Grading updates

- Starting today, you need your i>clicker
  - If your quiz grade isn't appearing in Canvas, send me an email
- Sample questions are due at midnight **after every lecture**

Graded Quiz Question #1

- Which macromolecule has the highest Atwater factor
    A. Carbohydrate
    B. Protein
    C. Fat
    D. They are all the same

Graded Quiz Question #2

- Basal metabolic rate decreases with age
    A. Due to increases in fat mass
    B. Largely explained by reductions in fat free mass
    C. Due to decreases in physical activity
    D. Because of increased thermic effect of food

Graded Quiz Question #3

- Which **is not** an example of how a gene could be controlelled at the mRNA level by a nutrient.
  A. Changes in DNA methylation affect the ability of transcription factors to bind a promotor sequence
  B. A nutrient-dependent receptor such as the Vitamin D receptor binds to promotor sequences in a gene
  C. A microRNA causes degradation of a transcript
  D. A nutrient causes changes in the activity of an enzyme

Metabolic Control Systems

Learning Objectives

- Understand what a rate limiting enzyme is, what a committed enzyme step is and what a reversible reaction is.
- Explain the differences in speed and persistence of allosteric, post-translational and transcriptional regulation of metabolism.
- Describe the role of cellular transport in macromolecular regulation. Understand the differences between active and passive transport.
- Describe how hormones alter macronutrient metabolism after a meal.
- Explain the roles of hormones that maintain glucose levels in the fasting state.
- Understand how metabolic rates are changed in response to diets and overfeeding.

Nutrient Regulation is About Two Things

- Metabolism
  - Catabolism
  - Anabolism
- Transport

What statement about enzymes is **<u>untrue</u>**?

A. Enzymes stabilize a transition state intermediate

B. Enzymes change the equilibrium levels of products and substrates

C. Enzymes can accelerate a chemical reaction

D. Enzymes can be proteins or mRNA

(Very) Quick Review of Enzymes

Thermodynamics and kinetics

Thermodynamics of Metabolic Pathways

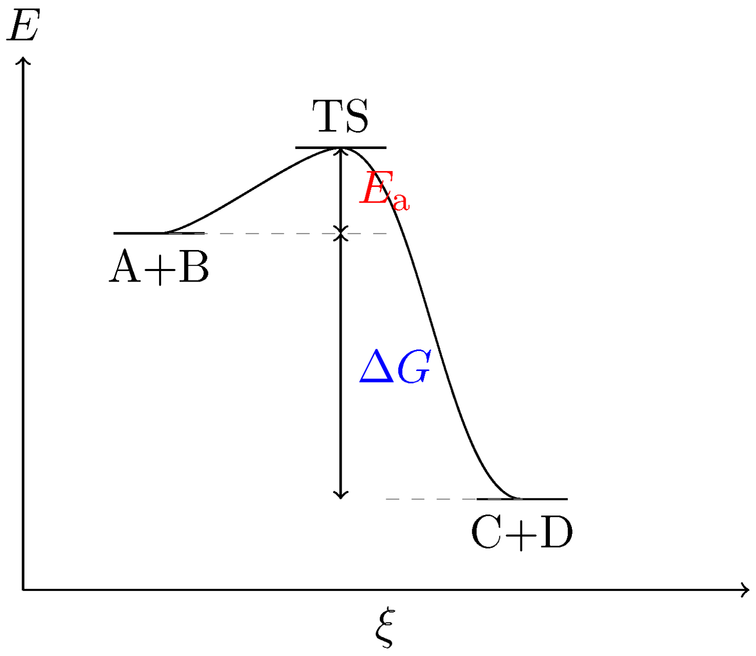


Figure 1: irreversible reaction

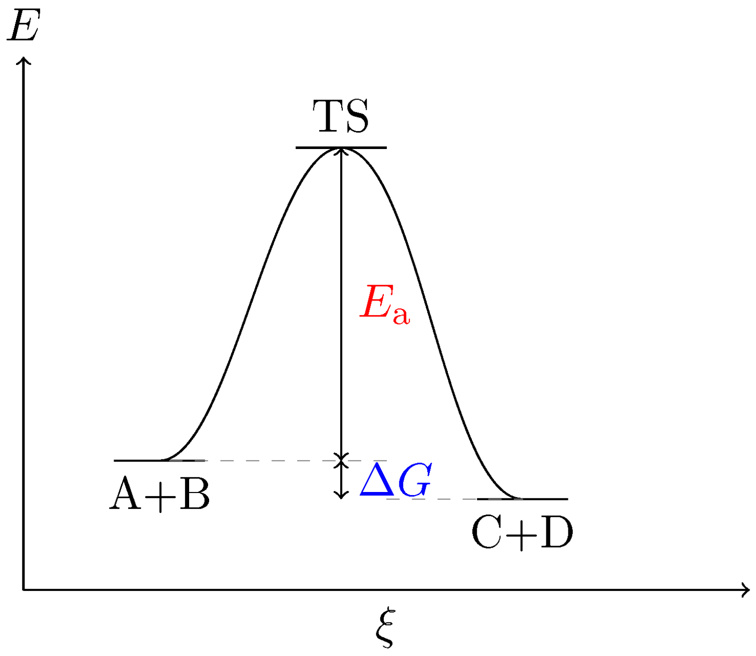
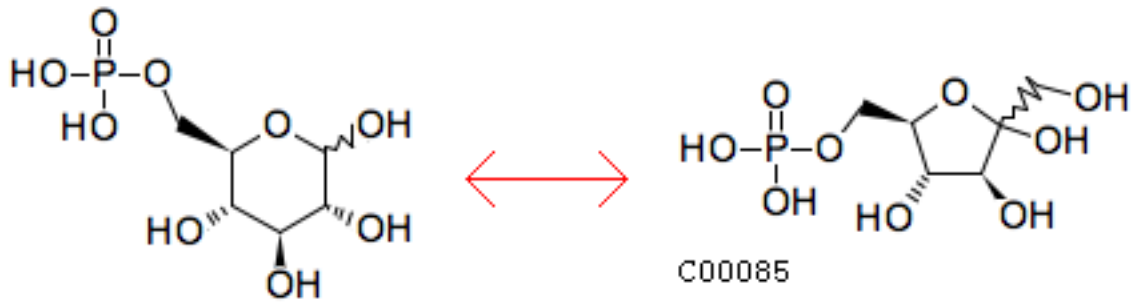


Figure 2: reversible reaction

$$\Delta G = \Delta G'^{\circ} + RT ln K_{eq}$$

$$K_{eq} = \frac{[C]\,[D]}{[A]\,[B]}$$

These chemicals are at nearly equal levels at equilibrium?



