

Quantitative flux analysis of energy metabolism

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HONG KONG BAPTIST UNIVERSITY

May 18, 2021

**The Analysis of Metabolism in
Saccharomyces cerevisiae with
Genome-scale Gene Expression Data**

HUI Sheng

A thesis submitted in partial fulfillment of the requirements
for degree of
Master of Philosophy

Principal Supervisor: Dr. TANG Lei Han

Hong Kong Baptist University

April 2005

中文

festival of Physics 1999 - 2000

Welcome Message

Samuel Ting
丁肇中



[Professor Hu](#)

Distinguished Lecture Series

[Professor Samuel C.C. Ting](#)

Lecture 1 : Search for antimatter and dark matter in the universe

October 28, 1999 (Thu) 4:00pm

[Wing Lung Bank Building Room 203 & 204](#)

Lecture 2 : Encounter with 20th century physics

October 29, 1999 (Fri) 4:30pm

[Wing Lung Bank Building Room 203 & 204](#)

During these two days, Prof. Ting left us lots of memories, his face, his speech and

To recall his visit in Physics Department, please [follow me](#).

Public Lecture

[Professor C.N. Yang](#)

What is Physics?

C.N. Yang
楊振寧

Paul Chu
朱經武

Daniel Tsui
崔琦







Chinatown, Manhattan



Chinatown, Manhattan



Chinatown, Boston

Energy metabolism: Burning the food we eat into CO₂



CO₂

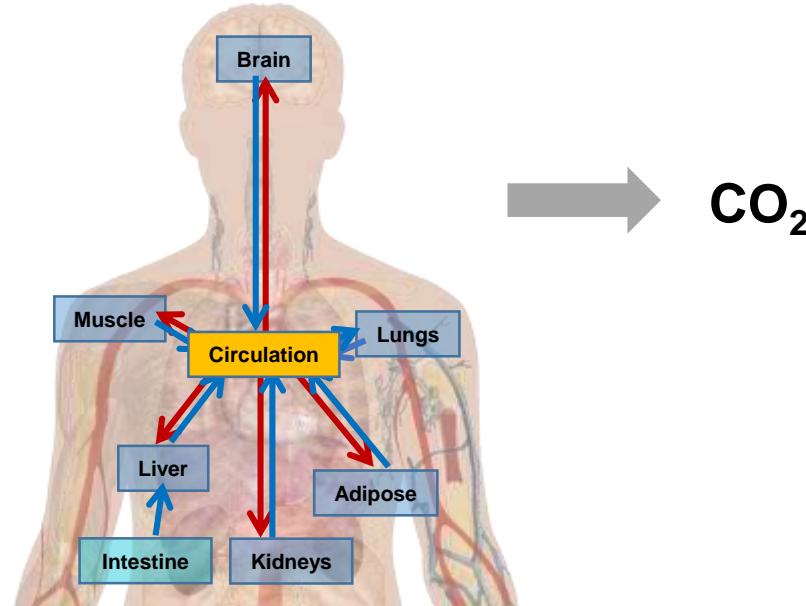


Energy metabolism: Burning the food we eat into CO₂



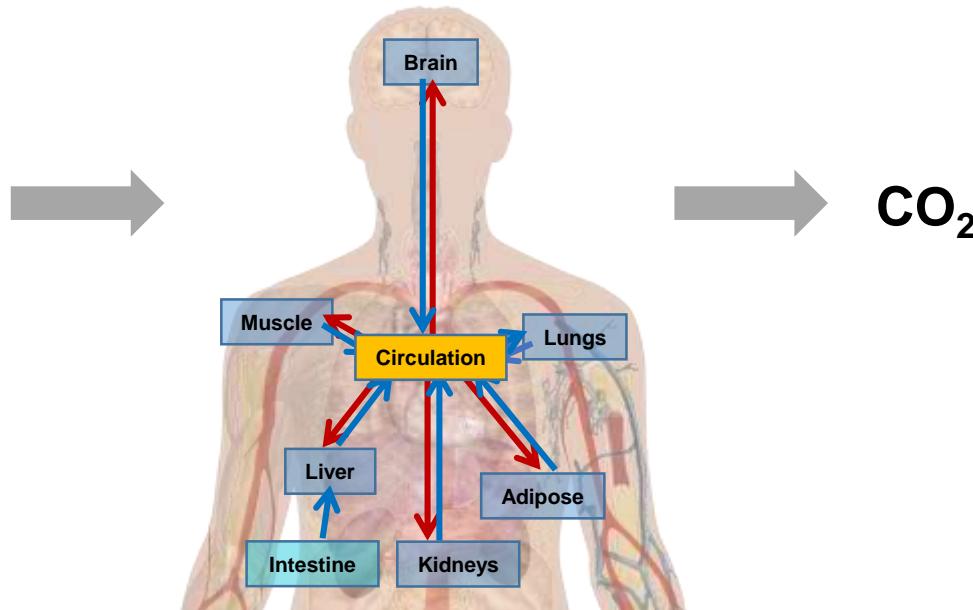
What do our organs/tissues eat?

Organs/tissues are fueled by *circulating metabolites*



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Organs/tissues are fueled by *circulating metabolites*



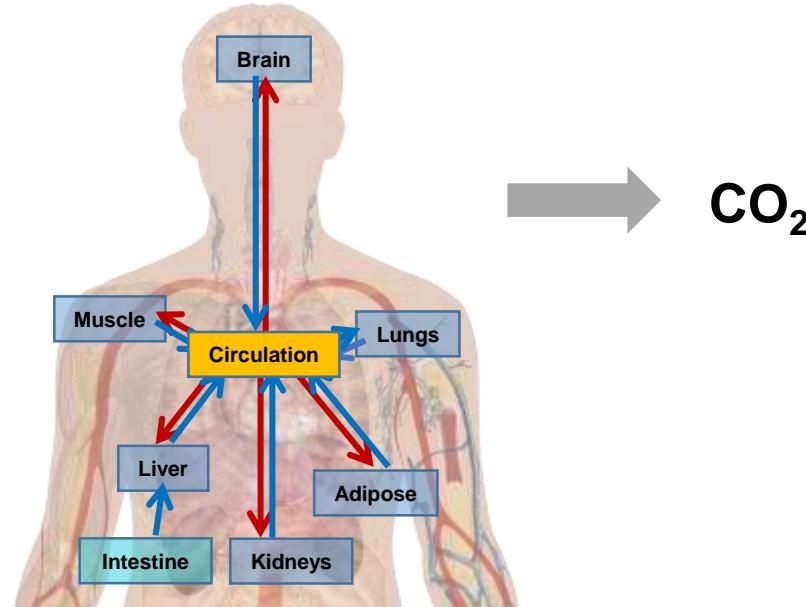
Serum Metabolome Statistics

Metabolite Statistics

Total Metabolites

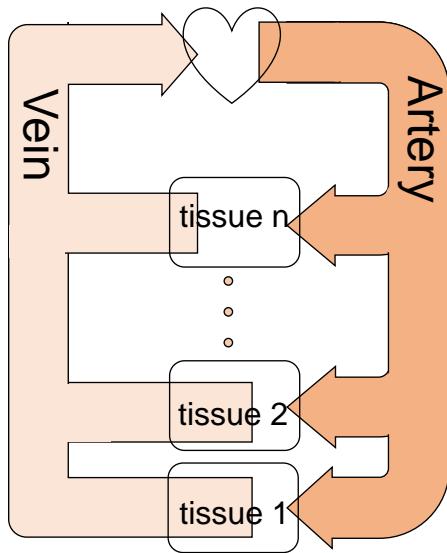
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Organs/tissues are fueled by *circulating metabolites*

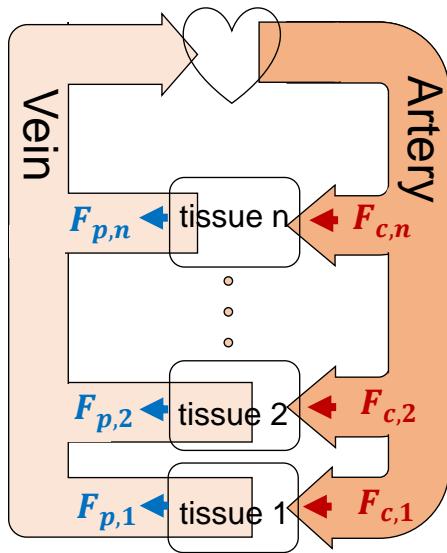


What are the important circulating metabolites?

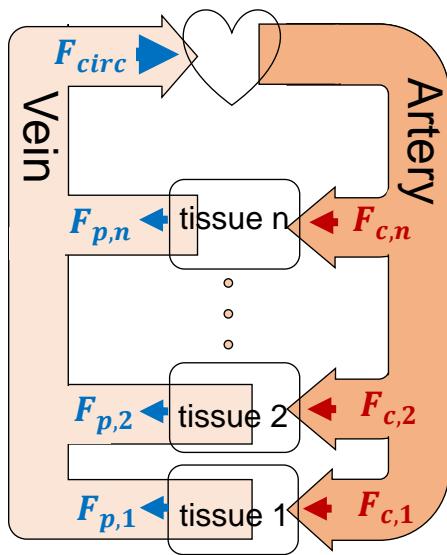
Circulatory turnover flux (F_{circ}) is a measure of nutrient importance



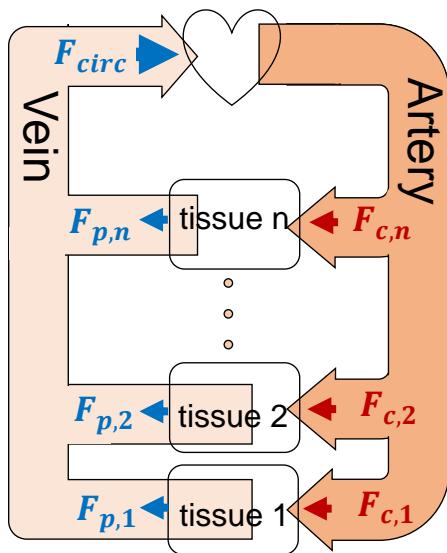
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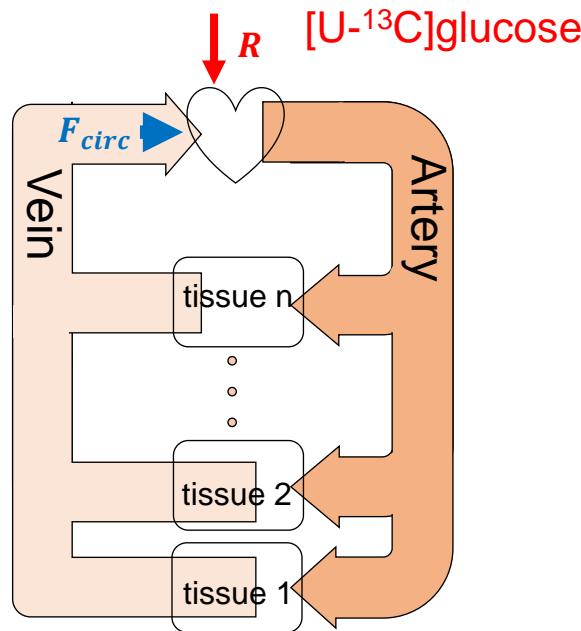


Circulatory turnover flux (F_{circ}) is a measure of nutrient importance



$$F_{circ} = \sum_{i=1}^n F_{p,i} = \sum_{i=1}^n F_{c,i}$$

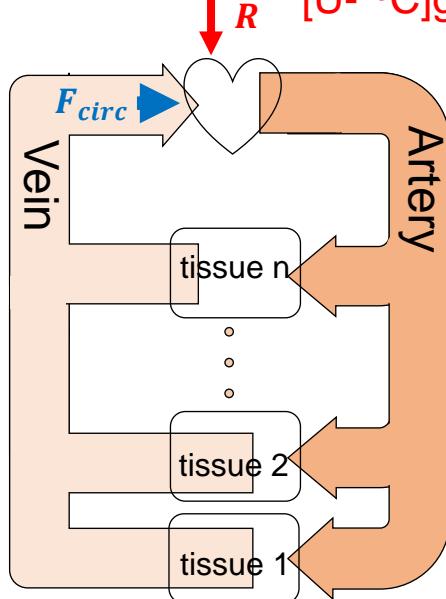
Quantifying F_{circ} by isotopic tracing



$$\frac{R}{F_{circ}} = \frac{L}{1 - L}$$

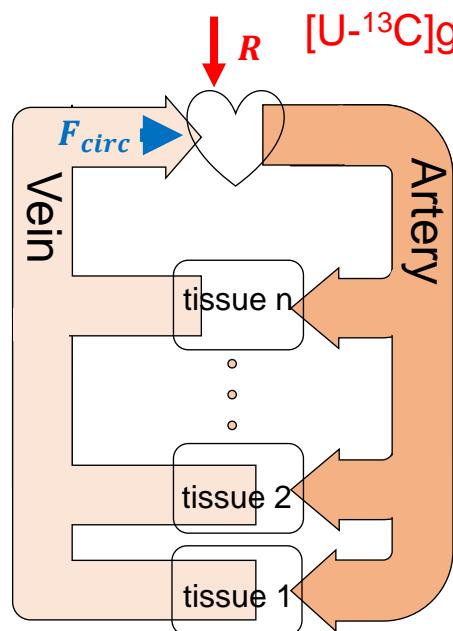
Quantifying F_{circ} by isotopic tracing

How many fish pass through the river per hour?



$$\frac{R}{F_{circ}} = \frac{L}{1 - L}$$

Quantifying F_{circ} by isotopic tracing

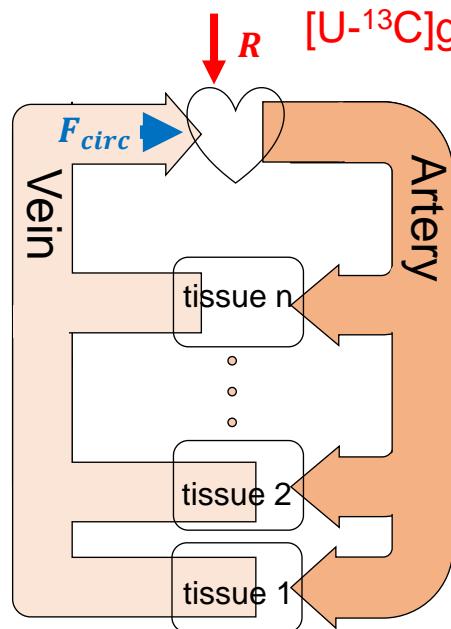


How many fish pass through the river per hour?



$$\frac{R}{F_{circ}} = \frac{L}{1 - L}$$

Quantifying F_{circ} by isotopic tracing



How many fish pass through the river per hour?



introduce 10 fish/hr



catch 10 fish

1

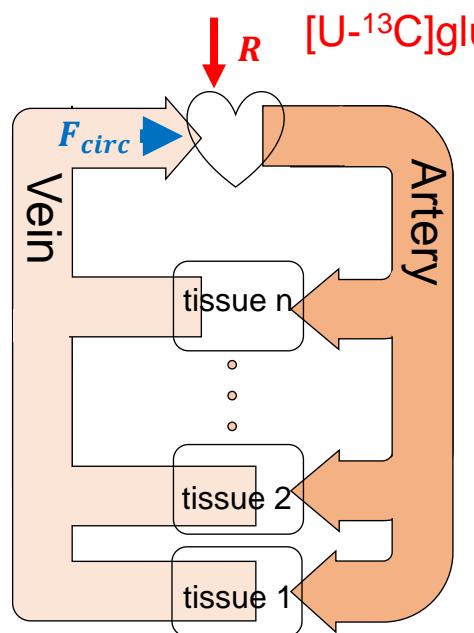


9



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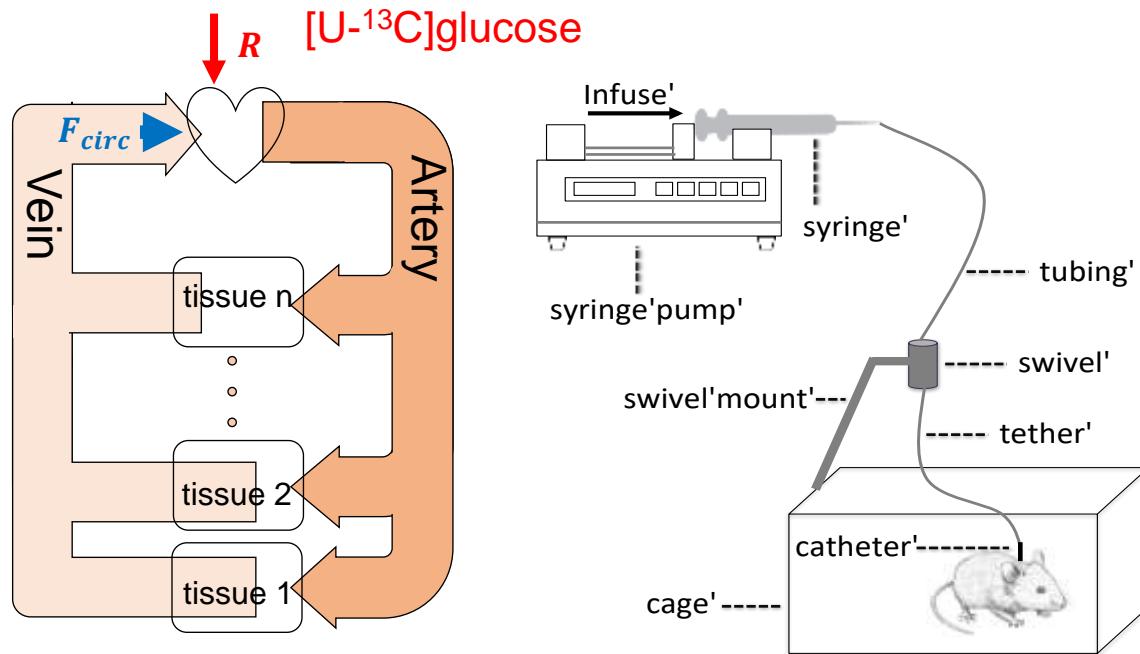
catch 10 fish



$$\frac{10}{90 \text{ fish}} = \frac{1}{9}$$

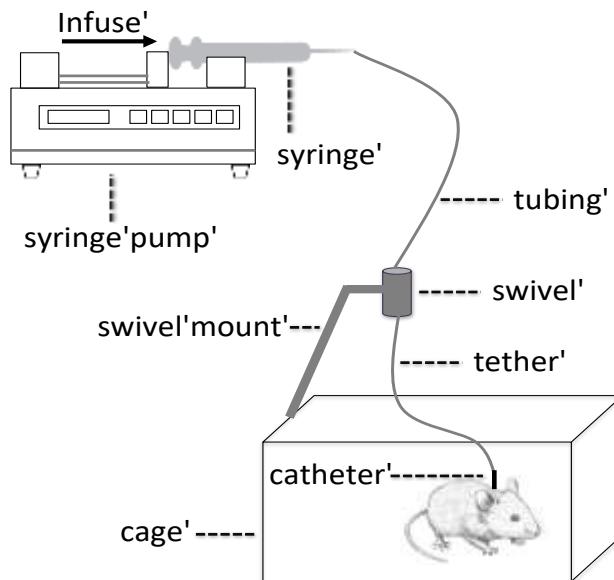
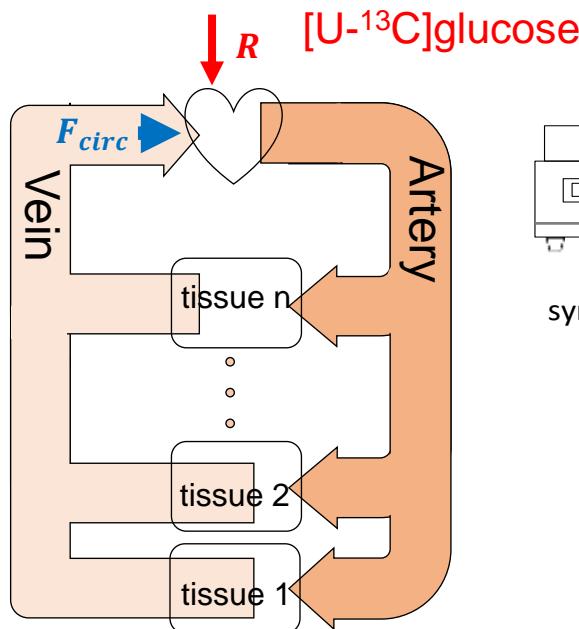
*pass through the
river per hour*

Quantifying F_{circ} by isotopic tracing



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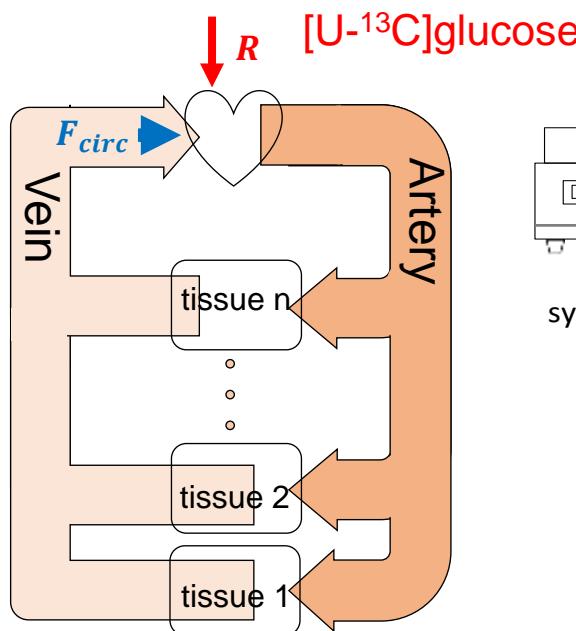
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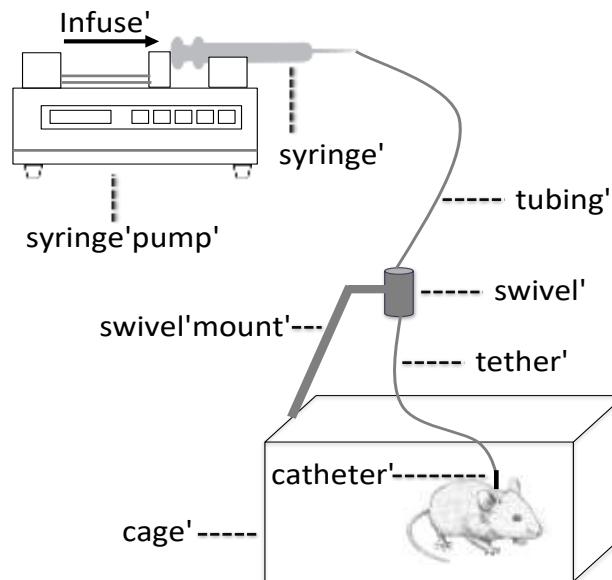
LC-MS

$$\frac{R}{F_{circ}} = \frac{L}{1 - L}$$

Quantifying F_{circ} by isotopic tracing



$$\frac{R}{F_{circ}} = \frac{L}{1 - L}$$



LC-MS

Serum Metabolome Statistics

Metabolite Statistics

Total Metabolites

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An upper bound for F_{circ}

$F_{circ} \leq \text{cardiac output} \times \text{concentration}$

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To be able to carry 10% of glucose F_{circ} , a metabolite's blood concentration has to be greater than 30 μM .

