

GEROSCIENCE EDUCATION & TRAINING

Energy and Metabolism: Metabolic Flux and Protein Metabolism



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GEROSCIENCE EDUCATION & TRAINING

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Metabolic flux and protein metabolism

- The limits of snapshots when trying to understand a moving picture.

Learning Objectives

- To understand the concept of metabolic flux.
- To understand the limitations of snapshots compared to moving pictures.
- Describe one approach for measuring flux.
- To understand important factors in the flux (turnover) of protein.
- Understand how to target protein turnover to slow aging.

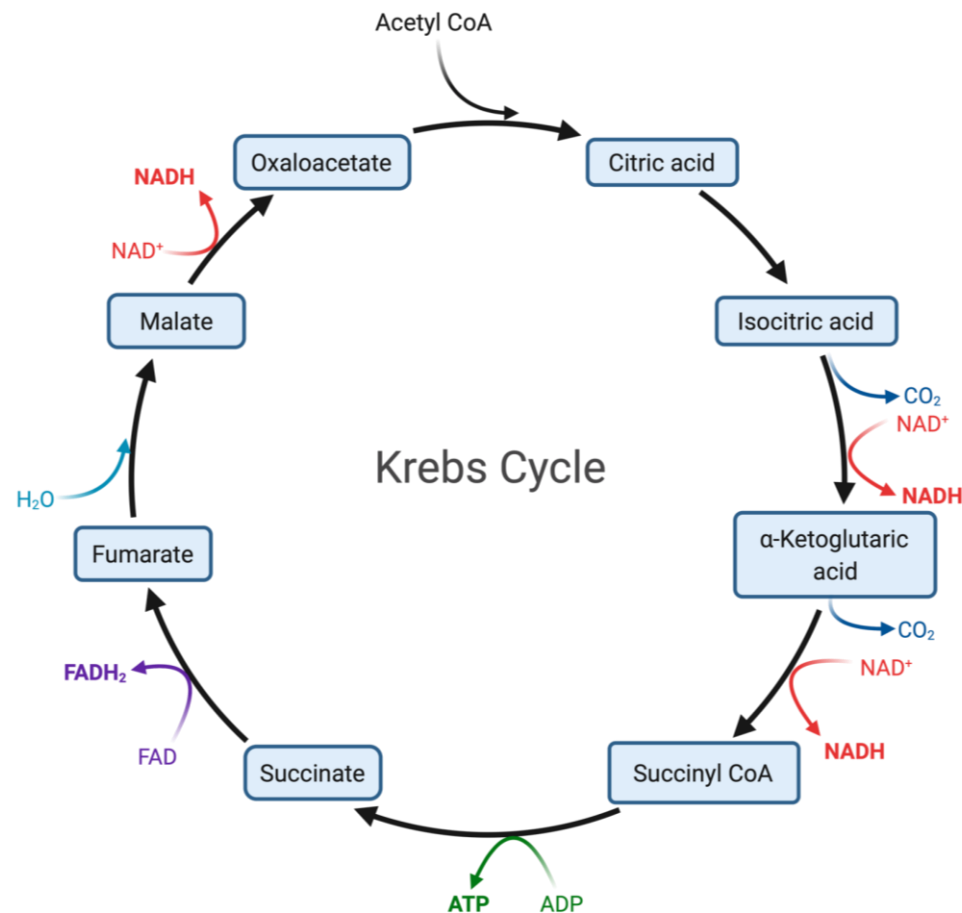
To understand the concept of metabolic flux

Objective 1

Flux - Continuous change, passage, or movement



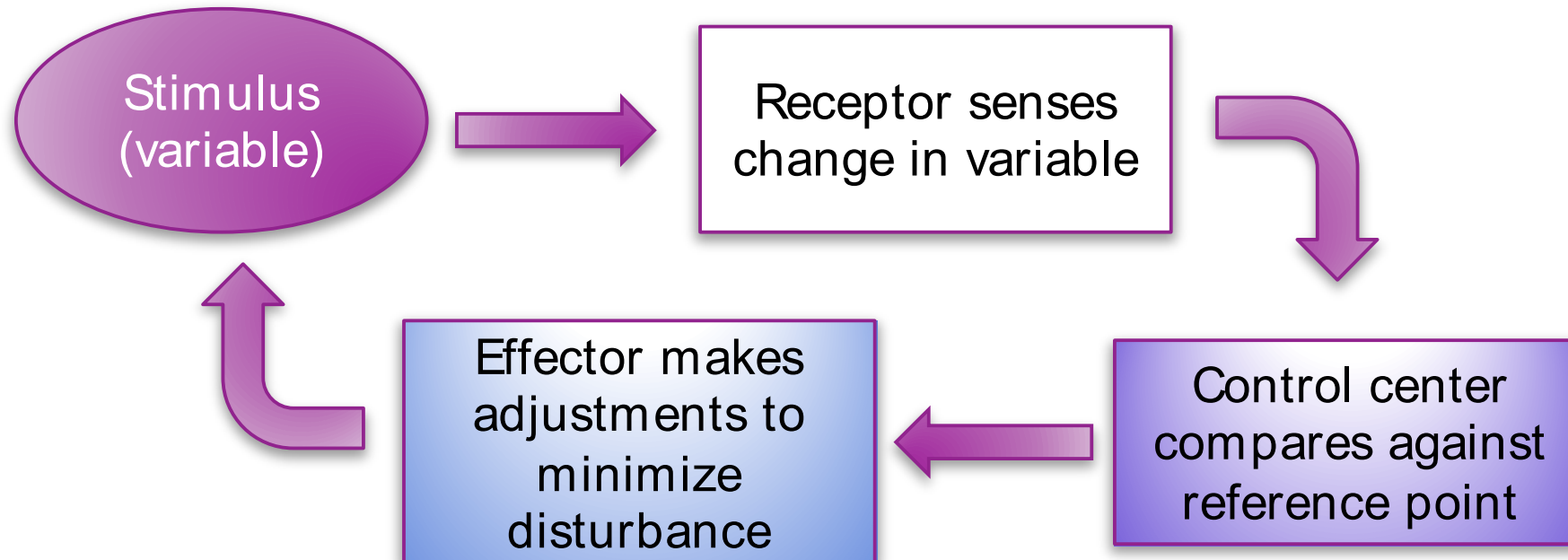
Metabolic flux- The rate of turnover of molecules through a metabolic pathway.



