THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

Energetics: Scientific Foundations of Obesity and Other Health Aspects

Energetics at the Molecular Level

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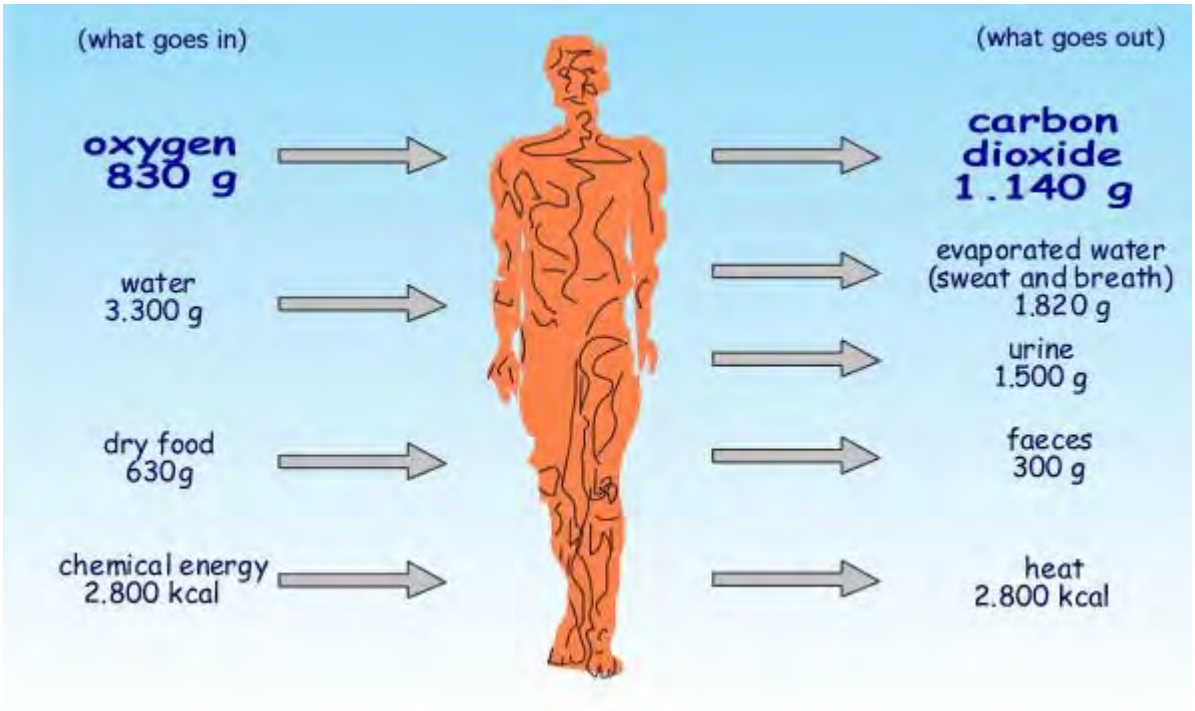
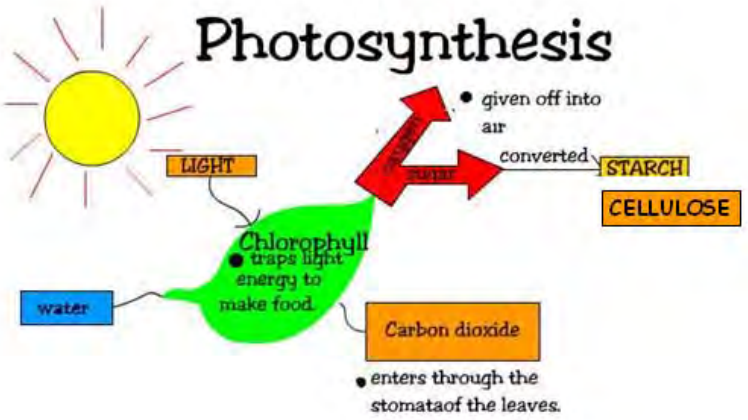
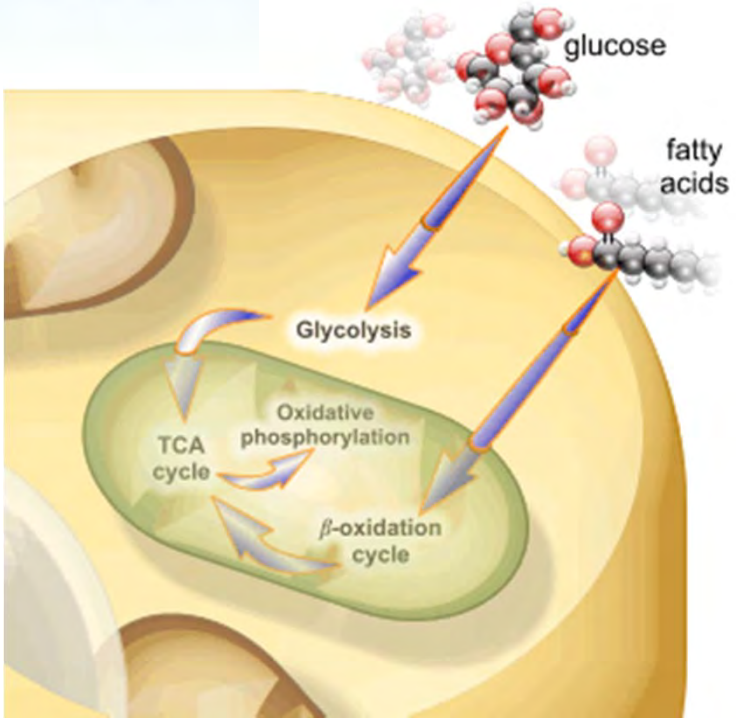
UAB Nutrition Sciences

UAB COMPREHENSIVE CENTER FOR HEALTHY AGING

UAB COMPREHENSIVE CARDIOVASCULAR CENTER


(what goes in)
(what goes out)
oxygen
830 g
carbon
dioxide
1.140 g
water
3.300 g
evaporated water
(sweat and breath)
1.820 g
urine
1.500 g
dry food
630g
faeces
300 g
chemical energy
2.800 kcal
heat
2.800 kcal


Photosynthesis
LIGHT
given off into
air
converted
STARCH
CELLULOSE
Chlorophyll
traps light
energy to
make food.
water
Carbon dioxide
enters through the
stomataof the leaves.

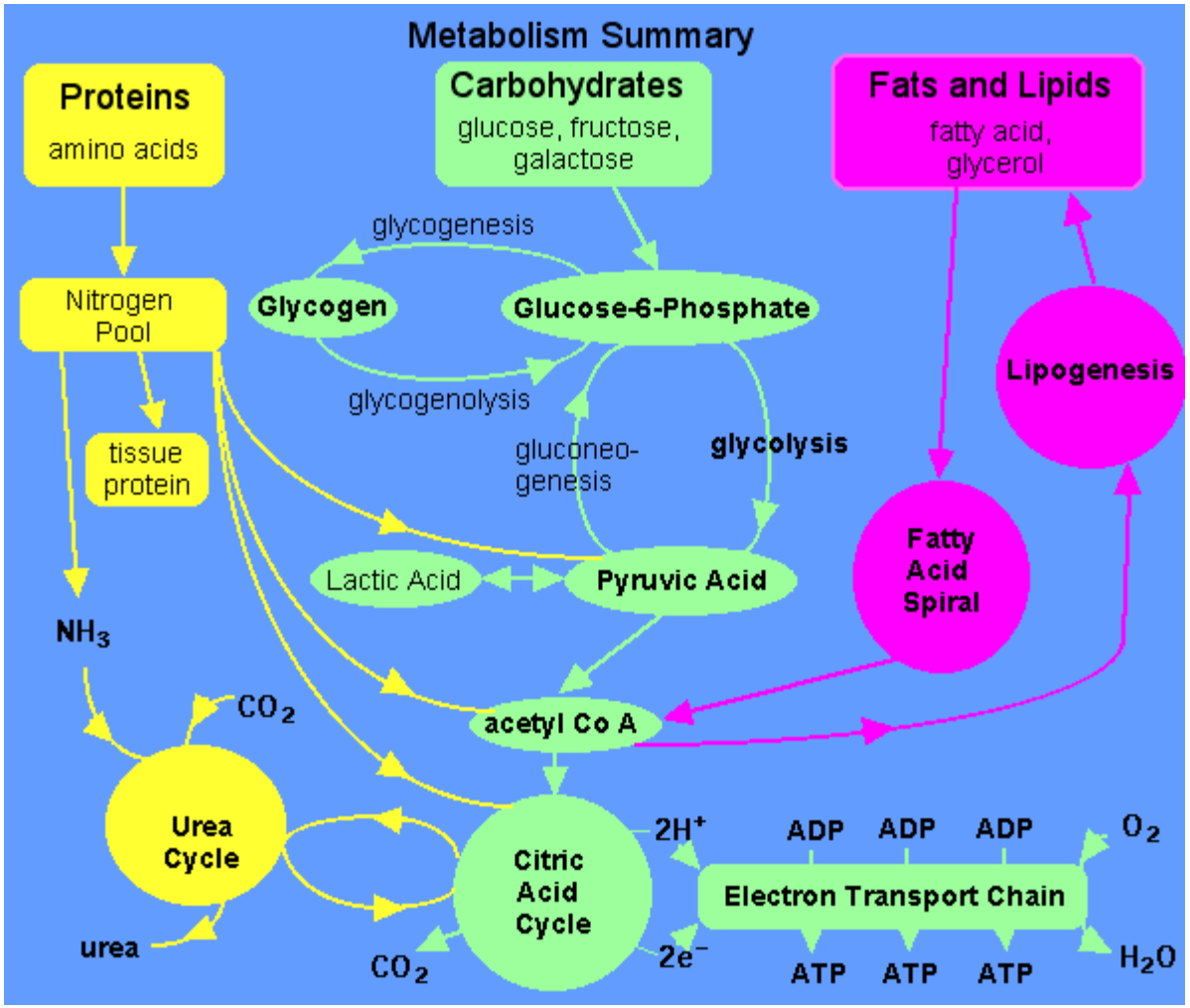

glucose
fatty
acids
Glycolysis
TCA
cycle
Oxidative
phosphorylation
β-oxidation
cycle

Overview of Metabolism

Water

Vitamins

Minerals



Organic Compounds:

Hydrogen: H

Oxygen: O

Carbon: C

Nitrogen: N

Phosphorous: P

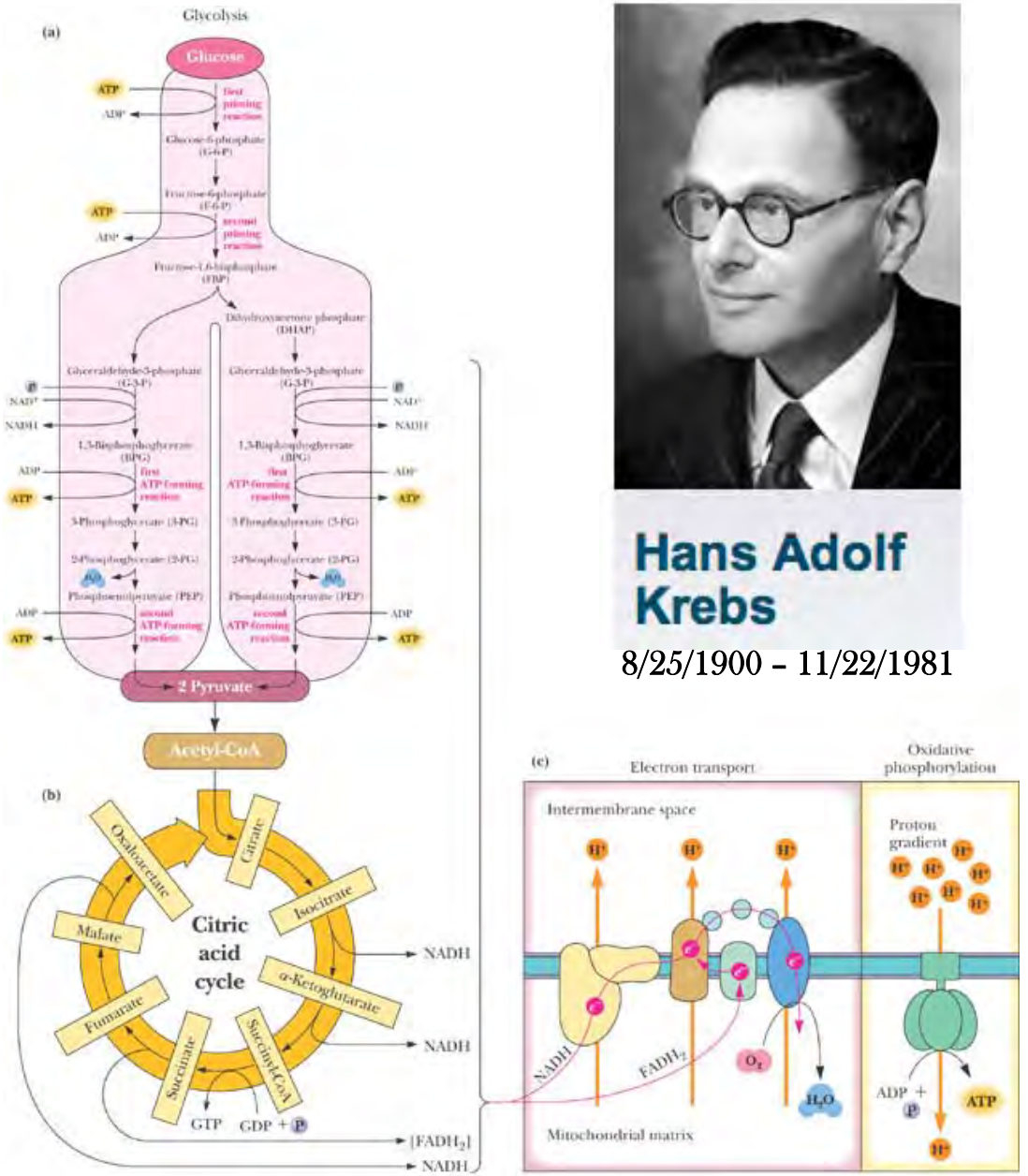
Sulfur: S

http://www.elmhurst.edu/~chm/vchembook/600glycolysis.html

Energy Metabolism Overview

(a) Pyruvate produced in glycolysis is oxidized in **(b)** the tricarboxylic acid (TCA) cycle. **(c)** Electrons liberated in this oxidation flow through the electron-transport chain and drive the synthesis of ATP in oxidative phosphorylation. In eukaryotic cells, this overall process occurs in mitochondria.