Systematic quantification of F_{circ}

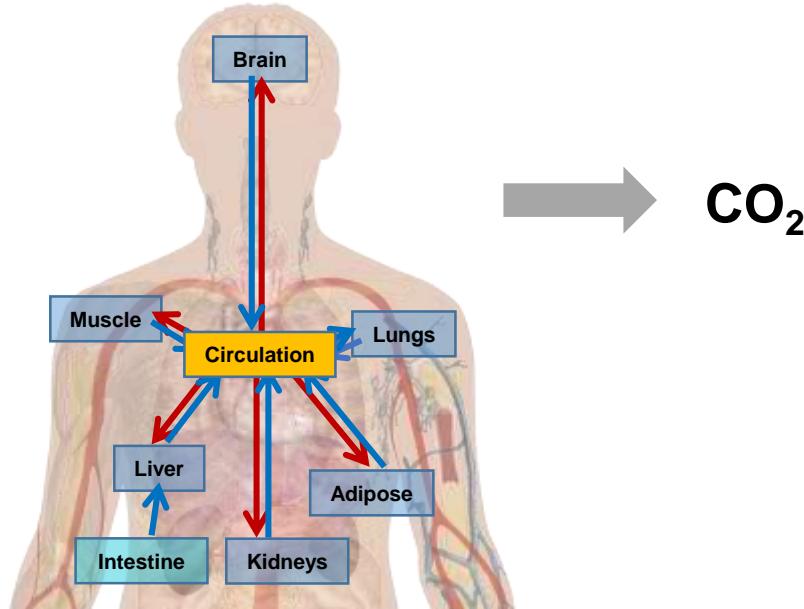
Metabolite	F_{circ} (nmol/min/g)	Metabolite	F_{circ} (nmol/min/g)	Metabolite	F_{circ} (nmol/min/g)
Lactate	374.4±112.4	Serine	19.3±4.2	Phenylalanine	5.9±0.8
Glucose	150.9±46.7	Citrate	16.2±6.6	2-Oxoglutarate	5.8±0.8
Acetate	72.7±17.5	Leucine	11.5±1.2	Histidine	5.0±0.4
Alanine	70.2±5.4	Valine	9.6±0.4	Methionine	3.9±1.6
Glycerol	53.3±2.1	Lysine	9.3±1.8	Succinate	3.1±1.1
Glutamine	45.6±4.7	Arginine	9.0±2.6	Creatine	2.6±0.5
3-Hydroxybutyrate	43.3±17.1	Tyrosine	8.0±2.2	Tryptophan	2.3±0.3
Linoleic acid	42.9±9.2	Threonine	7.6±0.8	Malate	2.0±0.4
Oleic acid	33.9±5.4	Proline	7.3±2.9	Betaine	1.6±0.2
Palmitic acid	24.6±4.2	Isoleucine	6.5±0.7		
Glycine	21.9±4.2	Asparagine	6.5±0.8		

Systematic quantification of F_{circ}

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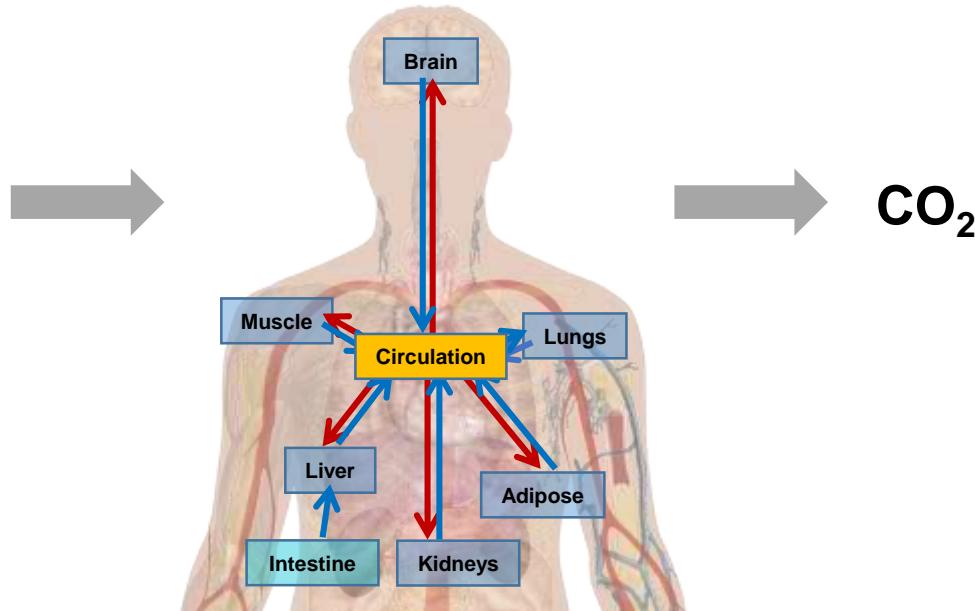
Only 13 metabolites actually carry more than 10% of glucose F_{circ} .

Organs/tissues are fueled by *circulating metabolites*



What are the important circulating metabolites?

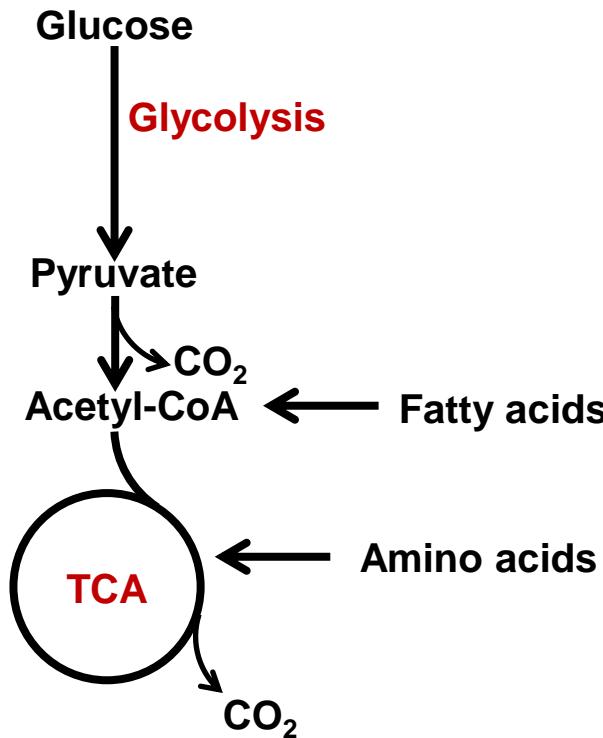
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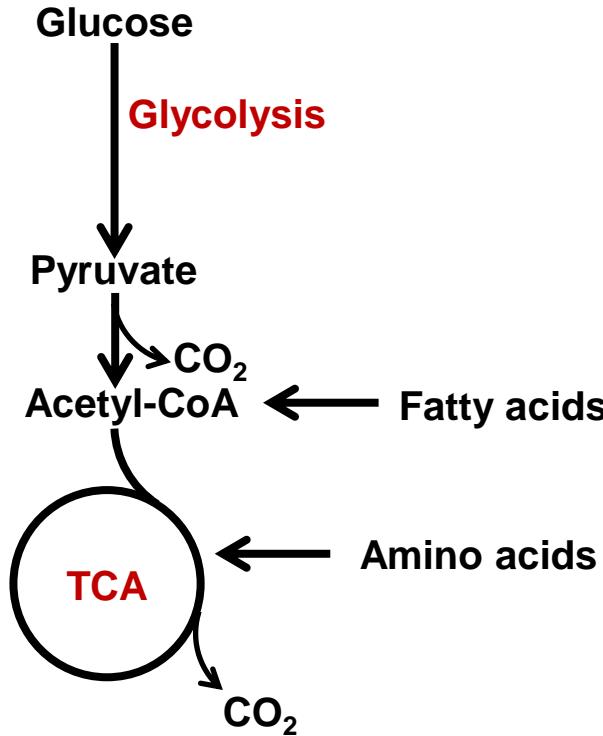
What are the important circulating metabolites?

How do they contribute as fuels to different tissues?

Energy production pathways: Glycolysis and TCA cycle

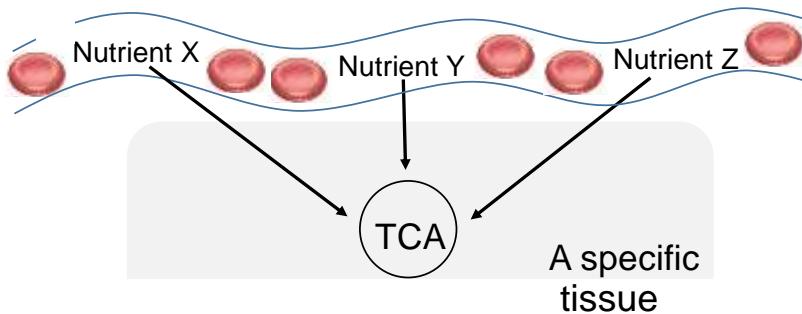


Energy production pathways: Glycolysis and TCA cycle

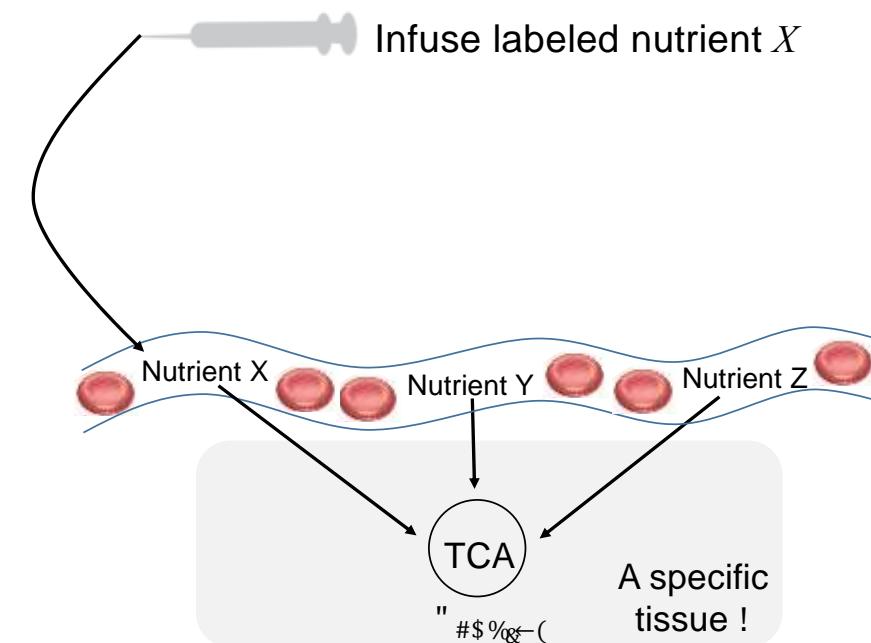


TCA cycle is the predominant energy production pathway.

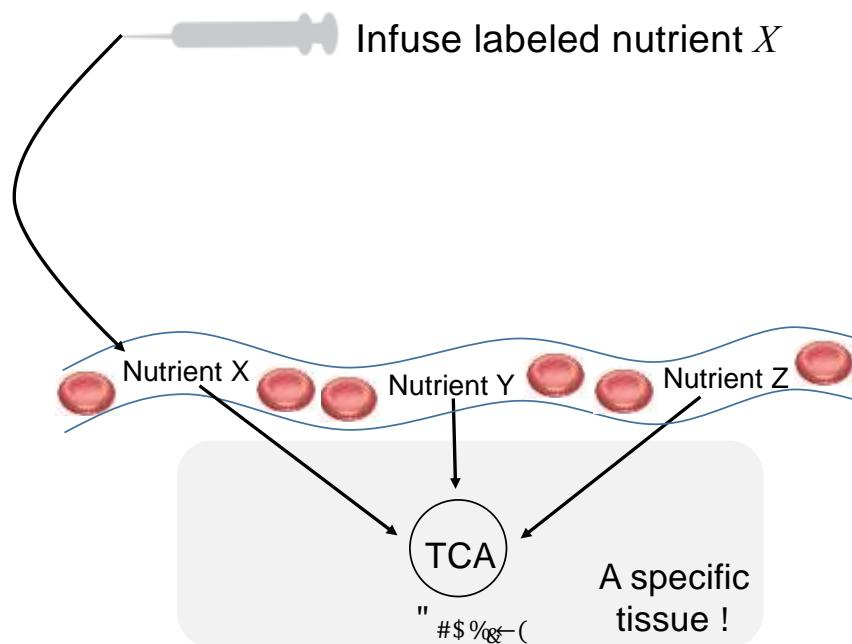
Contribution from circulating nutrients to tissue TCA cycle



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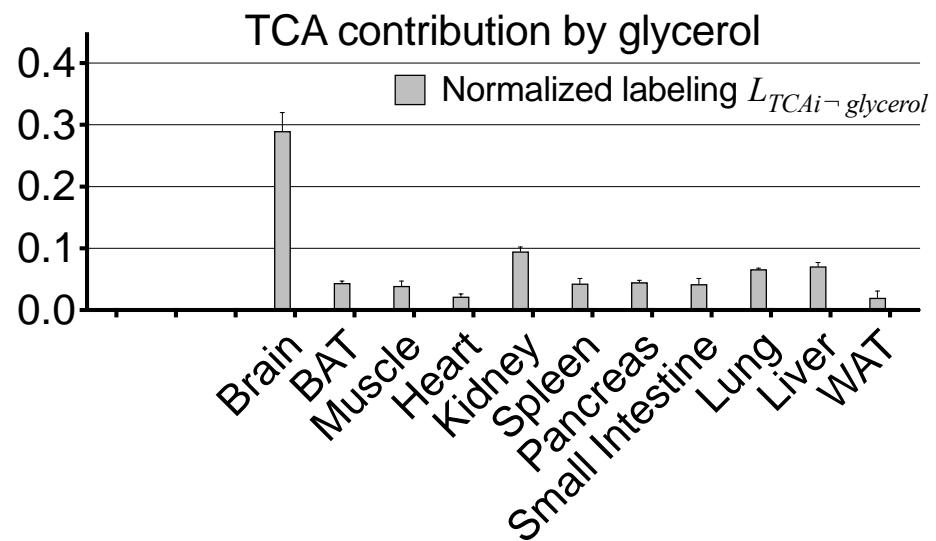
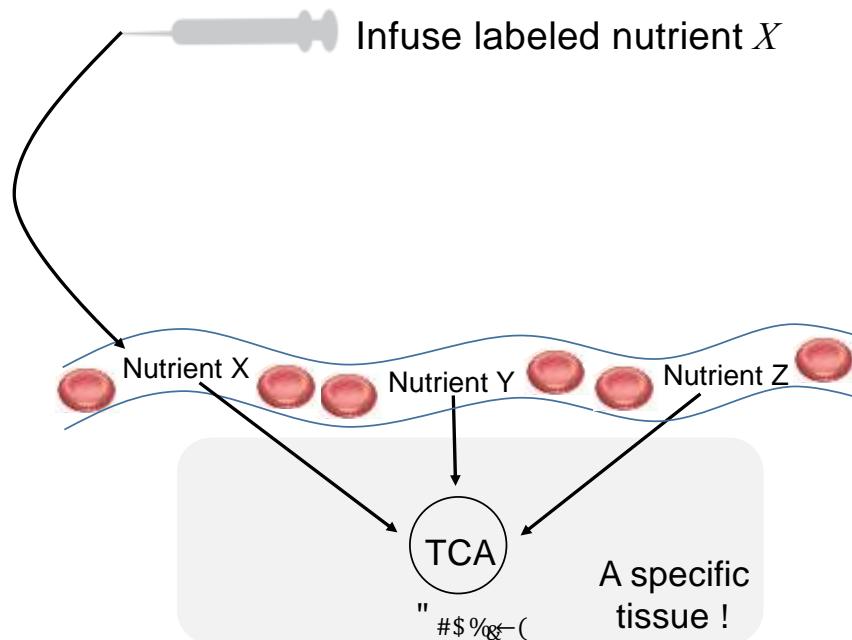


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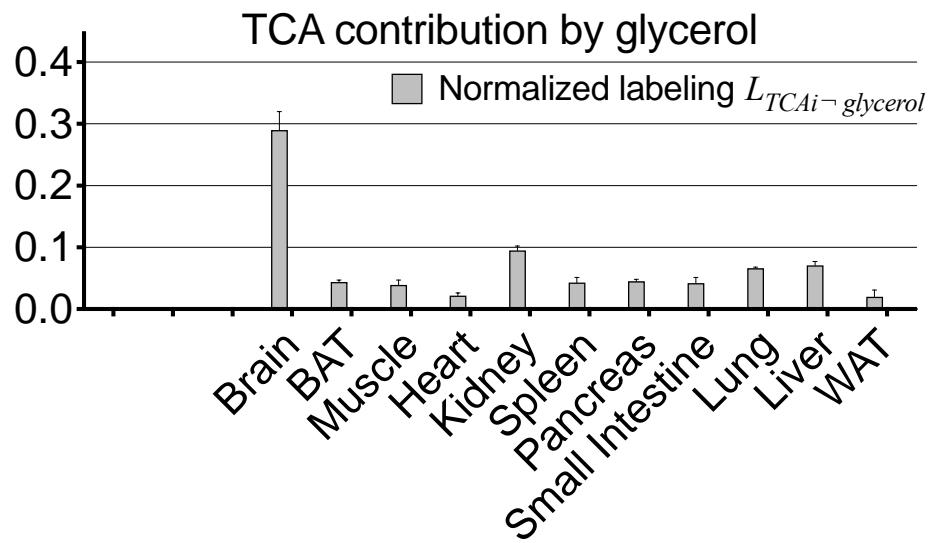
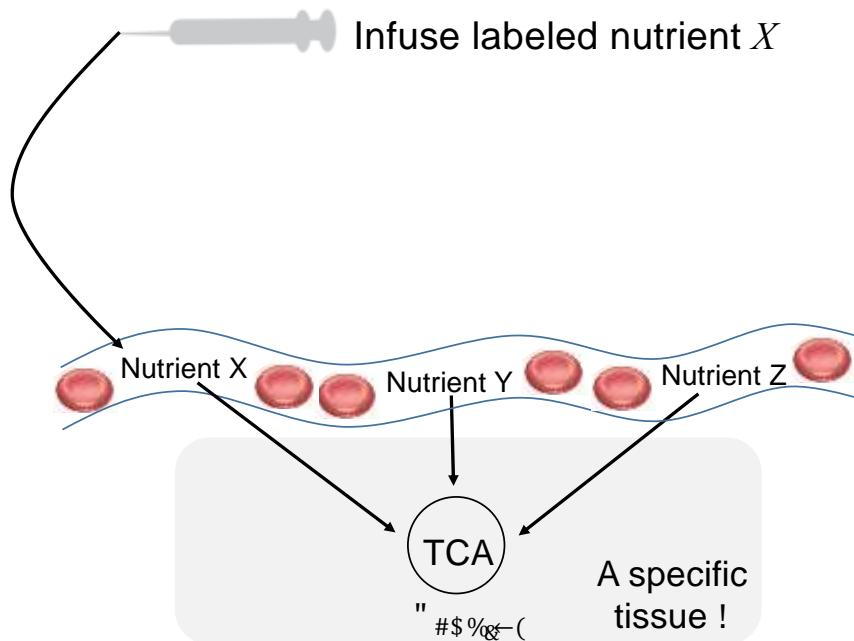


Normalized labeling $L_{TCA_i \leftarrow X} = \frac{L_{malate_i}}{L_X}$

Contribution from circulating nutrients to tissue TCA cycle

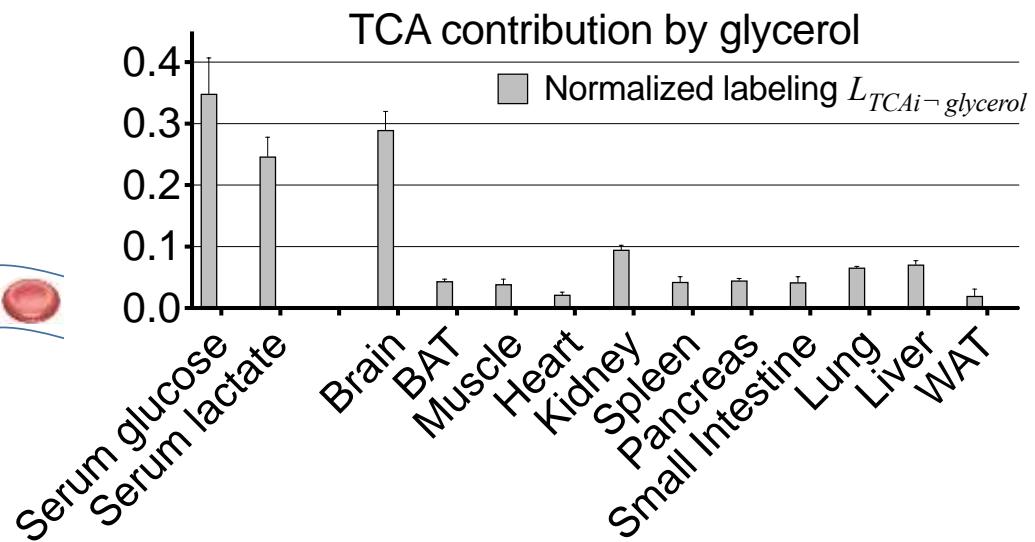
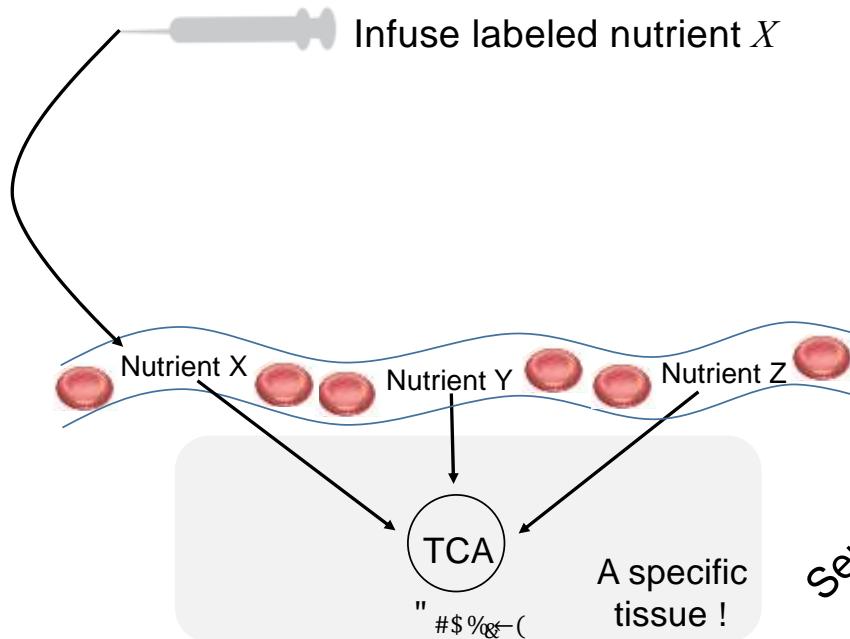


Contribution from circulating nutrients to tissue TCA cycle



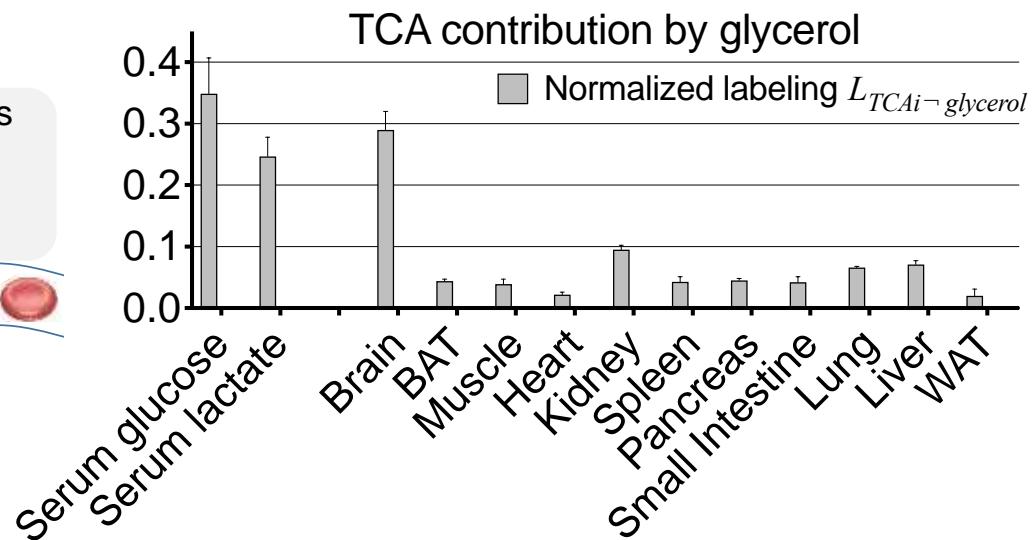
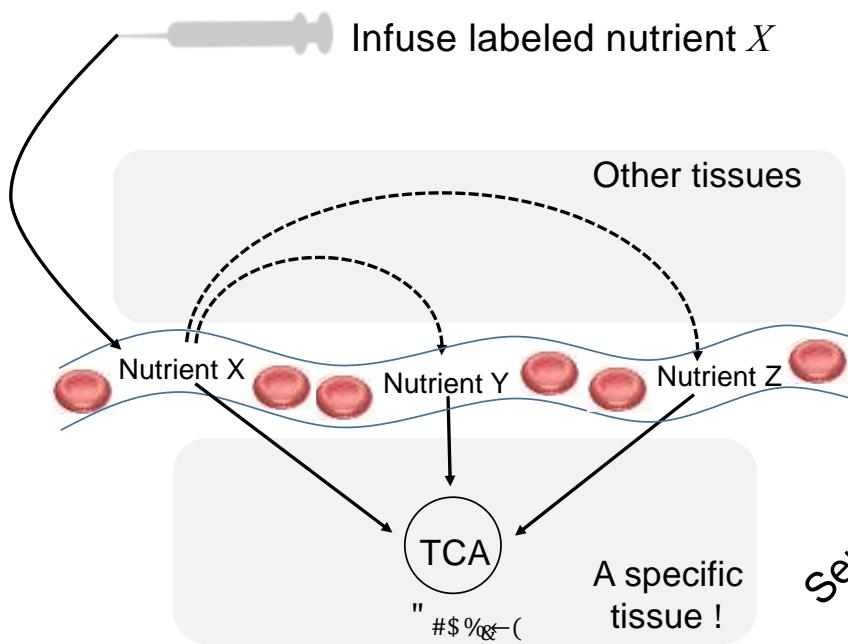
Normalized labeling is not *direct contribution*

