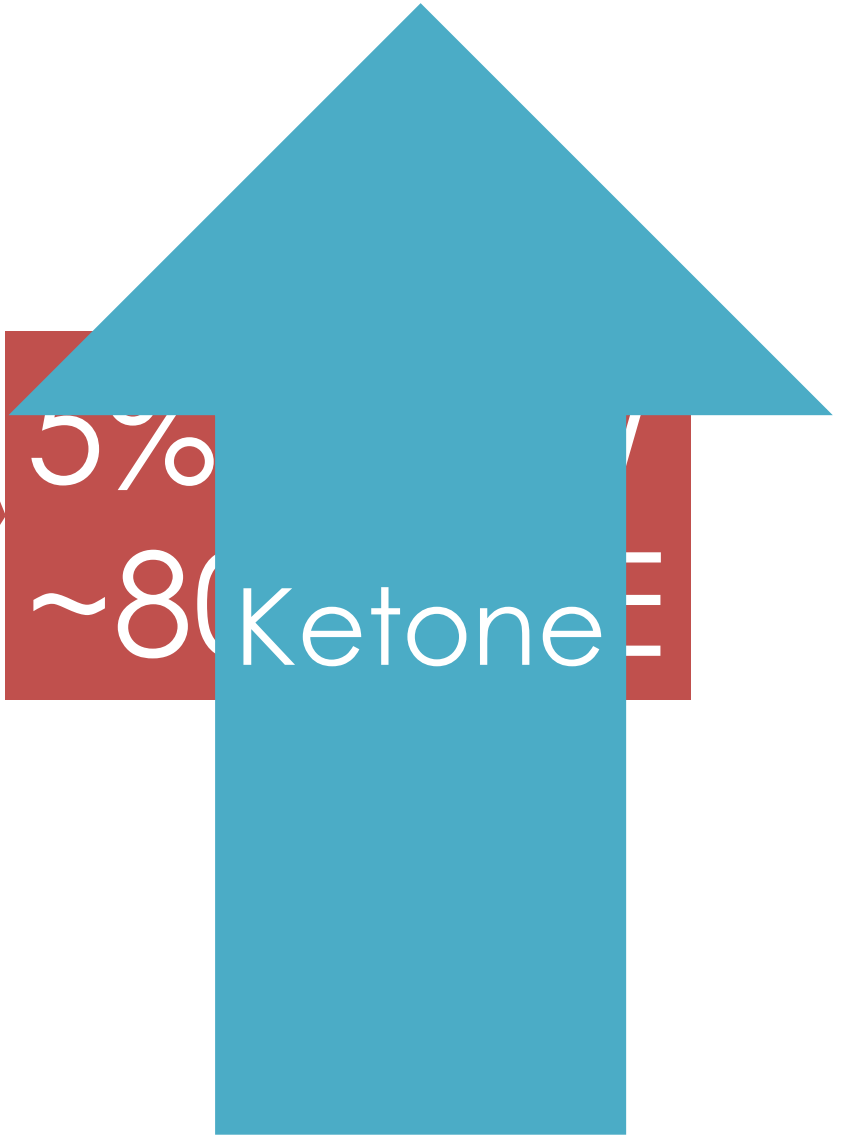
Does this even matter in real life?

~24% of BW  
~6% REE

~12% REE?