'1937' Krebs cycle =
TCA cycle =
Citric acid cycle



Hans Adolf Krebs

8/25/1900 – 11/22/1981

Overview: Harnessing Energy – Chemical Bonds

Complete oxidation of glucose:

$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O \quad \Delta G^{o\prime} = -2823\ kJ\ mol^{-1}$

Electron transfer:

1. **Oxidation of glucose carbon atoms**
   $C_6H_{12}O_6 + 6H_2O \rightarrow 6CO_2 + 24H^+ + 24e^-$

2. **Reduction of molecular oxygen**
   $6O_2 + 24H^+ + 24e^- \rightarrow 12H_2O$

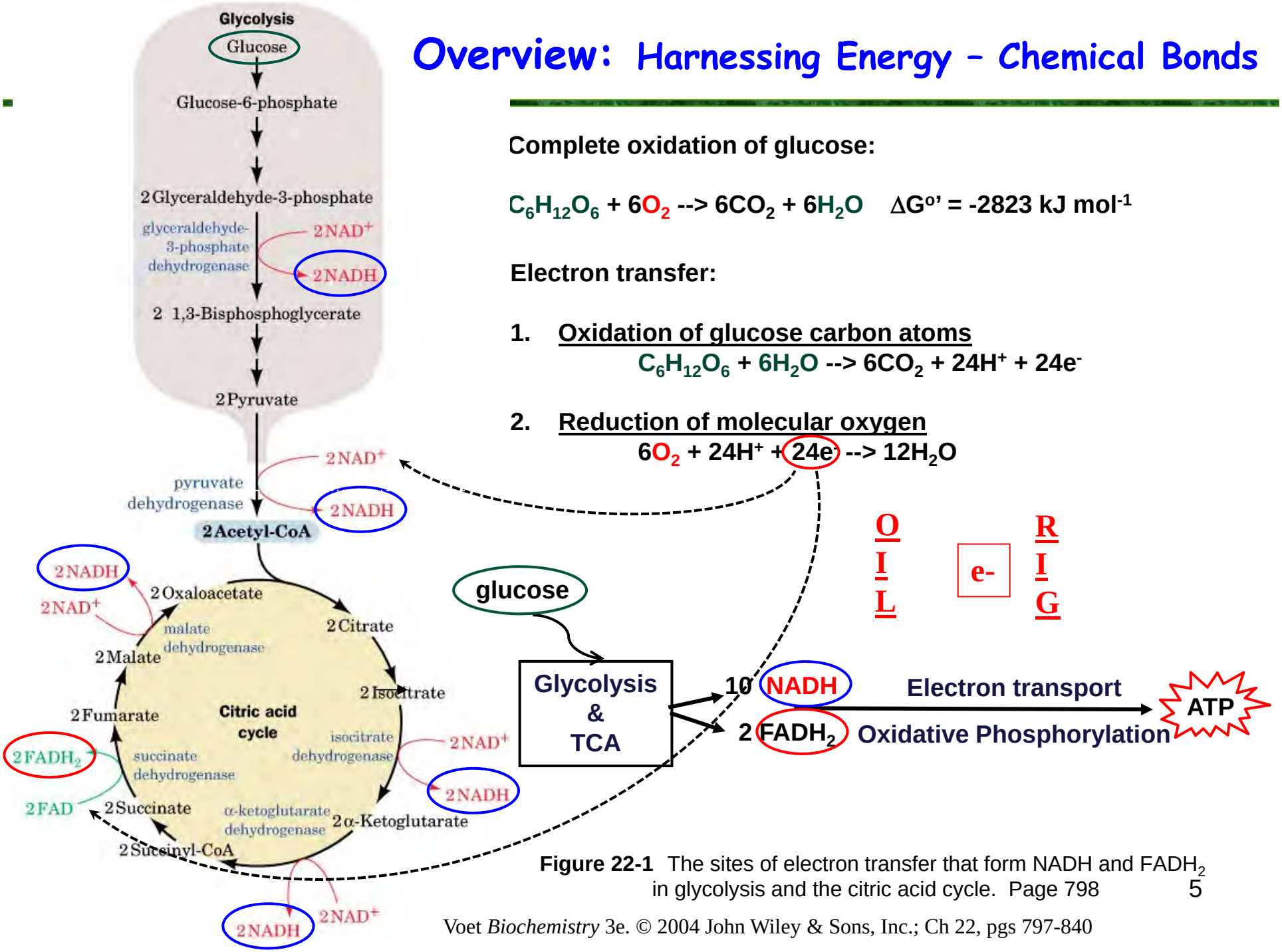
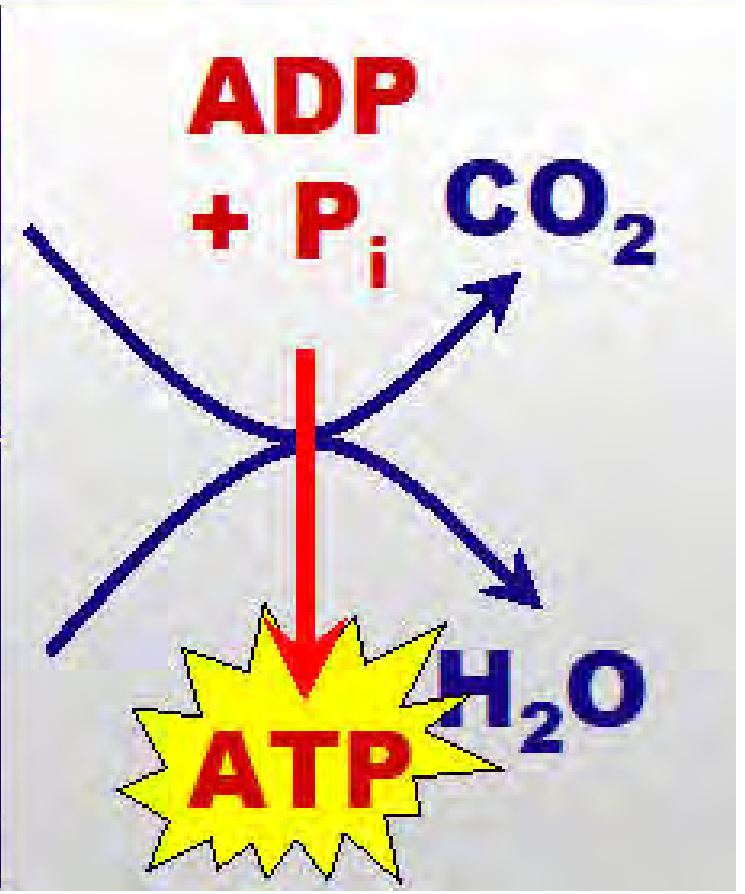


Figure 22-1 The sites of electron transfer that form NADH and $FADH_2$ in glycolysis and the citric acid cycle. Page 798

Where does Metabolism Start?

We Burn Food



http://www.medbio.info/Horn/Body%20Energy/body_energy.htm

Cellular Metabolism

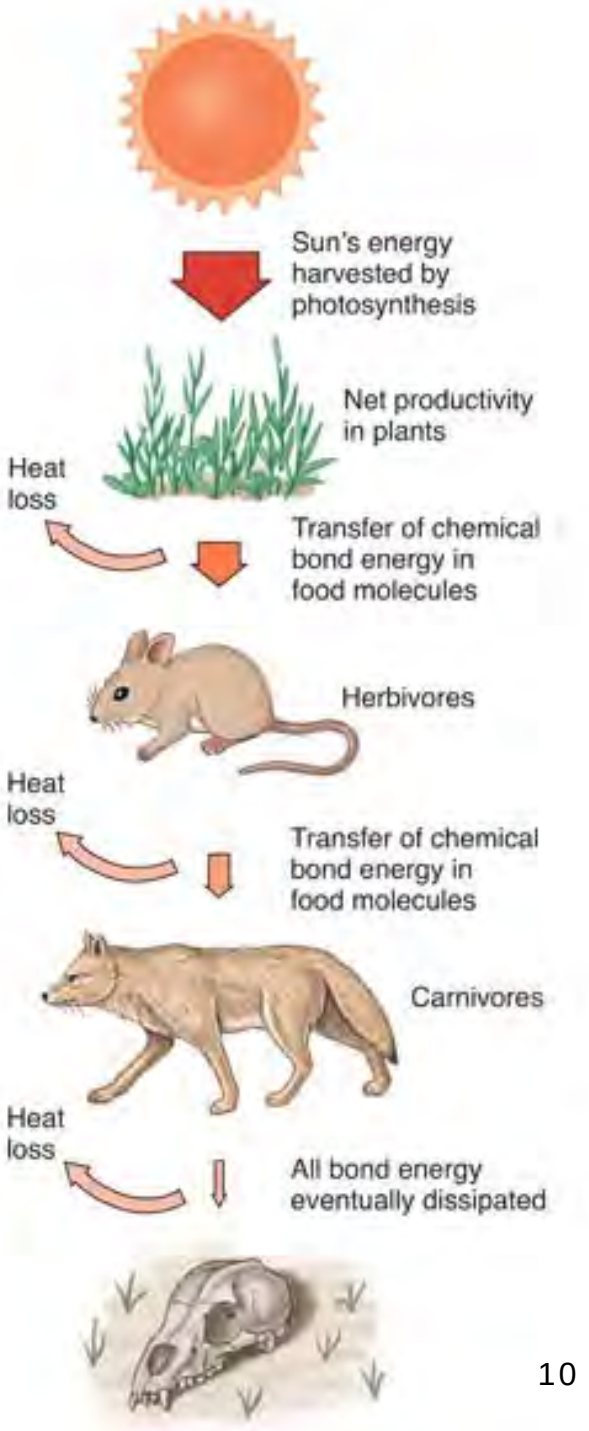
- **Cellular metabolism** refers to all of the chemical processes that occur inside living cells.

Energy

- Energy can exist in two states:
  - **Kinetic energy** – energy of motion.
  - **Potential energy** – stored energy.
    - Chemical energy – potential energy stored in bonds, released when bonds are broken.
- Energy can be transformed form one state to another.

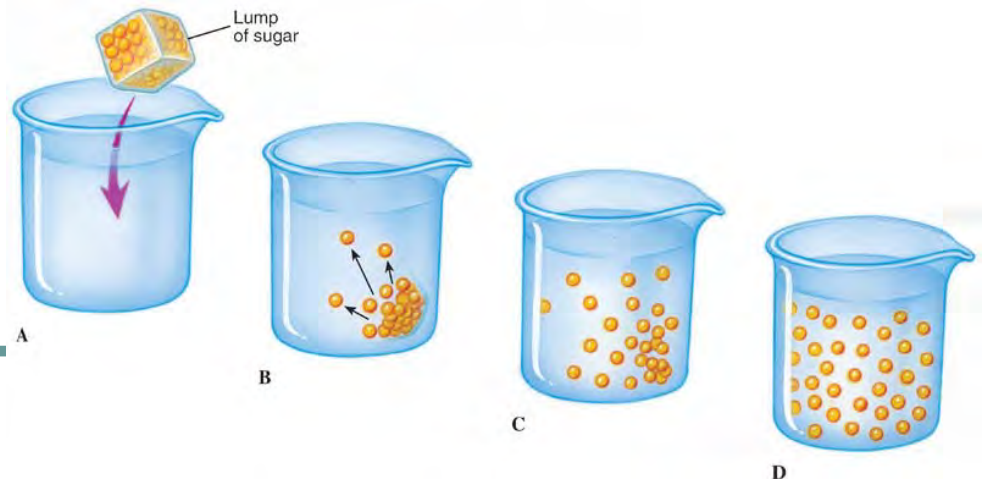
Energy

- The ultimate source of energy for most living things is the sun.



Laws of Thermodynamics

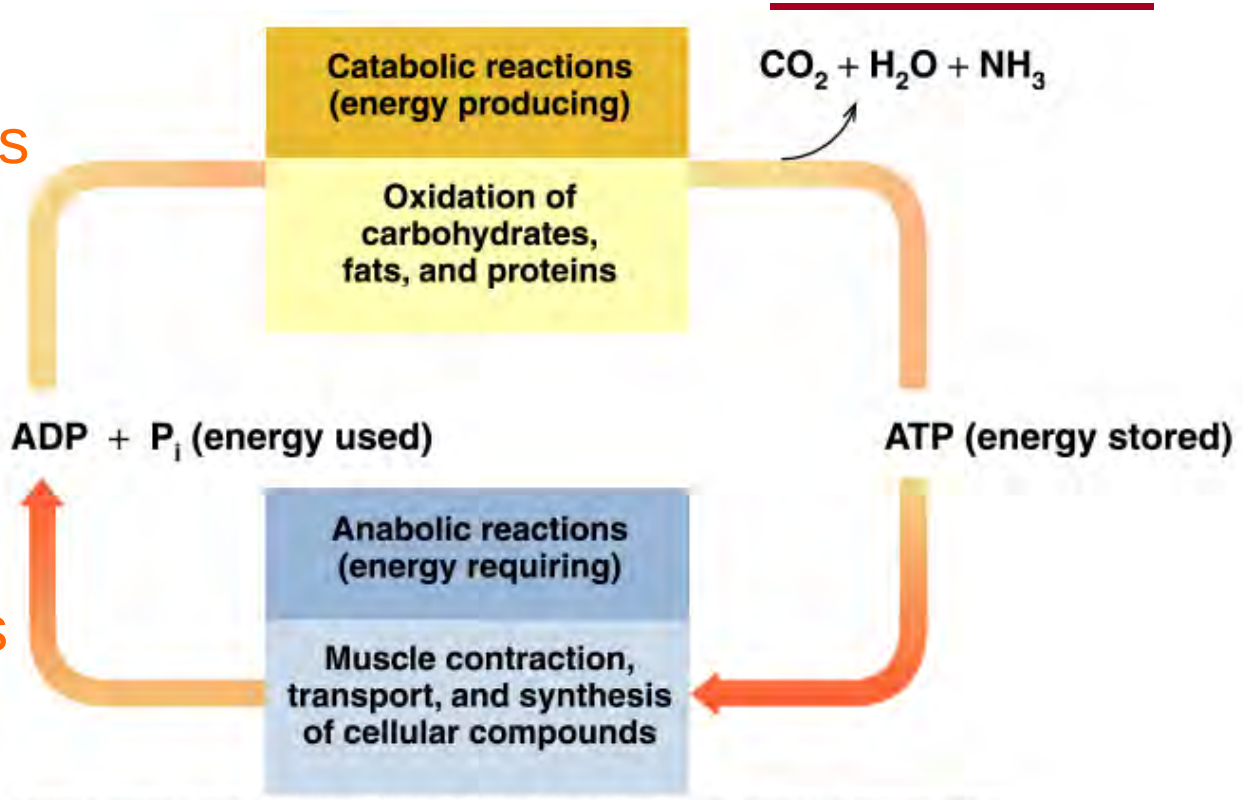
- **First law of thermodynamics** – energy cannot be created or destroyed – only transformed.
- **Second law of thermodynamics** – a *closed* system moves toward entropy, increasing disorder.
  - Living systems are open systems that maintain organization and increase it during development.