C00092

C00085

ΔG = +2 kJ/mol

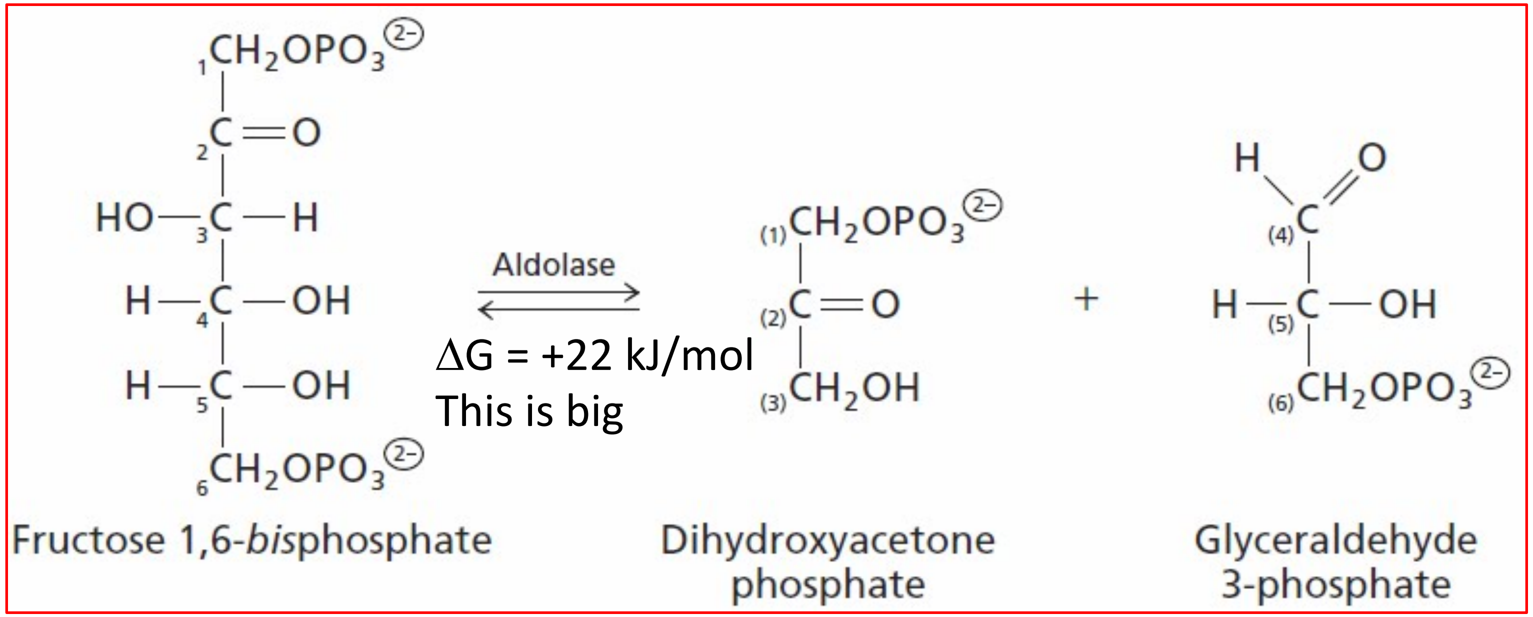
This is small

Glucose – 6 – Phosphate

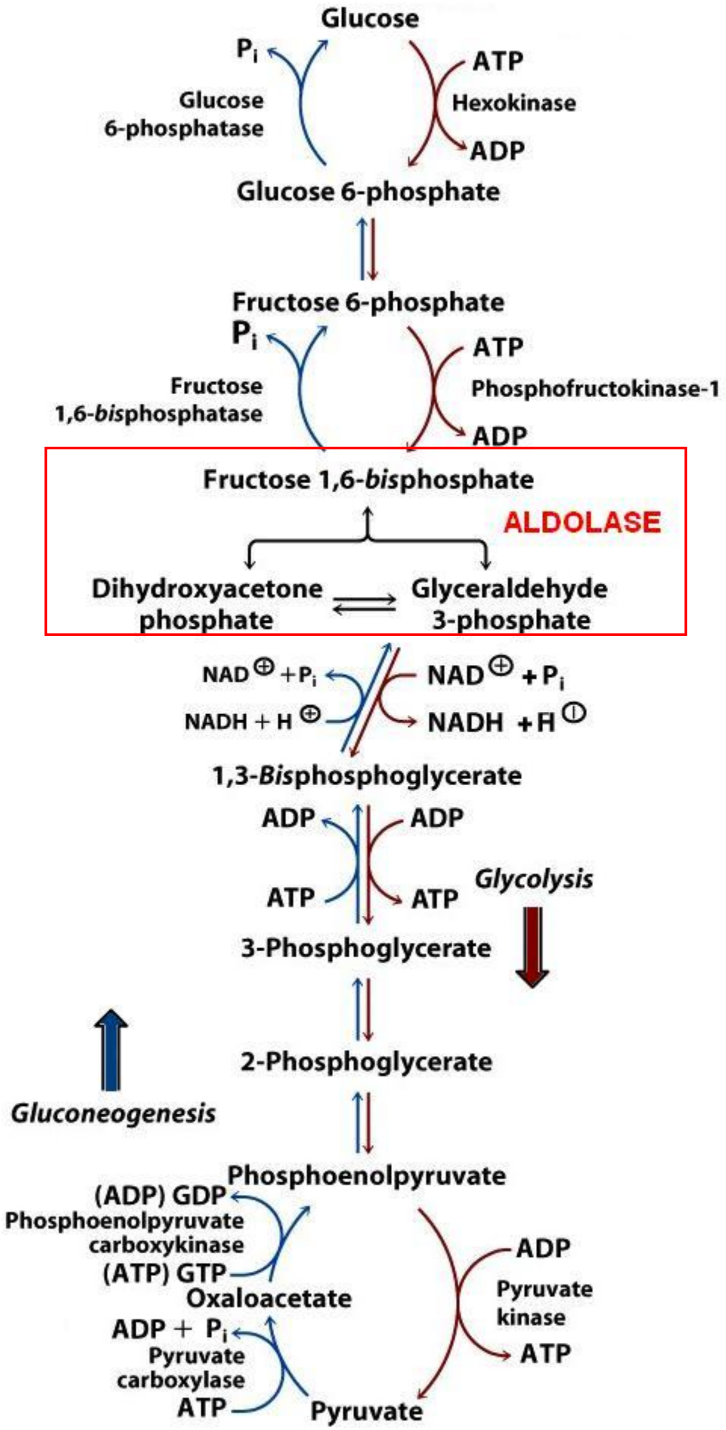
Fructose– 6 – Phosphate

A. True
B. False

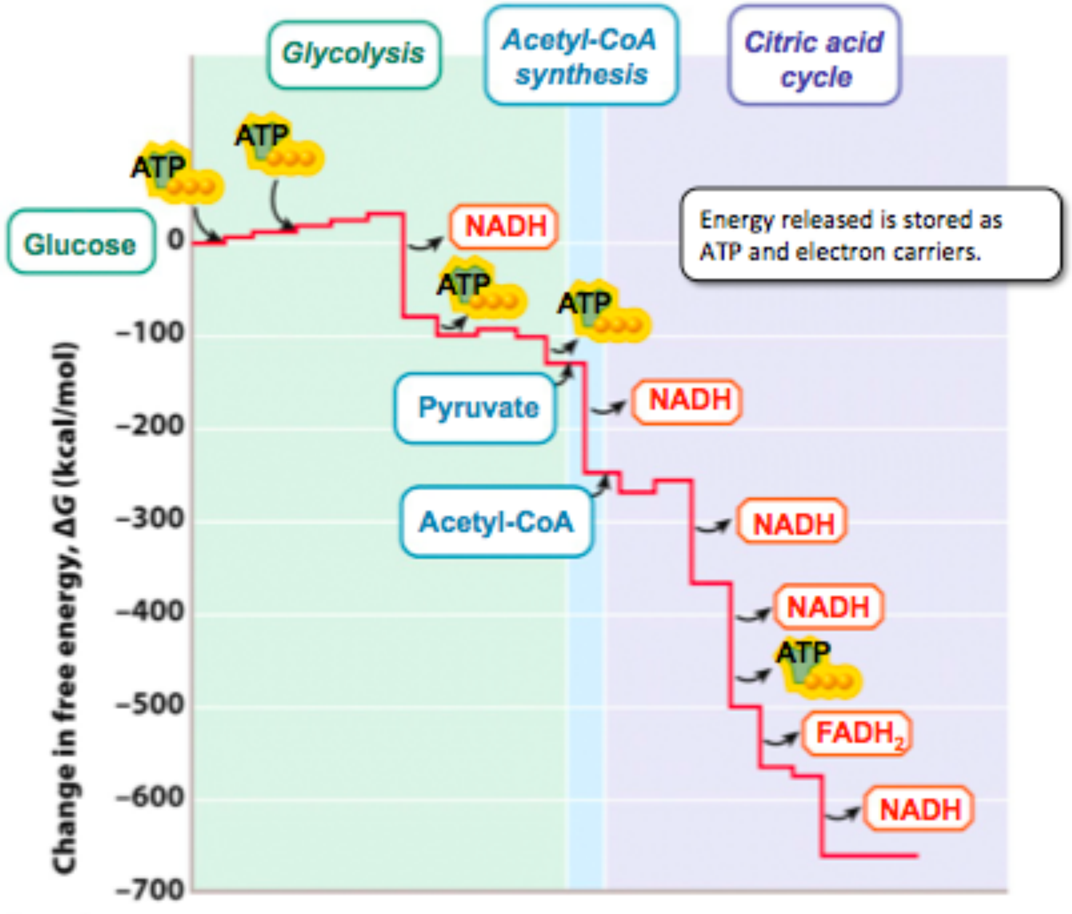
At equilibrium are these at the same levels?