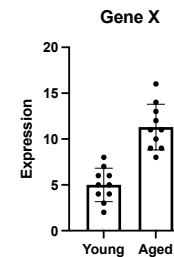
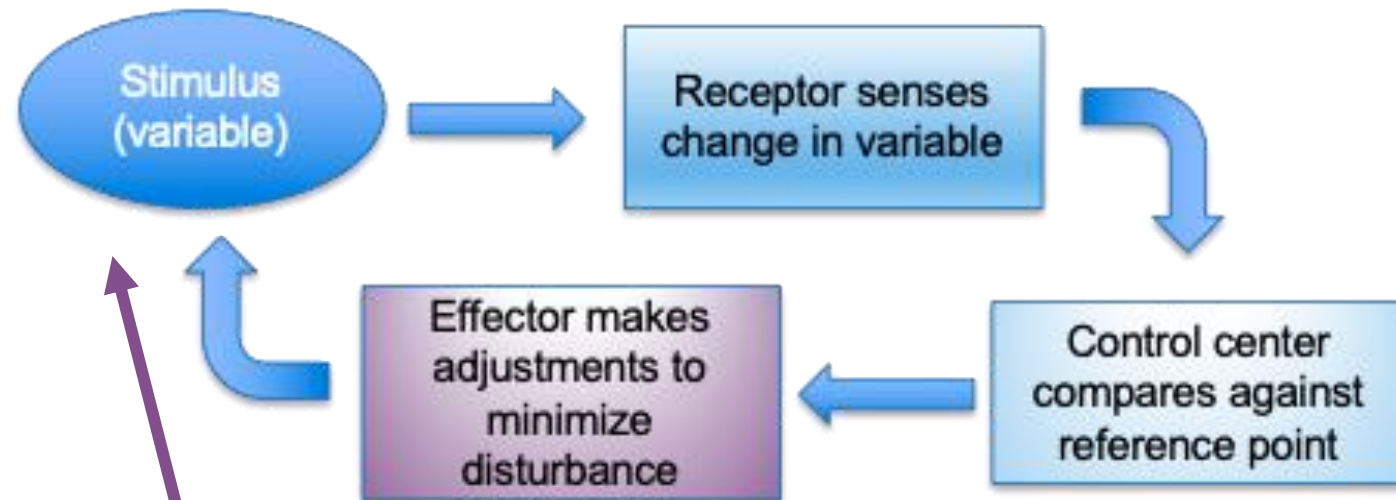
To understand the limitations of snapshots compared to moving pictures.

Objective 2

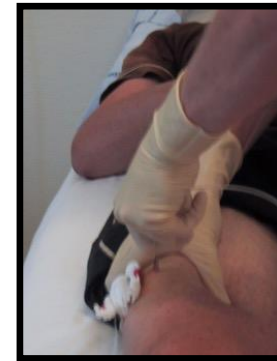
Adaptation is dynamic



Snapshot



6 months later

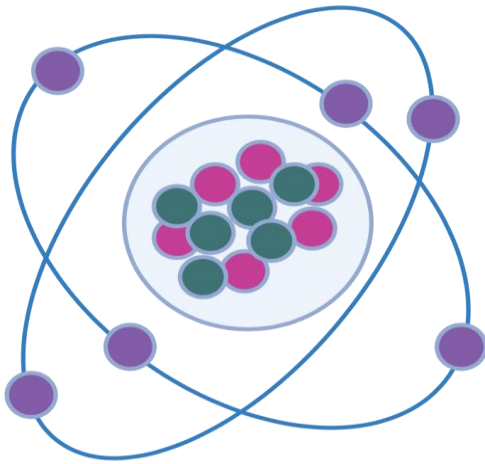




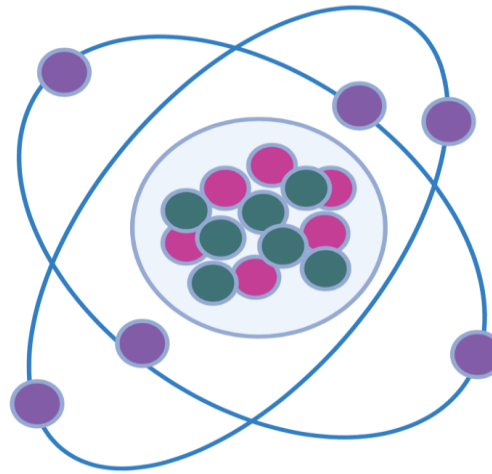
Describe one approach
for measuring metabolic
flux.

Objective 3

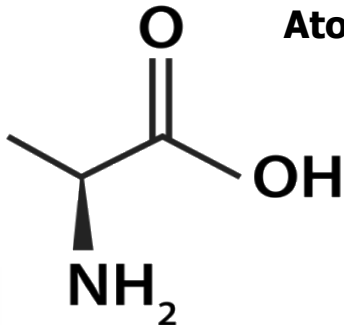
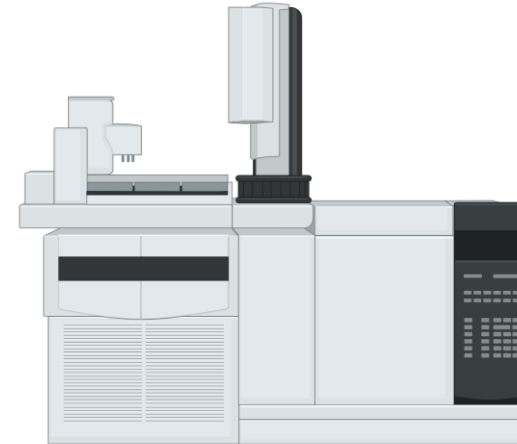
How do we measure metabolic flux?