Metabolism

Metabolism involves

- Catabolic reactions that break down large, complex molecules to provide energy and smaller molecules.
- Anabolic reactions that use ATP energy to build larger molecules.



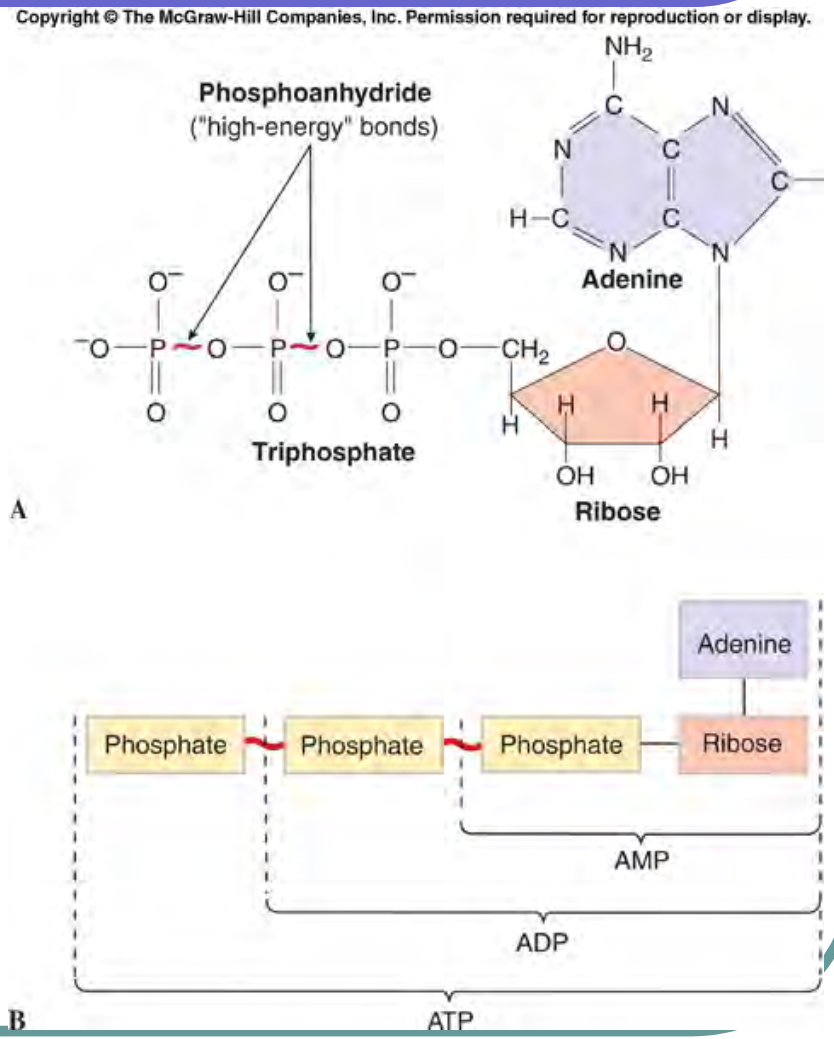
Timberlake, *General, Organic, and Biological Chemistry*, Copyright © Pearson Education Inc., publishing as Benjamin Cummings

Importance of ATP

- **Endergonic** reactions require energy to proceed.
- Coupling an energy-requiring reaction with an energy-yielding reaction can drive endergonic reactions.
- **ATP** is the most common intermediate in coupled reactions.

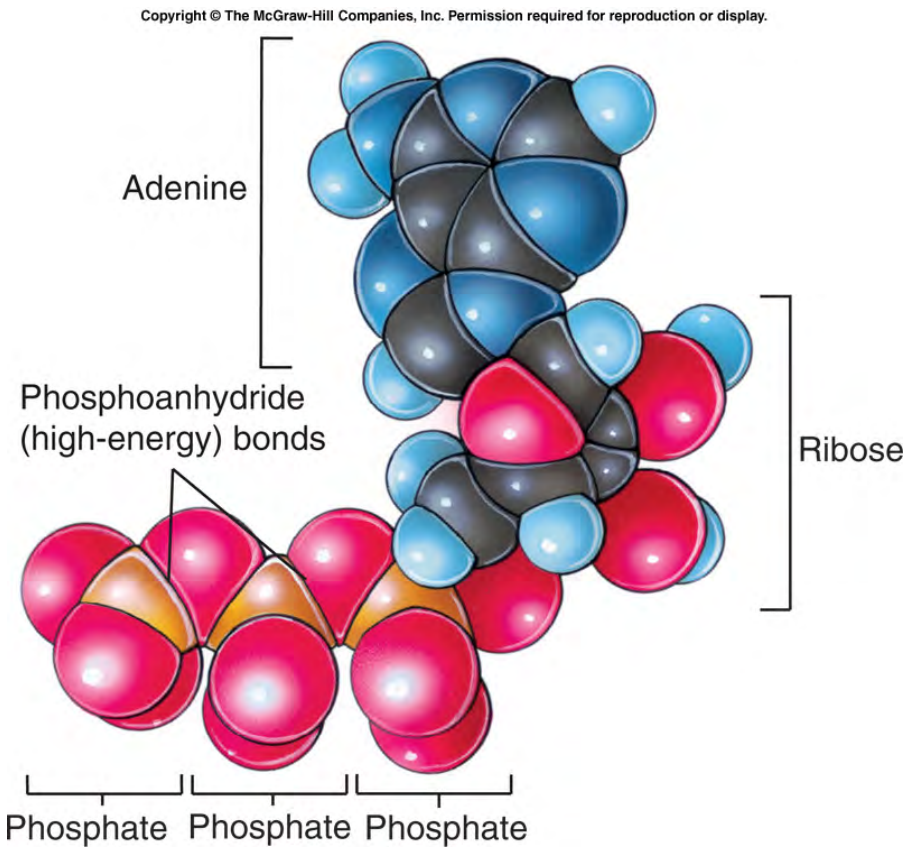
Importance of ATP

- ATP consists of adenosine (adenine + ribose) and a triphosphate group.
  - The bonds between the phosphate groups are high energy bonds.
  - A-P~P~P



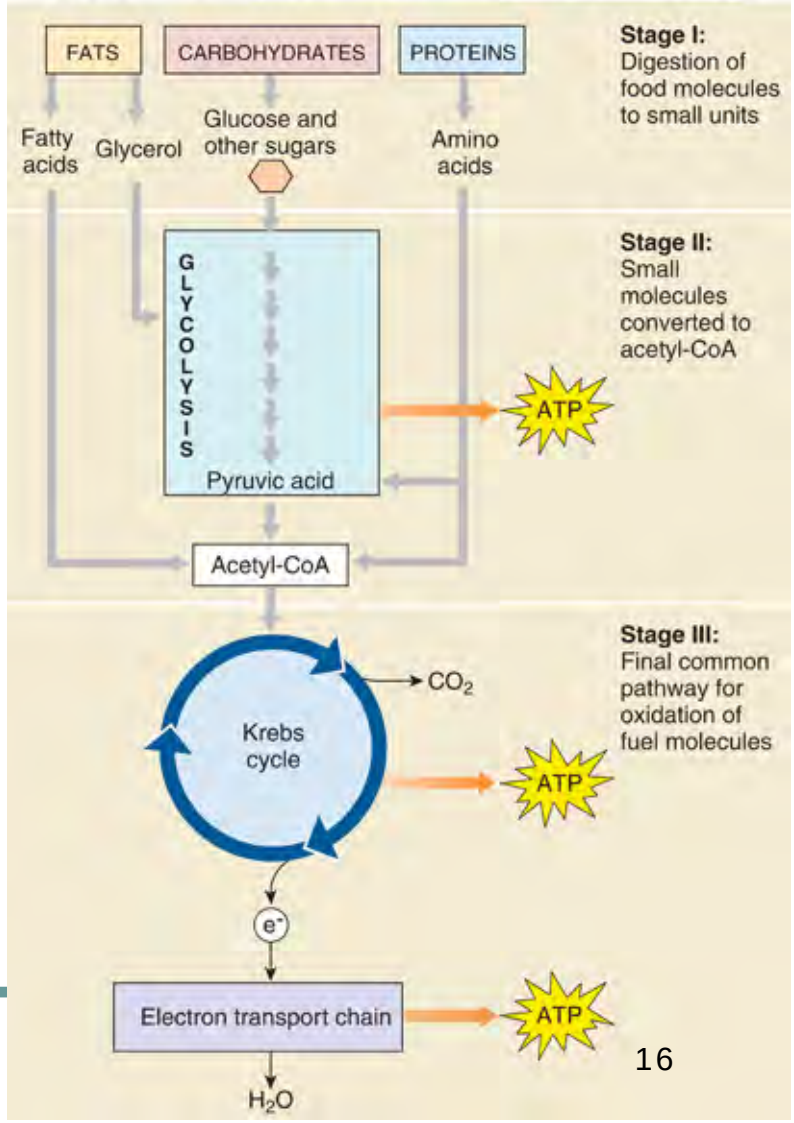
Importance of ATP

- Phosphates have negative charges.
  - Takes lots of energy to hold 3 in a row!
  - Ready to spring apart.
  - So, ATP is very reactive.



Cellular Respiration - 3 Stages

- Food is digested to break it into smaller pieces – no energy production here.
- **Glycolysis** – coupled reactions used to make ATP.
  - Occurs in cytoplasm
  - Doesn't require O_2
- **Oxidation** – harvests electrons and uses their energy to power ATP production.
  - Only in mitochondria
  - More powerful



Stages of Metabolism

Catabolic reactions:

Stage 1: Digestion and hydrolysis

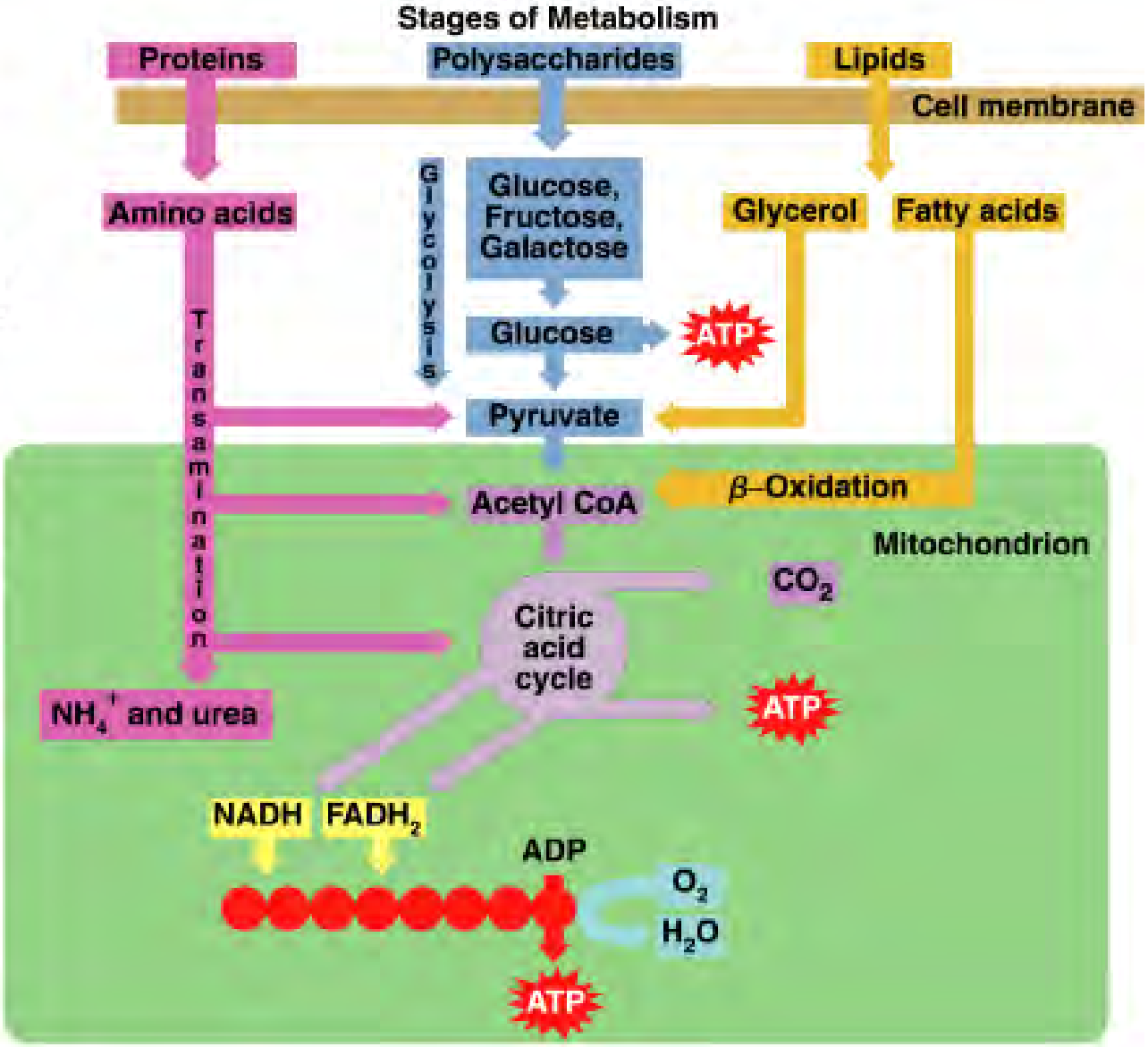
break down large molecules to smaller ones that enter the bloodstream.

Stage 2: Degradation

Further breaking and some oxidation of molecules to 2 & 3-carbon compounds.

Stage 3: Oxidation

of small molecules to CO_2 & H_2O in the citric acid cycle and electron transport provides energy for ATP synthesis.