A. True
B. False



Gibbs Free Energy in a Metabolic Pathway

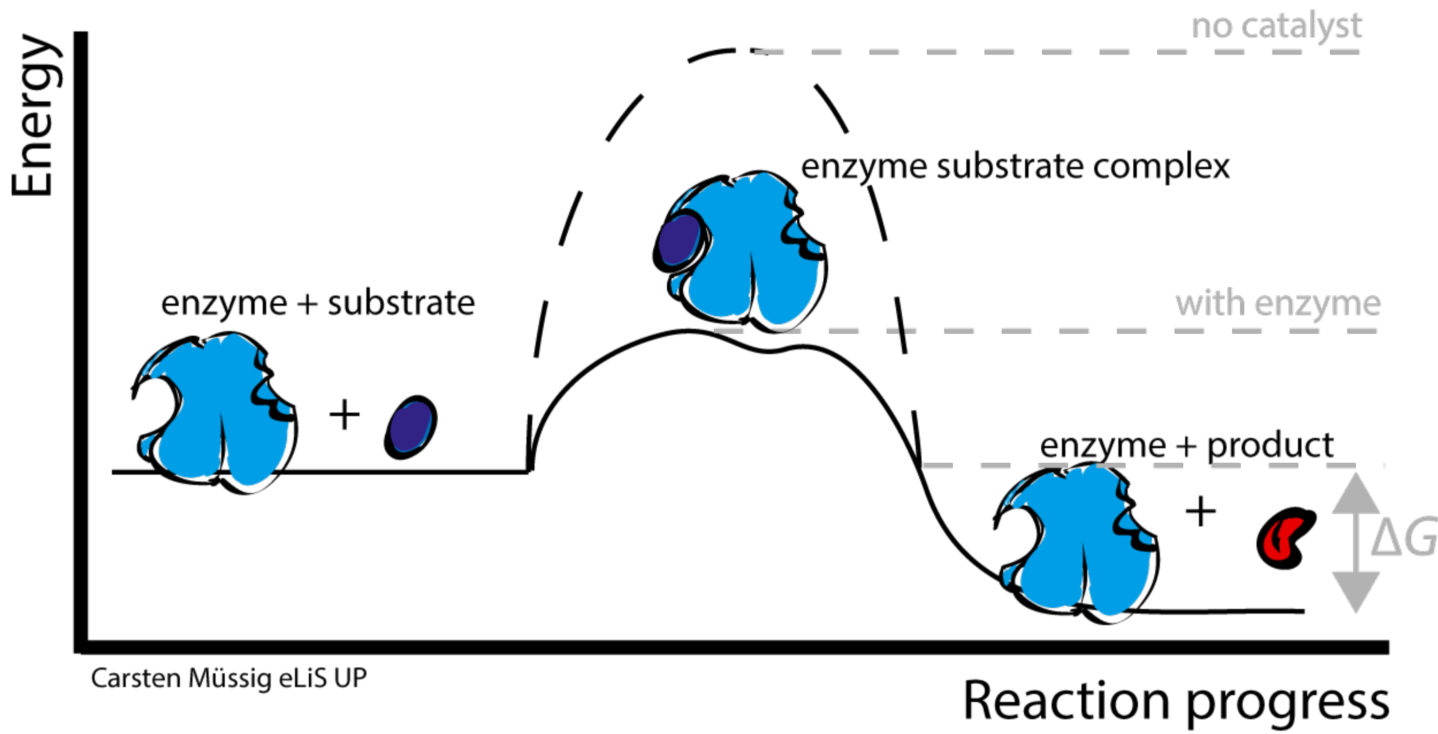


substrate	cofactors, enzymes	$\Delta G^{o\prime}$	ΔG
glucose, 5 mM;	ATP as donor		
	hexokinase, *glucokinase*	-16.5 kJ/mol	-33 kJ/mol
glucose-6-P, 83 μM;			
	glucose-6-P isomerase	+2.0 kJ/mol	-2 kJ/mol
fructose-6-P, 14 μM;	ATP as donor		
	phosphofructokinase	-13.7 kJ/mol	-26 kJ/mol
fructose-1,6-bisP, 35 μM;			
	*aldolase**	+22.0 kJ/mol	-1 kJ/mol
dihydroxyacetone-3-P, 150 μM;			
	triose phosphate isomerase	+5.6 kJ/mol	+0.7 kJ/mol
glyceraldehyde-3-P, 20 μM;	NAD^+ as e^- acceptor Pi as phosphate donor		
	glyceraldehyde-3-P dehydrogenase	+6.3 kJ/mol	+0.6 kJ/mol
1,3-bisphosphoglycerate, <1 μM;	ADP as acceptor		
	phosphoglycerate kinase	-18.8 kJ/mol	-1 kJ/mol
3-phosphoglycerate, 118 μM;			
	phosphoglyceromutase	+4.8 kJ/mol	+0.8 kJ/mol
2-phosphoglycerate, 30 μM;			
	enolase	+3.2 kJ/mol	+1 kJ/mol
phosphoenolpyruvate, 23 μM;	ADP as acceptor		
	pyruvate kinase	-31.6 kJ/mol	-17 kJ/mol
pyruvate, 51 μM;	NADH as e^- donor		
	lactate dehydrogenase	-26.2 kJ/mol	-0.8 kJ/mol
lactate, 2.9 mM;			

After adjusting for Concentrations of reactants

Kinetics of Enzyme Reactions

- Generally depends on amount of substrate/product
- Stabilization of transition state