Protons: 6
Neutrons: 6
Atomic mass: 12

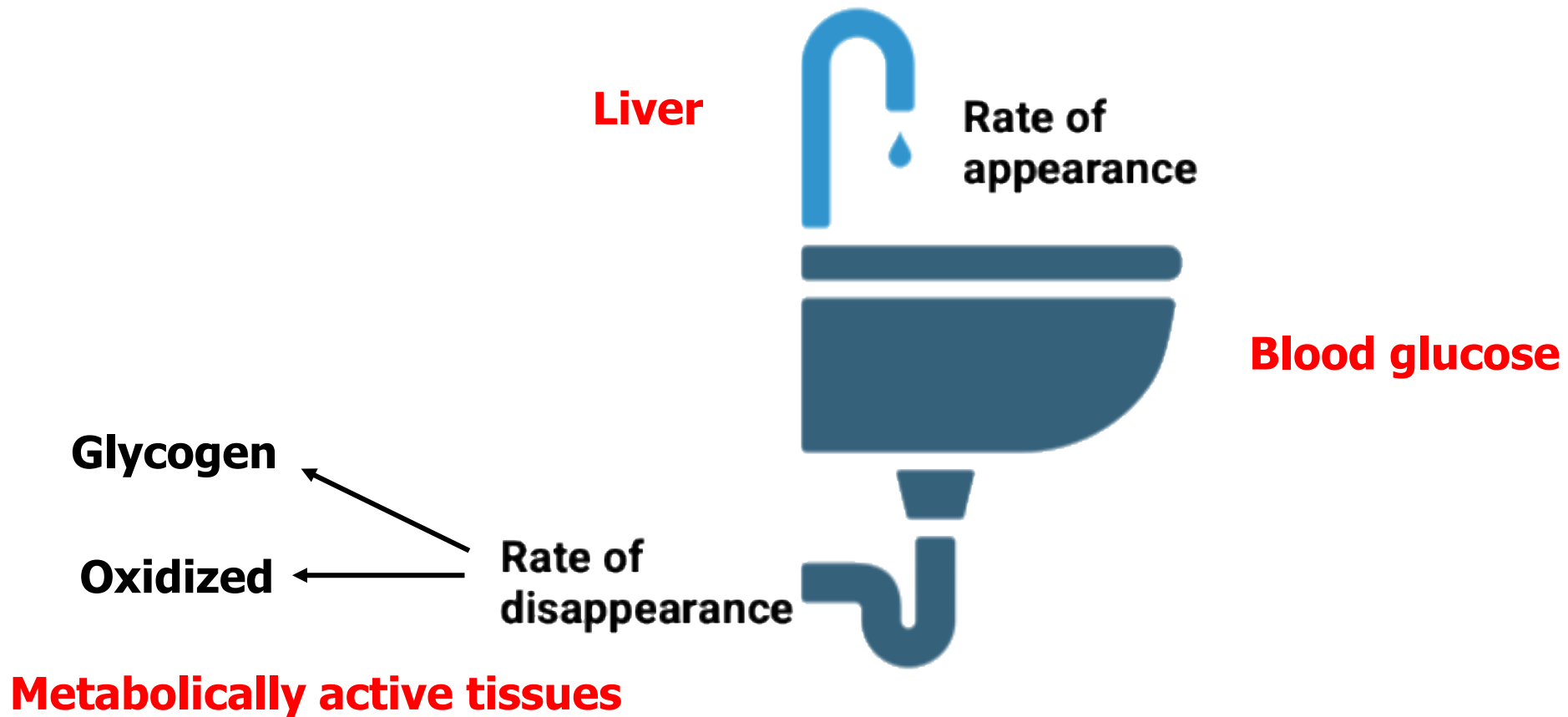


Protons: 6
Neutrons: 7
Atomic mass: 13

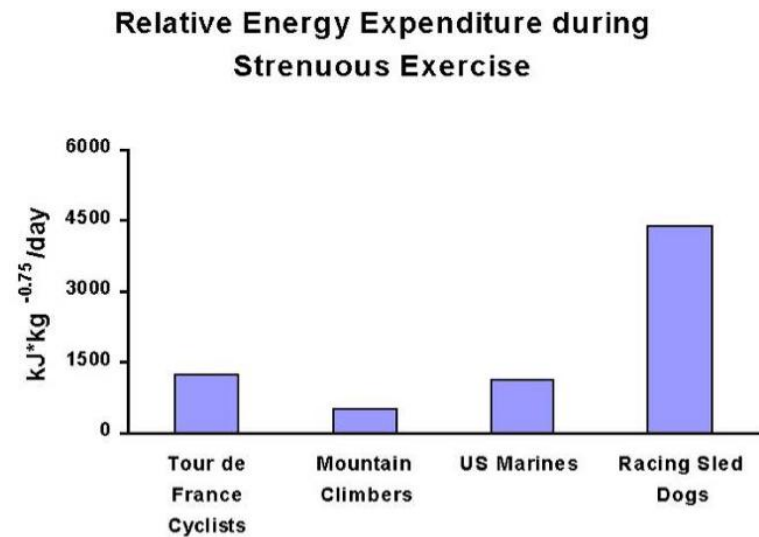


Molecules with stable isotopes are indistinguishable in physiological processes.

Tracer-measured metabolic flux



Example: Substrate use for energy metabolism



Participation in a 1,000-mile race increases the oxidation of carbohydrate in Alaskan sled dogs

Benjamin F. Miller,^{1*} Joshua C. Drake,¹ Frederick F. Peelor III,¹ Laurie M. Biela,¹ Raymond Geor,² Kenneth Hinchcliff,³ Michael Davis,^{4*} and Karyn L. Hamilton^{1*}

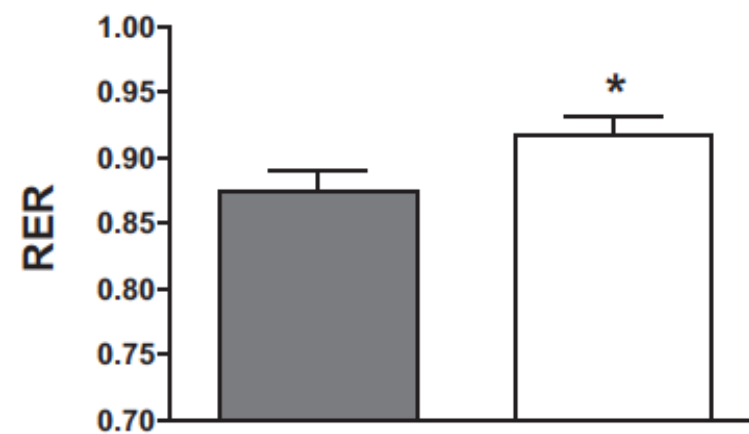
Table 2. *Isotope infusion rates*

Isotope	Infusion Rate	Dates of Testing
[1,1,2,3,3- ² H]glycerol		January 2013 and March 2013
Prime, mg	72	
Resting, mg/min	0.4	
Exercise, mg/min	1.6	
[3- ¹³ C]lactate		January 2013 and March 2013
Prime, mg	57.5	
Resting, mg/min	2.5	
Exercise, mg/min	10	
[6,6- ² H ₂]glucose		March 2013 and January 2014
Prime, mg	200	
Resting, mg/min	2.0	
Exercise, mg/min	8.0	
H ¹³ CO ₃ ⁻ (prime only), mg	100	All dates
H ¹³ CO ₃ ⁻ (primed continuous)		March 2013 and January 2014
Prime, mg	100	
Resting, mg/min	1.7	
Exercise, mg/min	10.3	