Glycolysis

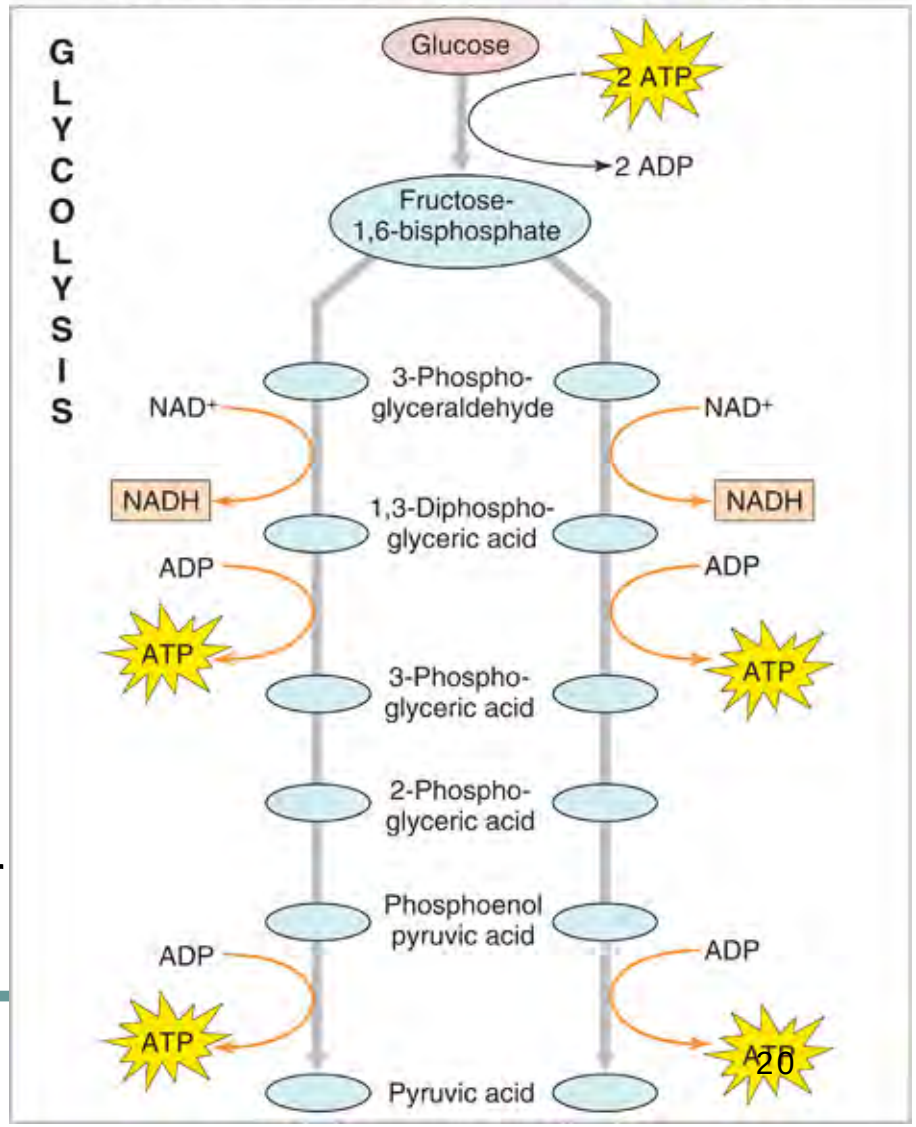
- **Glycolysis** – the first stage in cellular respiration.
  - A series of enzyme catalyzed reactions.
  - Glucose converted to pyruvic acid.
  - Small number of ATPs made (2 per glucose molecule), but it is possible in the absence of oxygen.
  - All living organisms use glycolysis.

Glycolysis: General Functions

- Provide ATP energy
- Generate intermediates for other pathways
  - Hexose monophosphate pathway
  - Glycogen synthesis
  - Pyruvate dehydrogenase
    - Fatty acid synthesis
    - Krebs' Cycle
  - Glycerol-phosphate (TG synthesis)

Glycolysis

- Uphill portion primes the fuel with phosphates.
  - *Uses* 2 ATPs
- Fuel is cleaved into 3-C sugars which undergo oxidation.
  - NAD^+ accepts e^-s & 1 H^+ to produce NADH
  - NADH serves as a carrier to move high energy e^-s to the final electron transport chain.
- Downhill portion produces 2 ATPs per 3-C sugar (4 total).
  - Net production of 2 ATPs per glucose molecule.



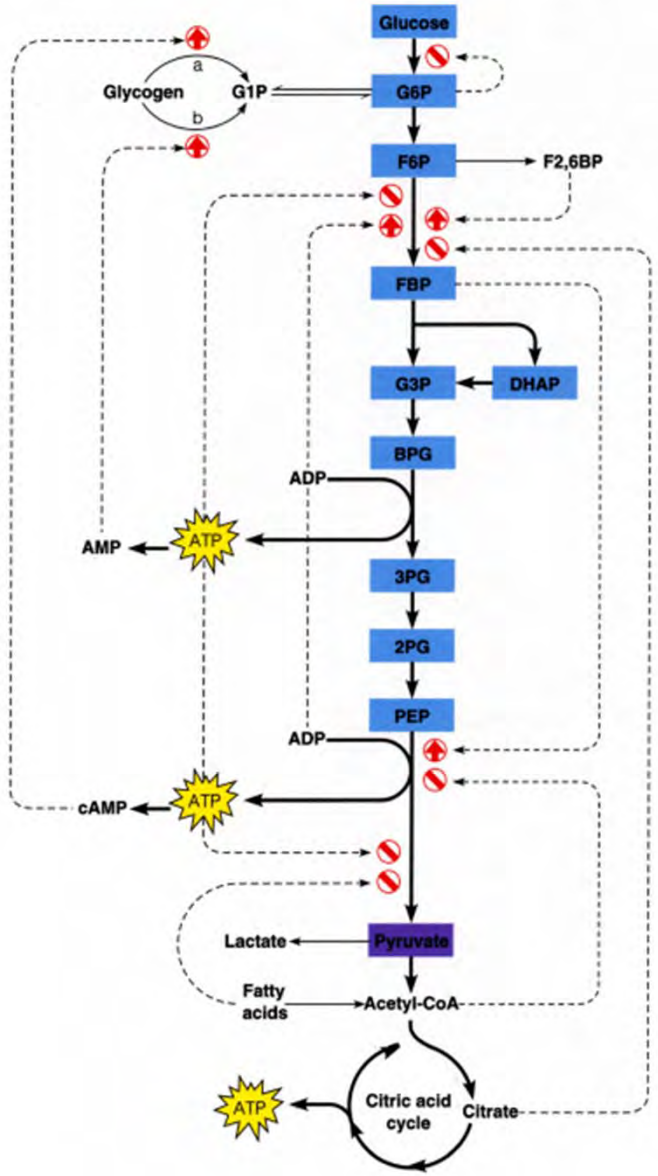
Glycolysis

- Summary of the enzymatically catalyzed reactions in glycolysis:

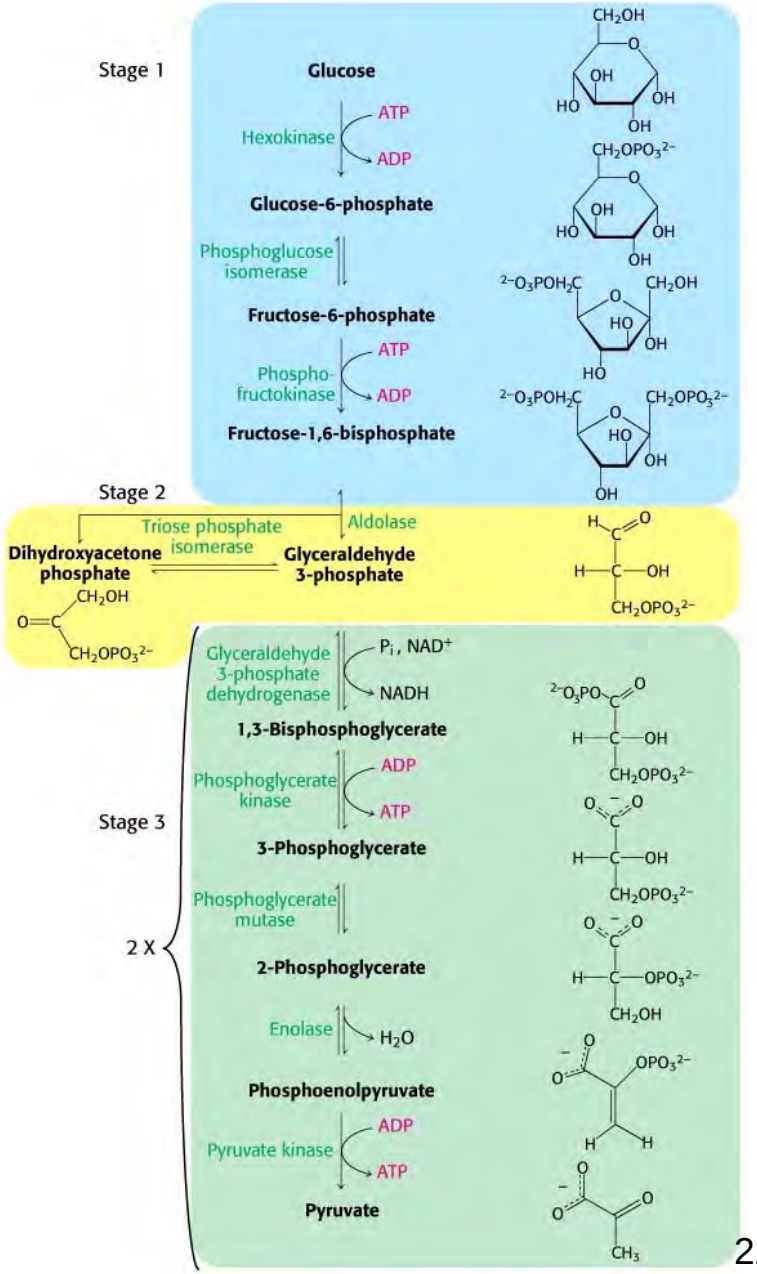
Glucose + 2ADP + 2P_i + 2 NAD^+ ⟶ 2 Pyruvic acid + 2 NADH + 2ATP

http://www.youtube.com/watch?v=3GTjQTqUuOw&list=FL9N_Px072WuVorSwDfqf-9w&index=4&feature=plpp

Figure 13.11 Overview of the regulation of glycolysis



From Mathews and van Holde: *Biochemistry 2/e.* © The Benjamin/Cummings Publishing Co., Inc.



Regulation of Glycolysis

Regulatory mechanisms controlling glycolysis include allosteric and covalent modification mechanisms.

Glycolysis is **regulated** reciprocally from **gluconeogenesis**. Molecules, such as **F2,6BP**, that turn on **glycolysis**, turn off gluconeogenesis. Conversely, **acetyl-CoA** turns on gluconeogenesis, but turns off **glycolysis**. See **Figure 16.6**

The principle enzymes of **glycolysis** involved in regulation are hexokinase (reaction 1), phosphofructokinase (reaction 3), and pyruvate kinase (reaction 10):

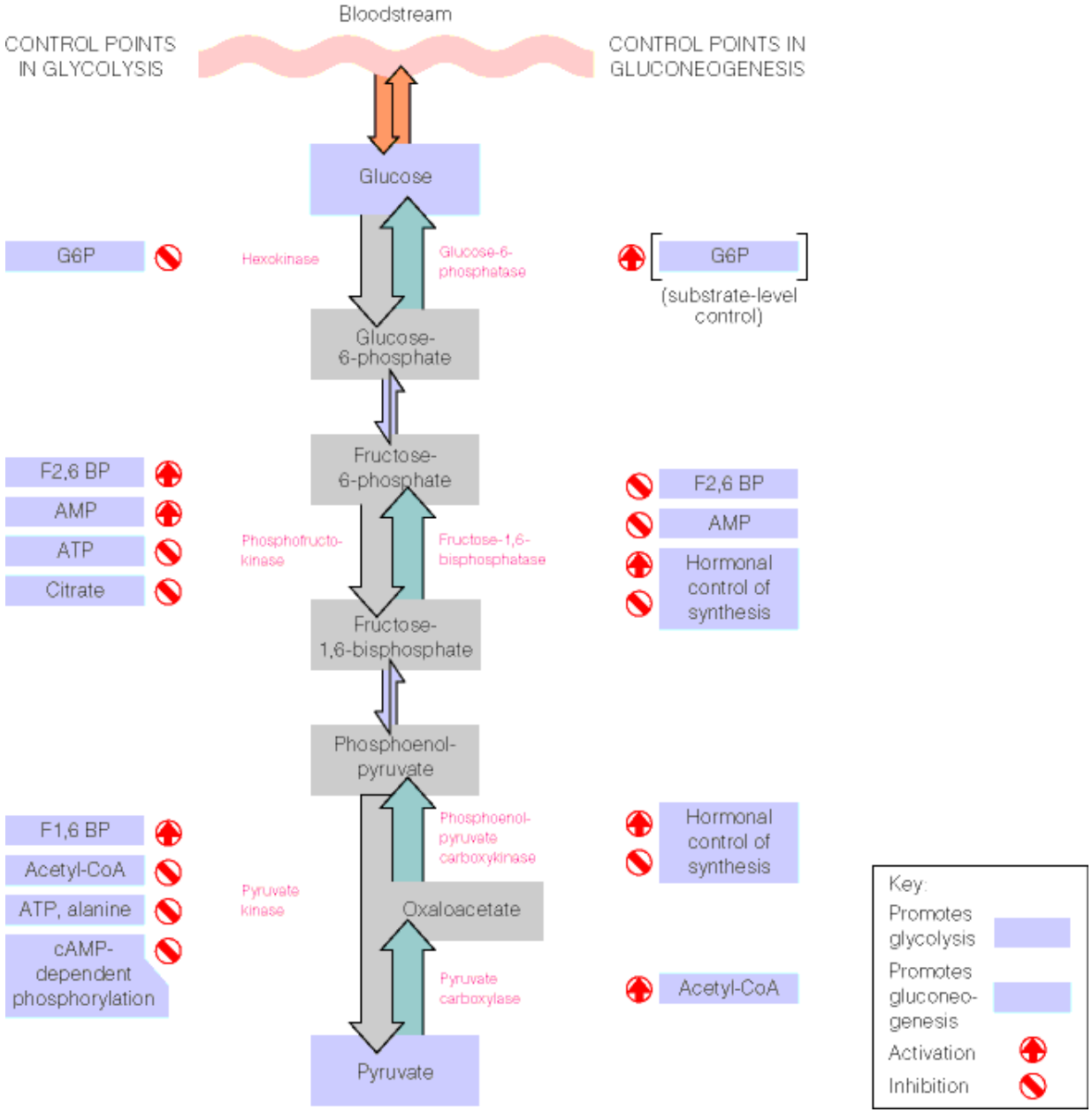
1. **Hexokinase** is allosterically inhibited by glucose-6-phosphate (**G6P**). That is, the enzyme for the first reaction of glycolysis is inhibited by the product of the first reaction. As a result, glucose and **ATP** (in reactions 1 and 3) are not committed to glycolysis unless necessary.