Contribution from circulating nutrients to tissue TCA cycle



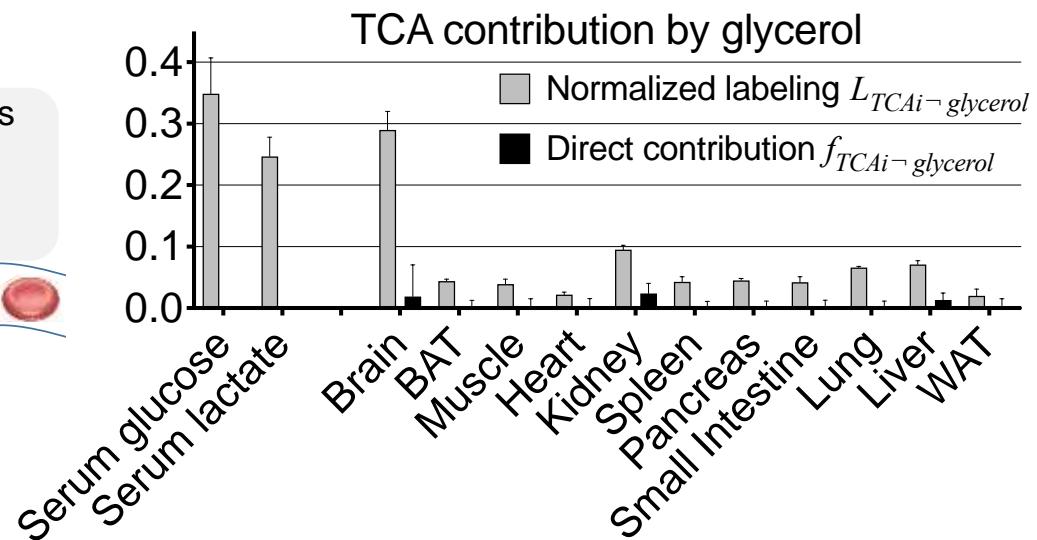
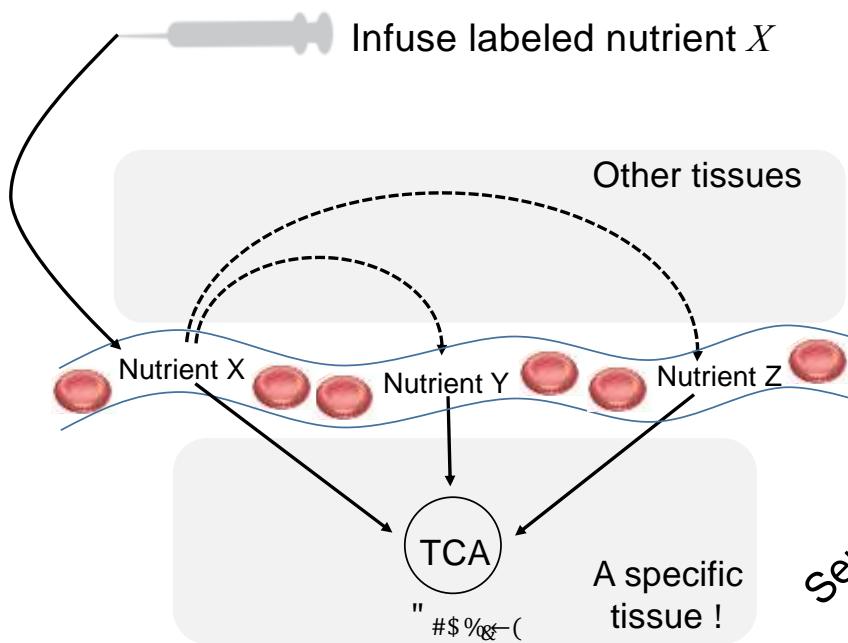
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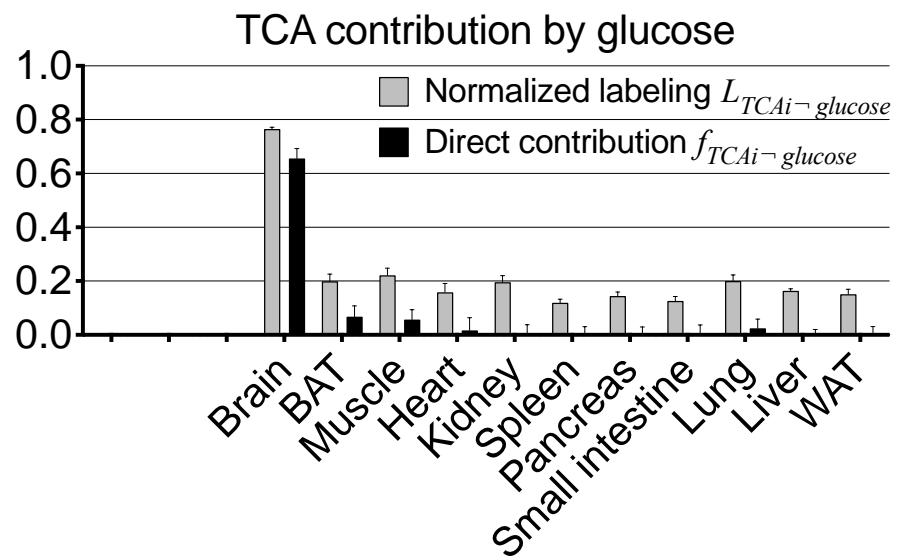
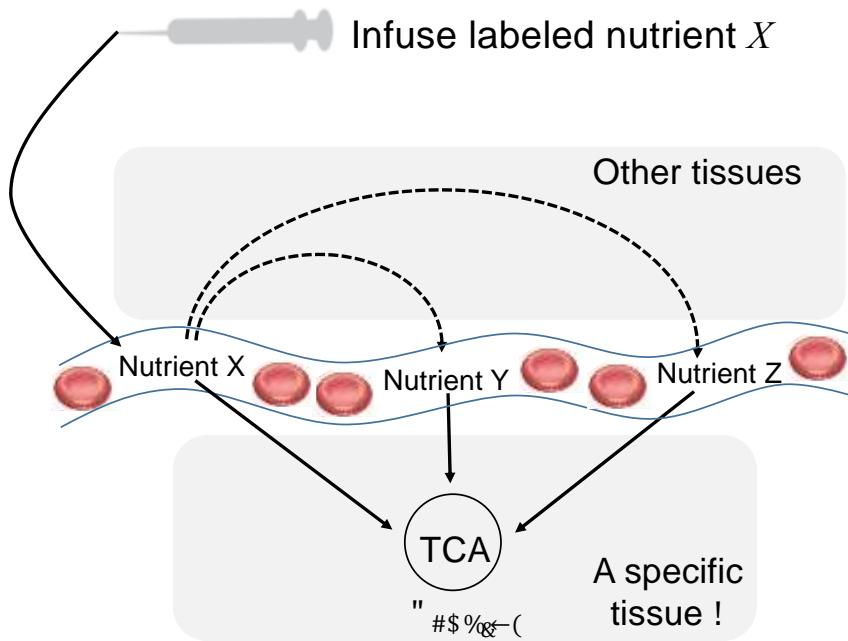
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Contribution from circulating nutrients to tissue TCA cycle



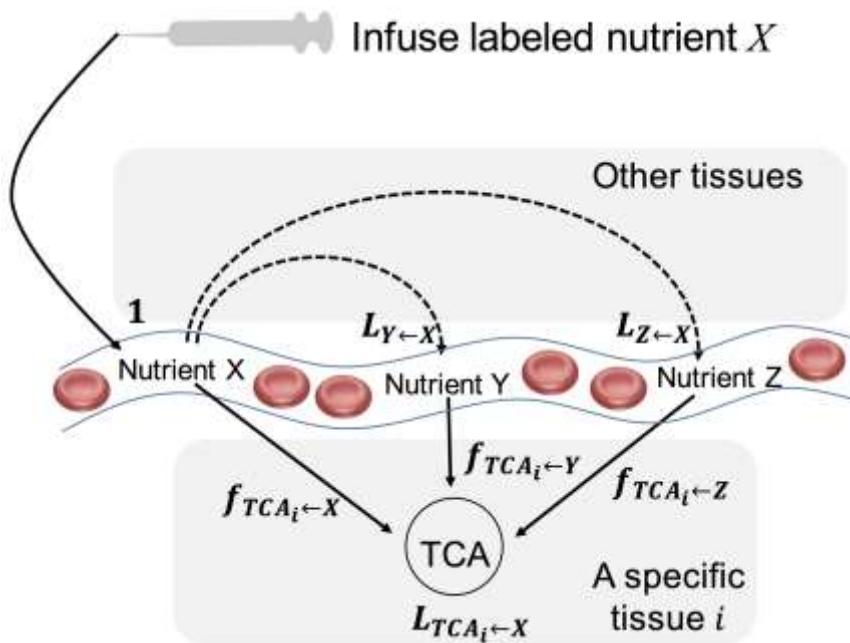
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Contribution from circulating nutrients to tissue TCA cycle



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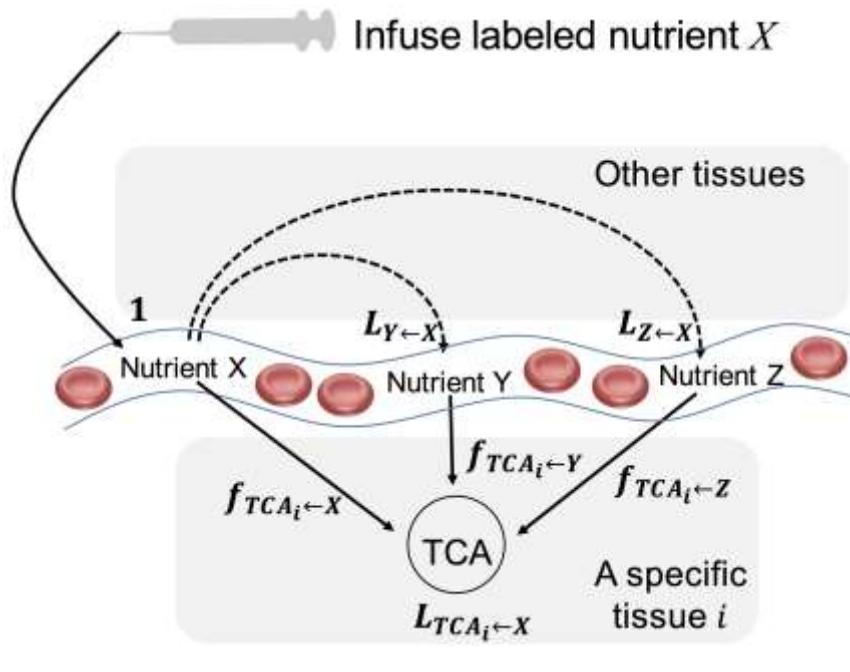
Contribution from circulating nutrients to tissue TCA cycle



Infusing X

$$f_{TCA_i \leftarrow X} + f_{TCA_i \leftarrow Y} \cdot L_{Y \leftarrow X} + f_{TCA_i \leftarrow Z} \cdot L_{Z \leftarrow X} = L_{TCA_i \leftarrow X}$$

Contribution from circulating nutrients to tissue TCA cycle



Infusing X

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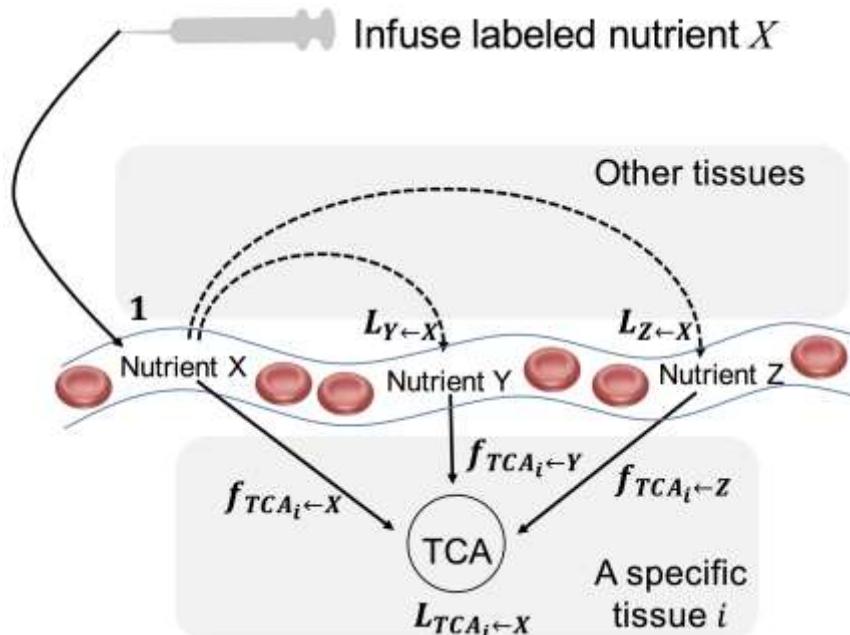
Infusing Y

$$f_{TCA_i \leftarrow X} \cdot L_{X \leftarrow i} + f_{TCA_i \leftarrow Y} + f_{TCA_i \leftarrow Z} \cdot L_{Z \leftarrow i} = L_{TCA_i \leftarrow Y}$$

Infusing Z

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Contribution from circulating nutrients to tissue TCA cycle

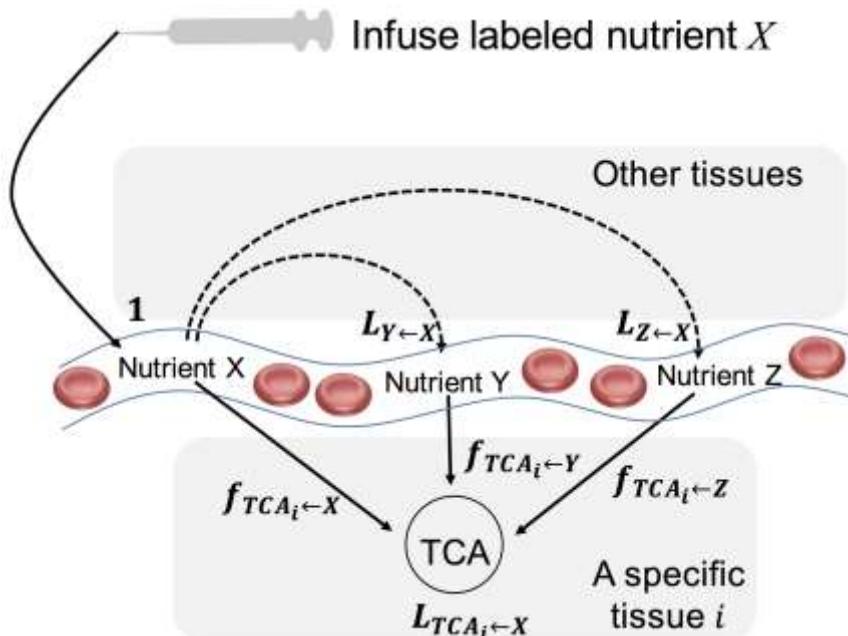


$$M \cdot \begin{pmatrix} f_{TCA_i \leftarrow glc} \\ f_{TCA_i \leftarrow lac} \\ \vdots \\ f_{TCA_i \leftarrow 6AAs} \end{pmatrix} = \begin{pmatrix} L_{TCA_i \leftarrow glc} \\ L_{TCA_i \leftarrow lac} \\ \vdots \\ L_{TCA_i \leftarrow 6AAs} \end{pmatrix}$$

Normalized TCA labeling by each of the 15 nutrients

15x15 matrix summarizing inter-labeling between every pair of the 15 nutrients

Contribution from circulating nutrients to tissue TCA cycle



Direct contribution to TCA
from each of the 15 nutrients

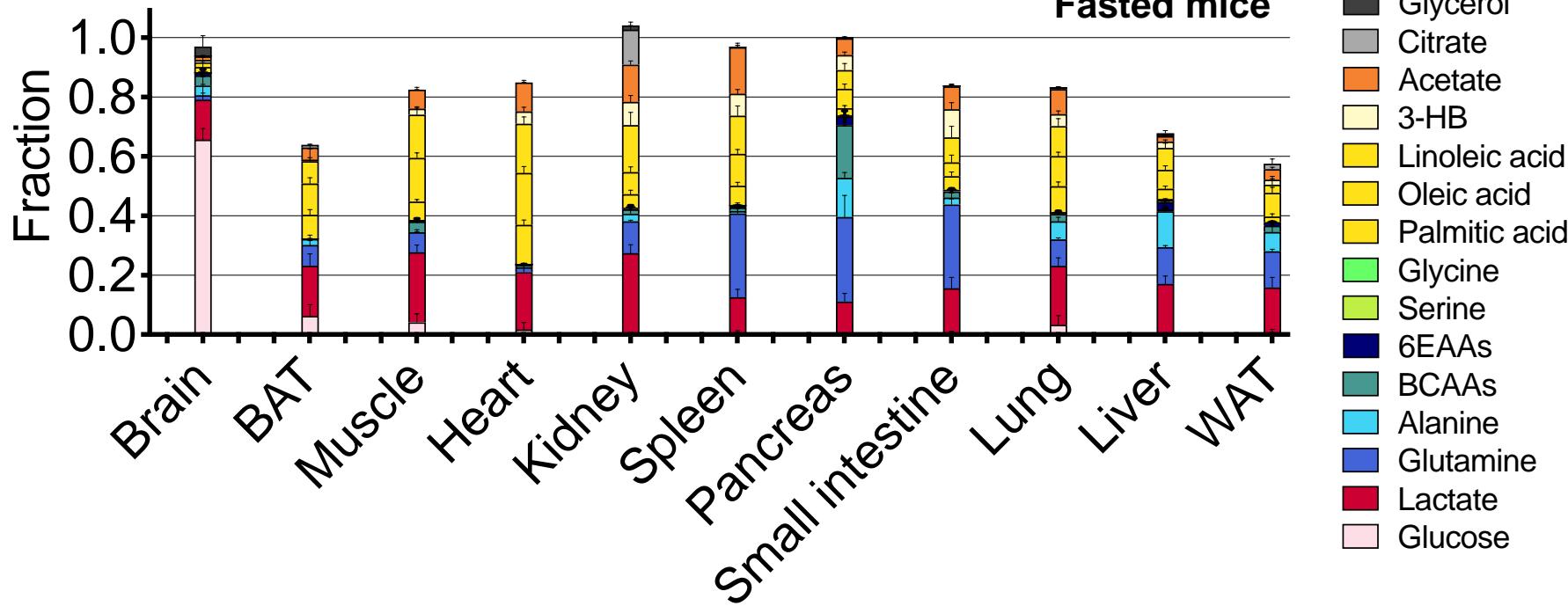
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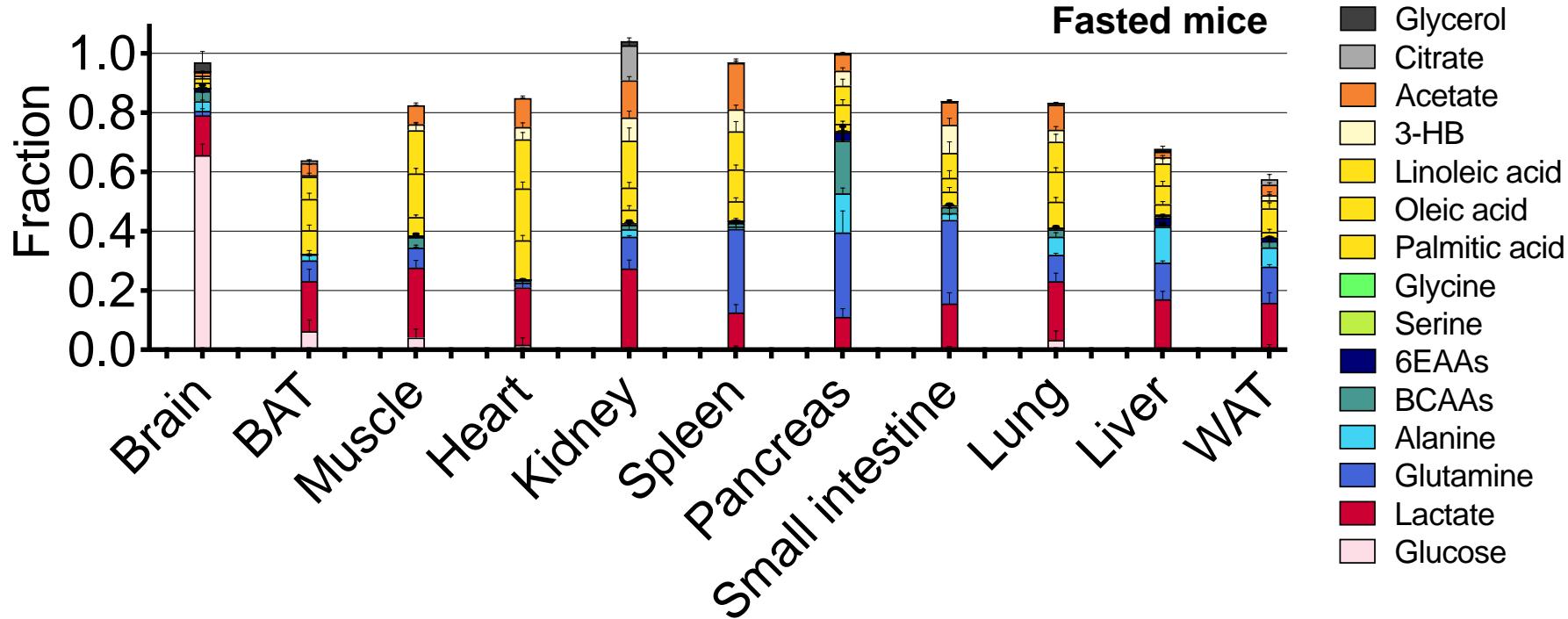
15x15 matrix summarizing inter-labeling
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Direct contributions to the tissue TCA