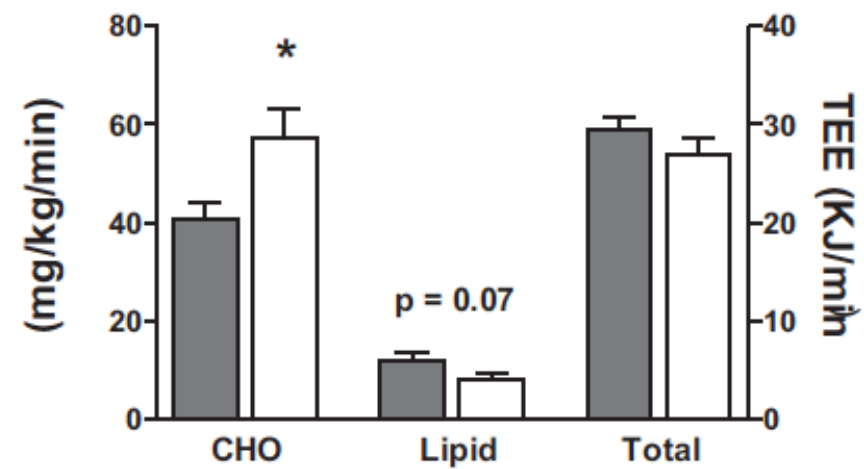
B

RER



D

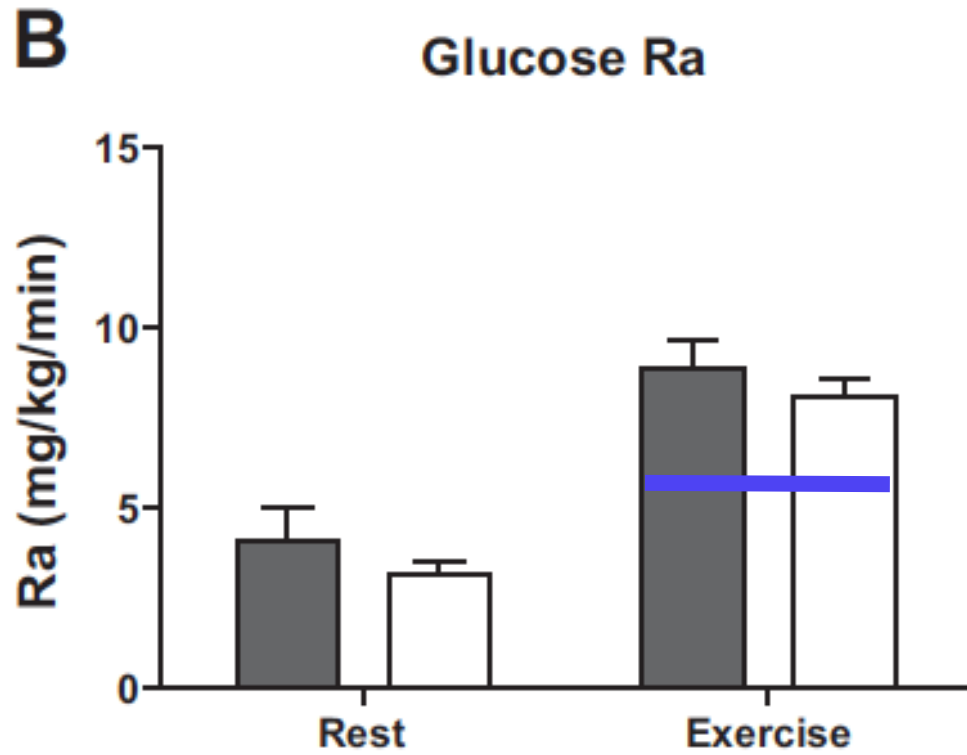
Rate of Oxidation



Non-Raced

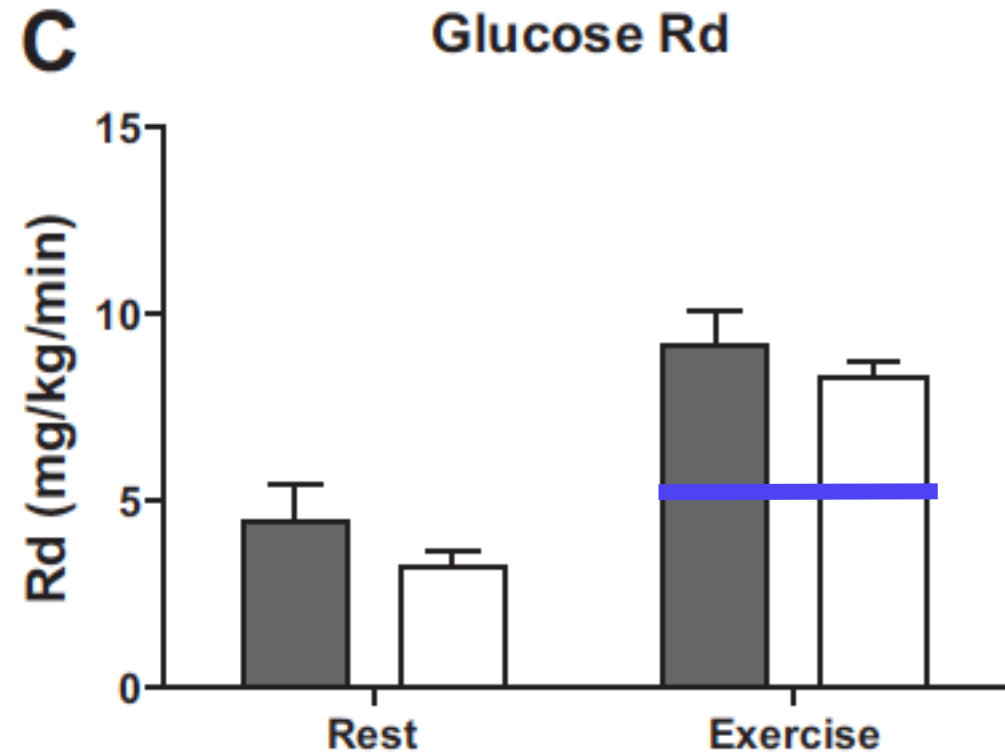


Raced



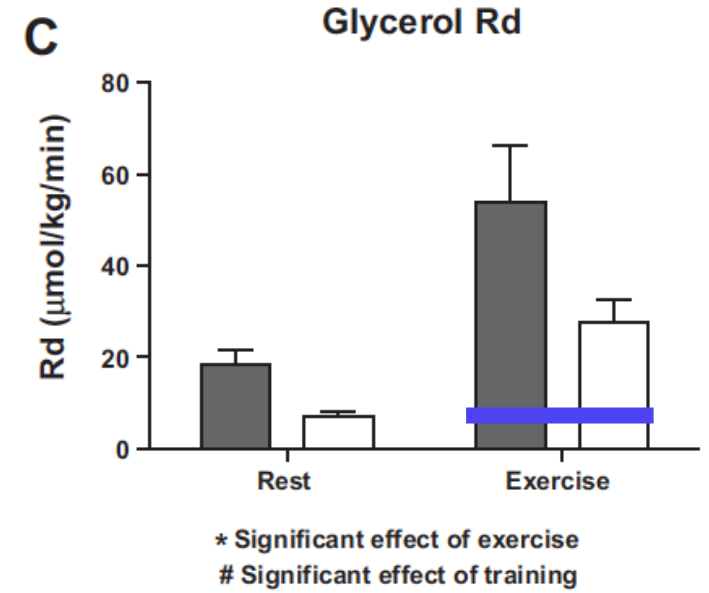
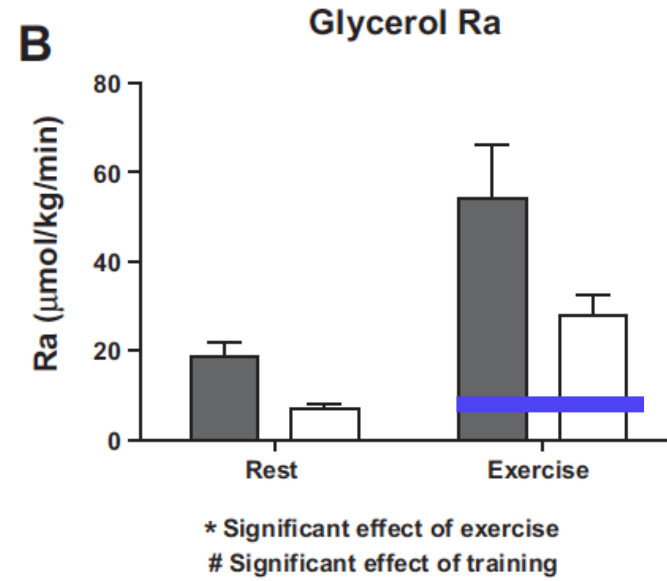
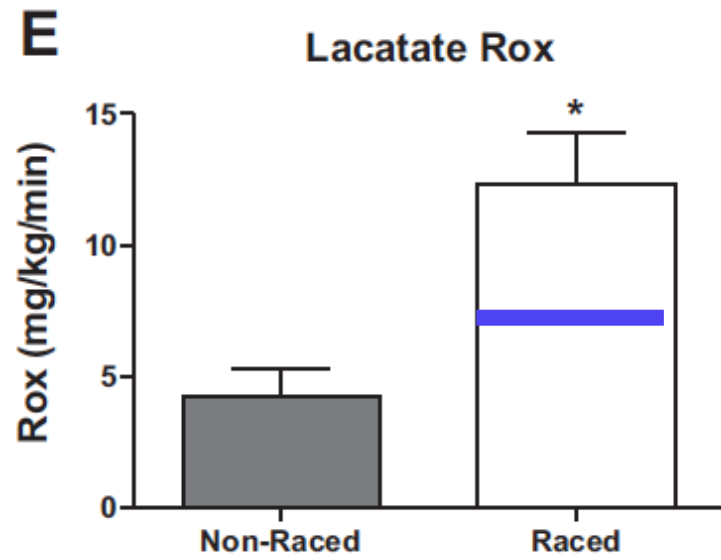
* Significant effect of exercise