2. **Phosphofructokinase** (PFK) is a major control point for glycolysis. PFK is allosterically inhibited by ATP and citrate, allosterically activated by **AMP**, **ADP**, and F2,6BP. Thus, carbon movement through glycolysis is inhibited at PFK when the cell contains ample stores of ATP and oxidizable substrates. Additionally, PFK is activated by AMP and ADP because they indicate low levels of ATP in the cell. F2,6BP is the major activator, though, because it reciprocally inhibits **fructose 1,6 bisphosphatase**, which is the gluconeogenic enzyme that catalyzes the reversal of this step.

3. **Pyruvate kinase** is allosterically inhibited by acetyl-CoA, ATP, and **Alanine**; allosterically activated by **F1,6BP**, and inhibited by cAMP-dependent phosphorylation.
   Note that several of the allosteric regulators are products of other metabolic pathways or are made in other metabolic pathways. These include acetyl-CoA, AMP, F2,6BP, and G1P, (readily converted into G6P). By having regulation dependent on other pathways, glycolysis is coordinately controlled with these pathways as well.

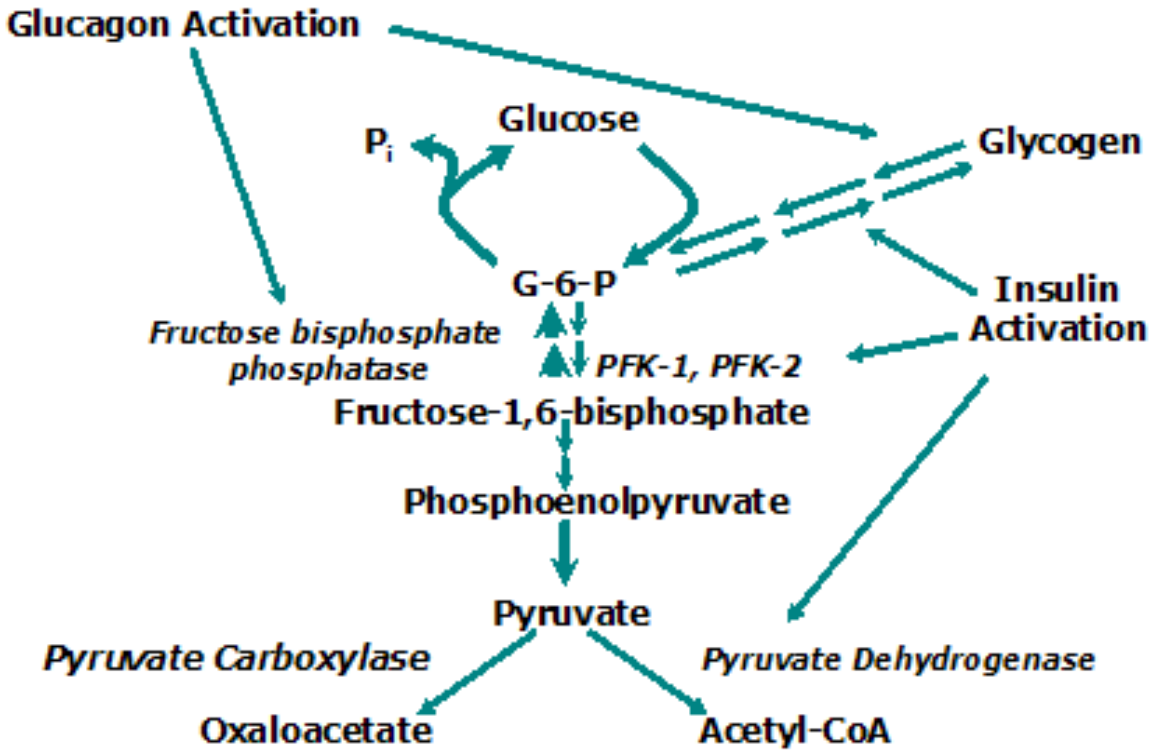
http://www.pearsonhighered.com/mathews/ch13/c13rog.htm

Figure 16.6: Major control mechanisms affecting glycolysis and gluconeogenesis



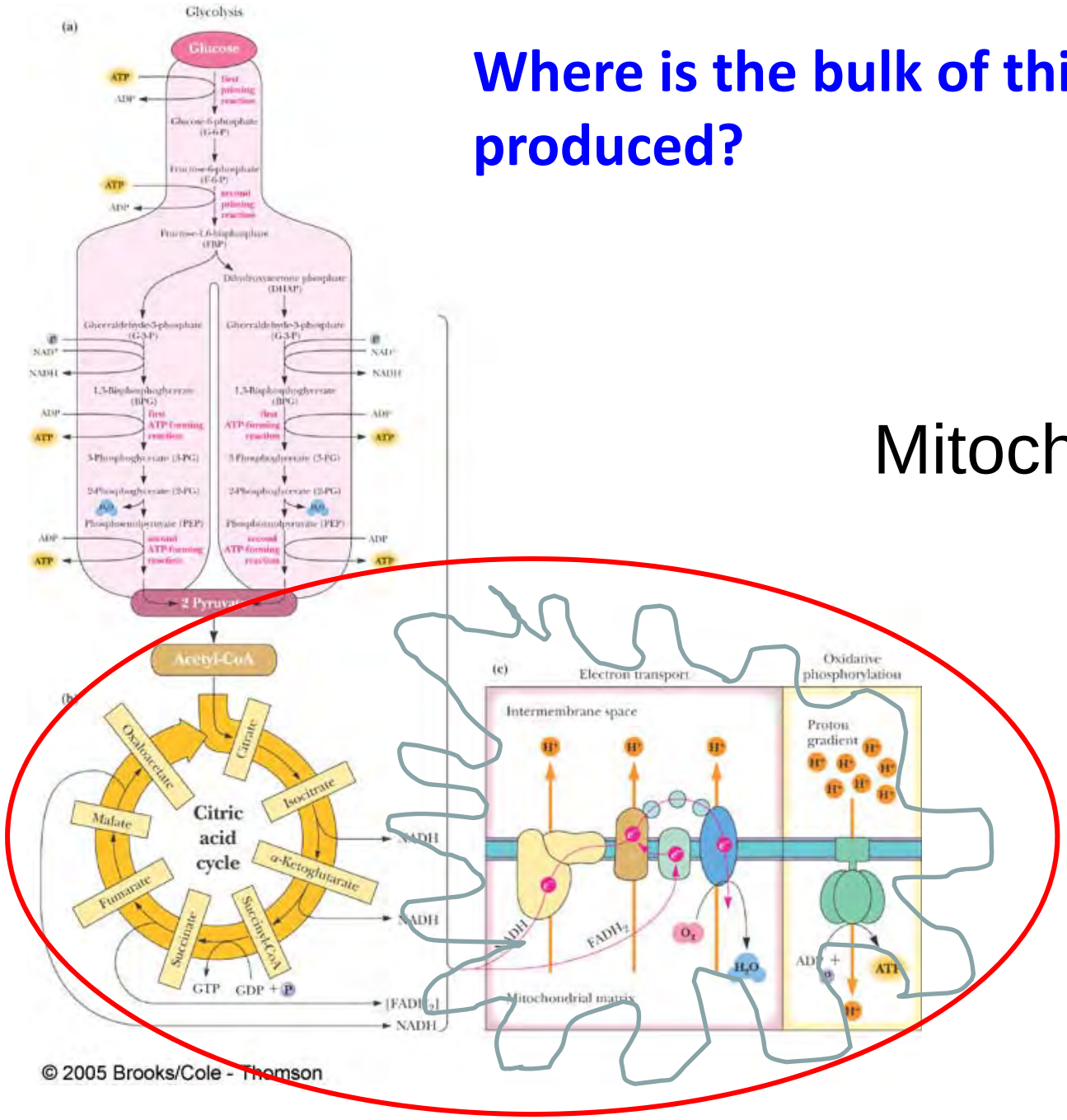
http://www.pearsonhighered.com/mathews/ch16/fi16p6.htm

Major Points of Hormone Regulation of Carbohydrate Metabolism



http://www.medbio.info/horn/intmet/integration_of_metabolism%20v4.htm

Where is the bulk of this energy (ATP) produced?



Mitochondria

Harvesting Electrons form Chemical Bonds

- When oxygen is available, a second oxidative stage of cellular respiration takes place.
  - First step – oxidize the 3-carbon **pyruvate** in the mitochondria forming **Acetyl-CoA**.
  - Next, Acetyl-CoA is oxidized in the **Krebs cycle**.

Multi-enzyme complexes:

- Groups of noncovalently associated enzymes that catalyze 2 or more sequential steps in a metabolic pathway

- Advantages:
  - Enhanced reaction rates
  - Reduction of side reactions
  - Reactions can be coordinately controlled

PDH Multienzyme Complex

The PDH complex contains multiple copies of 3 enzymes

Eukaryotic PDH:

~10,000 kDa Dodecahedron (12 pentagonal faces)

E_1 Pyruvate Dehydrogenase (30 E_1 $\alpha_2\beta_2$ heterotetramers)

E_2 Dihydrolipoyl transacetylase (20 E_2 trimers - core)

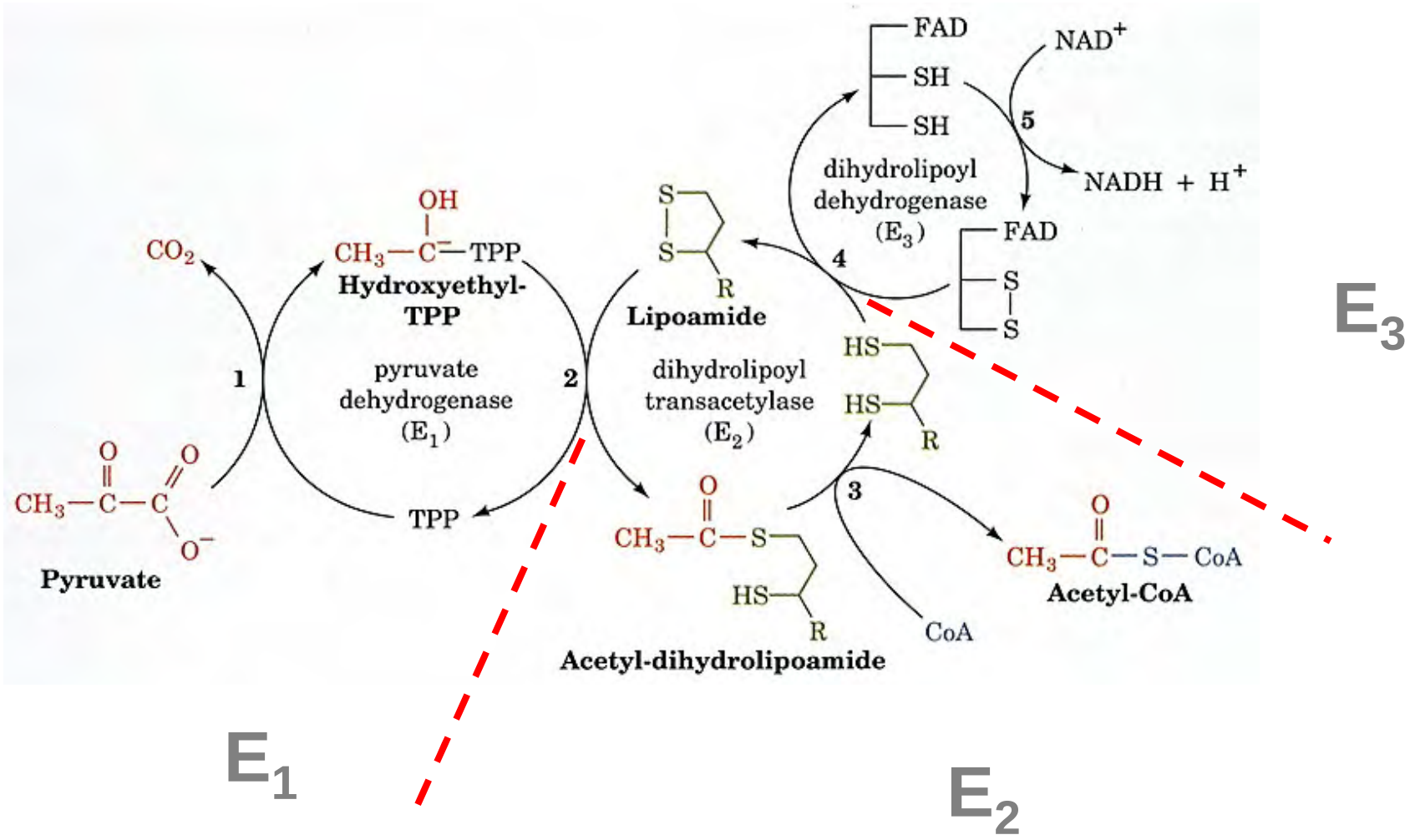
E_3 Dihidrolipoyl dehydrogenase (12 E_3 dimers)

Mammals also have:

- E_3 binding protein (a catalytically inactive E_2-like protein that may help bind E_3 to the complex)

- 1-3 copies each of PDH kinase and PDH phosphatase

PDH Multienzyme Complex

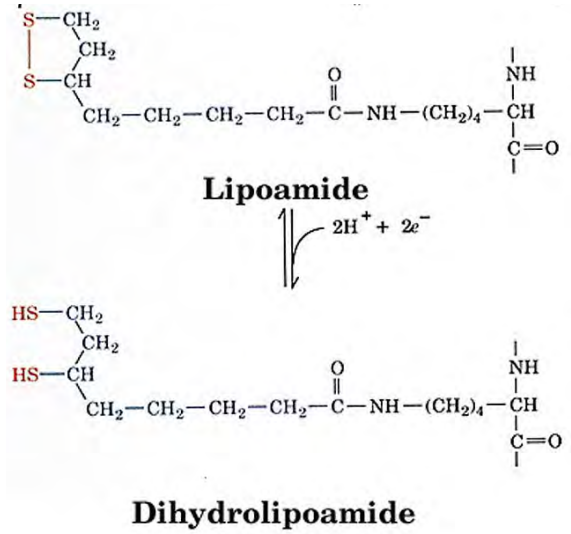


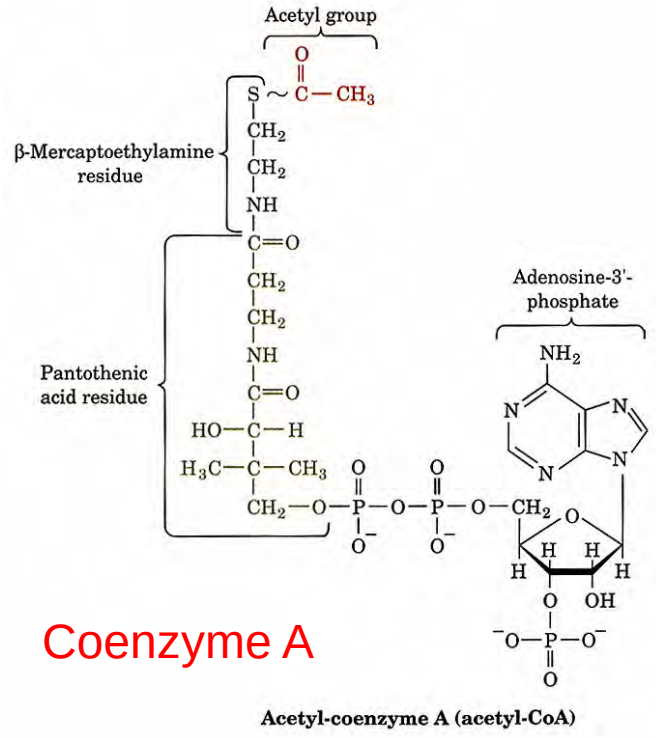
Catalyzes 5 sequential reactions – 5 coenzymes required

Pyruvate + CoA + NAD^+ ⟶ acetyl CoA + CO_2 + NADH

PDH Co-Factors

TPP: Thiamine PyroPhosphate (E_1) – (Vitamin B1 Thiamin)
Lipoamide: Lipoic Acid linked to ε-amino group of Lysine (E_2) – (α-lipoic acid)
FAD: Flavin Adenine Dinucleotide (E_3) – (Vitamin B2 Riboflavin)
NAD: Nicotinamide Adenine Dinucleotide (E_3) – (Vitamin B3 Niacin)
E_3 Thiols: Protein bound thiols oxidized to form a disulfide.