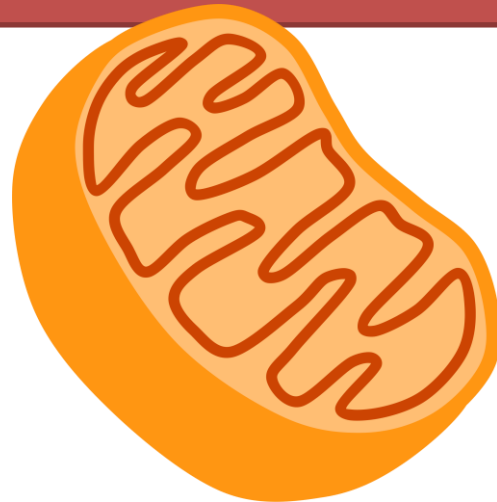
5%  
~80% Ketone



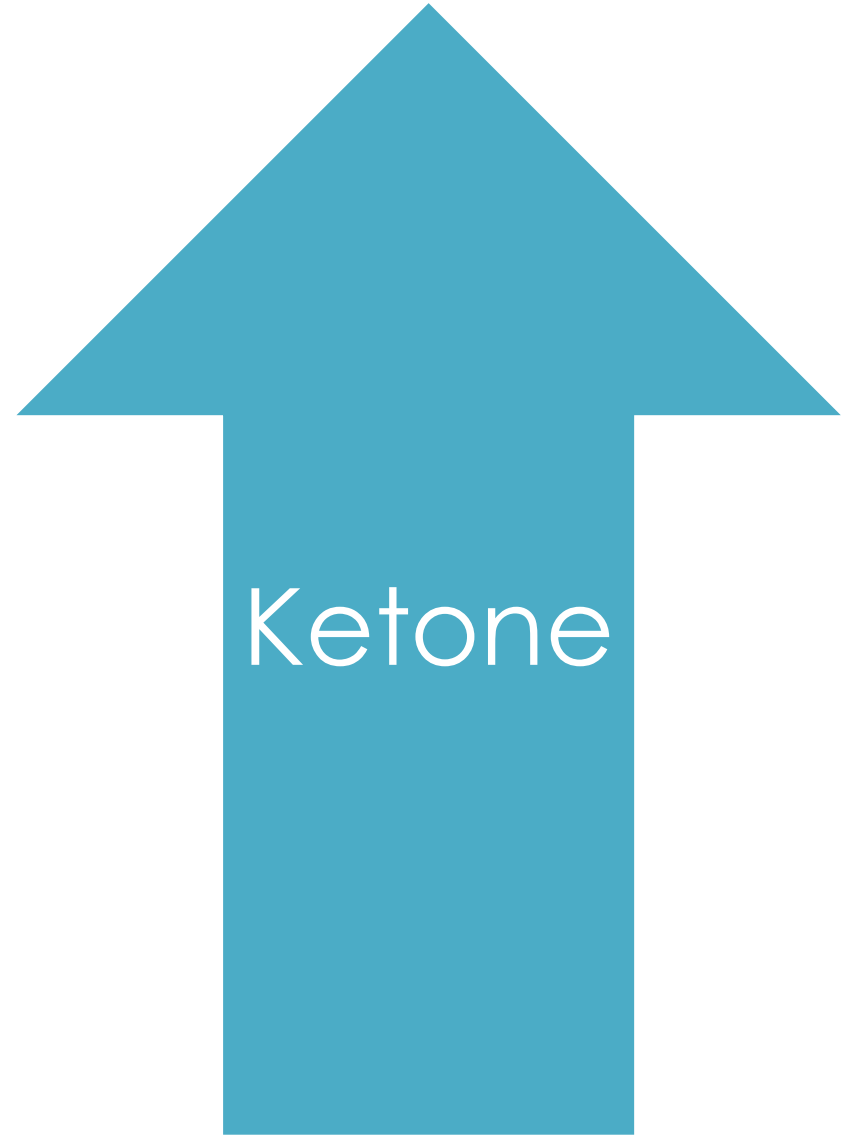


Does this happen  
in every tissue?