Fasted mice

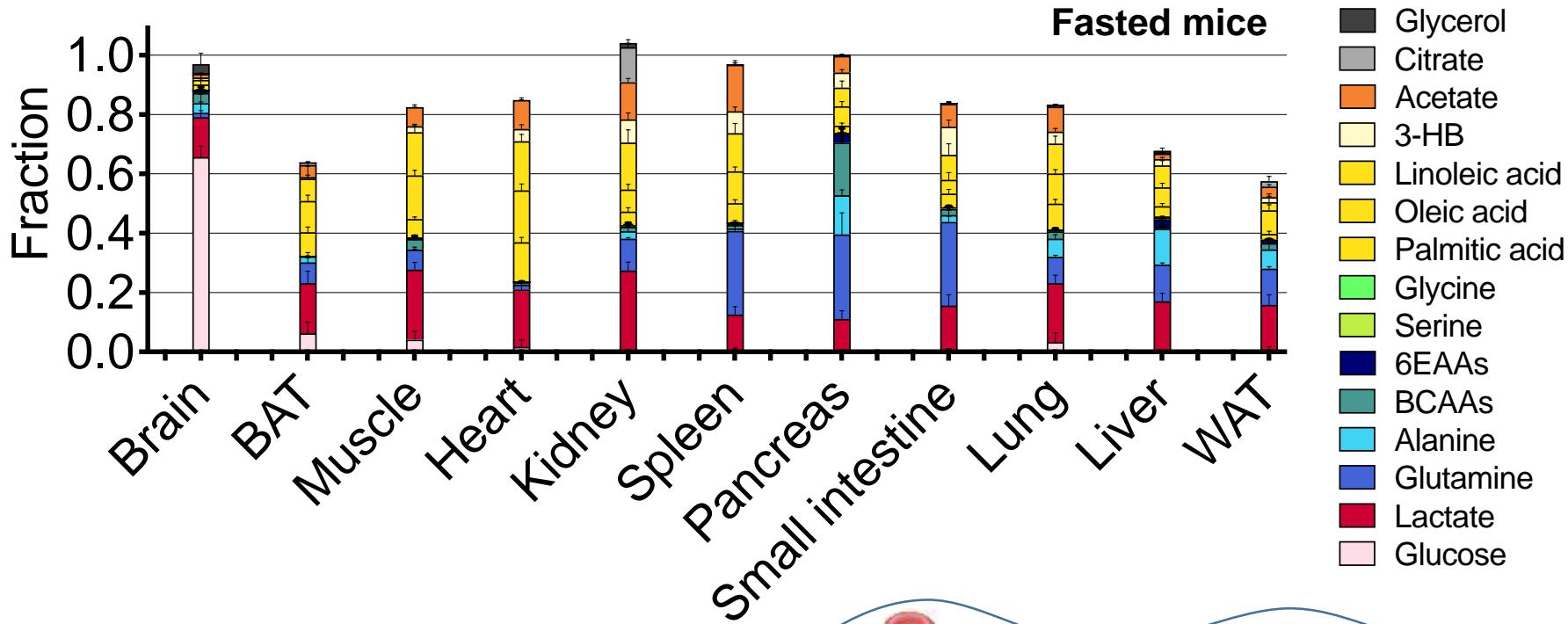


Direct contributions to the tissue TCA

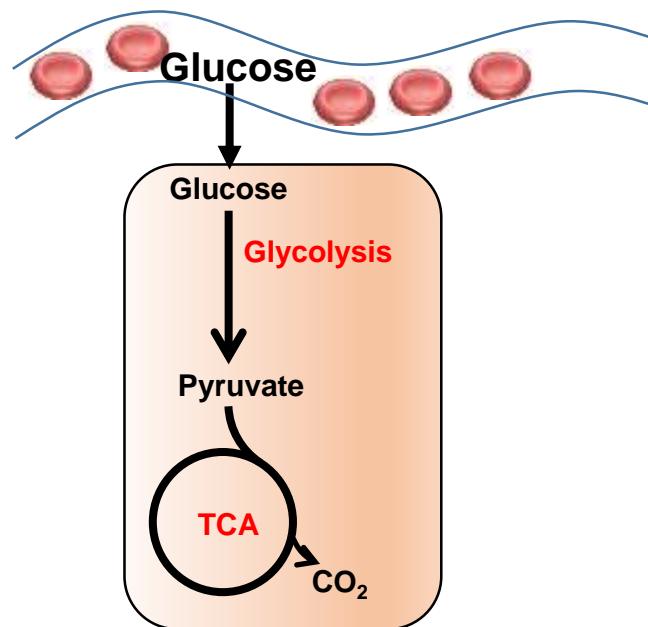


- **Glucose feeds the TCA cycle via circulating lactate.**

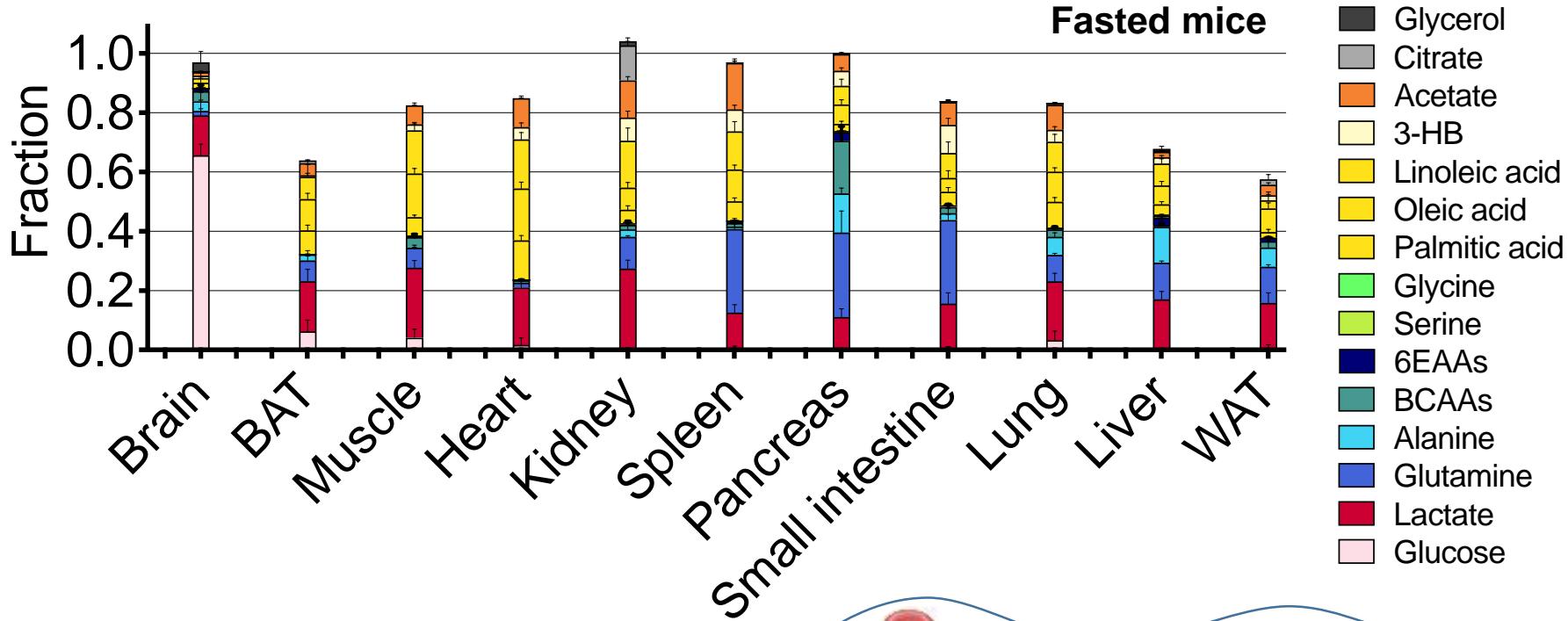
Direct contributions to the tissue TCA



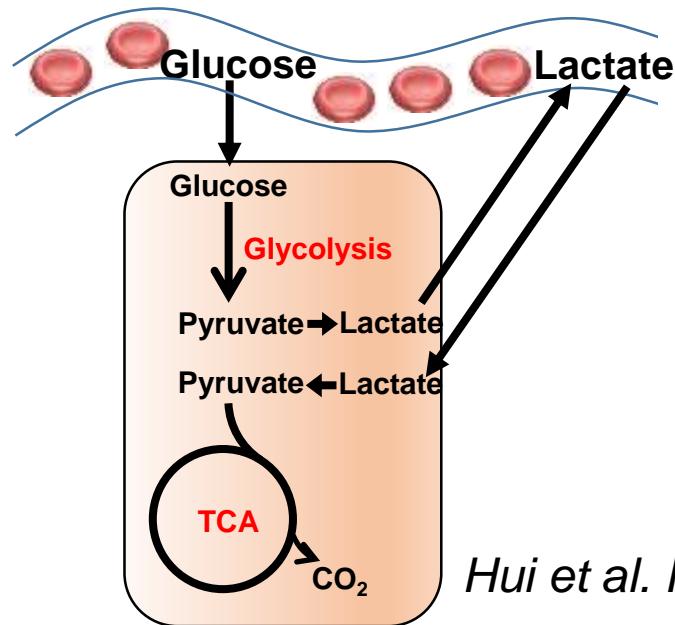
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Direct contributions to the tissue TCA

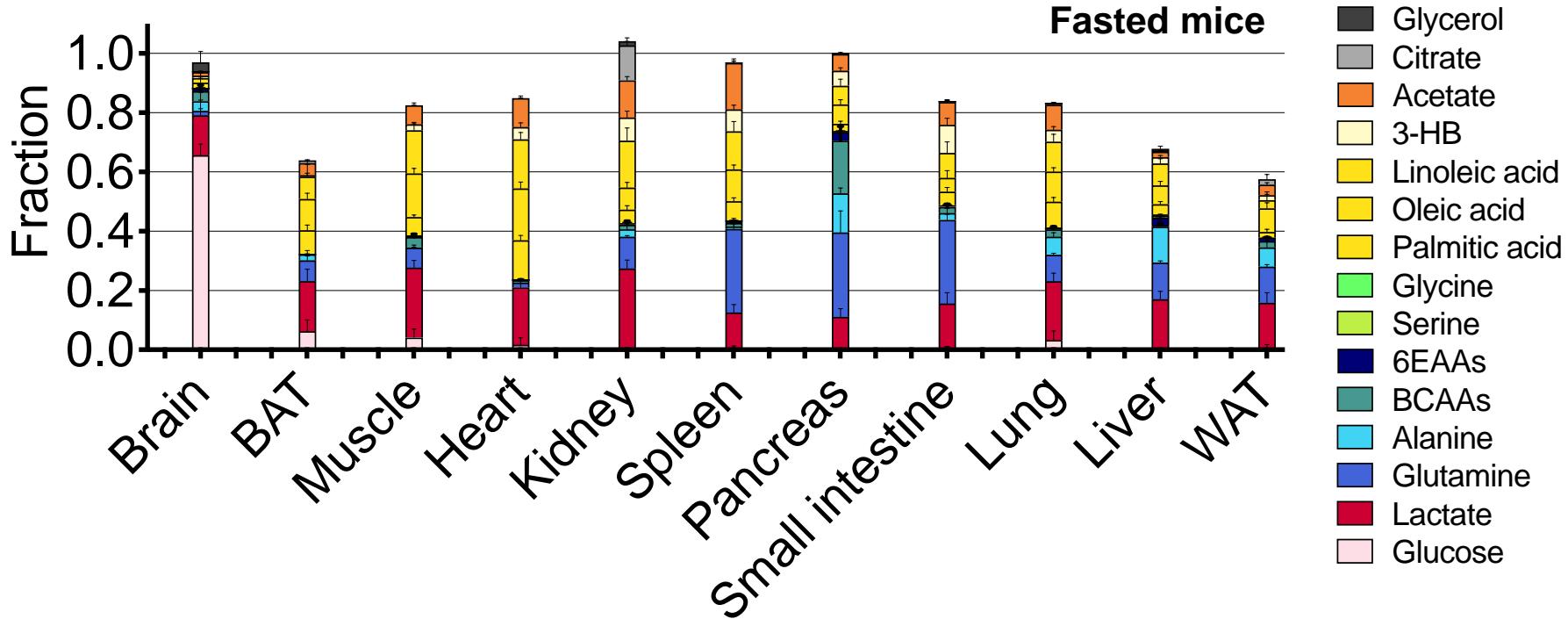


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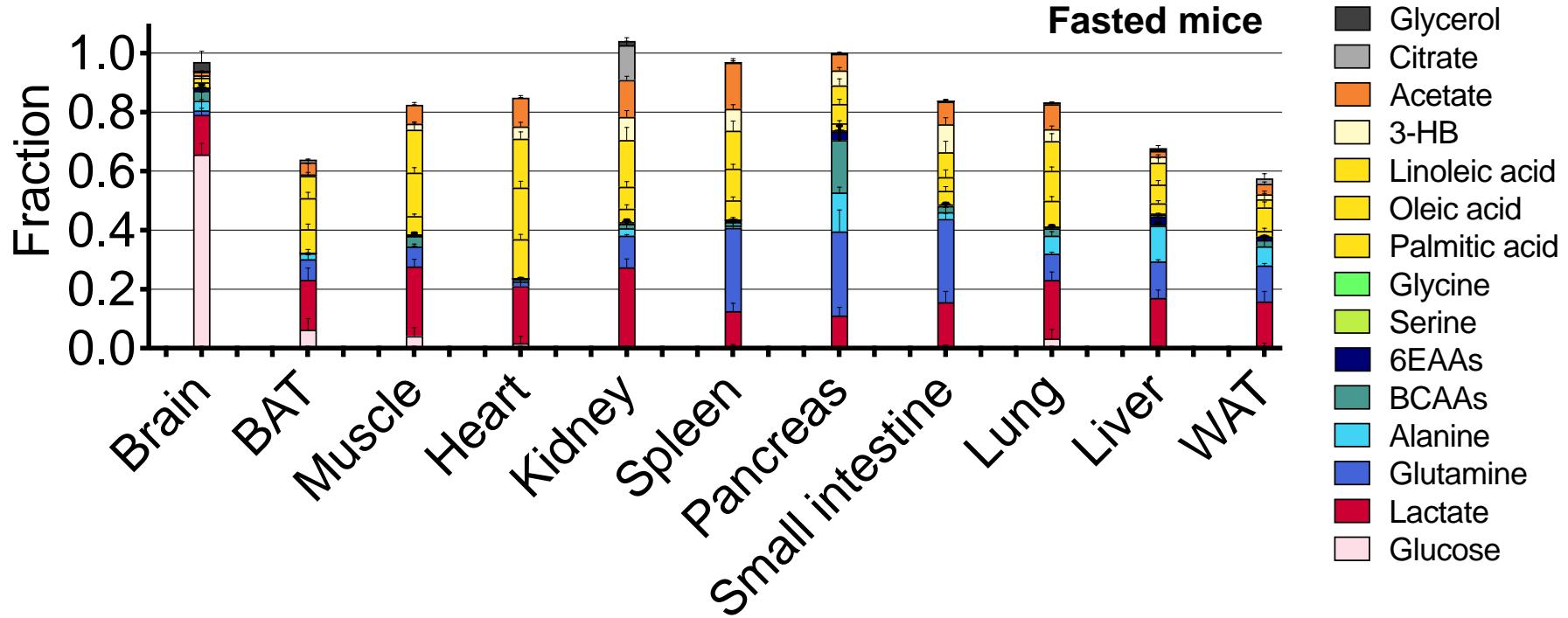
Hui et al. Nature 2017

Direct contributions to the tissue TCA



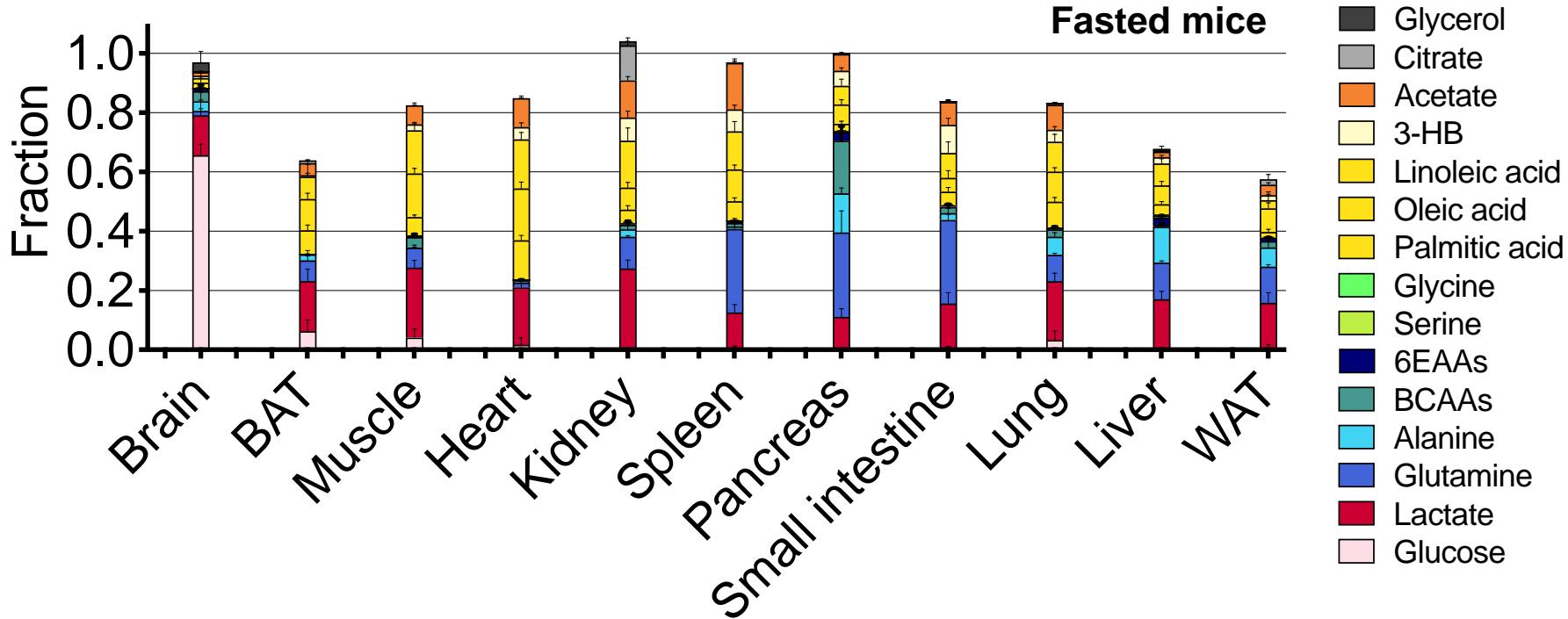
- **Glucose feeds the TCA cycle via circulating lactate.**
- **Glutamine is a major fuel for visceral tissues.**

Direct contributions to the tissue TCA



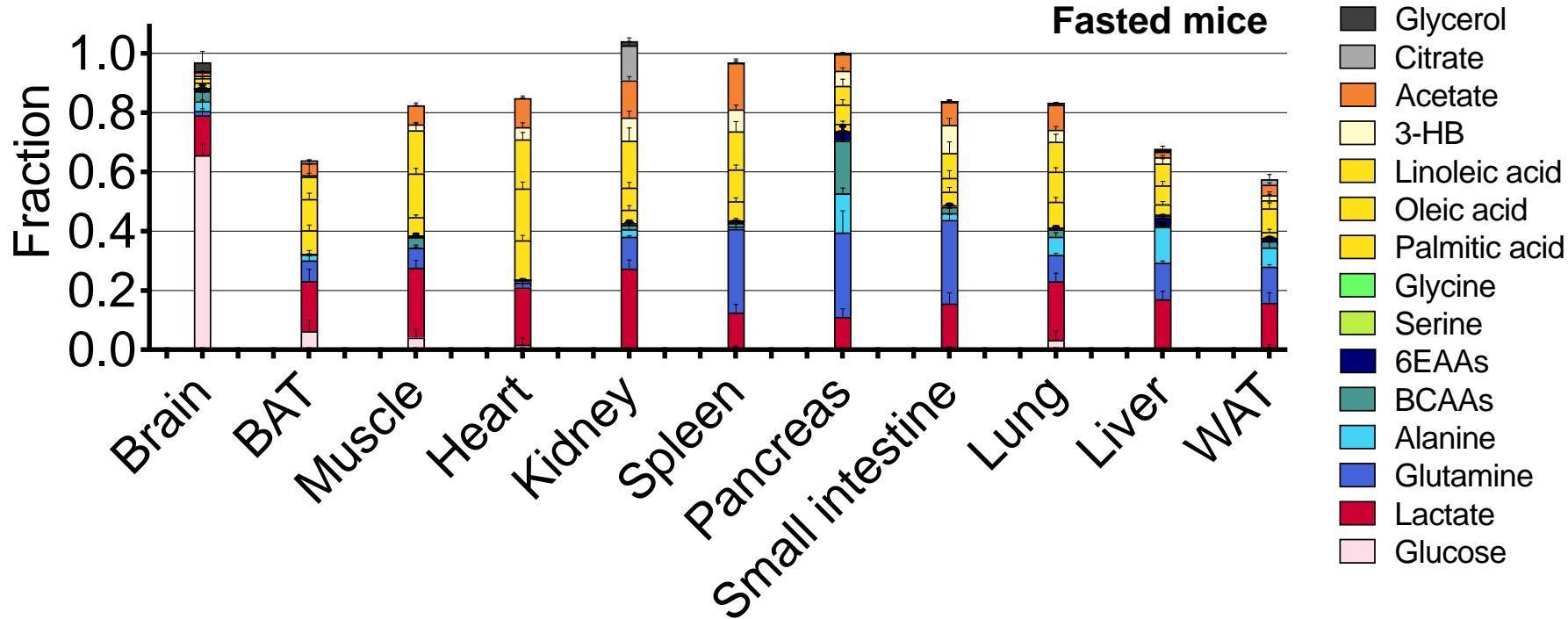
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- **BCAAs are a major fuel for pancreas.**

Direct contributions to the tissue TCA



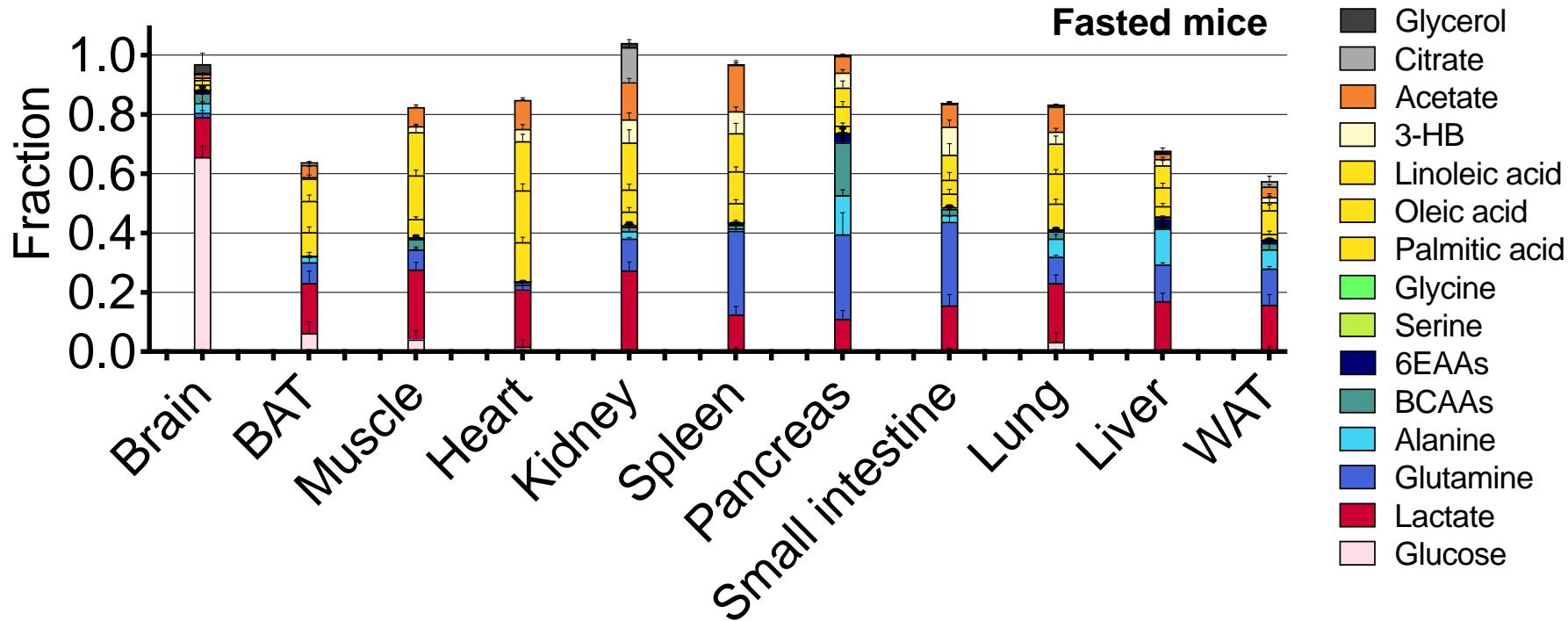
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- **Acetate is widely used by tissues.**