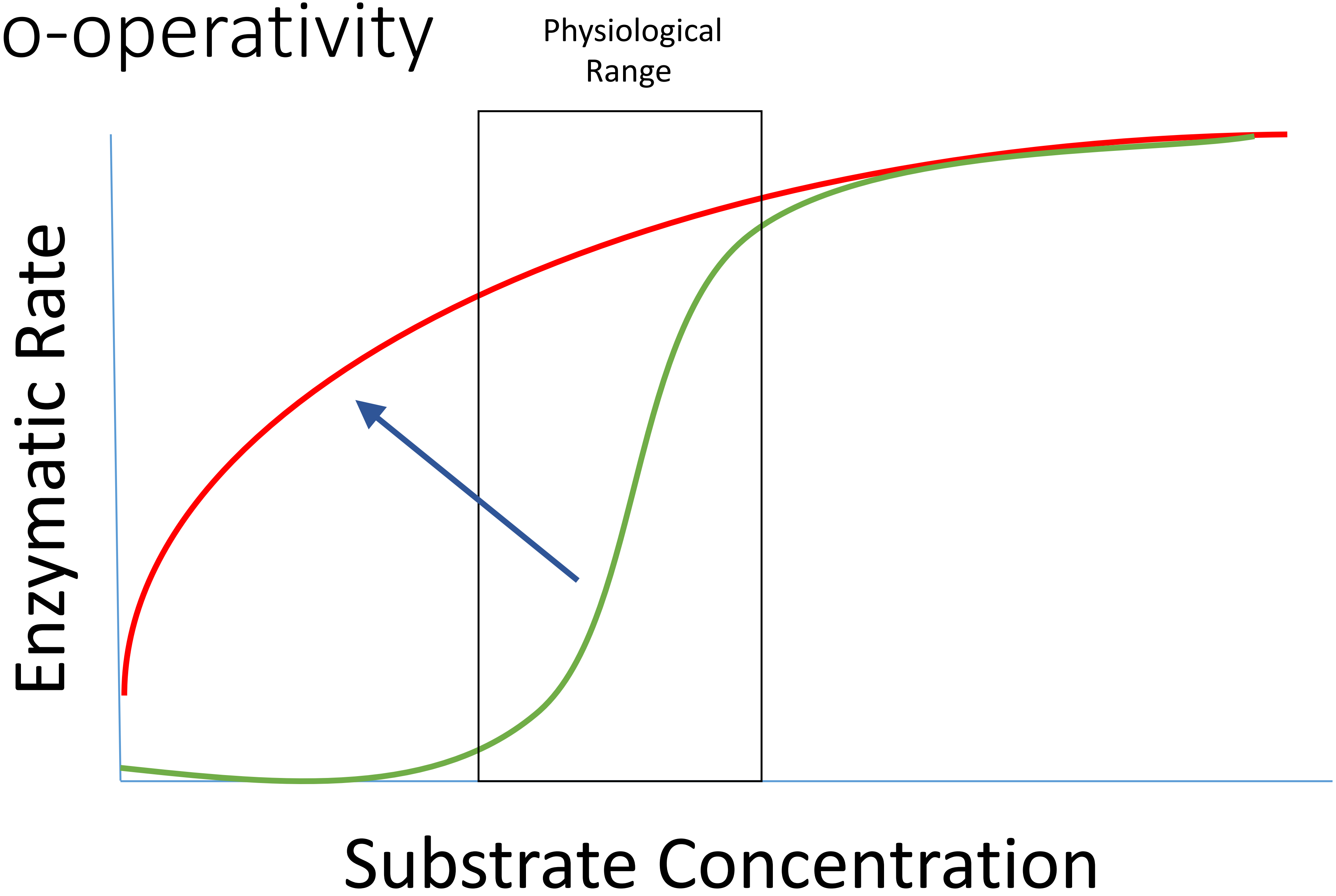


Rate Limiting Enzyme and Committed Steps

Recap committed or rate limiting steps?

- Reversible step:
  - Substrates and products can quickly move back and forth
- Committed step:
  - An effectively irreversible step along a metabolic pathway
- Rate limiting step:
  - The slowest enzymatic reaction in a pathway
- These steps are often the ones that regulate the flow of metabolites through the pathway

Co-operativity

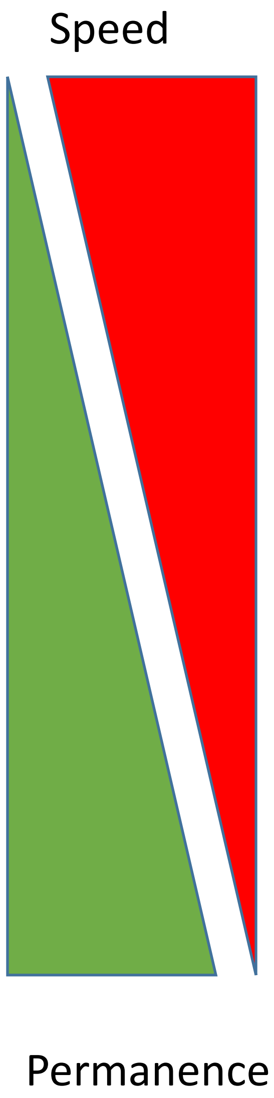


If an enzyme is catalytically activated…

A. It reduces ΔG of the reaction, but **does not** change the rate
B. It reduces ΔG of the reaction, and **does** changes the rate
C. It doesn’t change the ΔG of the reaction, and **does not** change the rate
D. It doesn't change the ΔG of the reaction, but **does** not change the rate

Enzymes are Regulated by Several Mechanisms

- Substrate/Product Concentrations
- Allosteric Control
- Catalytic Activation
- Enzyme Location
- Enzyme Levels
  - Protein Level -> Translation/Degradation
- Transcriptional Regulation



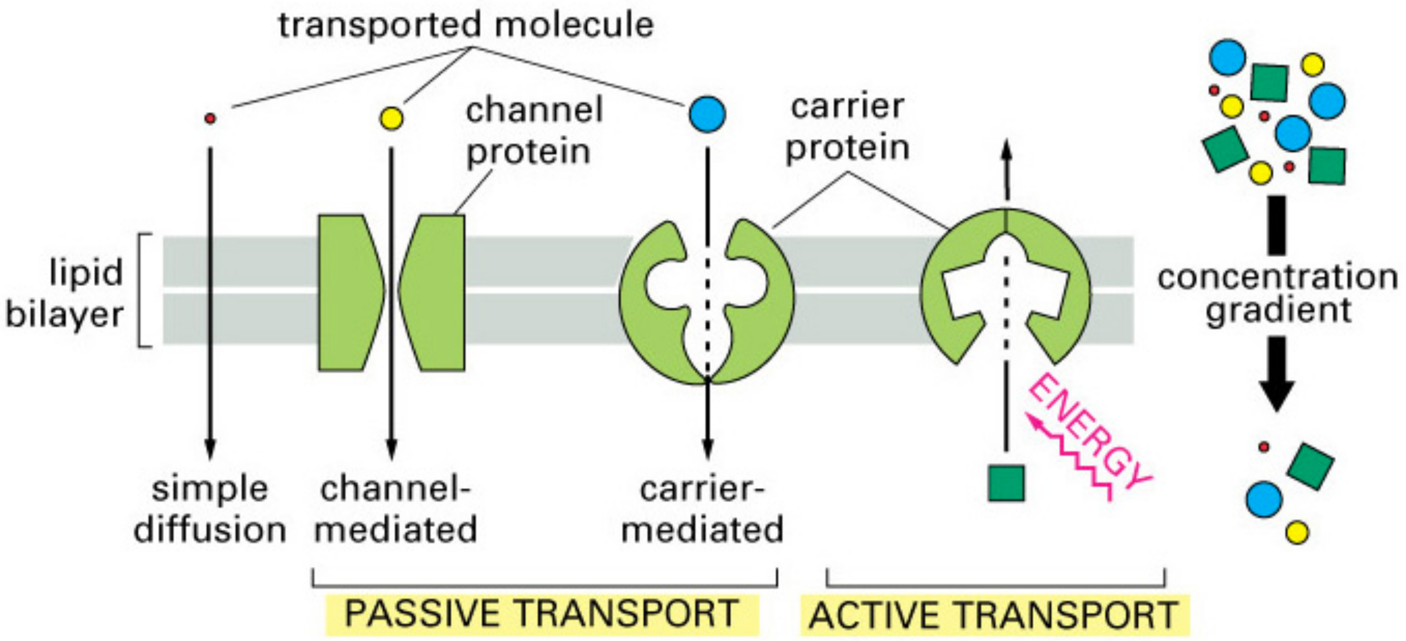
Which is an example of allosteric control of glycogen synthase?

A. Increasing the intracellular level of the substrate UDP-glucose makes GS add UDP-glucose to glycogen more rapidly
B. The transcription factor SREBP1c increases the amount of glycogen synthase in the cell
C. The non-substrate glucose-6-phosphate increases of GS activity
D. Both A and C