**Muscle**

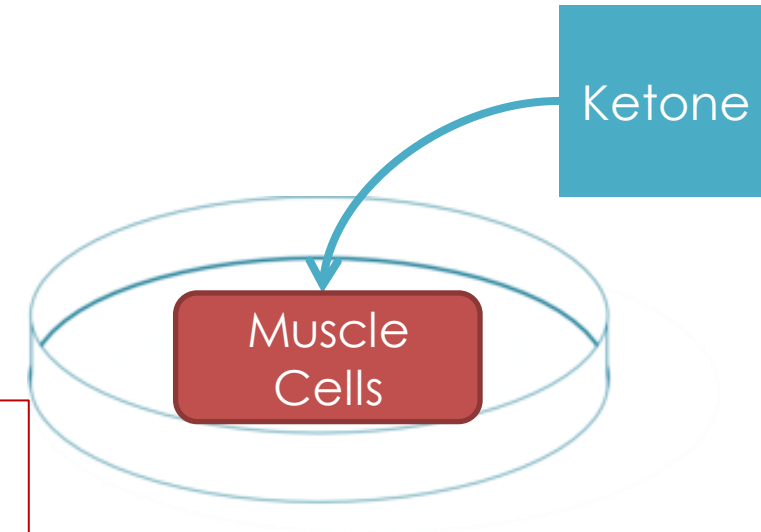
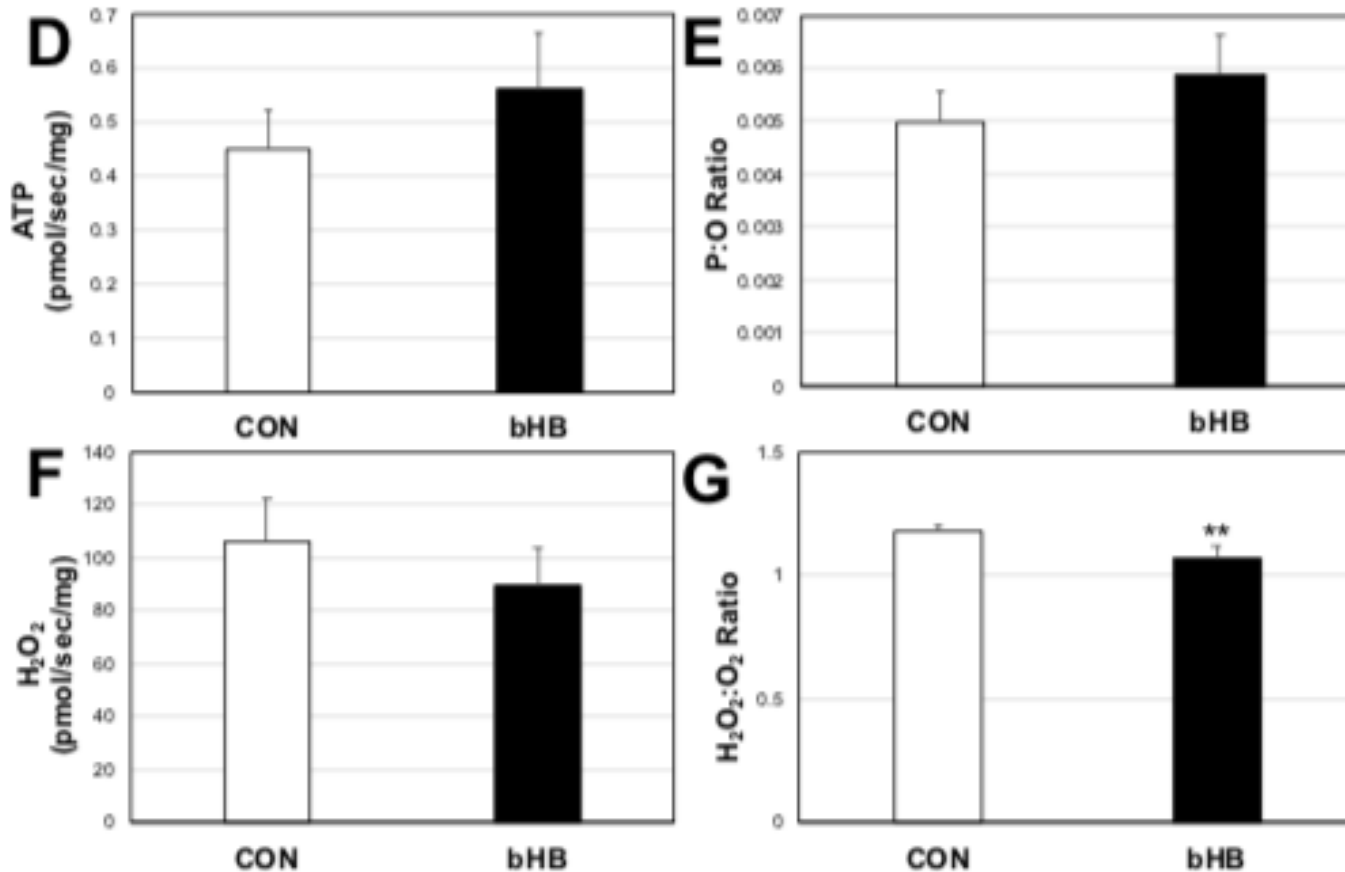


**Ketone**



# $\beta$ -Hydroxybutyrate Elicits Favorable Mitochondrial Changes in Skeletal Muscle

Brian A. Parker<sup>1</sup>, Chase M. Walton<sup>1</sup>, Sheryl T. Carr<sup>1</sup>, Jacob L. Andrus<sup>1</sup> , Eric C. K. Cheung<sup>1</sup>, Michael J. Duplisea<sup>1</sup>, Esther K. Wilson<sup>1</sup>, Carrie Draney<sup>2</sup>, Daniel R. Lathen<sup>2</sup> , Kyle B. Kenner<sup>2</sup>, David M. Thomson<sup>1</sup>, Jeffery S. Tessem<sup>2</sup>  and Benjamin T. Bikman<sup>1,\*</sup>



Ketones have **no effect on coupling**  
Ketones **reduce oxidative stress**