Direct contributions to the tissue TCA



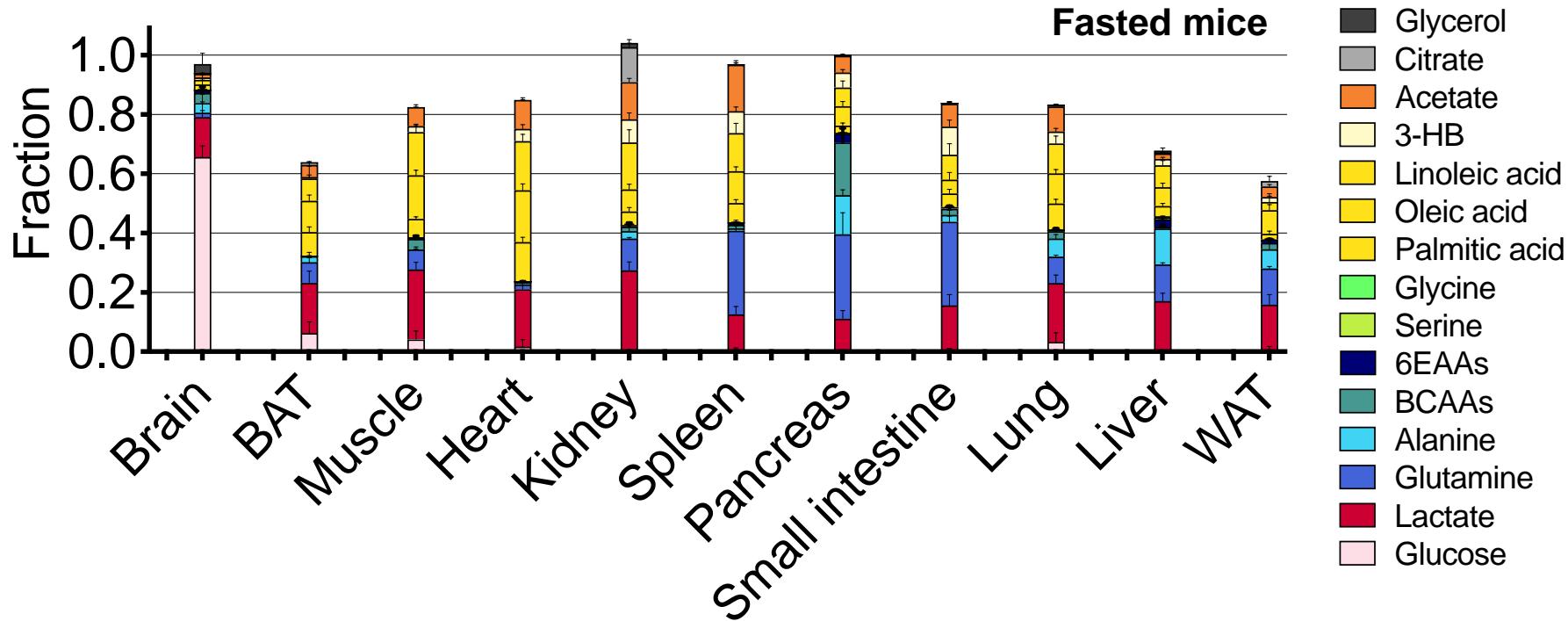
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Direct contributions to the tissue TCA



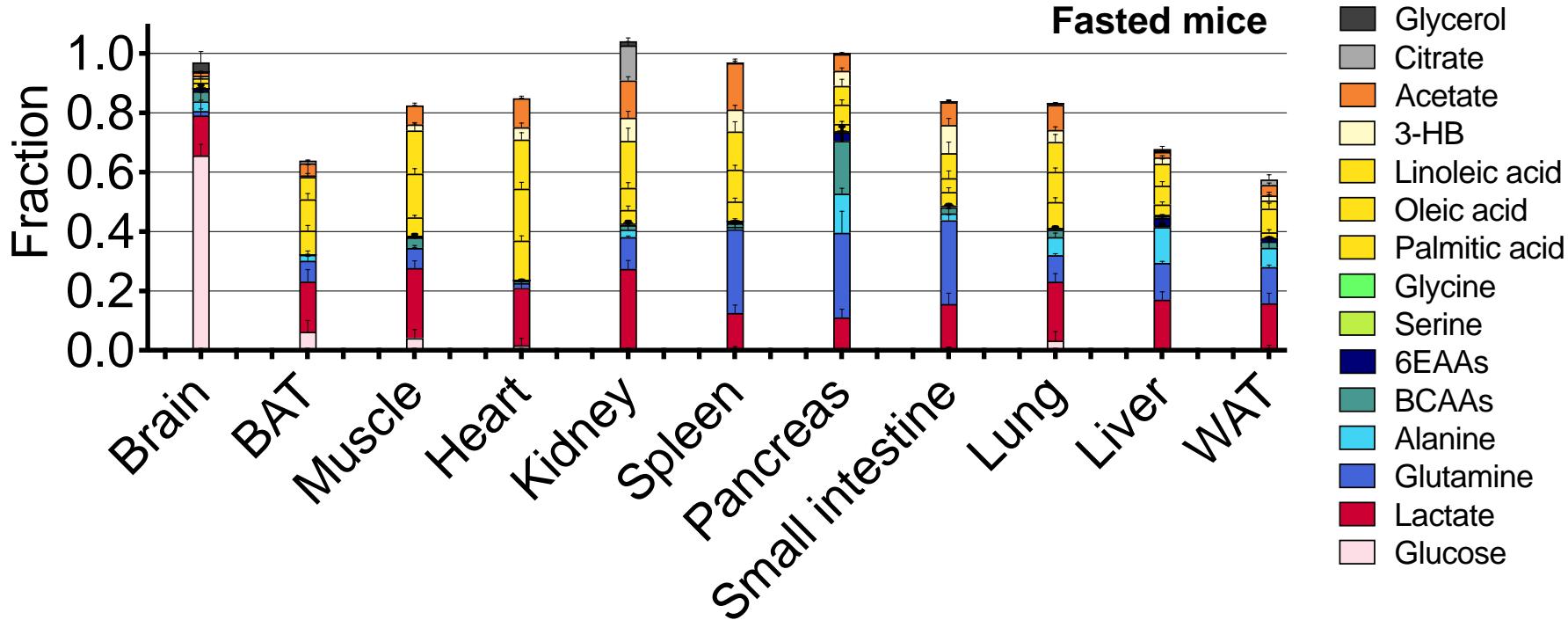
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- **Glycerol is not a TCA substrate.**

Direct contributions to the tissue TCA



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- **Glutamine is a major fuel for visceral tissues.**
- **BCAAs are a major fuel for pancreas.**
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- **Glycerol is not a TCA substrate.**
- **Heart does not burn amino acids.**

Direct contributions to the tissue TCA

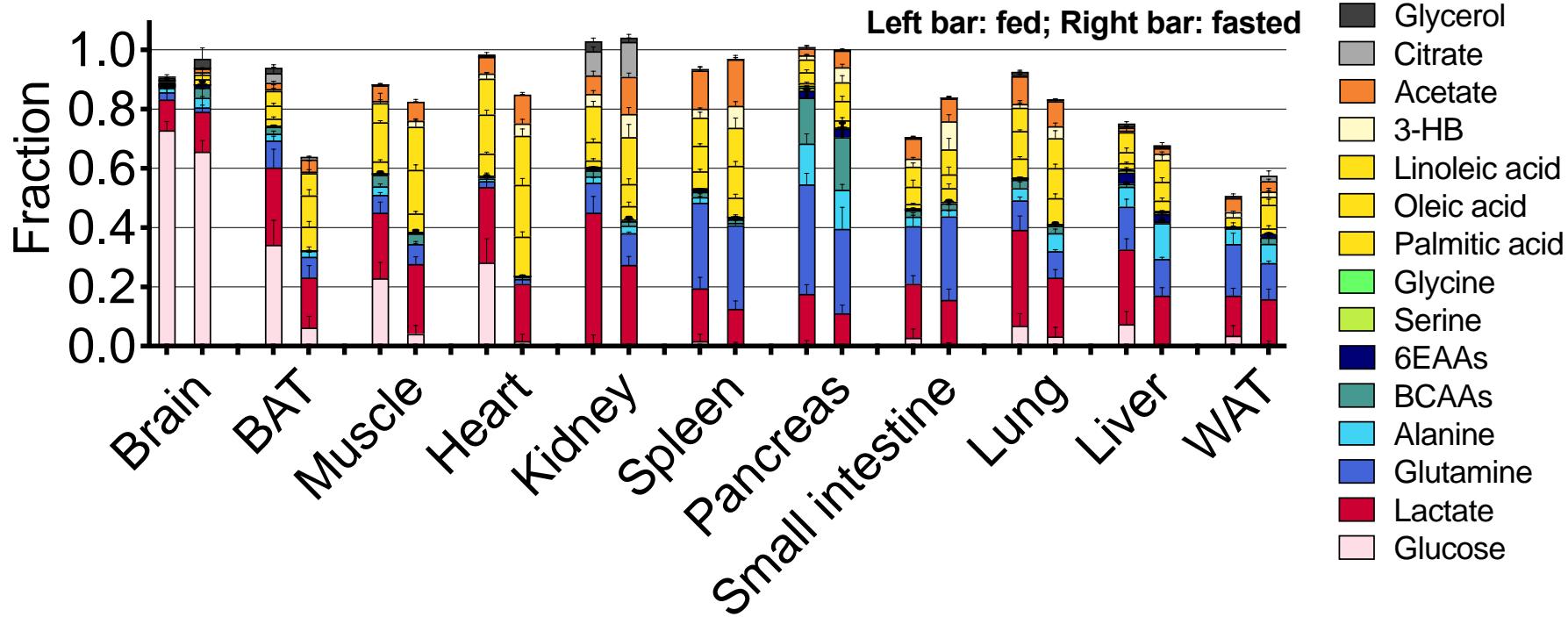


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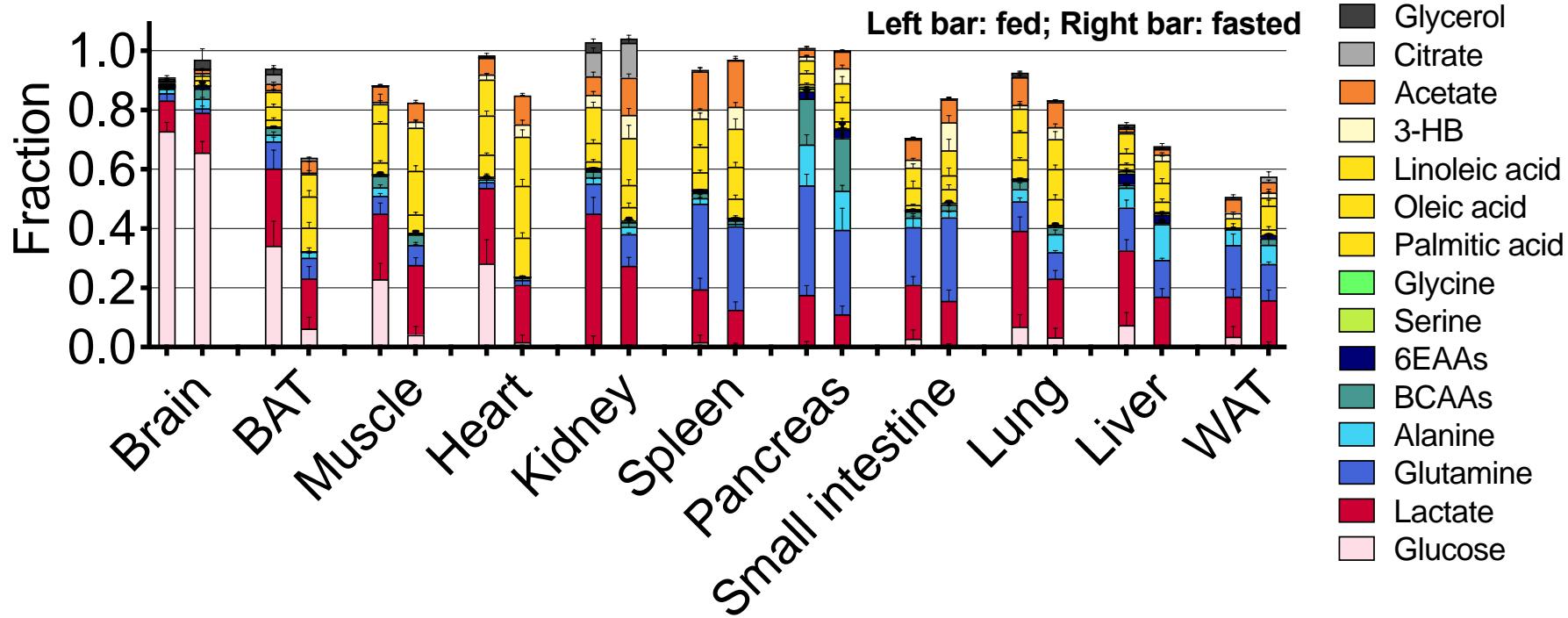
Take-home messages so far

- 1. Glucose feeds the TCA cycle via circulating lactate.**

Direct contributions to the tissue TCA

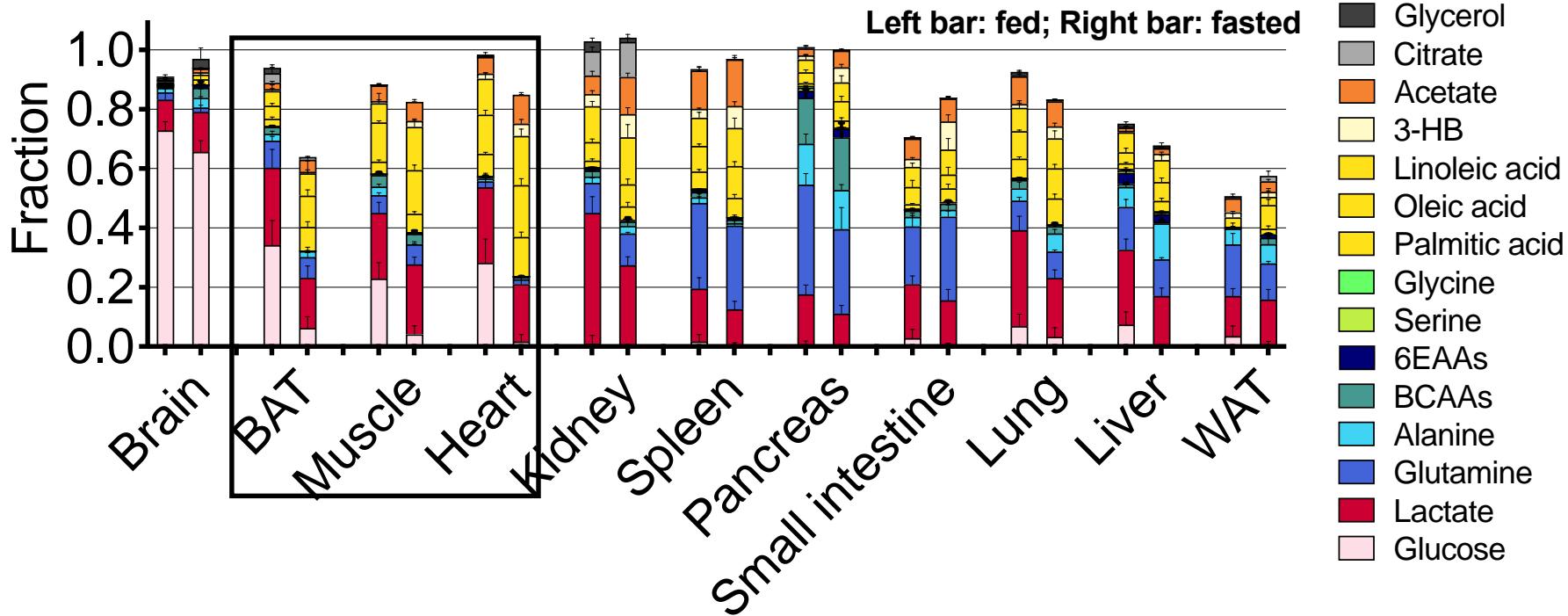


Direct contributions to the tissue TCA



- Fuel preferences are mostly maintained in most tissues.

Direct contributions to the tissue TCA

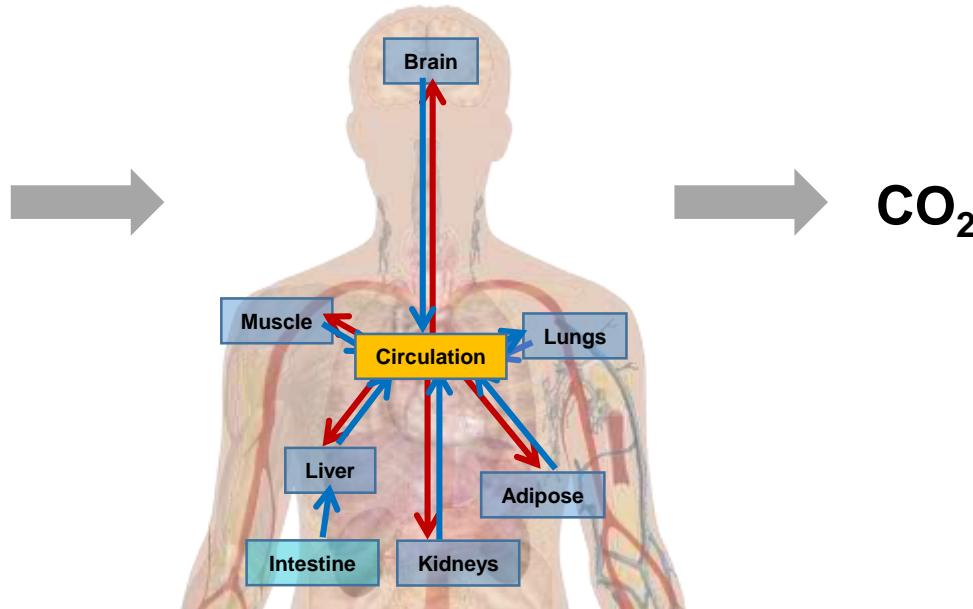


- Fuel preferences are mostly maintained in most tissues.
- Muscle, heart, and BAT are most responsive to the fed/fasting cycle.

Take-home messages so far

1. Glucose feeds the TCA cycle via circulating lactate.
2. Only muscle and brown adipose tissues adjust their fuel preferences in response to fasting/fed cycle.

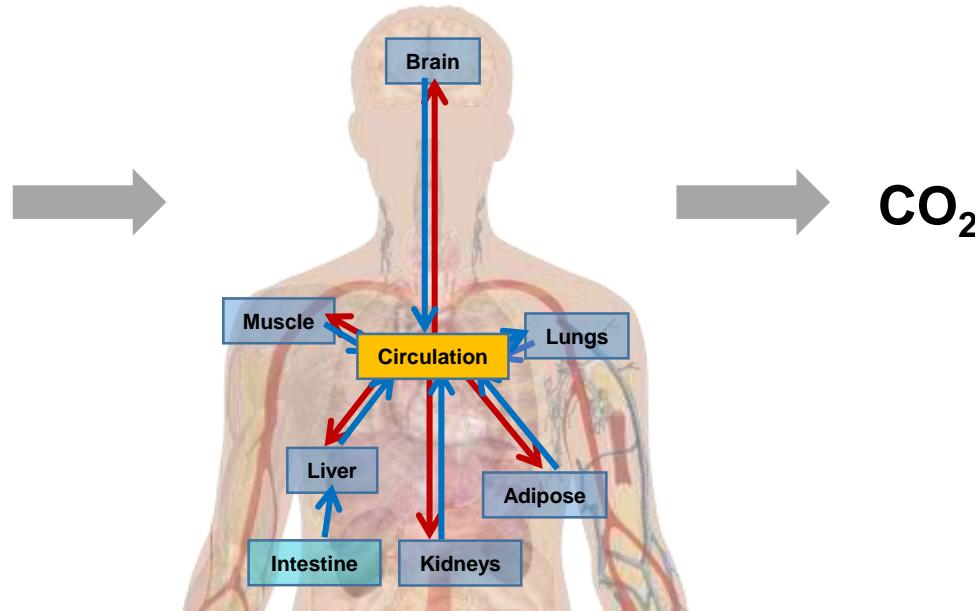
Organs/tissues are fueled by *circulating metabolites*



What are the important circulating metabolites?

How do they contribute as fuels to different tissues?

Organs/tissues are fueled by *circulating metabolites*

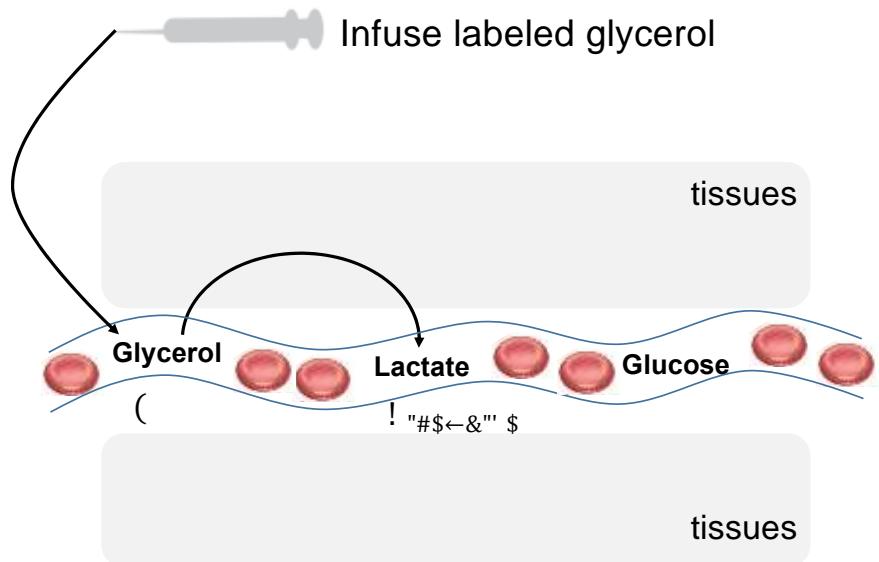


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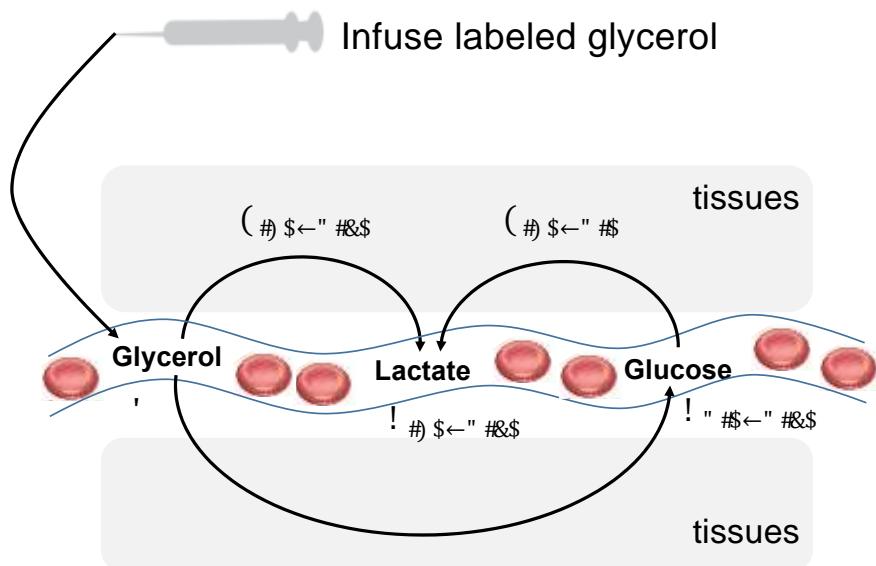
How do they contribute as fuels to different tissues?

How do they inter-convert with each other?