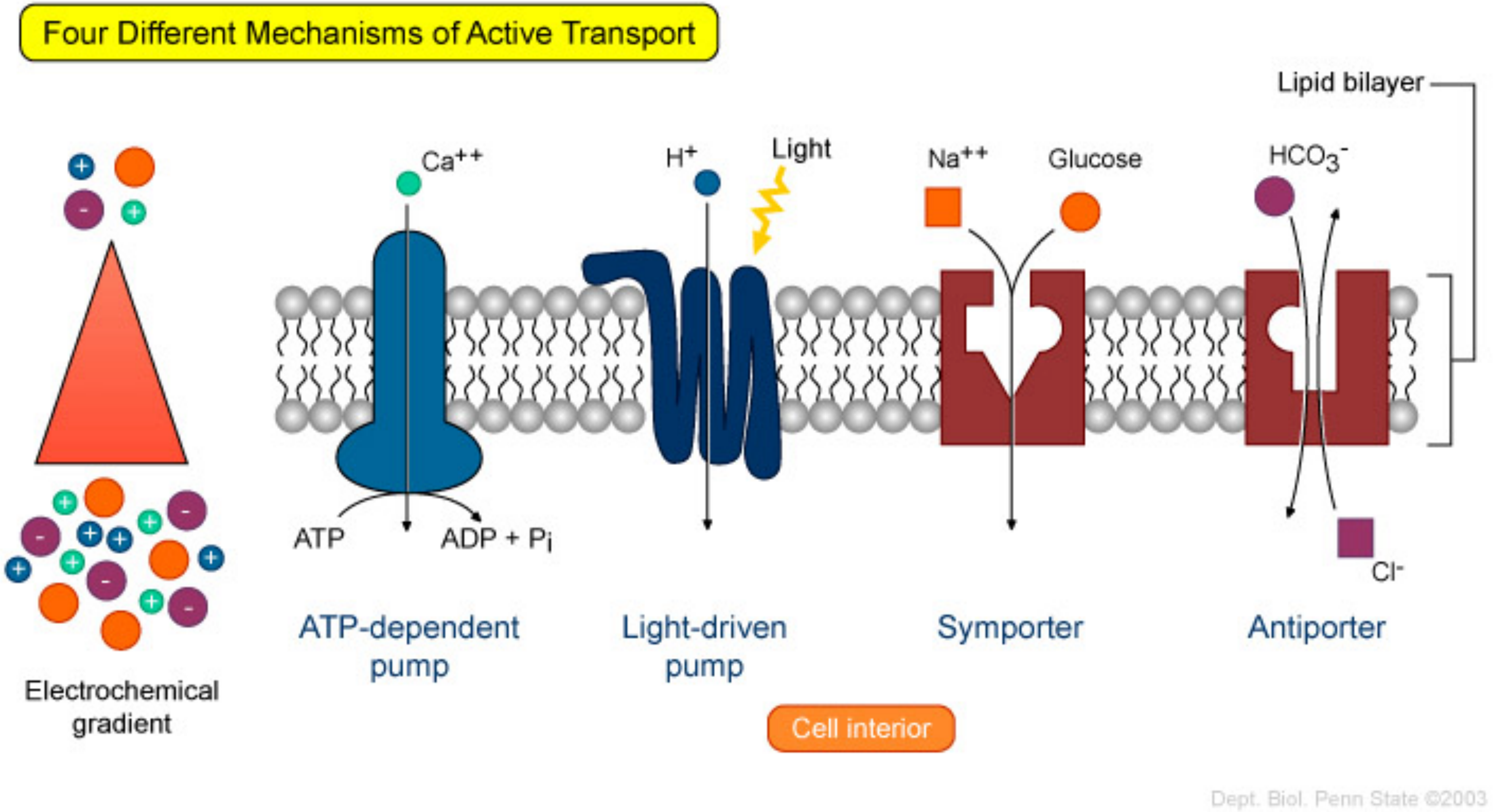
Cellular Transport Mechanisms

Cellular transport

- Cells are impermeable to many nutrients
- Transport can:
  - Follow concentration gradient
    - Passive transport
  - Push against concentration gradient
    - Active transport
- Same concepts are true for mitochondrial transport



The Energy from Active Transport Can Come from Several Sources



Altering Cellular Transport

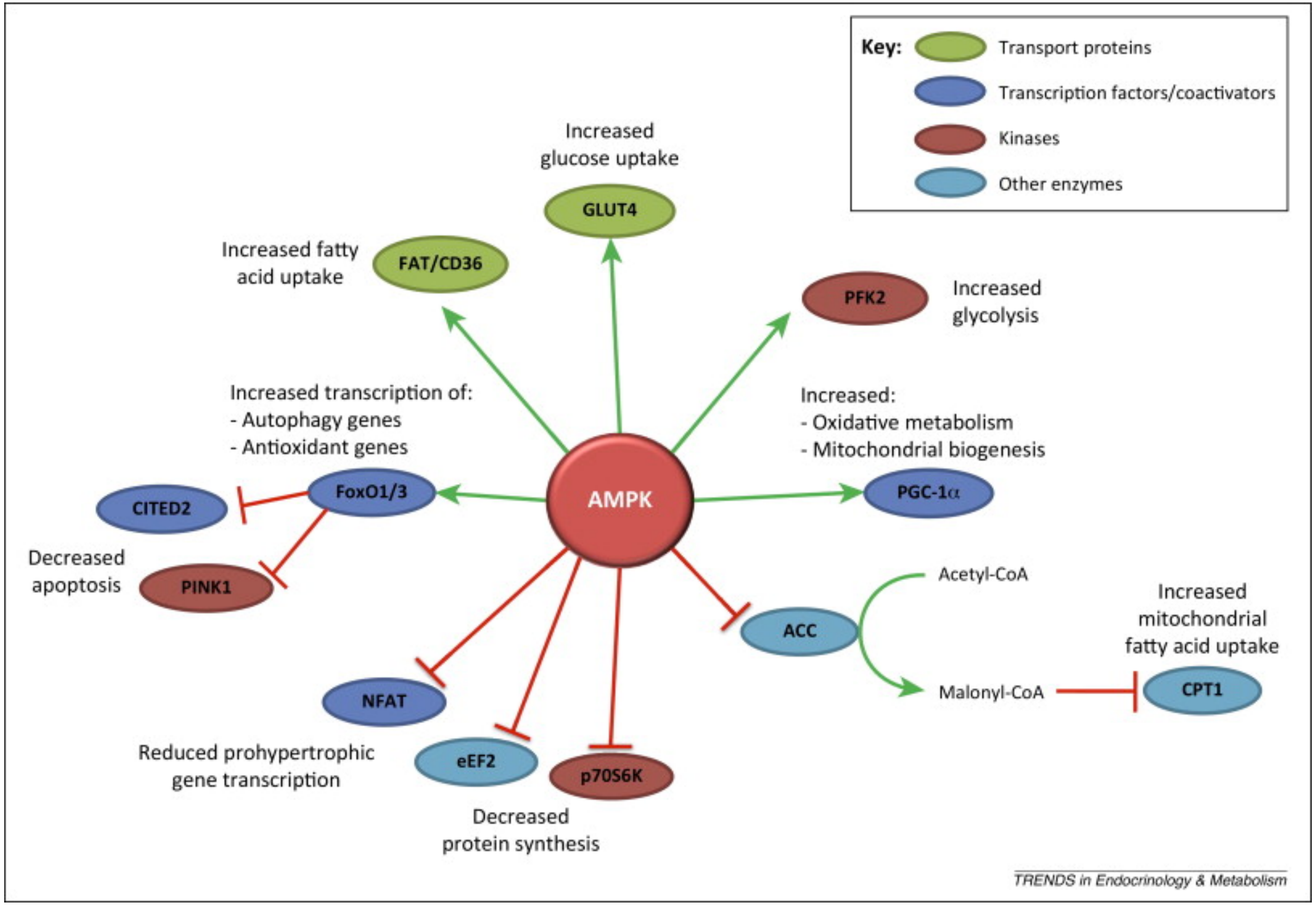
- With the folks nearby think of as many ways as you can by which you could increase cellular transport of a nutrient (I can think of 5)