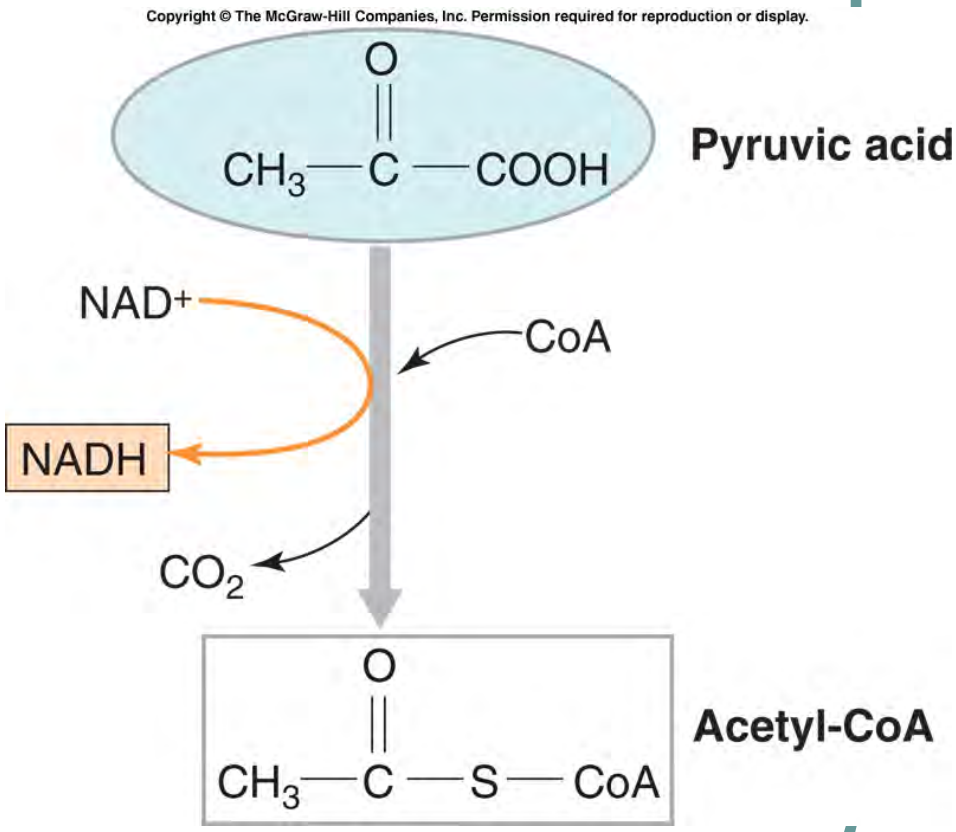
CoA-S-H

Ac

CoA-S-Ac

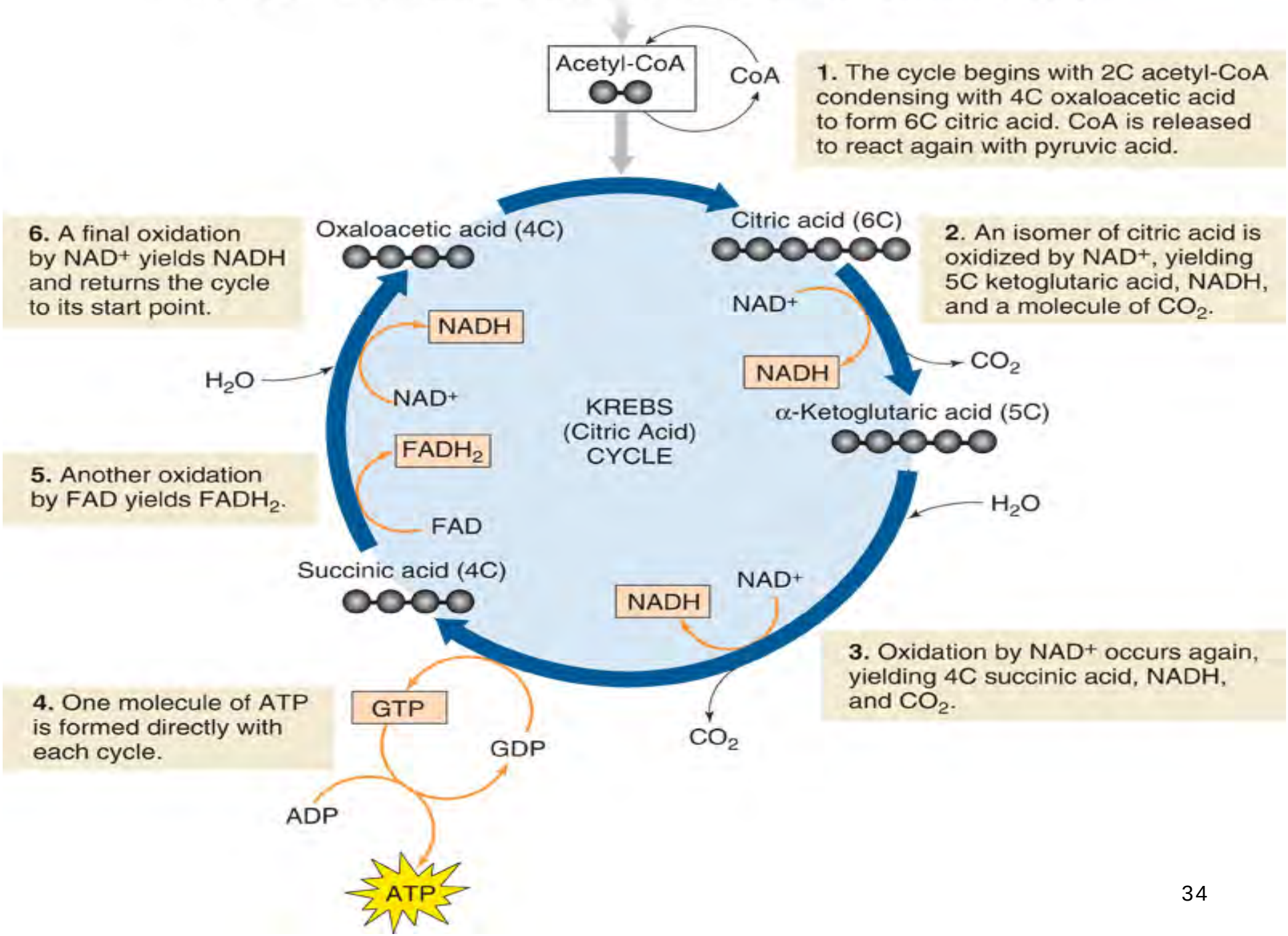
Producing Acetyl-CoA

- The 3-carbon pyruvate loses a carbon producing an acetyl group.
- Electrons are transferred to NAD^+ forming NADH.
- The acetyl group combines with CoA forming Acetyl-CoA.
- Ready for use in Krebs cycle.



The Krebs Cycle

- The **Krebs cycle** is the next stage in oxidative respiration and takes place in the **mitochondria**.
  - Acetyl-CoA joins cycle, binding to a 4-carbon molecule to form a 6-carbon molecule.
  - 2 carbons removed as CO_2, their electrons donated to NAD^+, 4-carbon molecules left.
    - 2 NADH produced.
  - More electrons are extracted and the original 4-carbon material is regenerated.
    - 1 ATP, 1 NADH, and 1 $FADH_2$ produced.



The Krebs Cycle

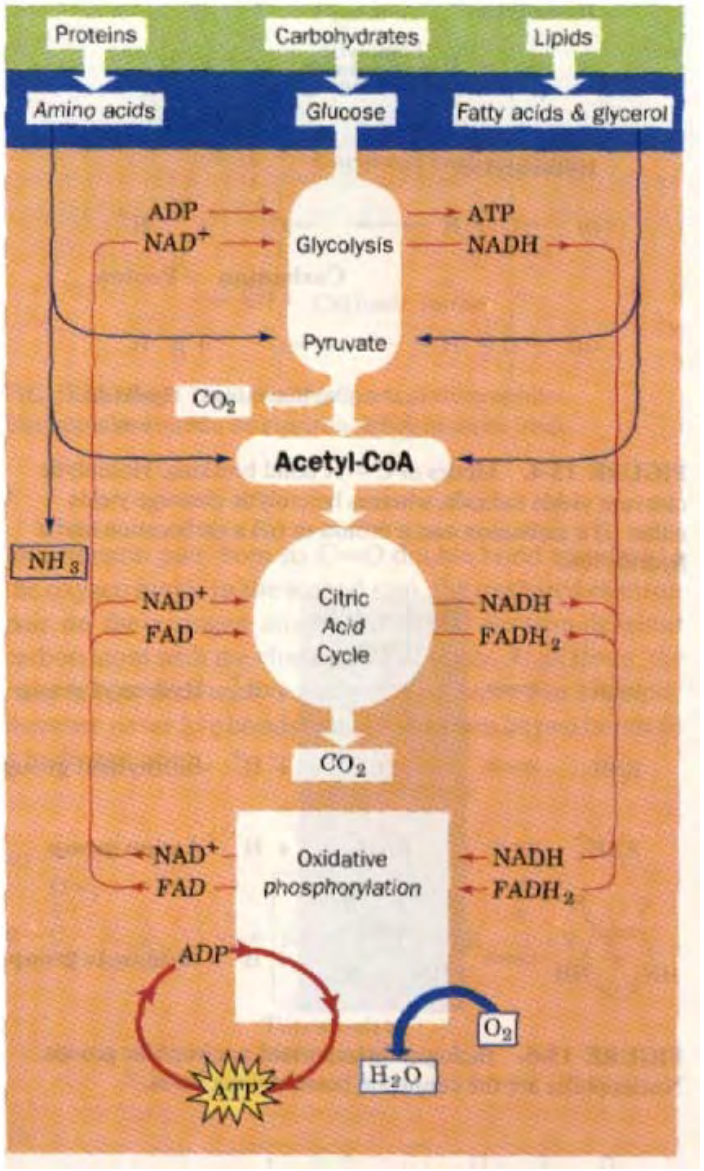
- Each glucose provides 2 pyruvates, therefore 2 turns of the Krebs cycle.
- Glucose is completely consumed during cellular respiration.