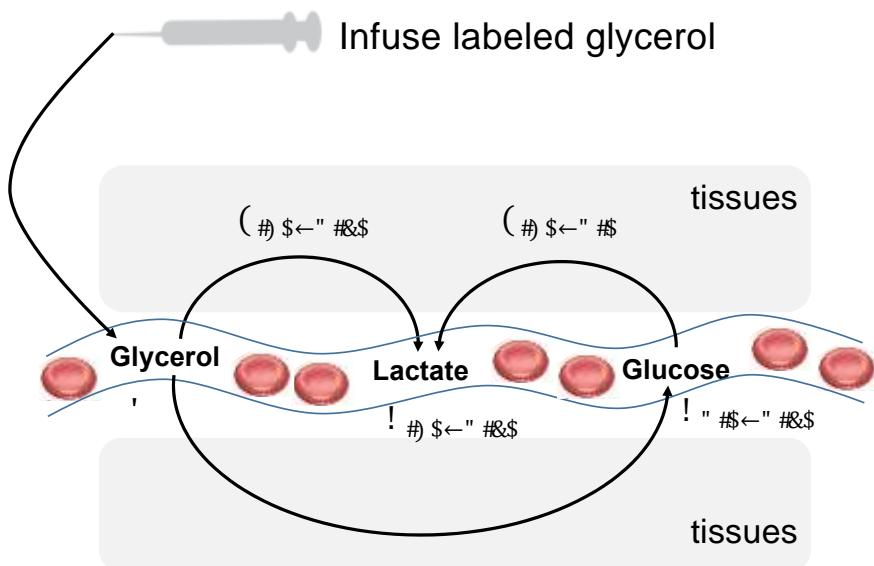
Contribution from one circulating metabolite to another



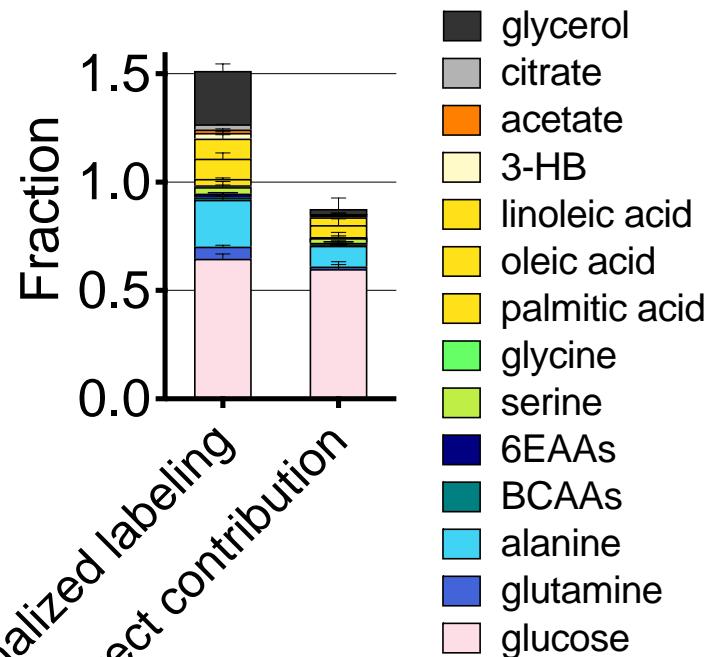
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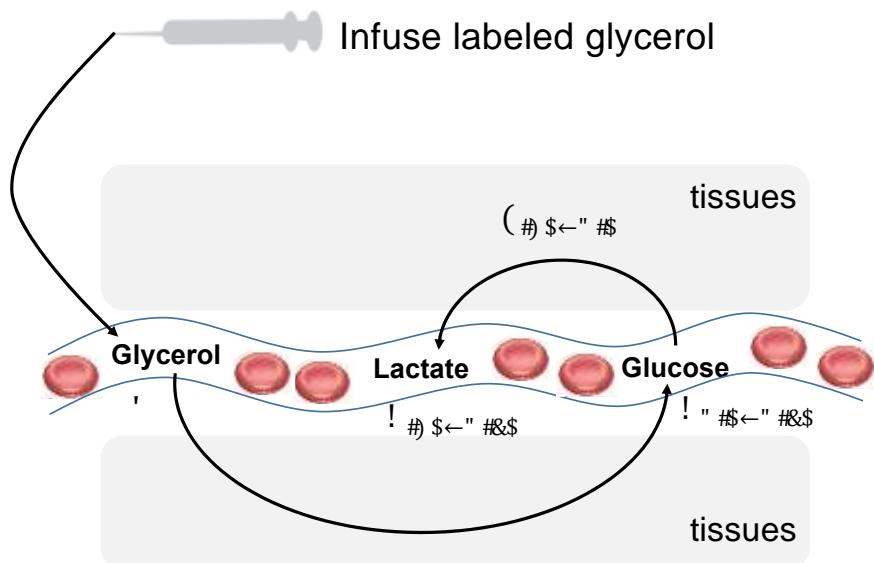
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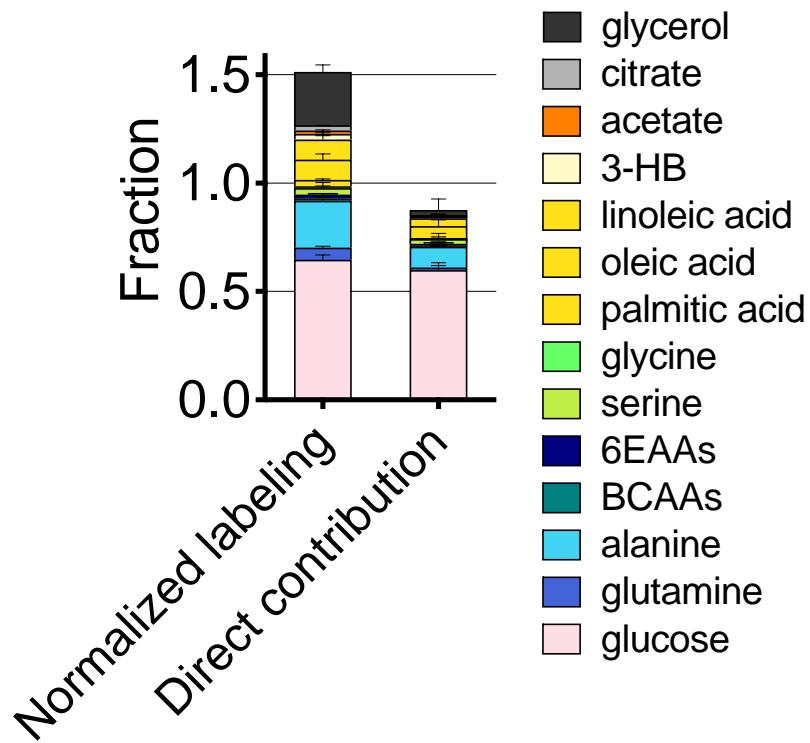
Sources of circulating lactate



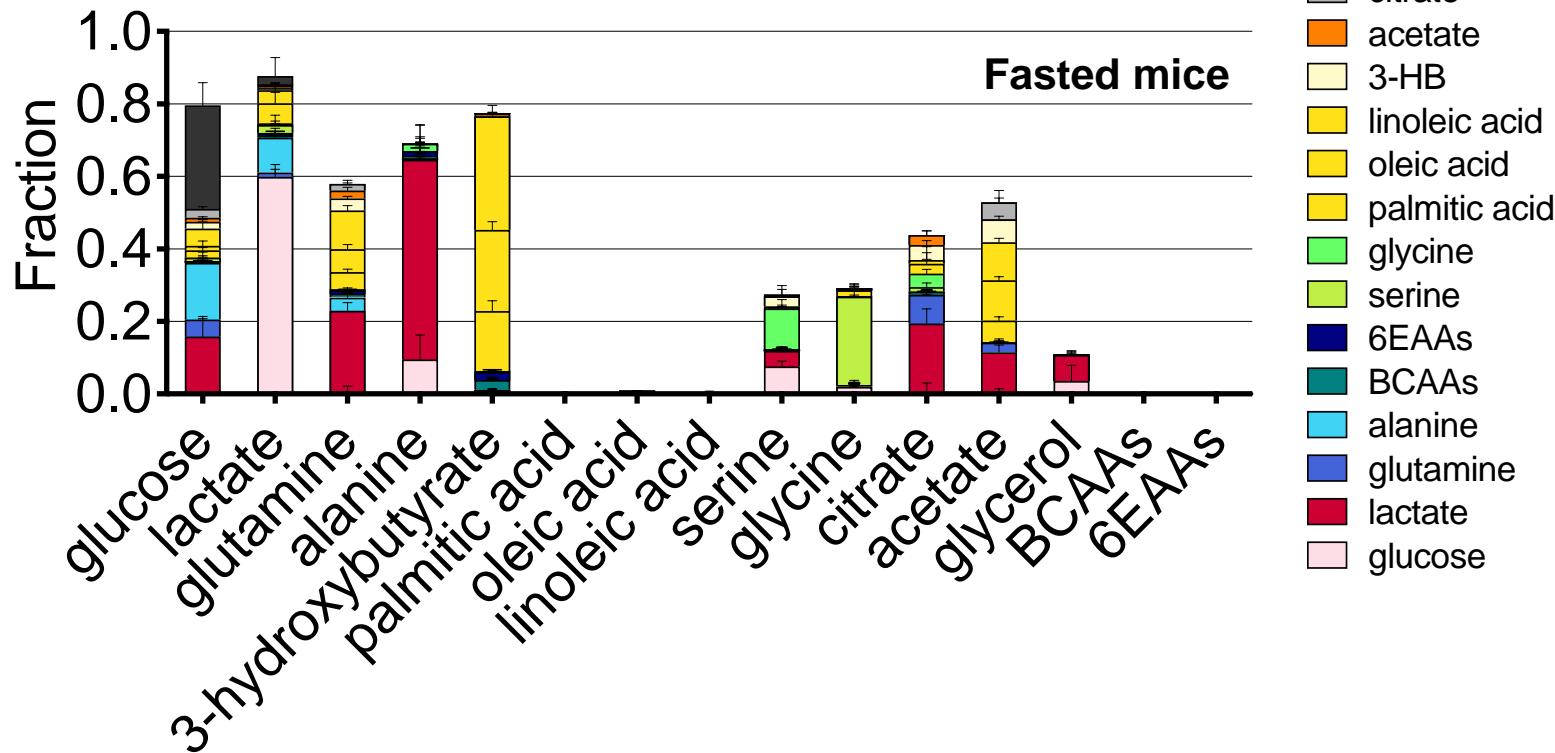
Contribution from one circulating metabolite to another



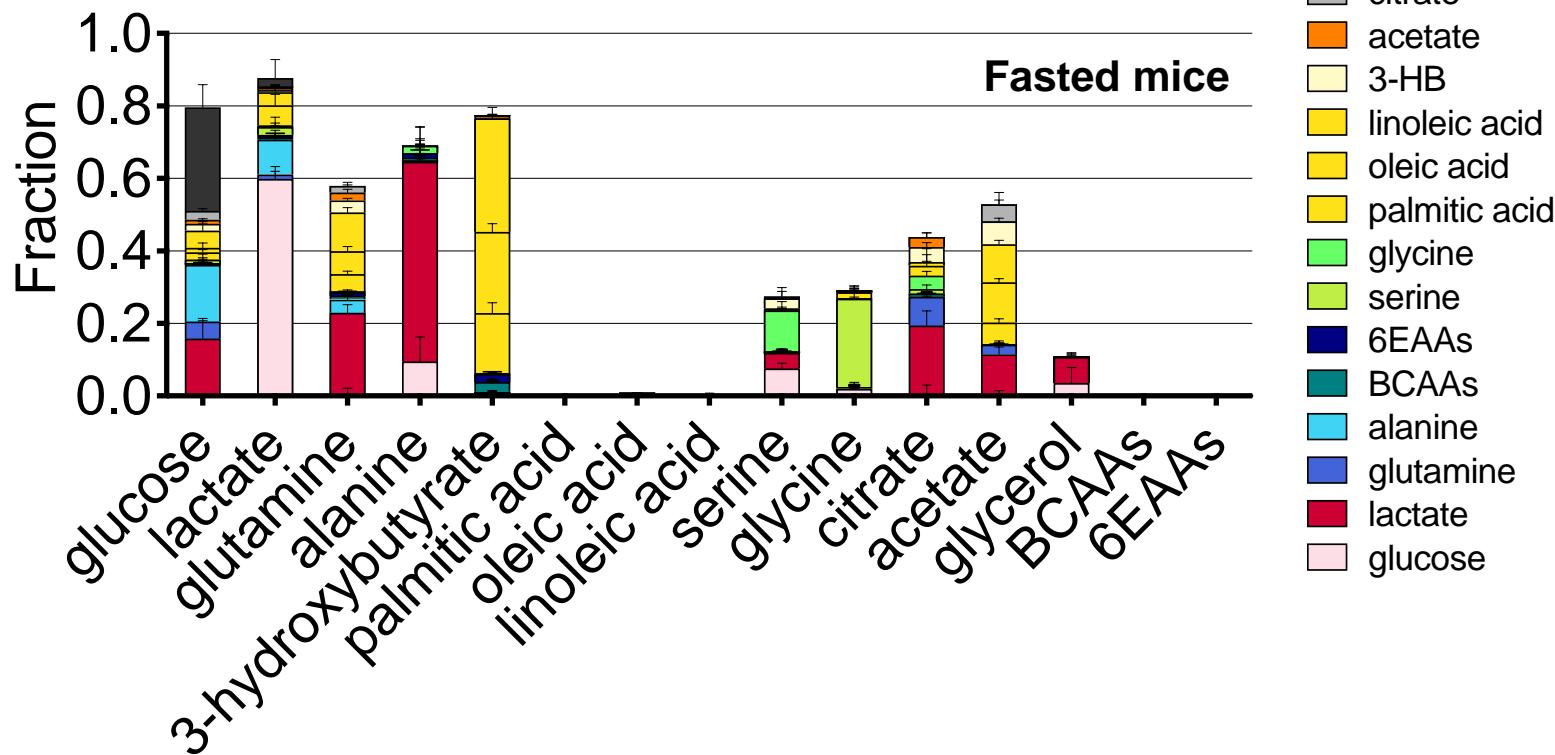
Sources of circulating lactate



Direct contribution to circulating nutrients

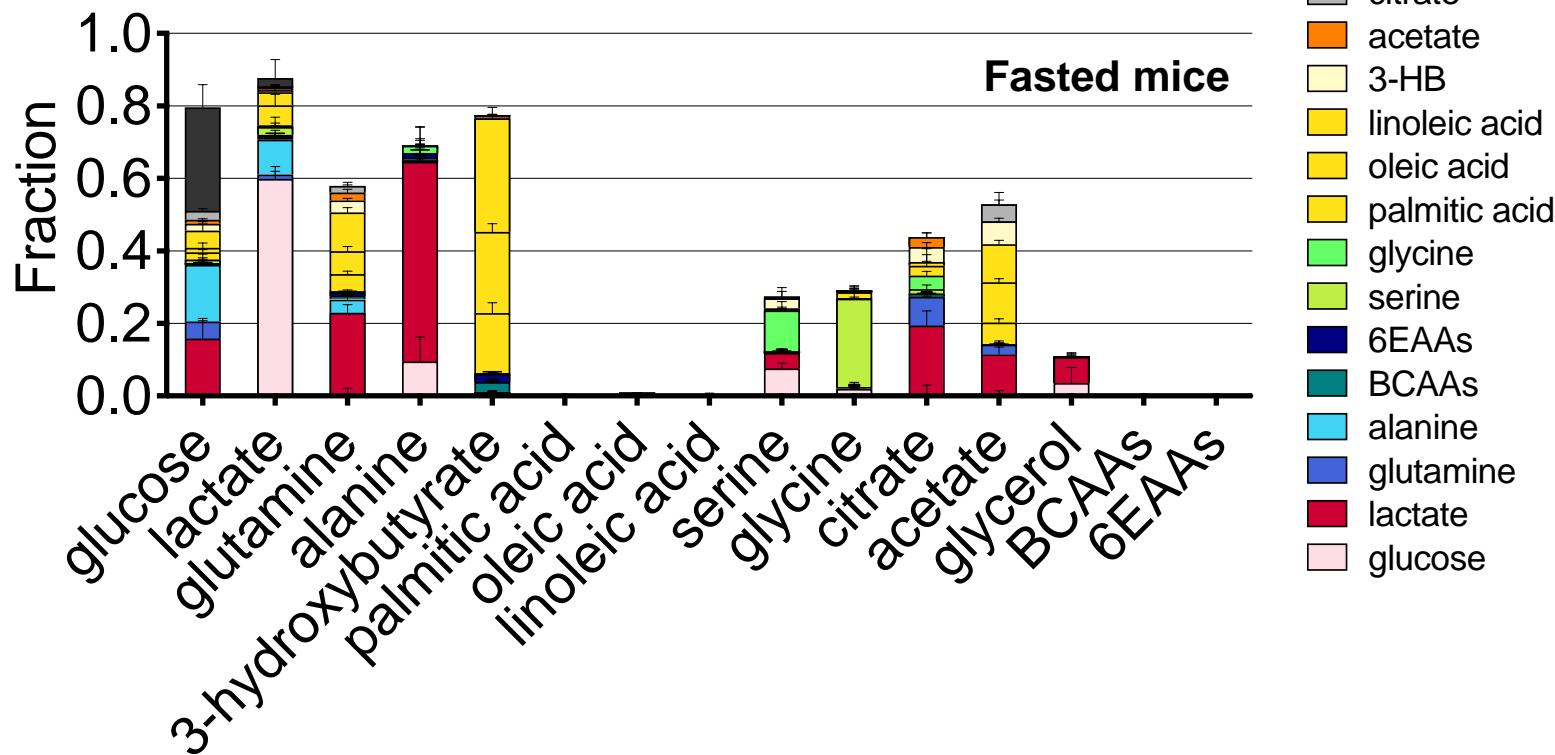


Direct contribution to circulating nutrients



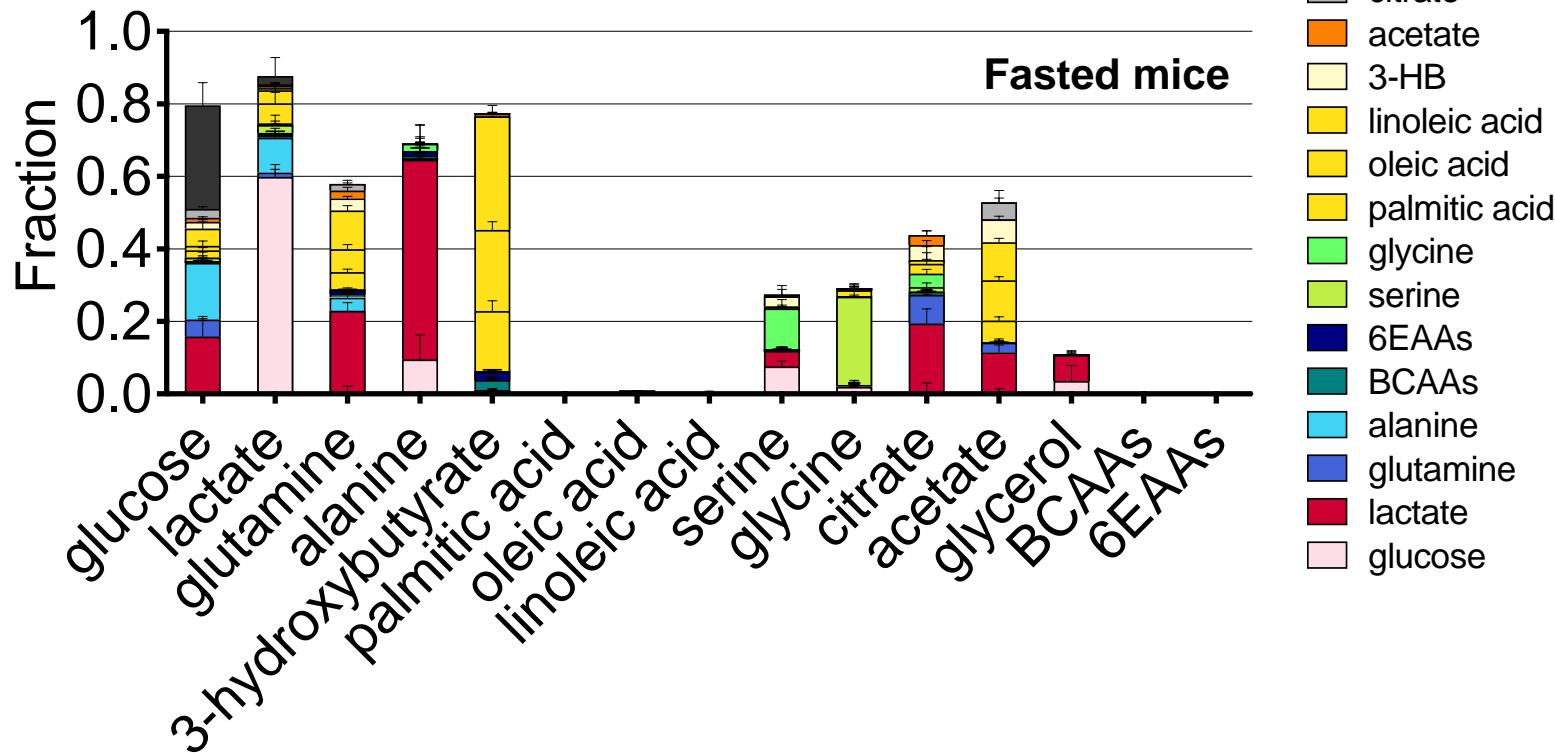
- No free palmitic acid is directly from *de novo* lipogenesis.