Several Levels of Metabolic Control

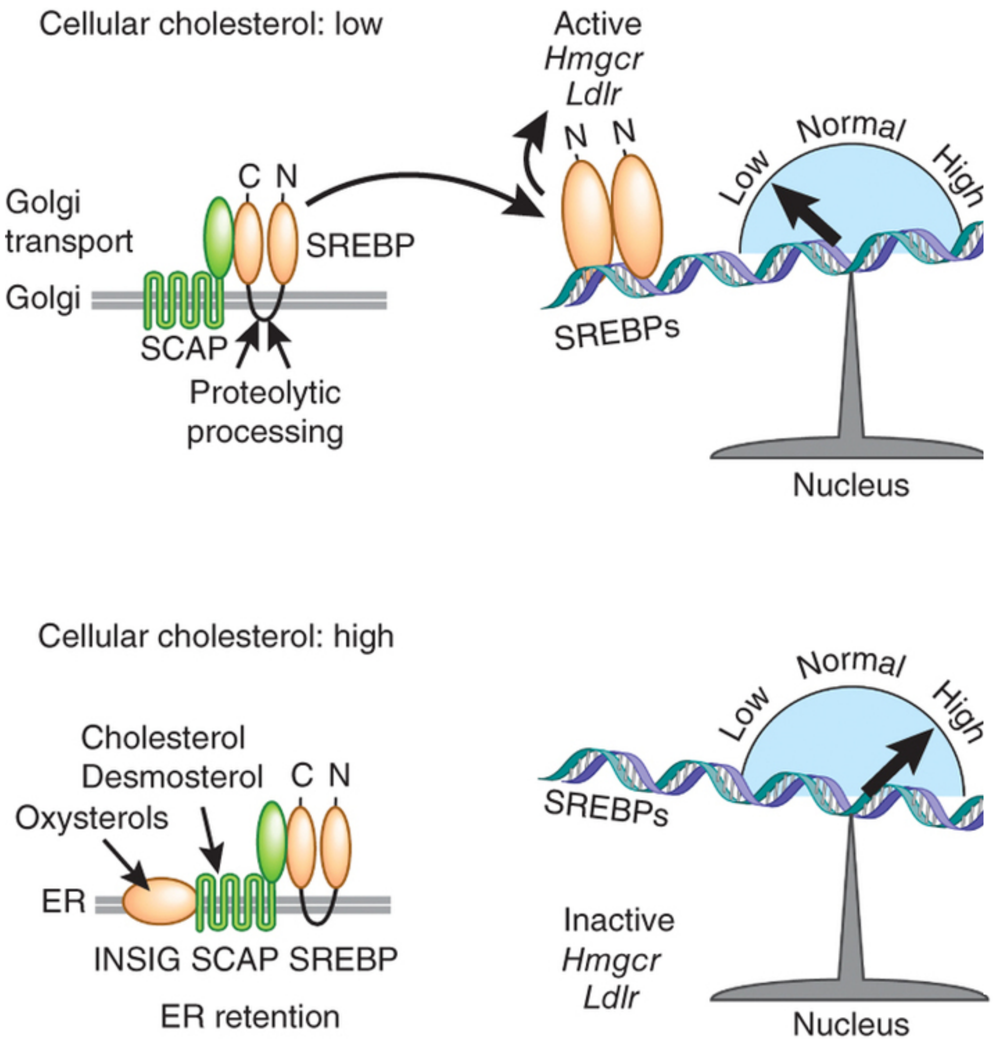
- Intracellular
  - Substrate and products
  - Allosteric activators/inhibitors
  - Metabolites that activate post-translational modifications
  - Transcription factors that respond to metabolite levels
- Integrated metabolic control
  - Endocrine signaling
  - Neural synapses

Example Post-Translational Metabolic Control System

- AMP activated protein kinase (AMPK)
- Activated when AMP/ATP level is high
- What sorts of things would you expect this kinase may regulate?



Example Transcriptional Control System



Basic endocrine regulation of nutrition

Hormones

- Postprandial
  - Insulin
- Fasting:
  - Glucagon – short term glucose
  - Adrenaline – glucose for muscle
  - Cortisol – glucose for brain

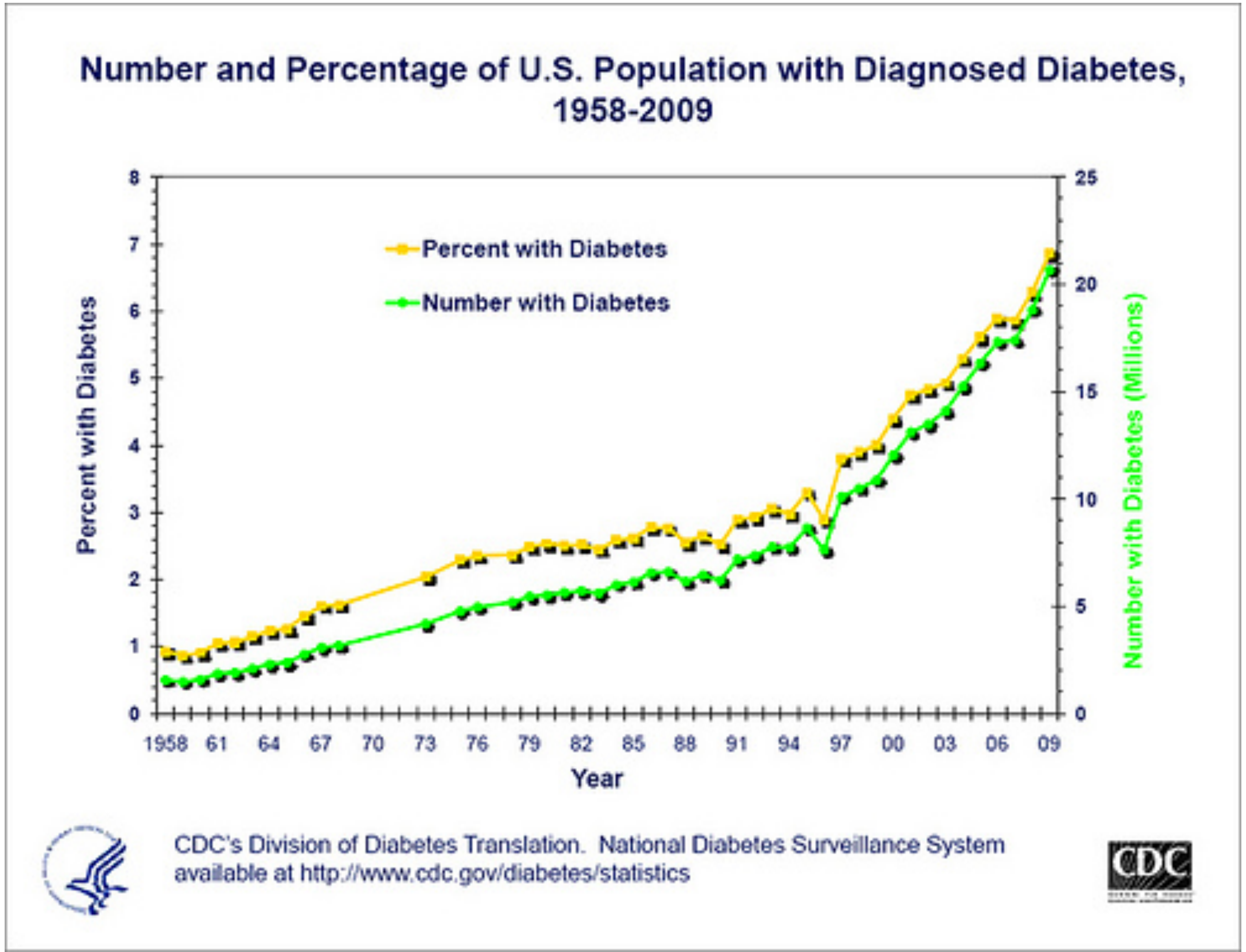
Metabolic Processes

- Glucose
  - Gluconeogenesis
  - Glucose Oxidation
  - Glycogen Storage
  - Glucose Transport (into Tissues)
- Lipids
  - Fatty Acid Release and Export (Lipolysis)
  - Fatty Acid Import
  - Triglyceride Synthesis
  - Fatty Acid Oxidation
- Proteins and Amino Acids
  - Protein Synthesis or Breakdown
  - Amino Acid Synthesis or Catabolism
  - Amino Acid Import or Export