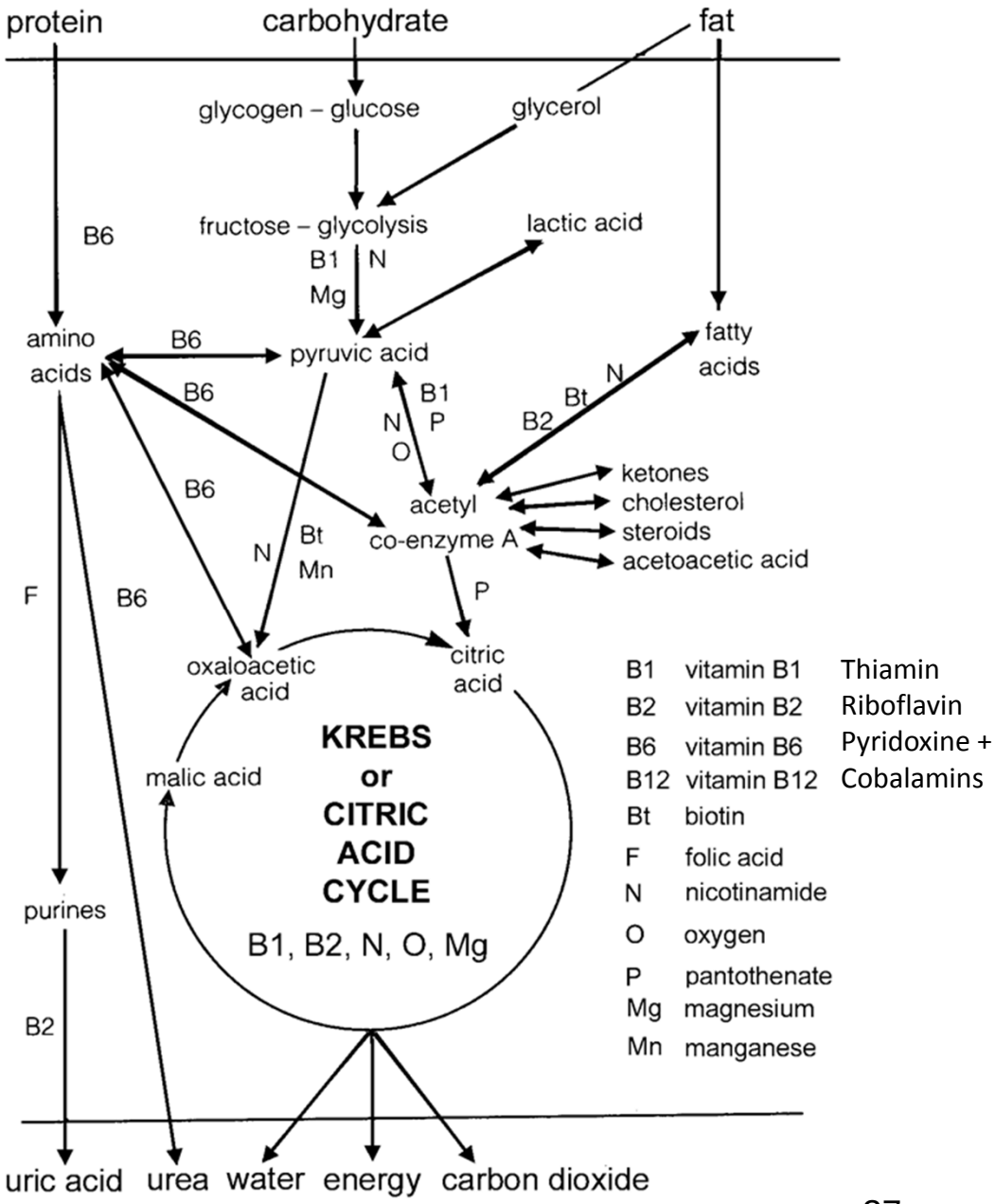
The Krebs Cycle

Acetyl unit + 3 NAD^+ + FAD + ADP + P_i

$\longrightarrow$ 2 CO_2 + 3 NADH + $FADH_2$ + ATP

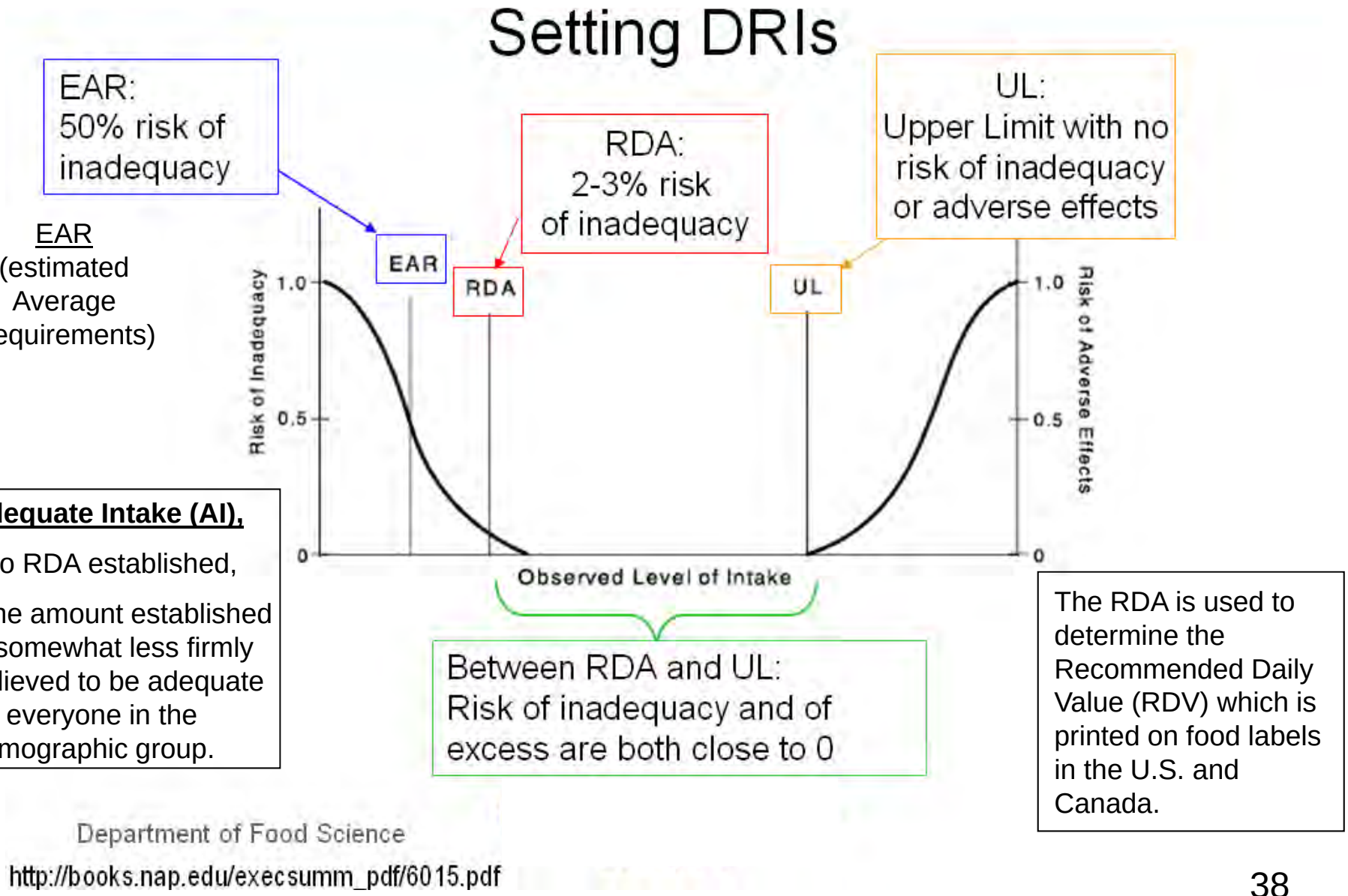
http://www.youtube.com/watch?v=-cDFYXc9Wko


Proteins
Carbohydrates
Lipids
Amino acids
Glucose
Fatty acids & glycerol
ADP
NAD+
Glycolysis
ATP
NADH
Pyruvate
CO2
Acetyl-CoA
NH3
NAD+
FAD
Citric Acid Cycle
NADH
FADH2
CO2
NAD+
FAD
Oxidative phosphorylation
NADH
FADH2
ADP
ATP
O2
H2O


protein
carbohydrate
fat
glycogen – glucose
glycerol
B6
fructose – glycolysis
lactic acid
B1
N
Mg
amino acids
B6
pyruvic acid
fatty acids
B6
B1
P
N
O
N
Bt
B2
ketones
cholesterol
steroids
acetoacetic acid
acetyl co-enzyme A
B6
N
Bt
Mn
F
B6
P
oxaloacetic acid
citric acid
malic acid
KREBS or CITRIC ACID CYCLE
B1, B2, N, O, Mg
purines
B2
B1 vitamin B1 Thiamin
B2 vitamin B2 Riboflavin
B6 vitamin B6 Pyridoxine +
B12 vitamin B12 Cobalamins
Bt biotin
F folic acid
N nicotinamide
O oxygen
P pantothenate
Mg magnesium
Mn manganese
uric acid
urea
water
energy
carbon dioxide

Current Dietary Reference Intake (DRI)

composed of:



EAR
(estimated Average Requirements)

Adequate Intake (AI),

- no RDA established,
- the amount established is somewhat less firmly believed to be adequate for everyone in the demographic group.

The RDA is used to determine the Recommended Daily Value (RDV) which is printed on food labels in the U.S. and Canada.

Department of Food Science

http://books.nap.edu/execsumm_pdf/6015.pdf

http://foodsci.rutgers.edu/fs104/2009Lecture9WEB-%20WaterSolVits.ppt#390,8,Setting DRIs

Vitamin B complex: * 8 water-soluble vitamins:

Vitamin B1 (thiamine)

Vitamin B2 (riboflavin)

Vitamin B3 (niacin or niacinamide)

Vitamin B5 (pantothenic acid)

Vitamin B6 (pyridoxine, pyridoxal, or pyridoxamine, or pyridoxine hydrochloride)

Vitamin B7 (biotin)

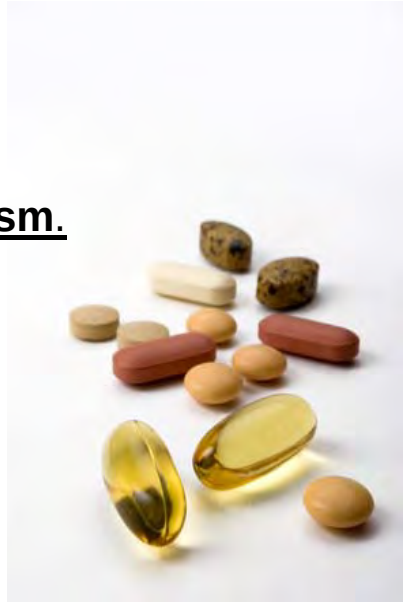
Vitamin B9 (folic acid)

Vitamin B12 (various cobalamins; commonly cyanocobalamin in vitamin supplements)

- each B vitamin has distinguishing character and chemical composition.

- They work in a group as well as individually to help and regulate numerous body functions including metabolizing glucose to release energy.

Vitamins for Metabolic Health
'THE BIG B'



B-complex vitamins are absolutely essential to your body's metabolism.

• Without even just one of them, don't expect the food you're eating to go down the drain anytime soon.

• Vitamin B 1 / Thiamine – for proper metabolism of starch and sugars. Found in eggs, whole grain flour, potatoes, oranges and asparagus.

• Vitamin B 2 / Riboflavin – for proper metabolism of fats, proteins and carbohydrates. Found in milk, cheese, leafy green vegetables and almonds.

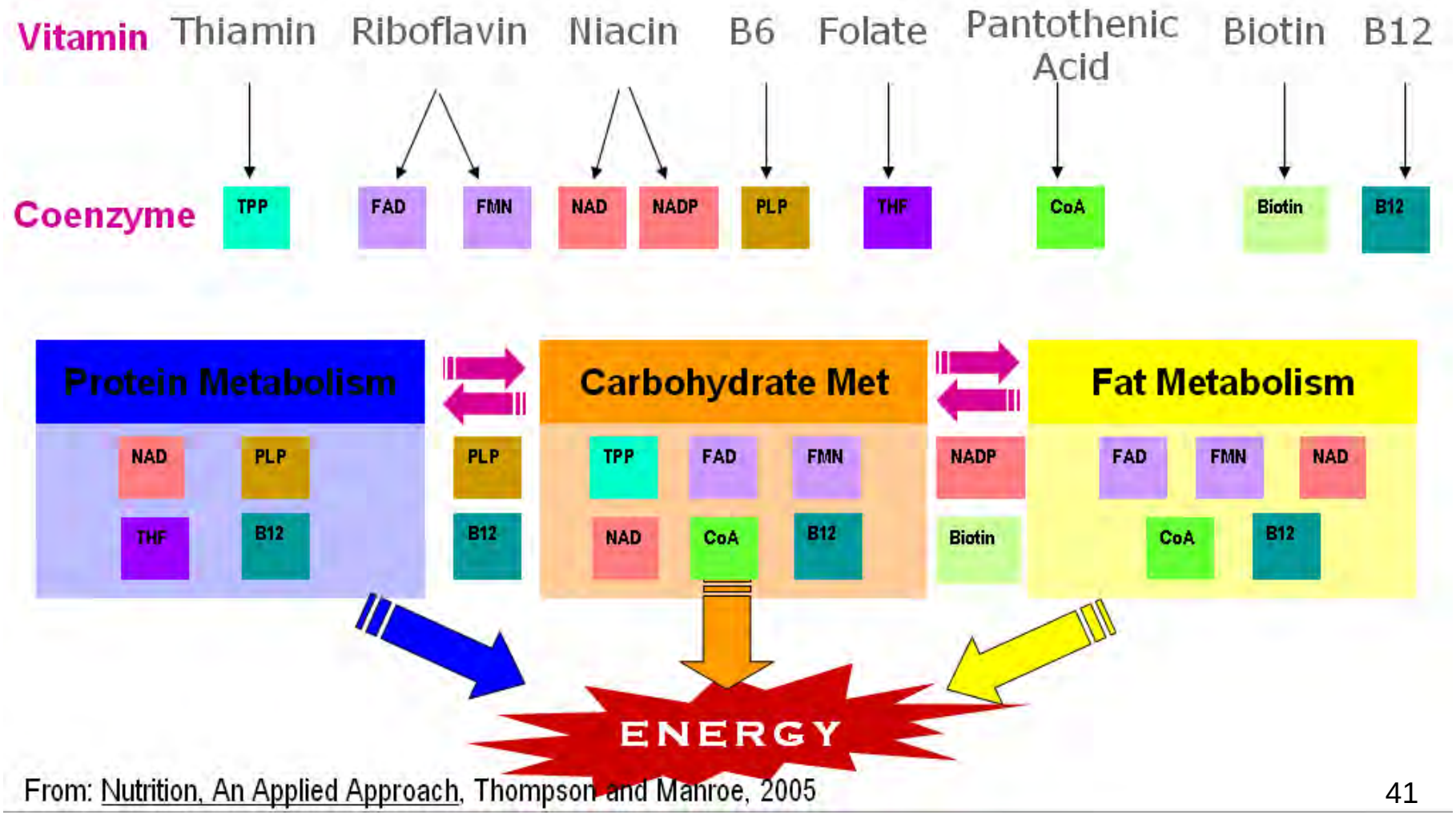
• Vitamin B 5 / Pantothenic Acid – for the generation of energy to be used in the body. Found in green vegetables, whole grain flour, chicken, eggs, beans and green vegetables.

• Vitamin B 6 / Pyridoxine – for the metabolism of unsaturated fatty acids. Found in eggs, beef, chicken, bananas and avocados.

• Vitamin B 12 / Cyanocobalamin – for the whole gamut of metabolism: digestion, protein synthesis, food absorption and general metabolism. Found in meat, fish and eggs.

While the B-complex family is the star of the "vitamins for weight loss," there are some other vitamins that can help you reach your goal of losing weight in the long run. Vit C, Vit E, Choline

B Vitamins Coenzyme Roles



From: Nutrition, An Applied Approach, Thompson and Manroe, 2005

http://foodsci.rutgers.edu/fs104/2009Lecture9WEB-%20WaterSolVits.ppt#340,20,B Vitamins Coenzyme Roles

Vitamins: Cooking, Storage, other considerations

• Vitamins A, D, E and K, riboflavin and beta carotene are destroyed when exposed to light.

• Vitamins C, A, B12, folic acid and thiamin are destroyed by heat.

• Vitamins C, A, D, E, K, B12 and folic acid are destroyed by exposure to air.

• Vitamins C, B6, thiamin, riboflavin, niacin, selenium, potassium and magnesium leach into cooking water.

• Vitamins C, B12, folic acid, thiamin and riboflavin are destroyed when combined with acid or alkaline substances.