Direct contribution to circulating nutrients



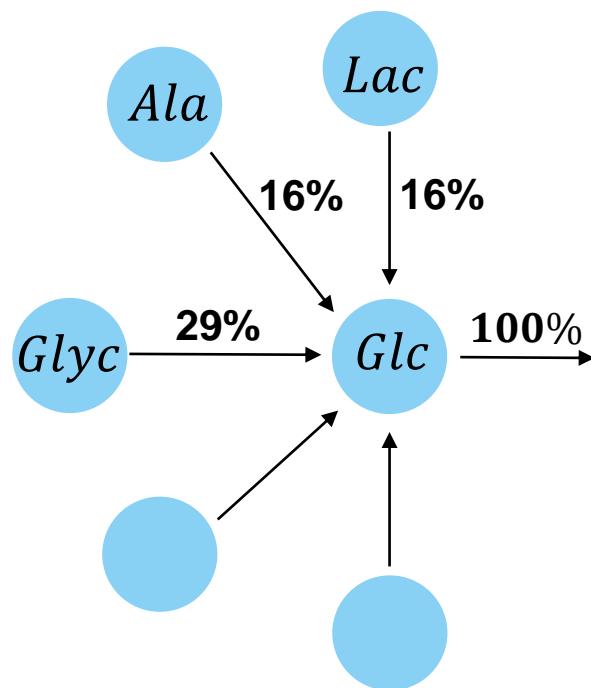
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Direct contribution to circulating nutrients



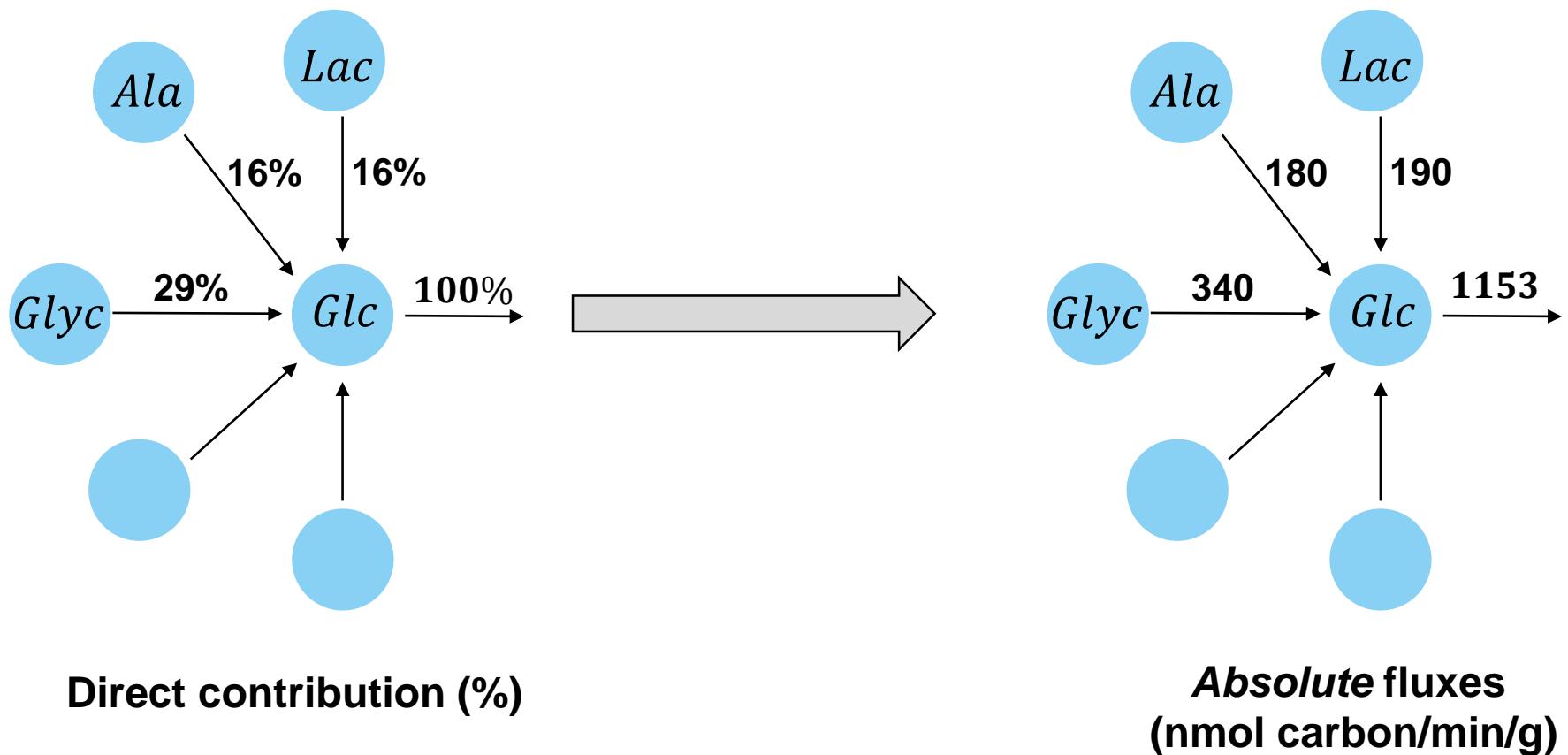
- No free palmitic acid is directly from *de novo* lipogenesis.
- Glycerol mostly comes from storage (adipose triglyceride)
- Fatty acids are a major source for acetate

Inter-converting fluxes between circulating metabolites

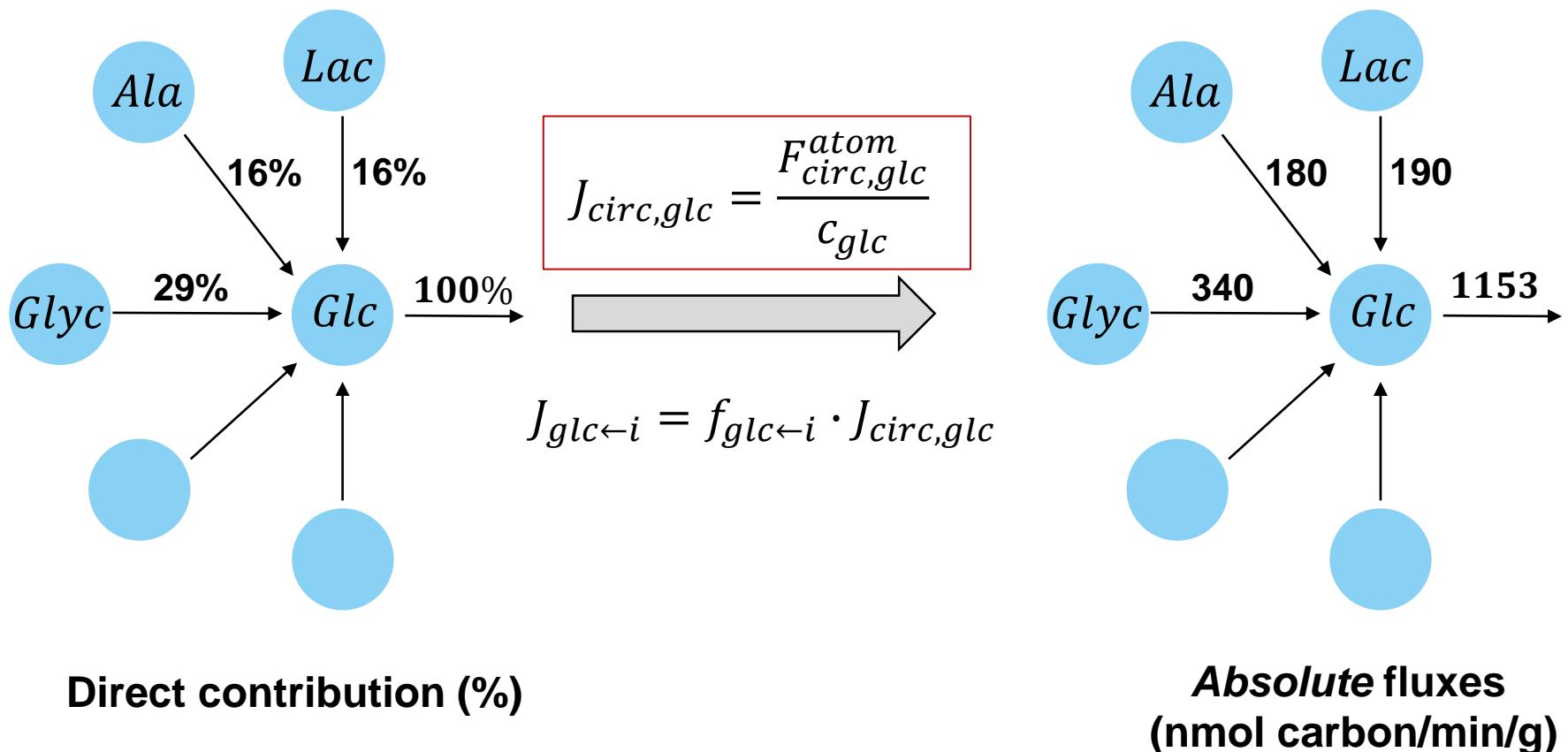


Direct contribution (%)

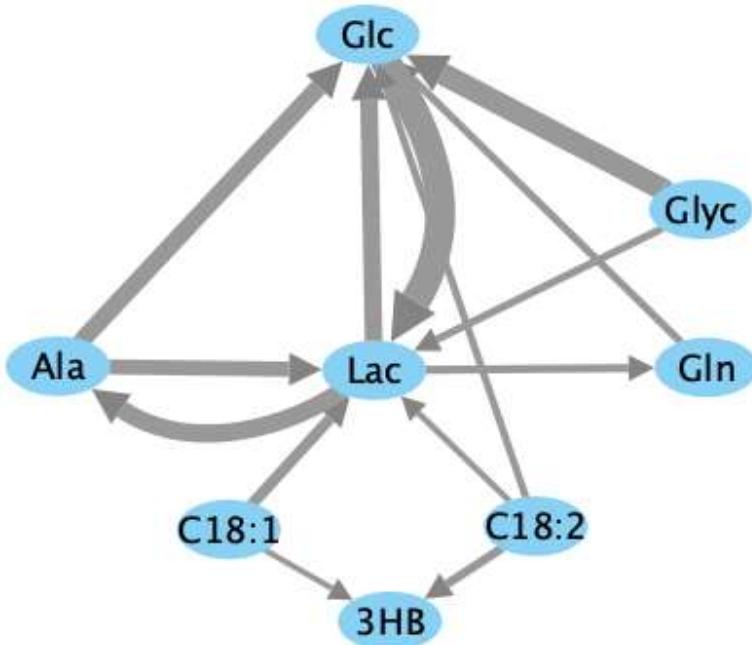
Inter-converting fluxes between circulating metabolites



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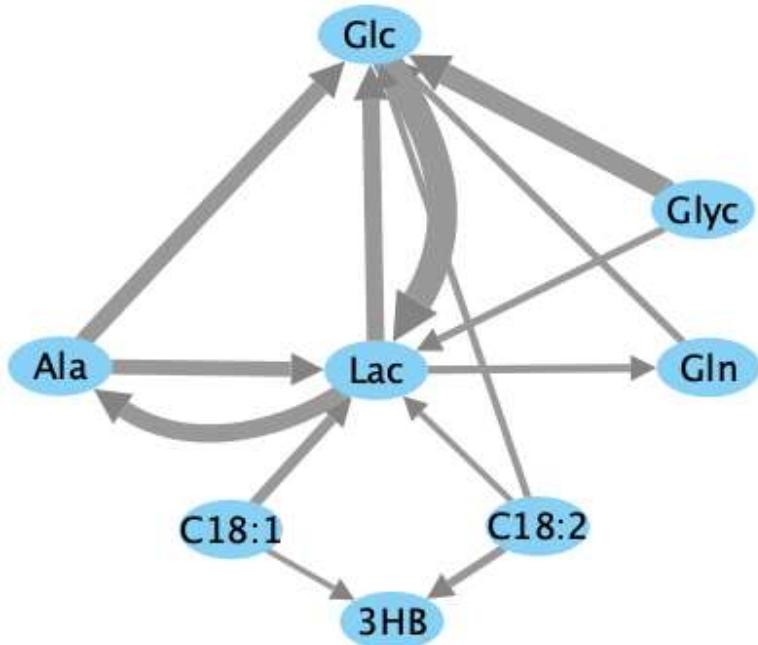


A flux network of circulating metabolites

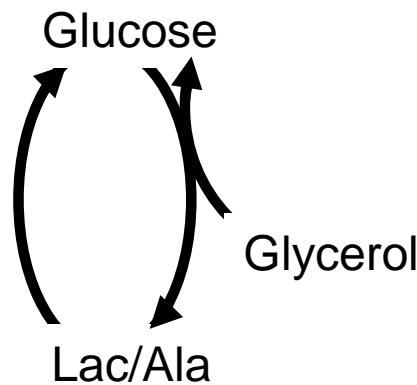


Fasted mice

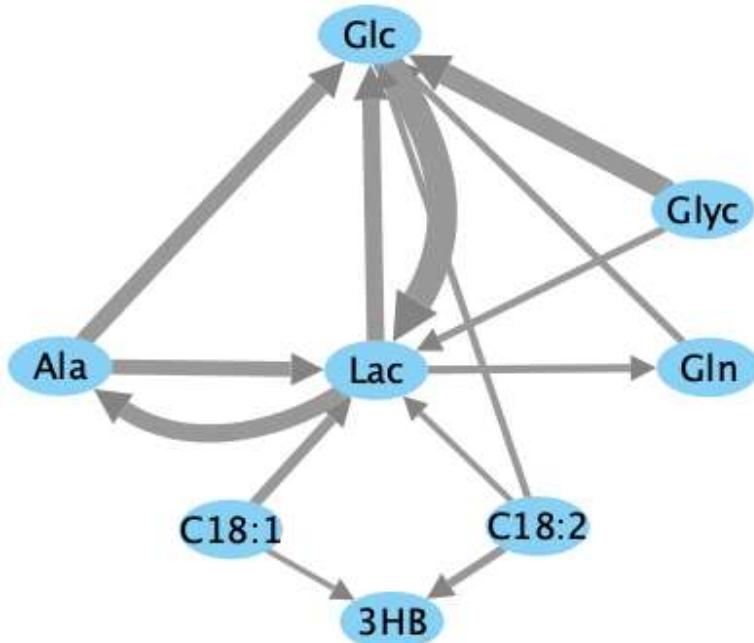
The major fluxes in the body



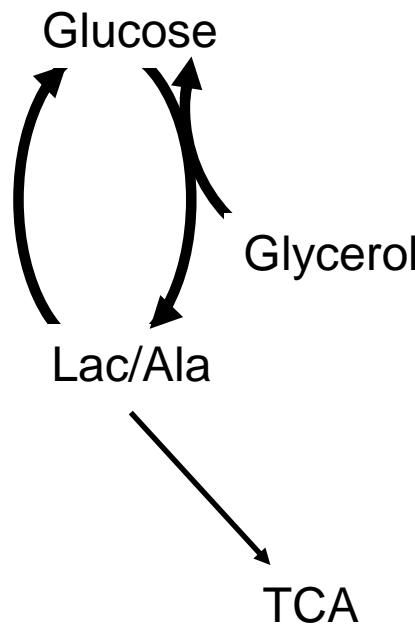
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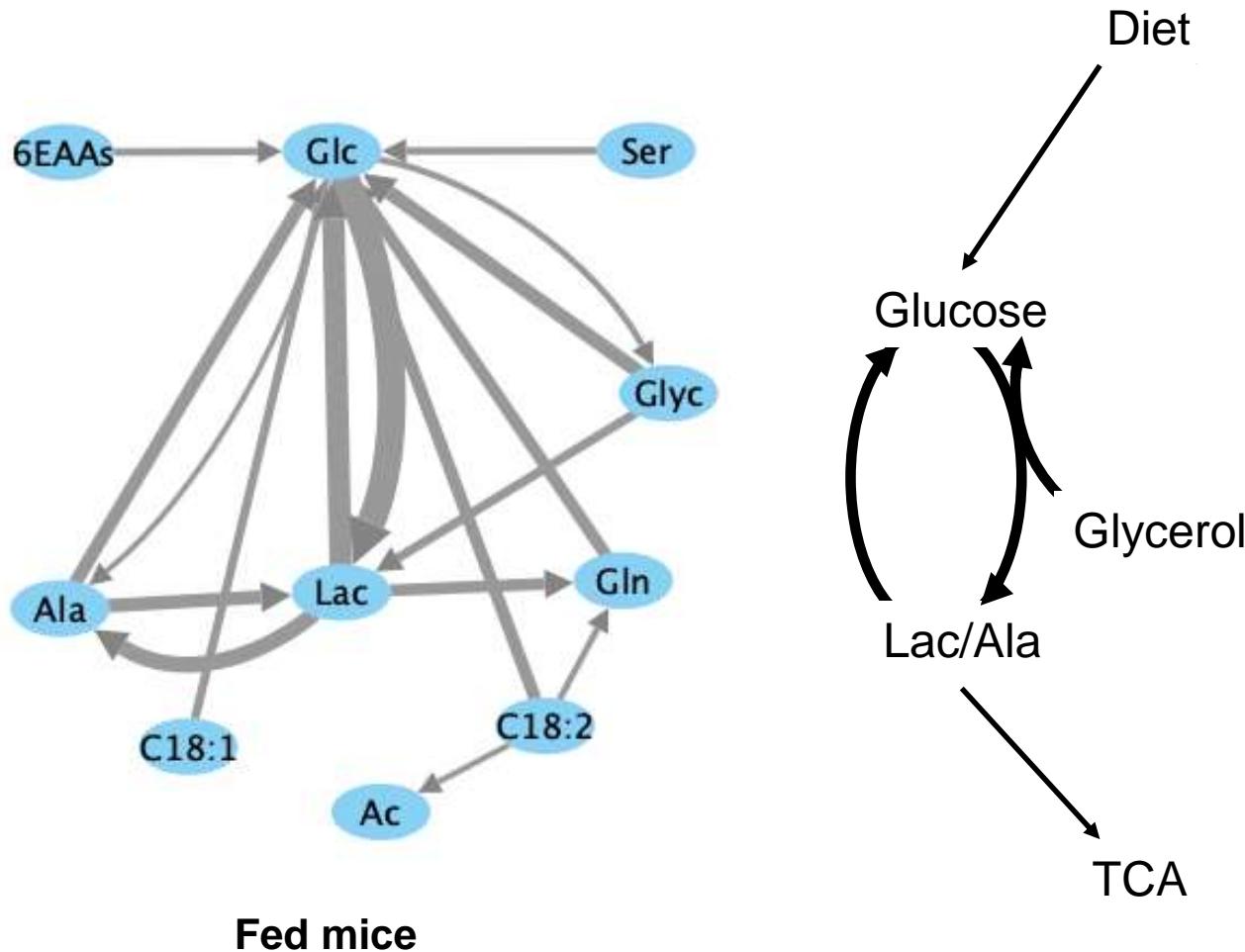
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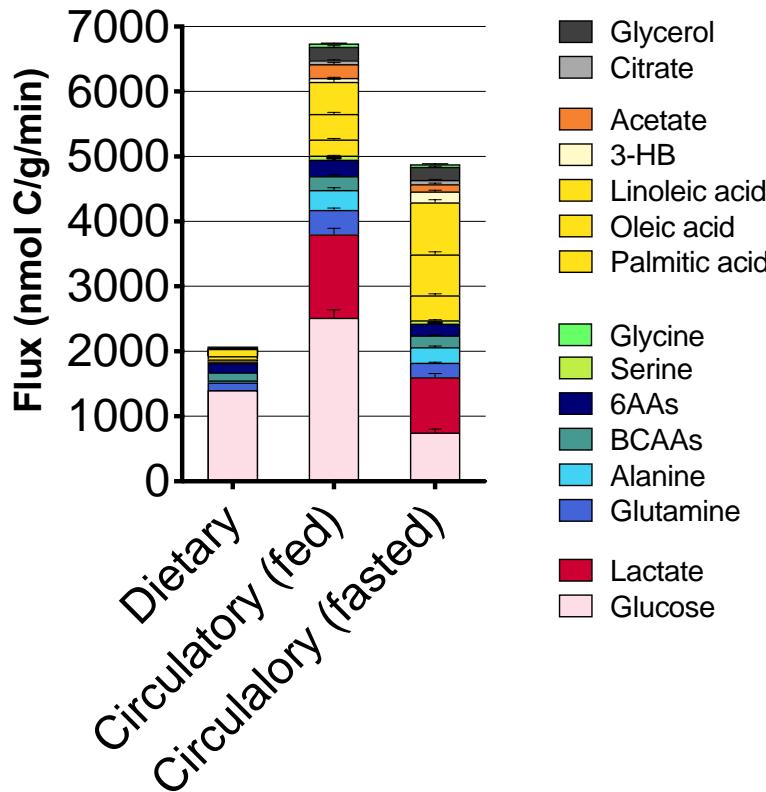
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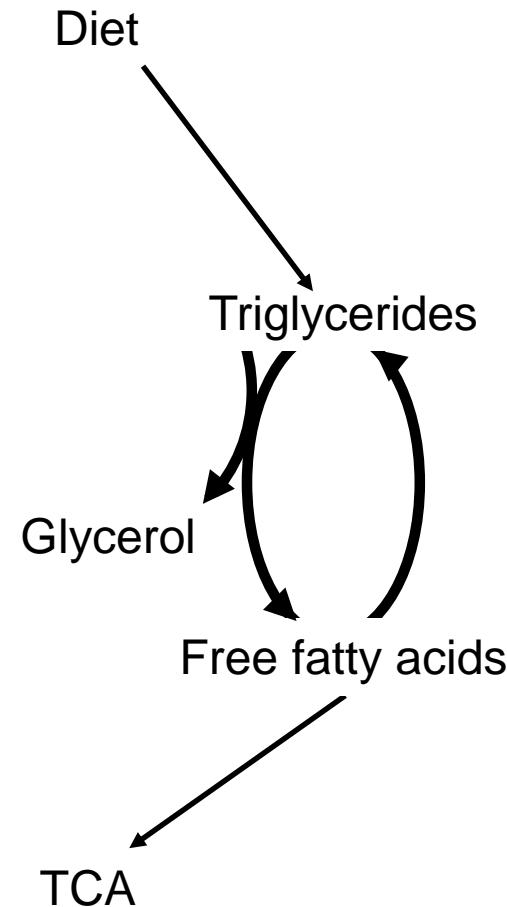
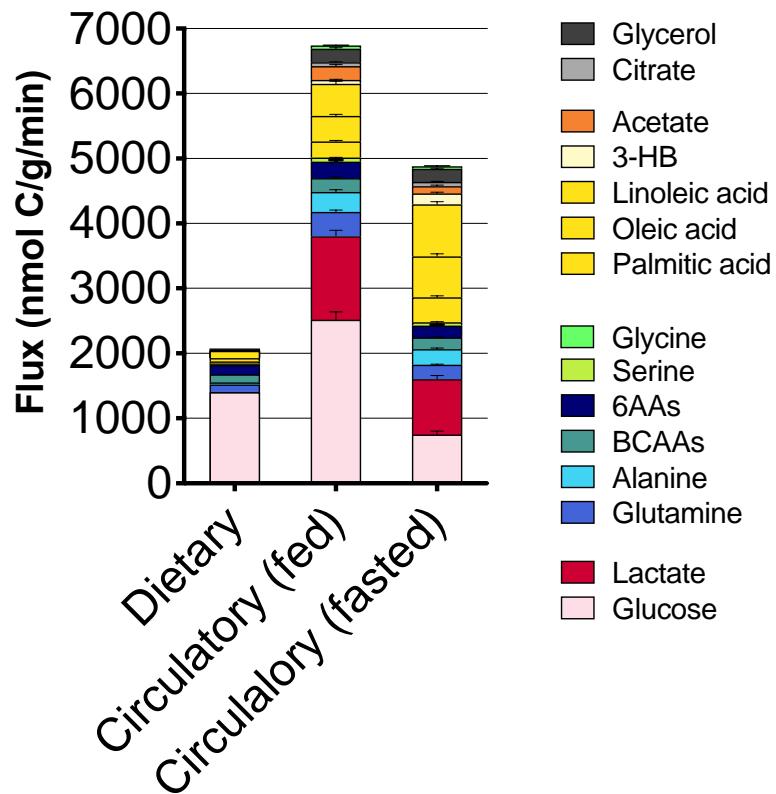
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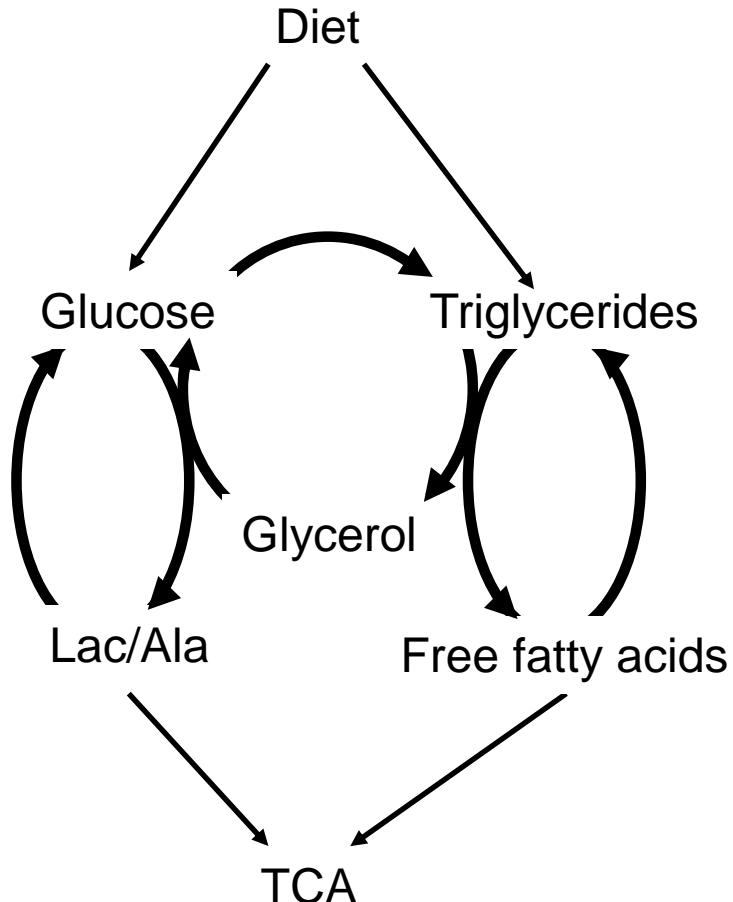
Another major cycle: the triglyceride – fatty acid cycle