■ Non-Raced



* Significant effect of exercise

□ Raced



■ Non-Raced □ Raced

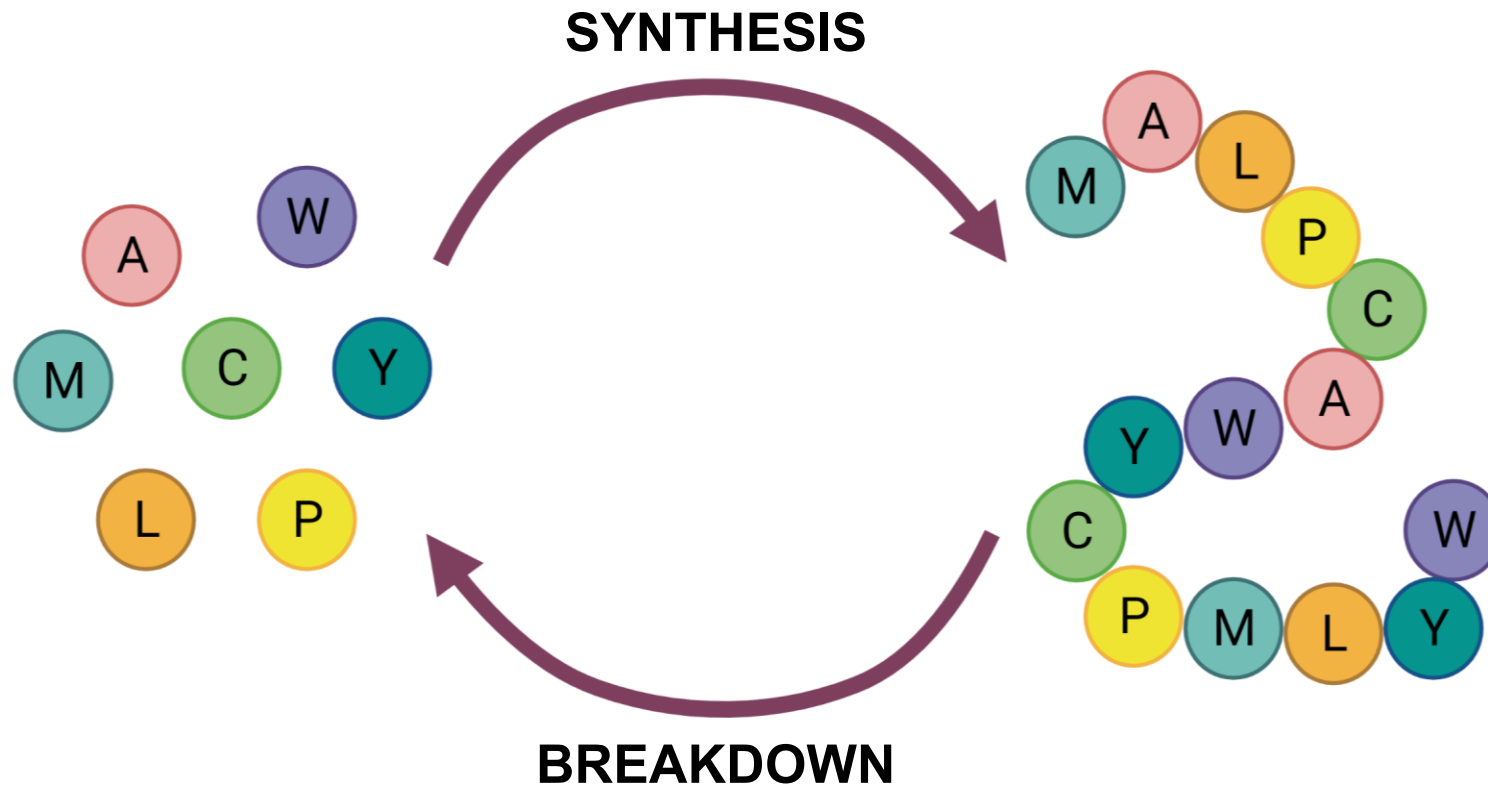
What was learned by measuring flux

- Contrary to what was assumed in the literature, Iditarod sled dogs are reliant on glucose during exercise.
- However, the glucose is made possible by a high rate of gluconeogenesis from the glycerol that comes from adipose tissue.

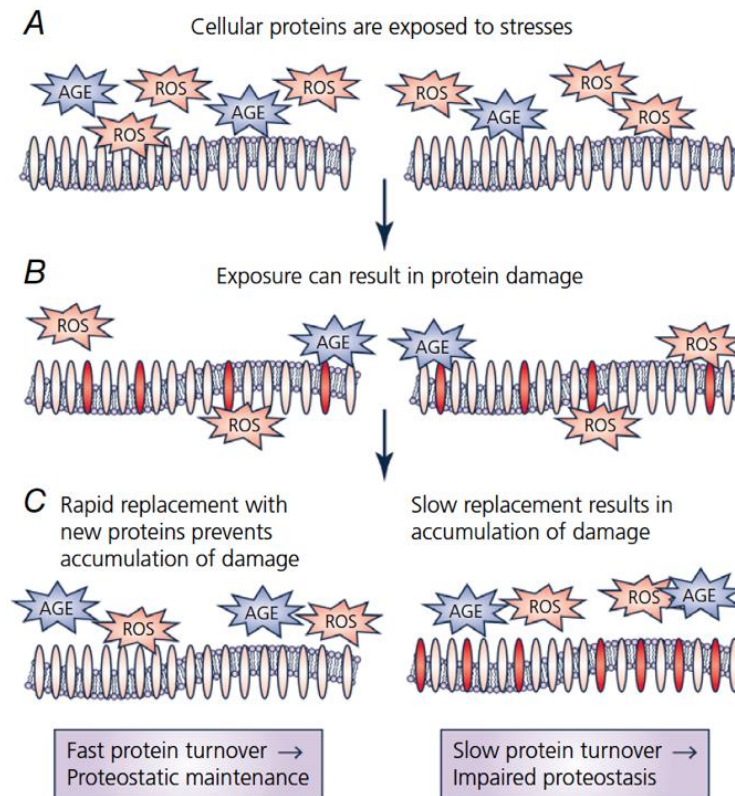
To understand
important factors in the
flux (turnover) of
protein

Objective 3

Turnover (a form of metabolic flux)



Initial paradigm of protein turnover with aging



J Physiol 000:00 (2017) pp 1-7
SYMPOSIUM REVIEW

Mitochondrial proteostasis as a shared characteristic of slowed aging: the importance of considering cell proliferation