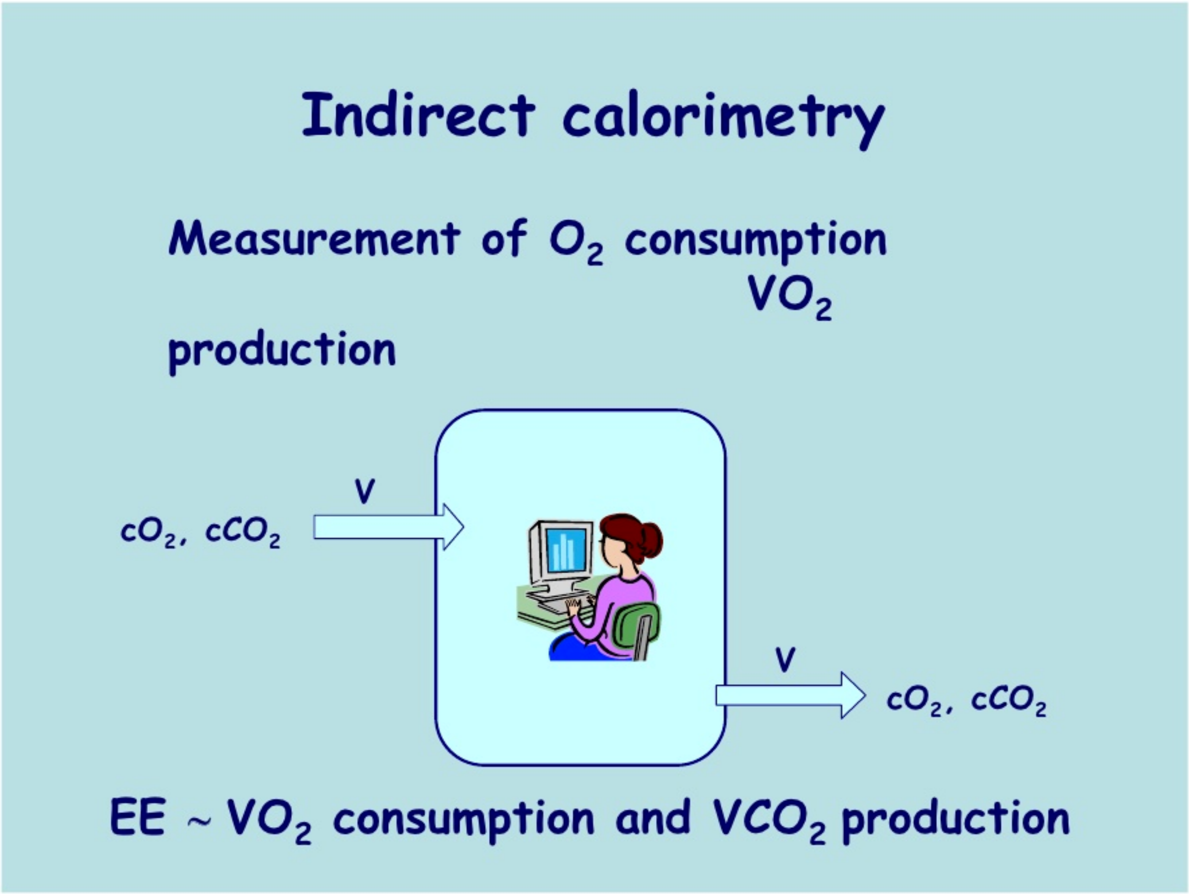
What should these hormones do?

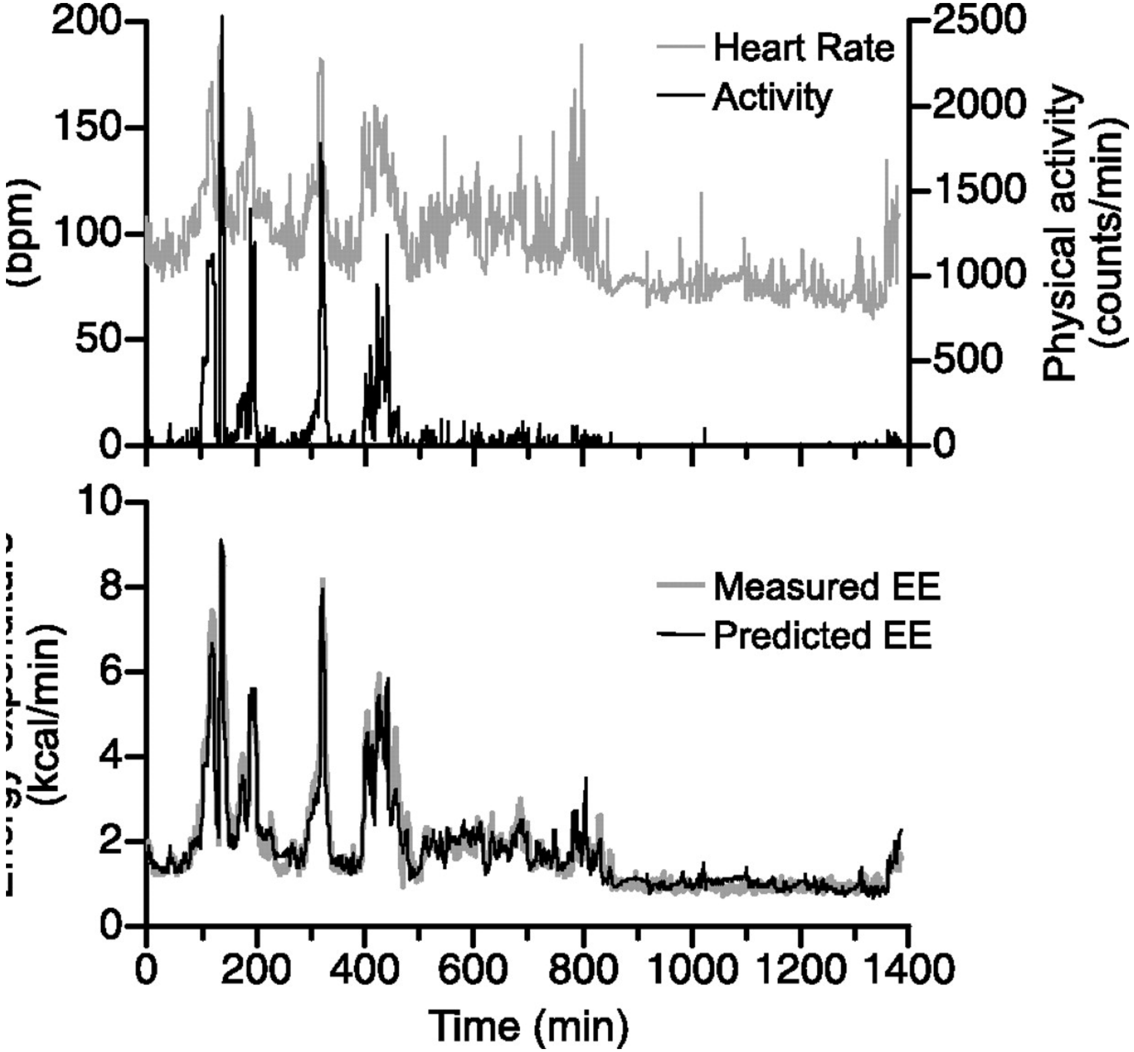
Tissue	Carbohydrate Metabolism	Protein Metabolism	Lipid Metabolism
Muscle			
Liver			
Fat			