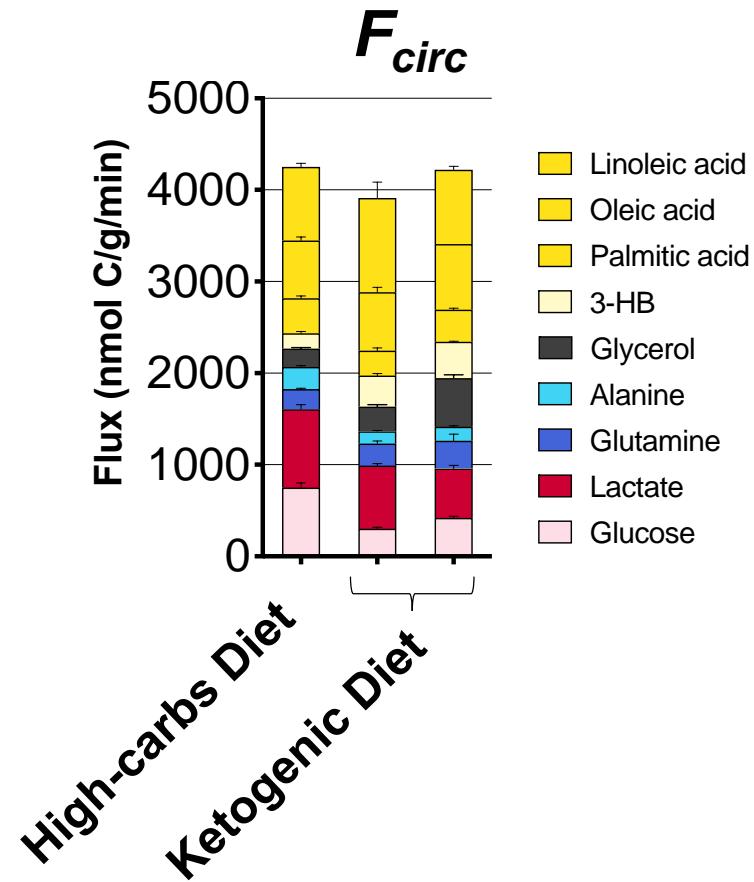
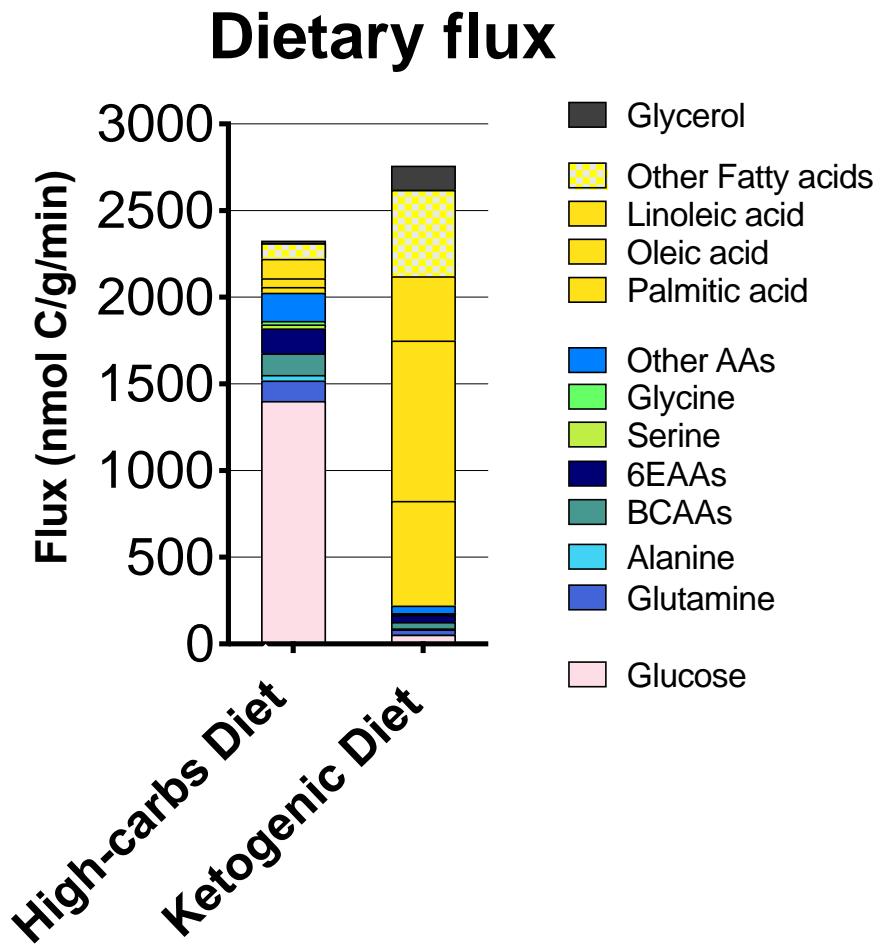
Another major cycle: the triglyceride – fatty acid cycle



The major fluxes in the body are two connected metabolic cycles



The cycling persists in ketogenic diet

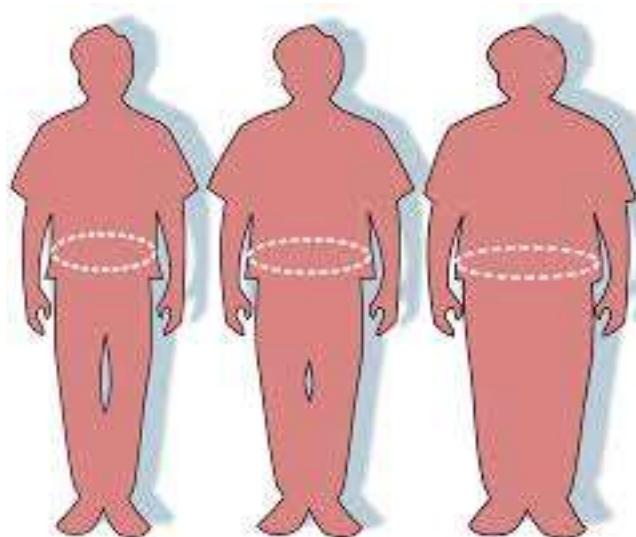


Take-home messages so far

1. Glucose feeds the TCA cycle via circulating lactate.
2. Only muscle and brown adipose tissues adjust their fuel preferences in response to fasting/fed cycle.
3. **Metabolic cycling helps render internal metabolic activity robust to food choice.**



Research goal: understand *the regulation of body weight*



**Does the microbiome in obesity
contribute more energy to the host?**

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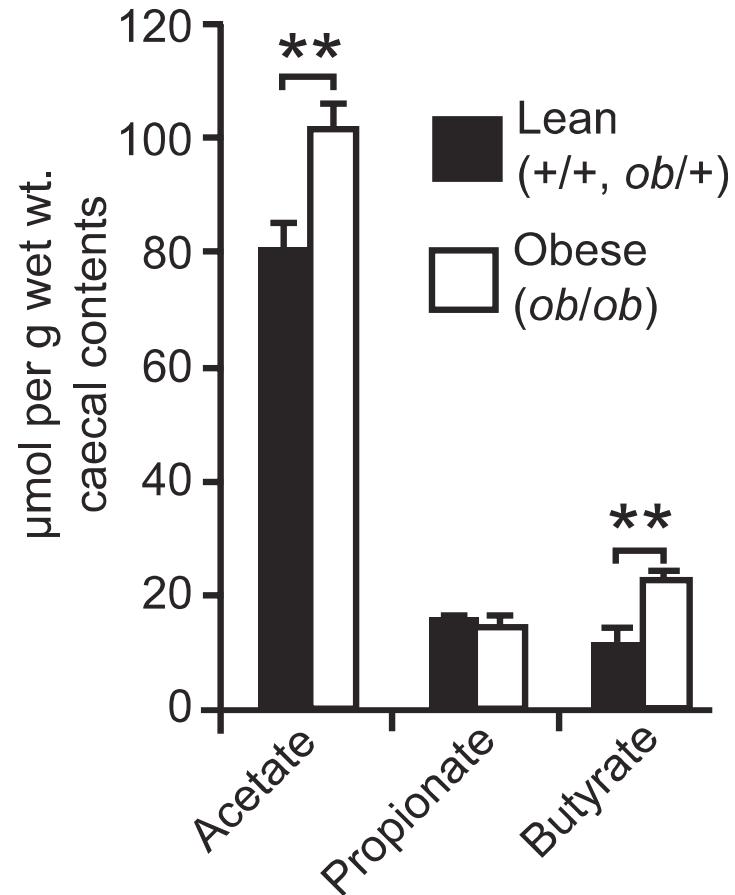
Vol 444 | 21/28 December 2006 | doi:10.1038/nature05414

nature

ARTICLES

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Peter J. Turnbaugh¹, Ruth E. Ley¹, Michael A. Mahowald¹, Vincent Magrini², Elaine R. Mardis^{1,2} & Jeffrey I. Gordon¹



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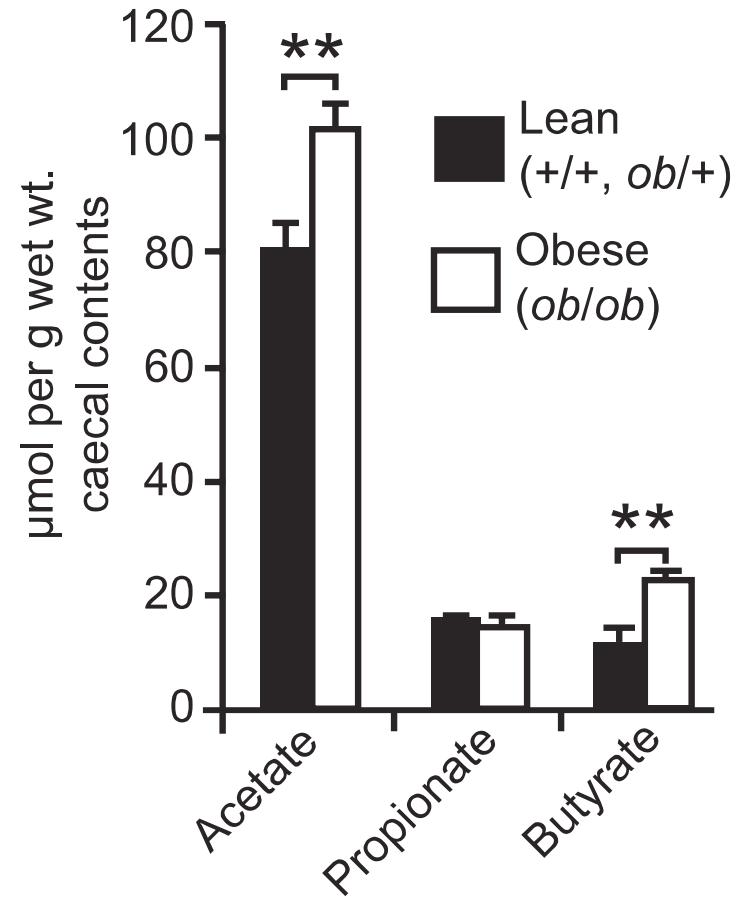
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Higher concentration does not necessarily mean higher flux!



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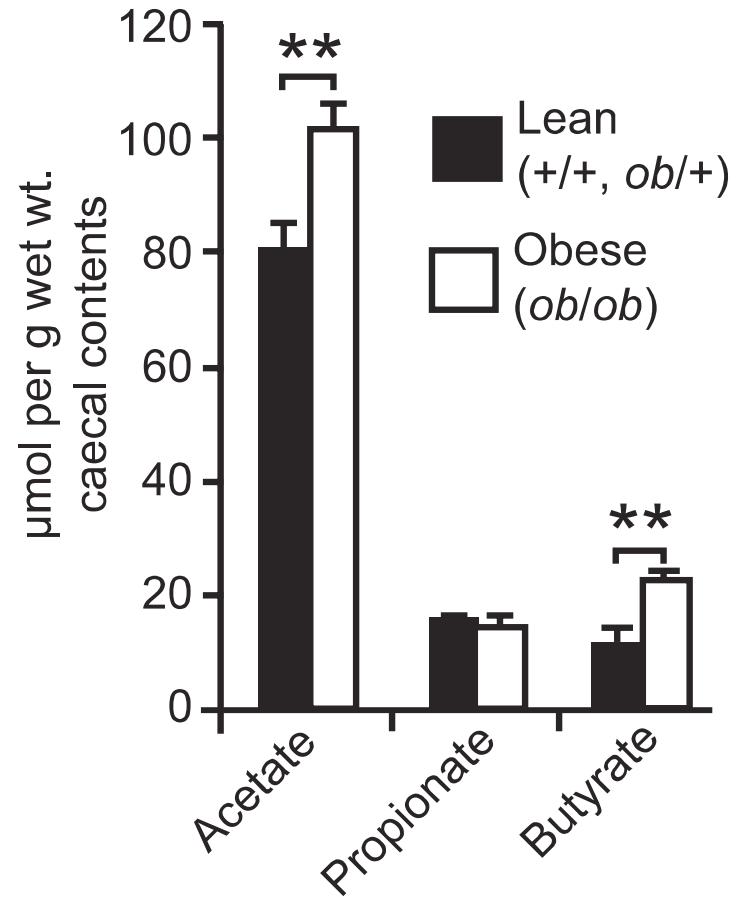
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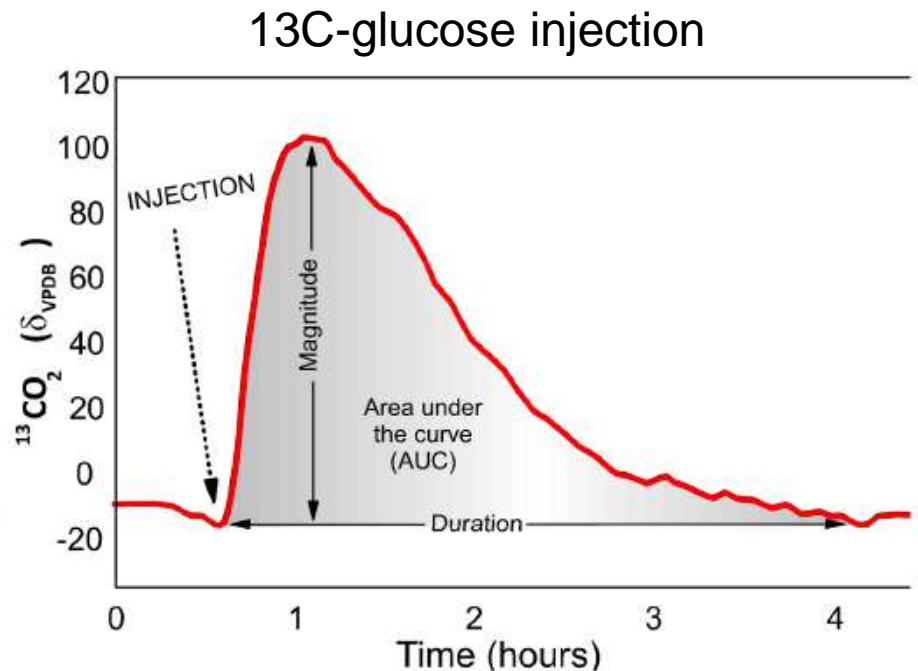
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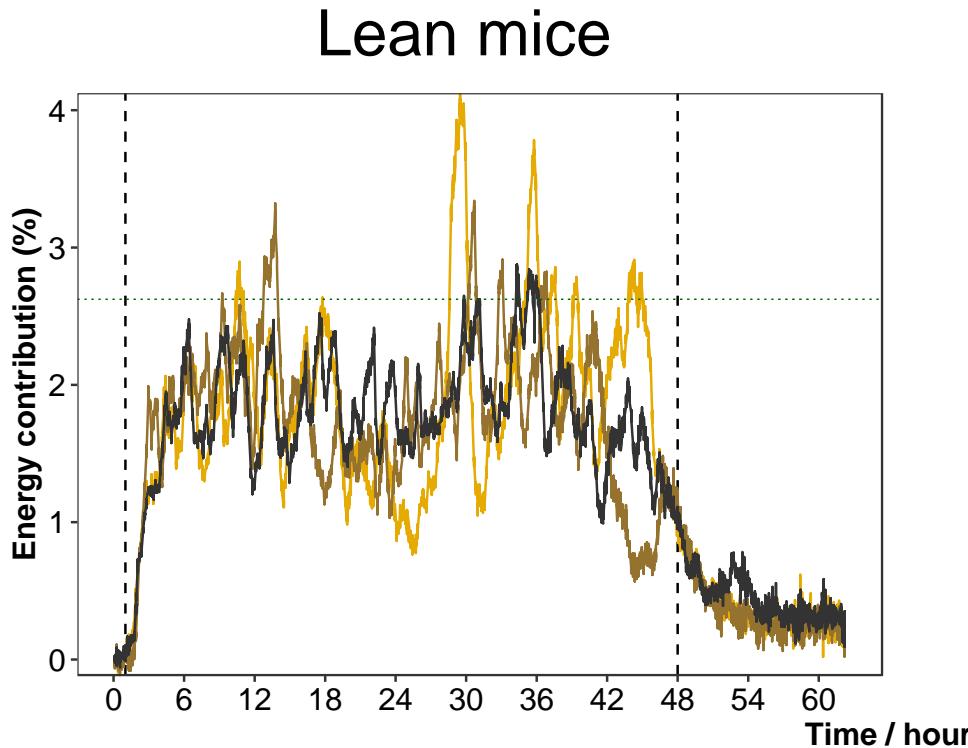


Stable isotope gas analyzer



<https://www.sablesys.com/products/promethion-line/stable-isotope-gas-analyzer/>

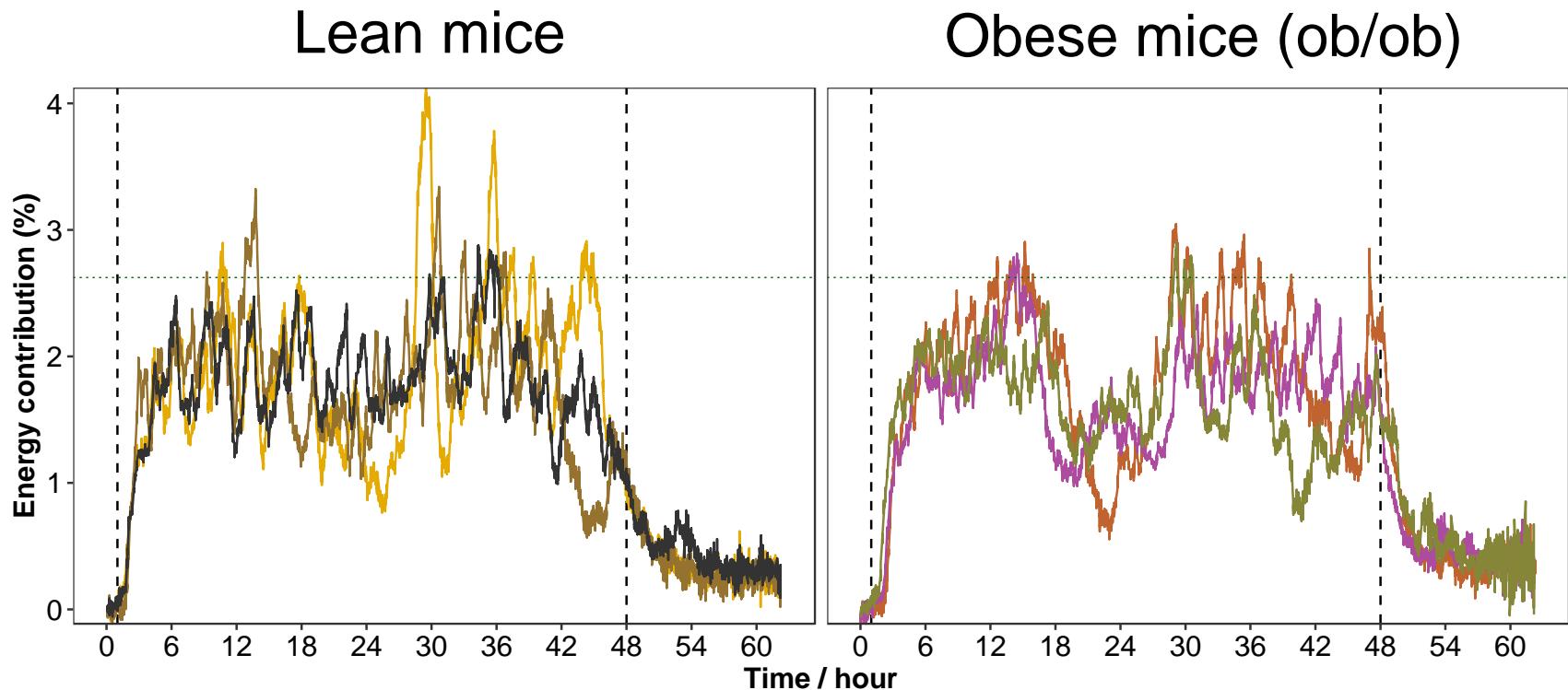
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Experiment:

Feed mice with ^{13}C labeled inulin, and measure the fraction of ^{13}C labeled CO_2 .

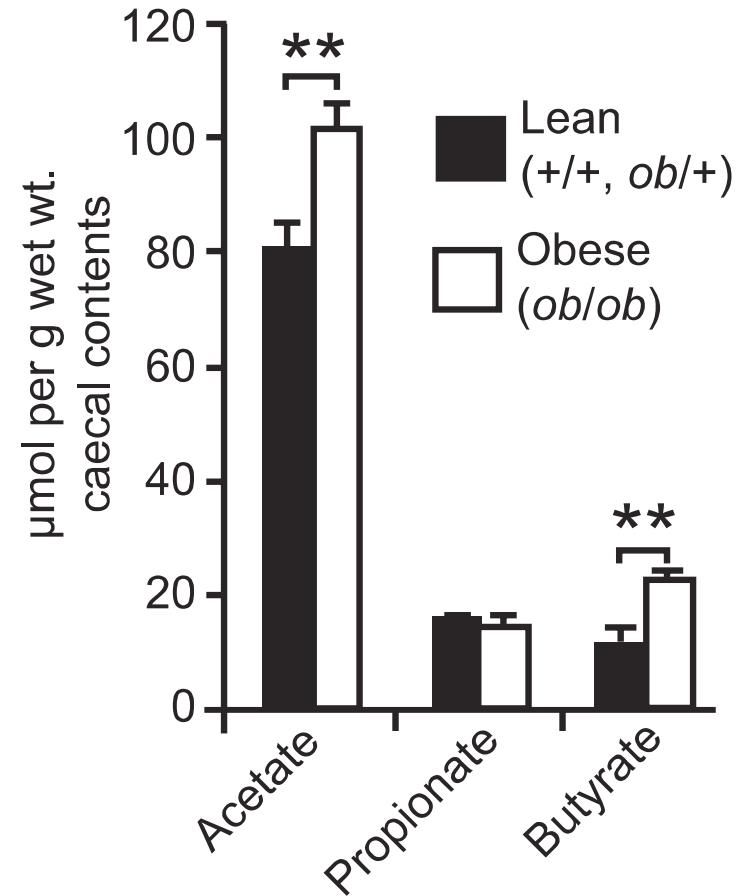
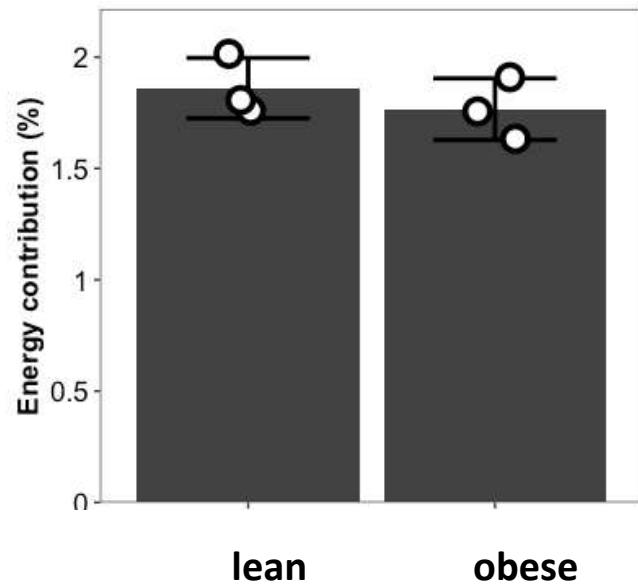
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No, the microbiome in obesity is NOT better at energy harvesting.

Turnbaugh et al. 2006

Acknowledgements

Hui lab

- Young Yon Kwon
- Bo Yuan
- Clement Rosique
- Nathan Heinzman



National Institute of
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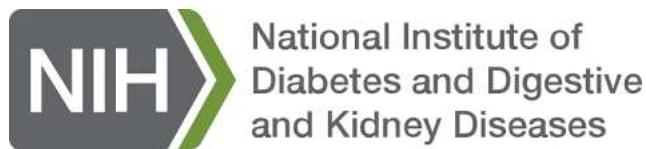
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