Karyn L. Hamilton and Benjamin F. Miller

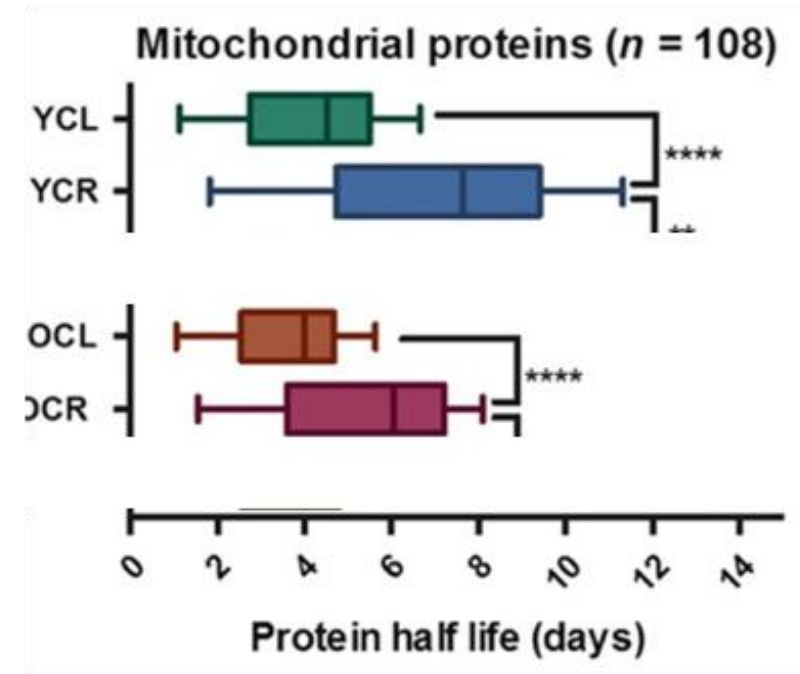
The Journal of
Physiology

Impact of gerotherapeutics on protein turnover

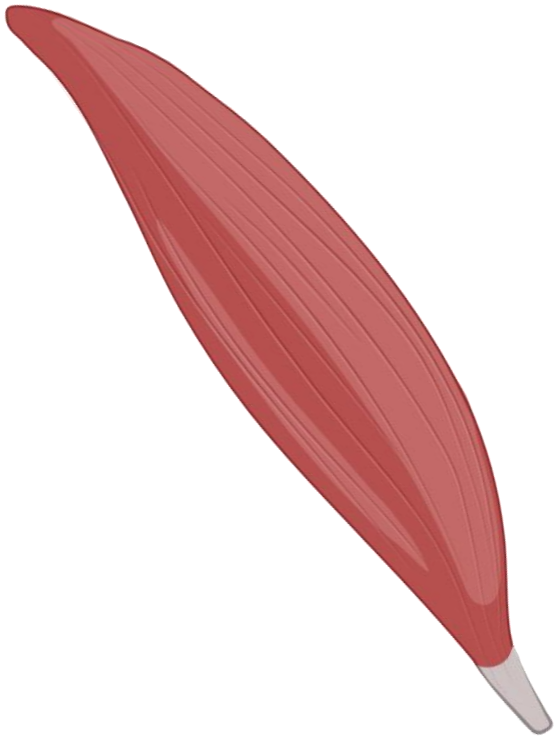
Aging slows protein turnover resulting in the accumulation of damaged proteins.

Treatments that slow aging (like rapamycin and CR) slow protein synthesis.

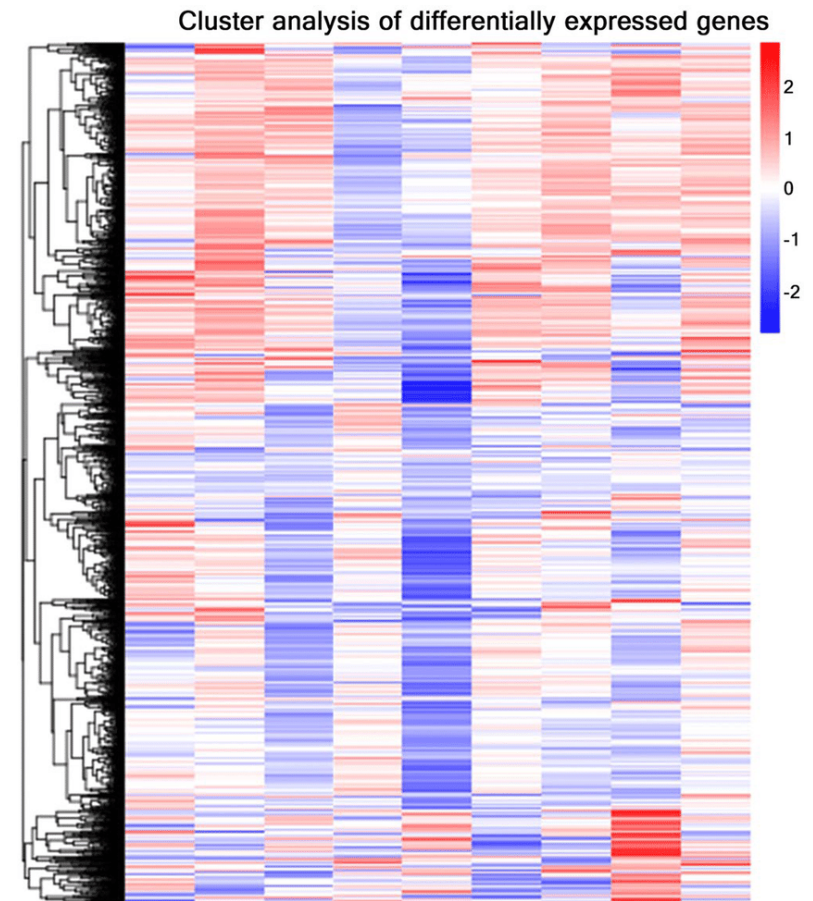
Treatments that slow aging increase protein breakdown (e.g. autophagy).