Metabolic Control Gone Awry, the Case of Type 2 Diabetes

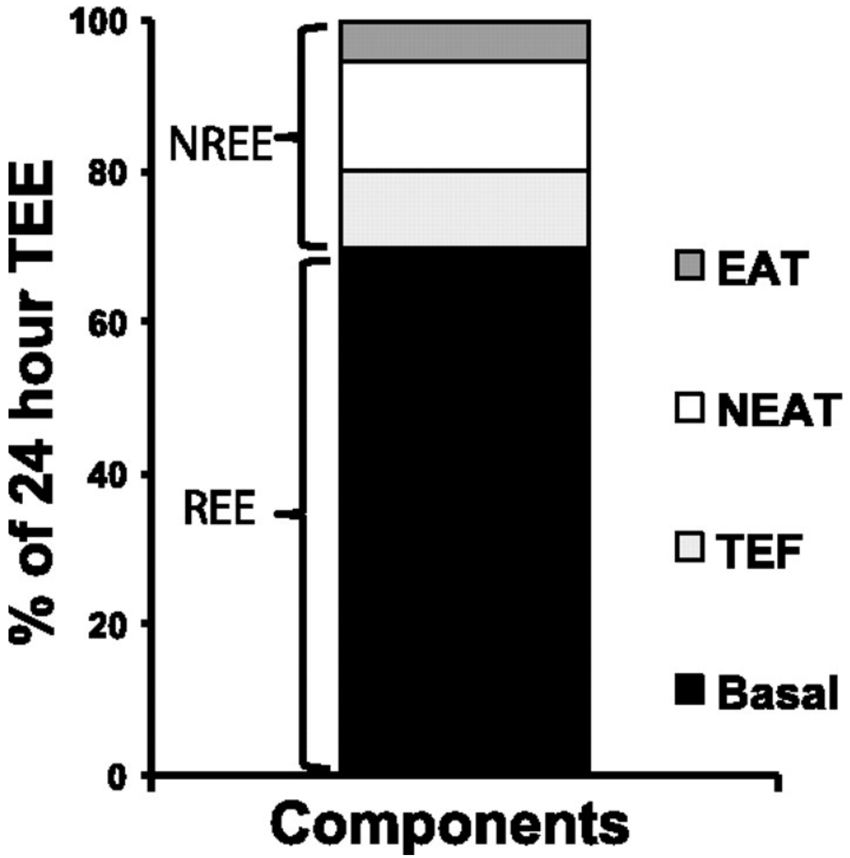


How do we measure metabolic rates





Parts of the Metabolic Rate Metabolic Rate

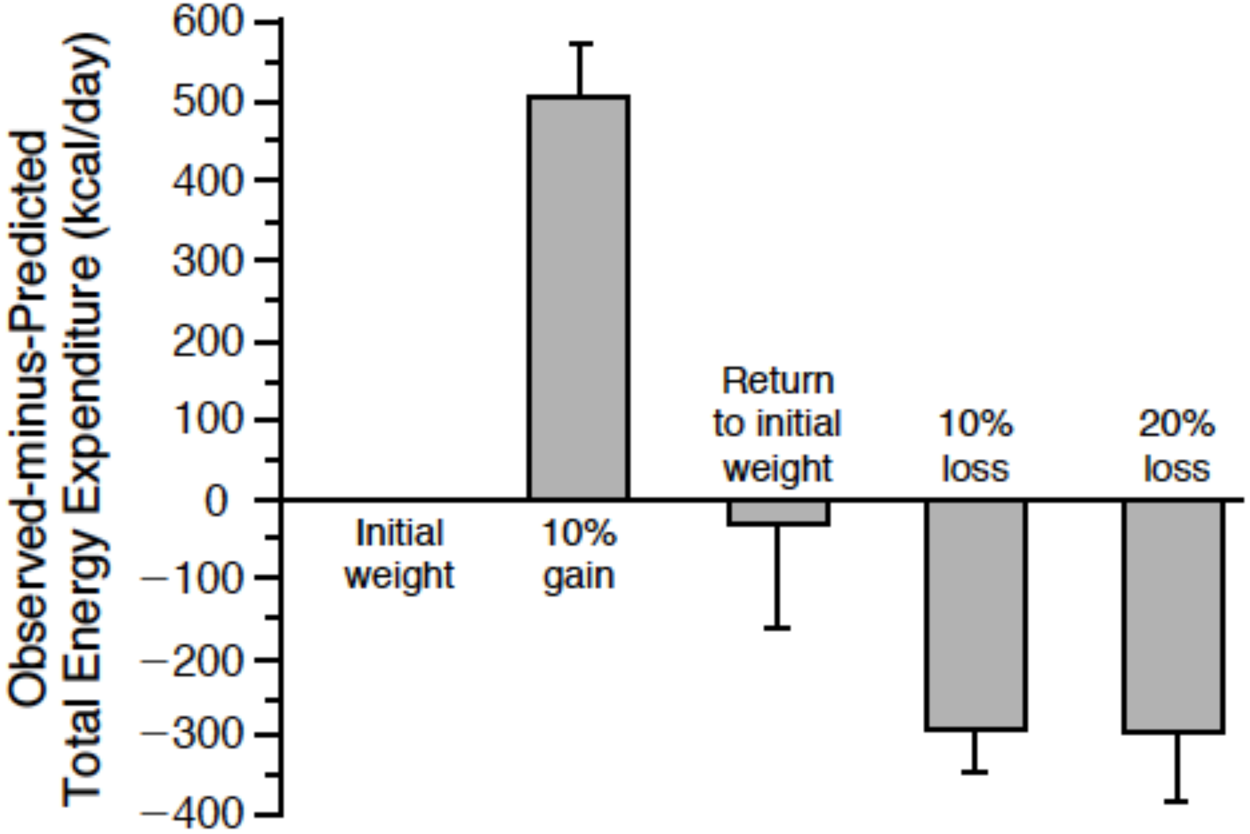


Maclean PS, Bergouignan A, Cornier M-A, Jackman MR. Biology's response to dieting: the impetus for weight regain. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2011;301(3):R581–R600. http://dx.doi.org/10.1152/ajpregu.00755.2010

How do you think over-eating alters the basal metabolic rate?

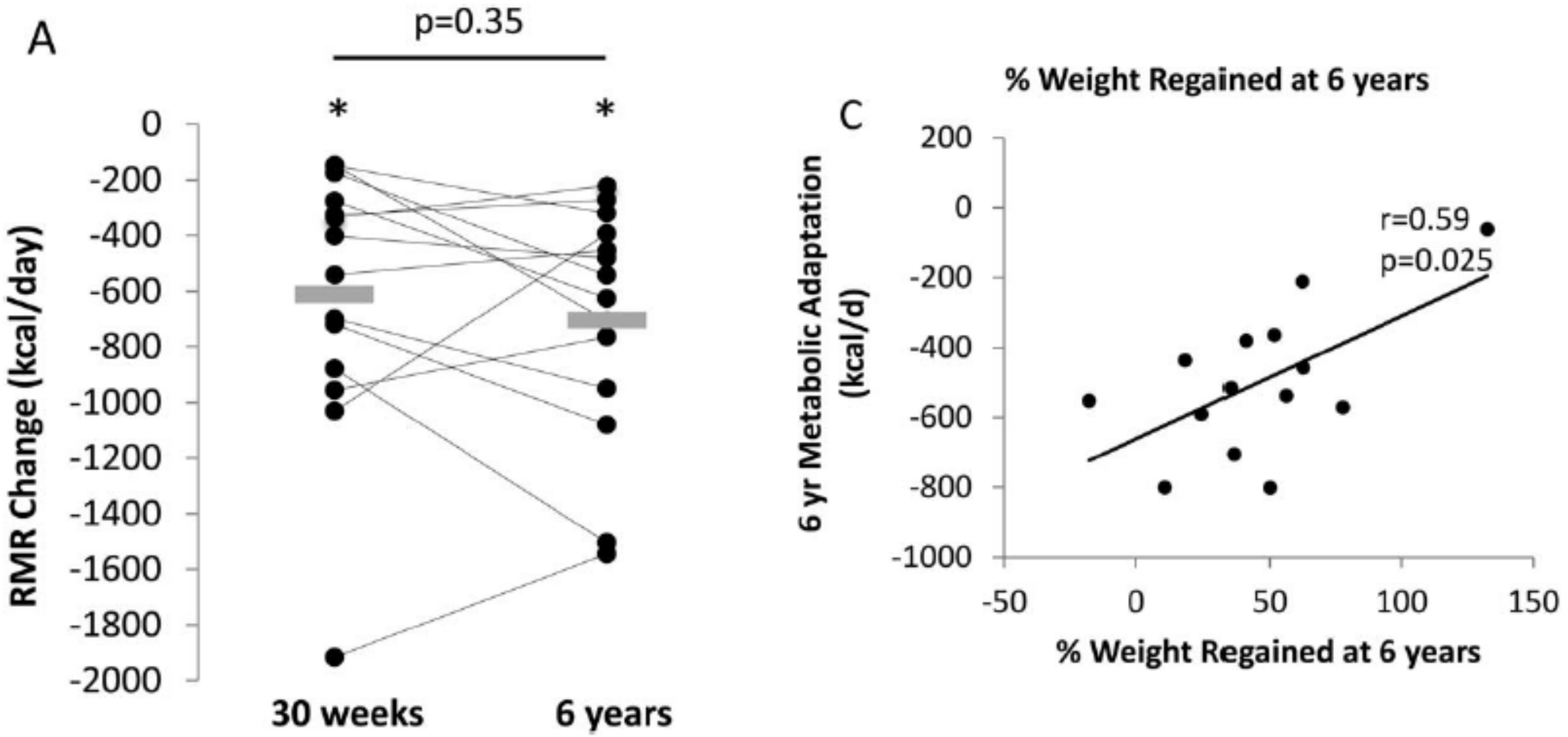
- I think metabolic rate would be lower after over-eating
- I think metabolic rate would be higher after over-eating
- What do you think fasting or caloric restriction would do to the metabolic rate?

Over/underfeeding and metabolic rates



Leibel R, Osenbaum MIR, Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. *N. Engl. J. Med.* 1995;332(10):621–8. http://dx.doi.org/10.1056/NEJM199503093321001

The Biggest Loser Follow-Up Study



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