“Protein synthesis” is not a thing

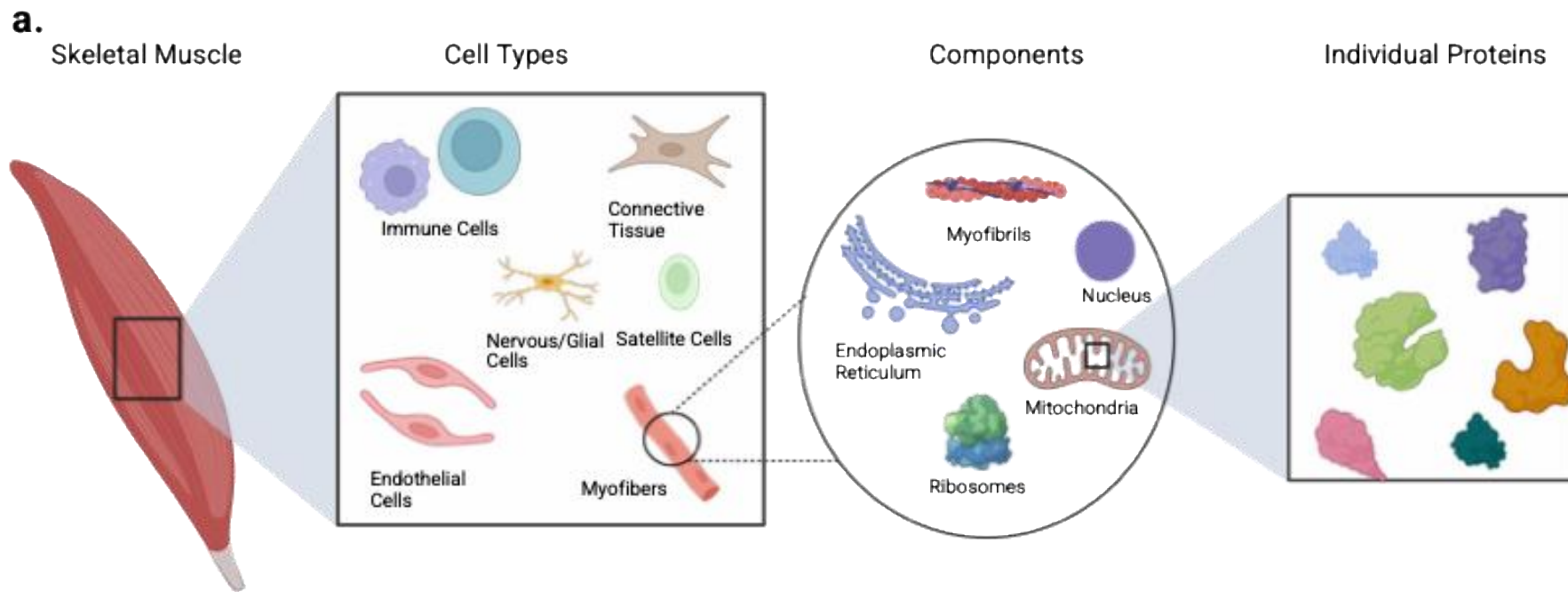


Muscle Protein Synthesis (FSR) = 2.8%/hr



Protein turnover is heterogenous

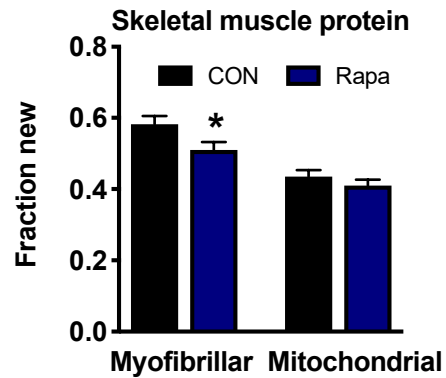
Hard to conclude that protein synthesis is up or down with aging.



Current limitations and future opportunities of tracer studies of muscle ageing

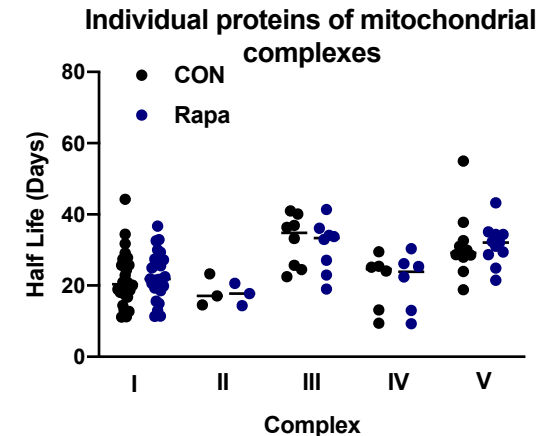
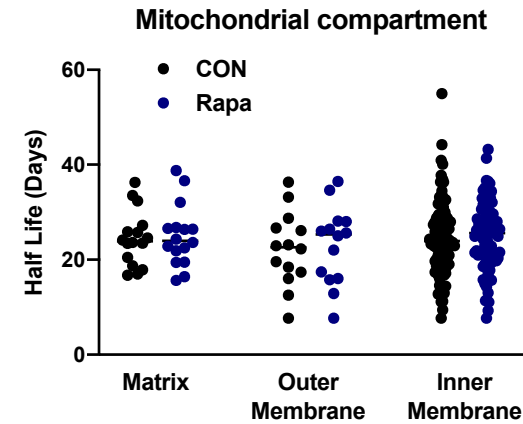
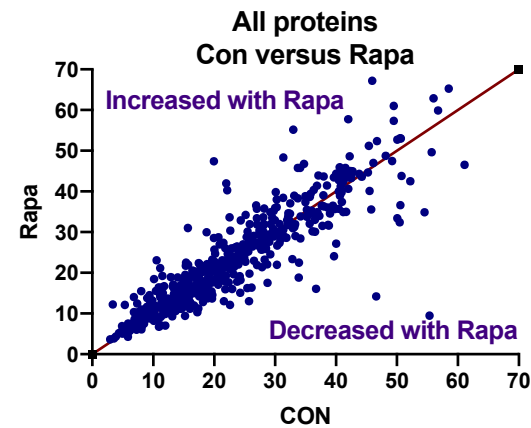
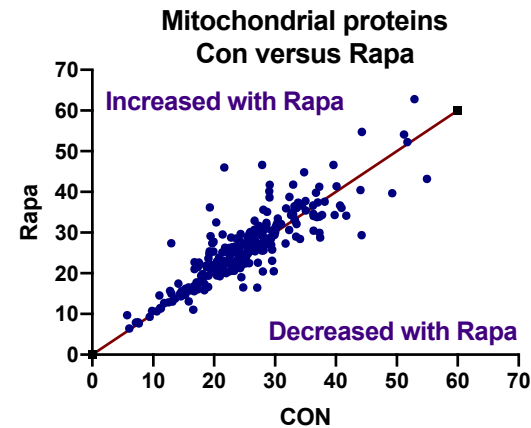
Colleen L. O'Reilly¹, Sue C. Bodine^{1,2} 
and Benjamin F. Miller^{1,2} 

Protein turnover is heterogenous

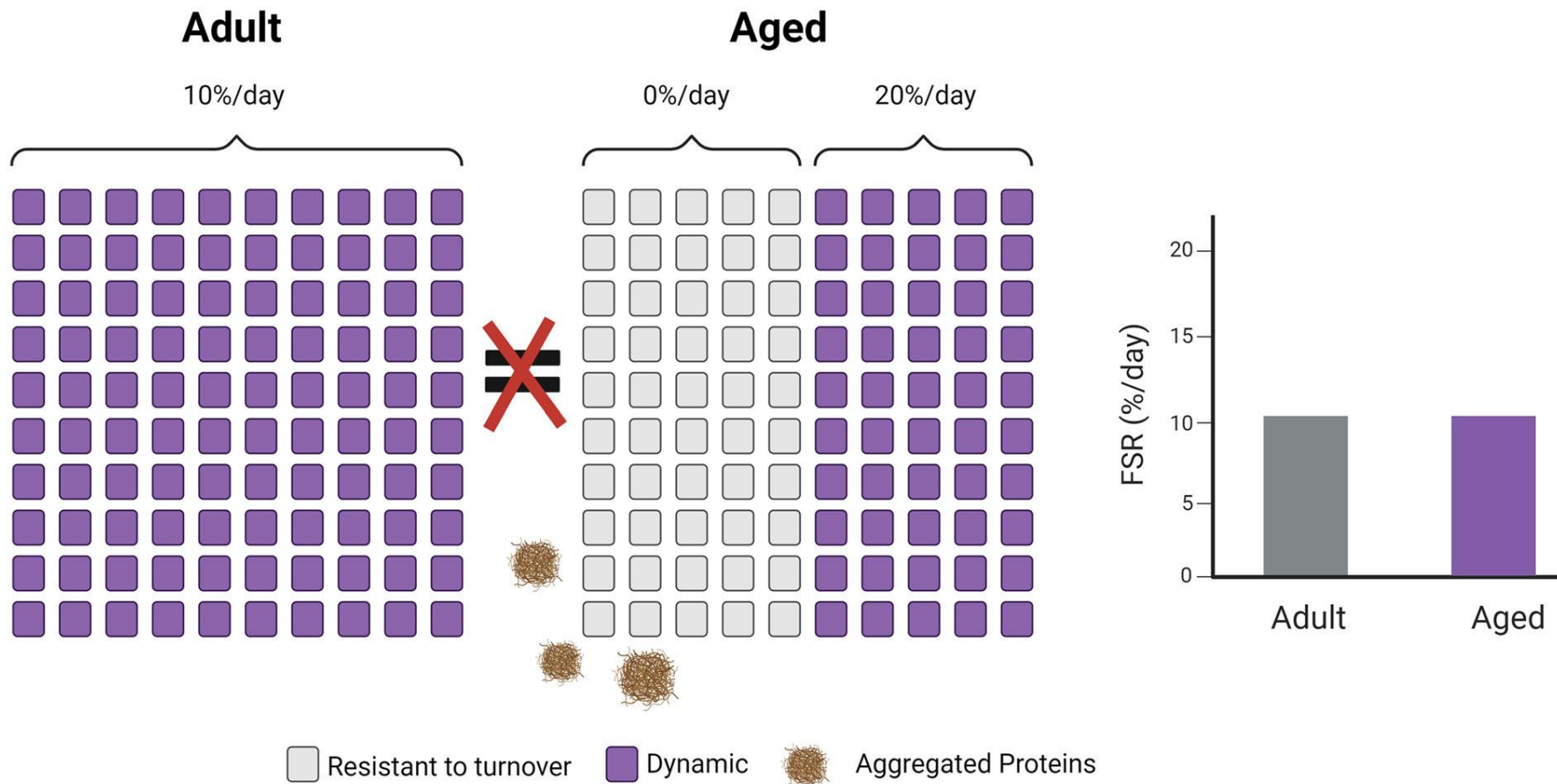


Sex differences in changes of protein synthesis with rapamycin treatment are minimized when metformin is added to rapamycin

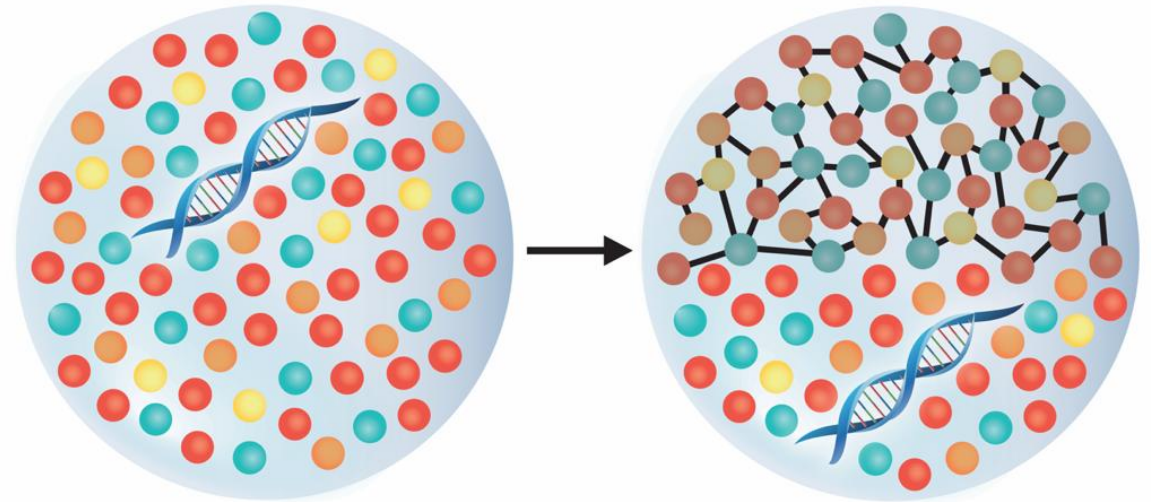
Christopher A. Wolff • Marcus M. Lawrence • Hunter Porter • Qian Zhang • Justin J. Reid • Jaime L. Laurin • Robert V. Musci • Melissa A. Linden • Frederick F. Peelor III • Jonathan D. Wren • Joseph S. Creery • Kyle J. Cutler • Richard H. Carson • John C. Price • Karyn L. Hamilton • Benjamin F. Miller



Not all proteins fully renew



Not all proteins fully renew



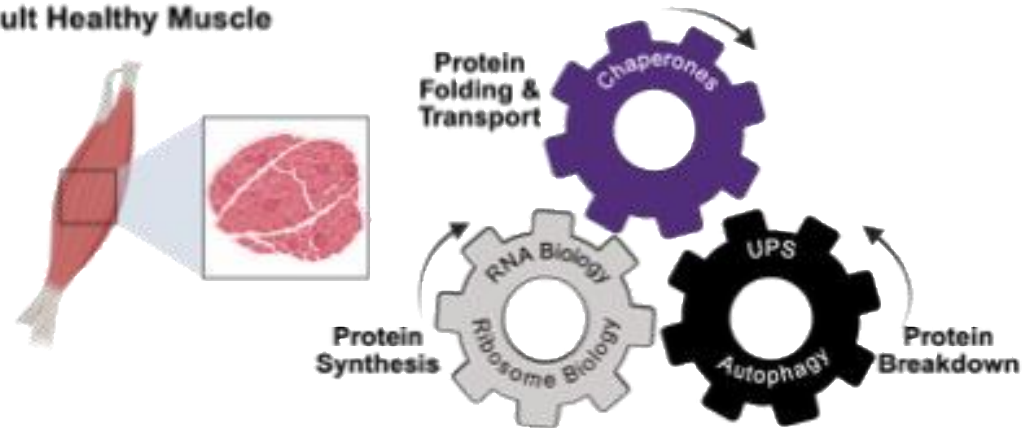
To say that “protein turnover” increases or decreases with age or gerotherapeutic interventions is overly simplistic.

Understand how to
target protein turnover
to slow aging.

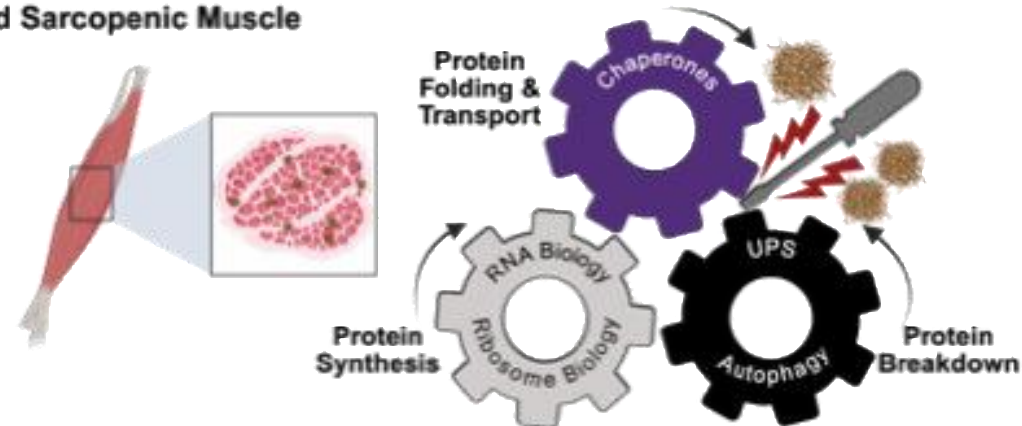
Objective 4

Turnover and proteostasis

Adult Healthy Muscle



Old Sarcopenic Muscle



Learning Objectives (revisted)

- To understand the concept of metabolic flux.
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- Understand how to target protein turnover to slow aging.

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