Recommended dietary allowances and suggested optimal intakes

	Men	Women	**Suggested intake**
Vitamin A	1000 mcg RE	800 mcg RE	**1500 mcg RE**
Beta carotene			**10 to 30 mg**
Thiamin	1.2 mg	1.1 mg	**5 to 10 mg**
Riboflavin	1.3 mg	1.1 mg	**5 to 10 mg**
Niacin	16 mg	14mg	**10 to 100 mg**
Vitamin B6 (under 50)	1.3 mg	1.3 mg	**2 to 50 mg**
Vitamin B6 (over 50)	1.7 mg	1.5 mg	
Vitamin B12	2.4 mg	2.4 mg	**11 to 100 mg**
Pantothenic acid	5 mg	5 mg	**10 mg**
Biotin	30 mcg	30 mcg	**30 to 300 mcg**
Folic acid	400 mcg	400 mcg	**400 mcg**
Vitamin C	60 mg	60 mg	**100 to 1000 mg**
Vitamin D (under 50)	200 IU	200 IU	**100 to 600 IU**
Vitamin D (over 50)	400 IU	400 IU	
Vitamin D (over 70)	600 IU	600 IU	
Vitamin E	10 mg alpha TE	8 mg alpha TE	**67 to 500 mg alpha TE**
Vitamin K	80 mcg	65 mcg	**60 to 300 mcg**
Calcium (under 50)	1000 mg	1000 mg	**1200 to 1500 mg**
Calcium (over 50)	1200 mg	1200 mg	
Chromium	20 to 200 mcg	20 to 200 mcg	200 to 400 mcg
Copper	1.5 to 3 mg	1.5 to 3 mg	3 mg
Fluoride	3.8 mg	3.1 mg	
Iodine	150 mcg	150 mcg	200 mcg
Iron	10 mg	15 mg	15 to 30 mg
Magnesium	420 mg	320 mg	350 to 500 mg
Manganese	2 to 5 mg	2 to 5 mg	10 mg
Molybdenum	75 to 250 mcg	75 to 250 mcg	250 mcg
Phosphorus	700 mg	700 mg	700 mg
Potassium	2000 mg	2000 mg	**2000 to 5000 mg**
Selenium	70 mcg	55 mcg	**100 to 200 mcg**
Vanadium	10 to 60 mcg	10 to 60 mcg	50 to 100 mcg
Zinc	15 mg	12 mg	**15 to 30 mg**

Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes, Vitamins

Food and Nutrition Board, Institute of Medicine, National Academies

Life Stage Group	Vitamin A (µg/d)[a]	Vitamin C (mg/d)	Vitamin D (µg/d)[b,c]	Vitamin E (mg/d)[d]	Vitamin K (µg/d)	Thiamin (mg/d)	Riboflavin (mg/d)	Niacin (mg/d)[e]	Vitamin B_6 (mg/d)	Folate (µg/d)[f]	Vitamin B_{12} (µg/d)	Pantothenic Acid (mg/d)	Biotin (µg/d)	Choline (mg/d)[g]
Infants														
0 to 6 mo	400*	40*	10	4*	2.0*	0.2*	0.3*	2*	0.1*	65*	0.4*	1.7*	5*	125*
6 to 12 mo	500*	50*	10	5*	2.5*	0.3*	0.4*	4*	0.3*	80*	0.5*	1.8*	6*	150*
Children														
1–3 y	300	15	15	6	30*	0.5	0.5	6	0.5	150	0.9	2*	8*	200*
4–8 y	400	25	15	7	55*	0.6	0.6	8	0.6	200	1.2	3*	12*	250*
Males														
9–13 y	600	45	15	11	60*	0.9	0.9	12	1.0	300	1.8	4*	20*	375*
14–18 y	900	75	15	15	75*	1.2	1.3	16	1.3	400	2.4	5*	25*	550*
19–30 y	900	90	15	15	120*	1.2	1.3	16	1.3	400	2.4	5*	30*	550*
31–50 y	900	90	15	15	120*	1.2	1.3	16	1.3	400	2.4	5*	30*	550*
51–70 y	900	90	15	15	120*	1.2	1.3	16	1.7	400	2.4[h]	5*	30*	550*
> 70 y	900	90	20	15	120*	1.2	1.3	16	1.7	400	2.4[h]	5*	30*	550*
Females														
9–13 y	600	45	15	11	60*	0.9	0.9	12	1.0	300	1.8	4*	20*	375*
14–18 y	700	65	15	15	75*	1.0	1.0	14	1.2	400[i]	2.4	5*	25*	400*
19–30 y	700	75	15	15	90*	1.1	1.1	14	1.3	400[i]	2.4	5*	30*	425*
31–50 y	700	75	15	15	90*	1.1	1.1	14	1.3	400[i]	2.4	5*	30*	425*
51–70 y	700	75	15	15	90*	1.1	1.1	14	1.5	400	2.4[h]	5*	30*	425*
> 70 y	700	75	20	15	90*	1.1	1.1	14	1.5	400	2.4[h]	5*	30*	425*
Pregnancy														
14–18 y	750	80	15	15	75*	1.4	1.4	18	1.9	600[j]	2.6	6*	30*	450*
19–30 y	770	85	15	15	90*	1.4	1.4	18	1.9	600[j]	2.6	6*	30*	450*
31–50 y	770	85	15	15	90*	1.4	1.4	18	1.9	600[j]	2.6	6*	30*	450*
Lactation														
14–18 y	1,200	115	15	19	75*	1.4	1.6	17	2.0	500	2.8	7*	35*	550*
19–30 y	1,300	120	15	19	90*	1.4	1.6	17	2.0	500	2.8	7*	35*	550*
31–50 y	1,300	120	15	19	90*	1.4	1.6	17	2.0	500	2.8	7*	35*	550*

NOTE: This table (taken from the DRI reports, see www.nap.edu) presents Recommended Dietary Allowances (RDAs) in **bold type** and Adequate Intakes (AIs) in ordinary type followed by an asterisk (*). An RDA is the average daily dietary intake level; sufficient to meet the nutrient requirements of nearly all (97-98 percent) healthy individuals in a group. It is calculated from an Estimated Average Requirement (EAR). If sufficient scientific evidence is not available to establish an EAR, and thus calculate an RDA, an AI is usually developed. For healthy breastfed infants, an AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all healthy individuals in the groups, but lack of data or uncertainty in the data prevent being able to specify with confidence the percentage of individuals covered by this intake.

[a] As retinol activity equivalents (RAEs). 1 RAE = 1 µg retinol, 12 µg β-carotene, 24 µg α-carotene, or 24 µg β-cryptoxanthin. The RAE for dietary provitamin A carotenoids is two-fold greater than retinol equivalents (RE), whereas the RAE for preformed vitamin A is the same as RE.

[b] As cholecalciferol. 1 µg cholecalciferol = 40 IU vitamin D.

[c] Under the assumption of minimal sunlight.

[d] As α-tocopherol. α-Tocopherol includes *RRR*-α-tocopherol, the only form of α-tocopherol that occurs naturally in foods, and the *2R*-stereoisomeric forms of α-tocopherol (*RRR*-, *RSR*-, *RRS*-, and *RSS*-α-tocopherol) that occur in fortified foods and supplements. It does not include the *2S*-stereoisomeric forms of α-tocopherol (*SRR*-, *SSR*-, *SRS*-, and *SSS*-α-tocopherol), also found in fortified foods and supplements.

[e] As niacin equivalents (NE). 1 mg of niacin = 60 mg of tryptophan; 0–6 months = preformed niacin (not NE).

[f] As dietary folate equivalents (DFE). 1 DFE = 1 µg food folate = 0.6 µg of folic acid from fortified food or as a supplement consumed with food = 0.5 µg of a supplement taken on an empty stomach.

[g] Although AIs have been set for choline, there are few data to assess whether a dietary supply of choline is needed at all stages of the life cycle, and it may be that the choline requirement can be met by endogenous synthesis at some of these stages.

[h] Because 10 to 30 percent of older people may malabsorb food-bound B_{12}, it is advisable for those older than 50 years to meet their RDA mainly by consuming foods fortified with B_{12} or a supplement containing B_{12}.

[i] In view of evidence linking folate intake with neural tube defects in the fetus, it is recommended that all women capable of becoming pregnant consume 400 µg from supplements or fortified foods in addition to intake of food folate from a varied diet.

Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes, Total Water and Macronutrients

Food and Nutrition Board, Institute of Medicine, National Academies

Life Stage Group	*Total* Water[a] (L/d)	Carbohydrate (g/d)	Total Fiber (g/d)	Fat (g/d)	Linoleic Acid (g/d)	α-Linolenic Acid (g/d)	Protein[b] (g/d)
Infants							
0 to 6 mo	0.7*	60*	ND	31*	4.4*	0.5*	9.1*
6 to 12 mo	0.8*	95*	ND	30*	4.6*	0.5*	**11.0**
Children							
1–3 y	1.3*	**130**	19*	ND[c]	7*	0.7*	**13**
4–8 y	1.7*	**130**	25*	ND	10*	0.9*	**19**
Males							
9–13 y	2.4*	**130**	31*	ND	12*	1.2*	**34**
14–18 y	3.3*	**130**	38*	ND	16*	1.6*	**52**
19–30 y	3.7*	**130**	38*	ND	17*	1.6*	**56**
31–50 y	3.7*	**130**	38*	ND	17*	1.6*	**56**
51–70 y	3.7*	**130**	30*	ND	14*	1.6*	**56**
> 70 y	3.7*	**130**	30*	ND	14*	1.6*	**56**
Females							
9–13 y	2.1*	**130**	26*	ND	10*	1.0*	**34**
14–18 y	2.3*	**130**	26*	ND	11*	1.1*	**46**
19–30 y	2.7*	**130**	25*	ND	12*	1.1*	**46**
31–50 y	2.7*	**130**	25*	ND	12*	1.1*	**46**
51–70 y	2.7*	**130**	21*	ND	11*	1.1*	**46**
> 70 y	2.7*	**130**	21*	ND	11*	1.1*	**46**
Pregnancy							
14–18 y	3.0*	**175**	28*	ND	13*	1.4*	**71**
19–30 y	3.0*	**175**	28*	ND	13*	1.4*	**71**
31–50 y	3.0*	**175**	28*	ND	13*	1.4*	**71**
Lactation							
14–18	3.8*	**210**	29*	ND	13*	1.3*	**71**
19–30 y	3.8*	**210**	29*	ND	13*	1.3*	**71**
31–50 y	3.8*	**210**	29*	ND	13*	1.3*	**71**

NOTE: This table (take from the DRI reports, see www.nap.edu) presents Recommended Dietary Allowances (RDA) in **bold type** and Adequate Intakes (AI) in ordinary type followed by an asterisk (*). An RDA is the average daily dietary intake level; sufficient to meet the nutrient requirements of nearly all (97-98 percent) healthy individuals in a group. It is calculated from an Estimated Average Requirement (EAR). If sufficient scientific evidence is not available to establish an EAR, and thus calculate an RDA, an AI is usually developed. For healthy breastfed infants, an AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all healthy individuals in the groups, but lack of data or uncertainty in the data prevent being able to specify with confidence the percentage of individuals covered by this intake.

[a] *Total* water includes all water contained in food, beverages, and drinking water.

[b] Based on g protein per kg of body weight for the reference body weight, e.g., for adults 0.8 g/kg body weight for the reference body weight.

[c] Not determined.

SOURCE: *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids* (2002/2005) and *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate* (2005). The report may be accessed via www.nap.edu.

http://fnic.nal.usda.gov/dietary-guidance/dietary-reference-intakes/dri-tables

Dietary Reference Intakes : Electrolytes and Water

Nutrient	Function	Life Stage Group	AI	UL[a]	Selected Food Sources	Adverse Effects of Excessive Consumption	Special Considerations
Water	Maintains homeostasis in the body and allows for transport of nutrients to cells and removal and excretion of waste products of metabolism.		(L/d)	No UL.	All beverages, including water, as well as moisture in foods (high moisture foods include watermelon, meats, soups, etc.).	No UL because normally functioning kidneys can handle more than 0.7 L (24 oz) of fluid per hour; symptoms of water intoxication include hyponatremia which can result in heart failure and rhabdomyolosis (skeletal muscle tissue injury) which can lead to kidney failure.	Recommended intakes for water are based on median intakes of generally healthy individuals who are adequately hydrated; individuals can be adequately hydrated at levels below as well as above the AIs provided. The AIs provided are for total water in temperate climates. All sources can contribute to total water needs: beverages (including tea, coffee, juices, sodas, and drinking water) and moisture found in foods. Moisture in food accounts for about 20% of total water intake. Thirst and consumption of beverages at meals are adequate to maintain hydration.
		Infants					
		0–6 mo	0.7				
		7–12 mo	0.8				
		Children					
		1–3 y	1.3				
		4–8 y	1.7				
		Males					
		9–13 y	2.4				
		14–18 y	3.3				
		19–30 y	3.7				
		31–50 y	3.7				
		50–70 y	3.7				
		> 70 y	3.7				
		Females					
		9–13 y	2.1				
		14–18 y	2.3				
		19–30 y	2.7				
		31–50 y	2.7				
		50–70 y	2.7				
		> 70 y	2.7				
		Pregnancy					
		14–18 y	3.0				
		19–50 y	3.0				
		Lactation					
		14–18 y	3.8				
		19–50 y	3.8				

NOTE: The table is adapted from the DRI reports. See www.nap.edu. Adequate Intakes (AIs) may be used as a goal for individual intake. For healthy breastfed infants, the AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all individuals in the group, but lack of data prevent being able to specify with confidence the percentage of individuals covered by this intake; therefore, no Recommended Dietary Allowance (RDA) was set.

[a]UL = The maximum level of daily nutrient intake that is likely to pose no risk of adverse effects. Unless otherwise specified, the UL represents total intake from food, water, and supplements. Due to lack of suitable data, ULs could not be established for potassium, water, and inorganic sulfate. In the absence of ULs, extra caution may be warranted in consuming levels above recommended intakes.

[b]ND = Not determinable due to lack of data of adverse effects in this age group and concern with regard to lack of ability to handle excess amounts. Source of intake should be from food only to prevent high levels of intake.

SOURCE: *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate.* This reports may be accessed via www.nap.edu.

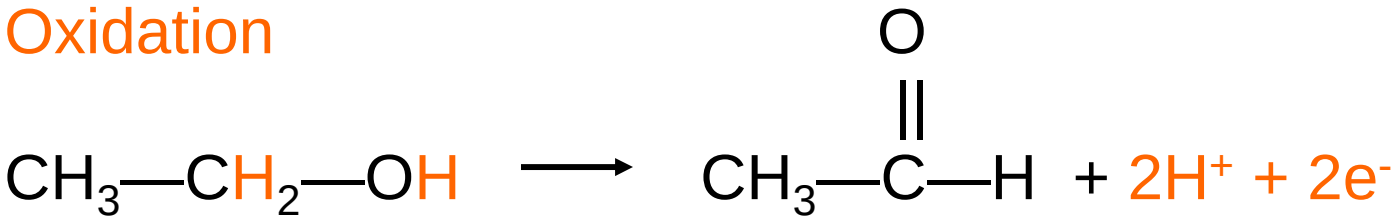
http://fnic.nal.usda.gov/dietary-guidance/dietary-reference-intakes/dri-tables

Coenzyme NAD^+

NAD^+ (nicotinamide adenine dinucleotide)

- Participates in reactions that produce a carbon-oxygen double bond (C=O).
- Is reduced when an oxidation provides $2H^+$ and $2e^-$.

Oxidation



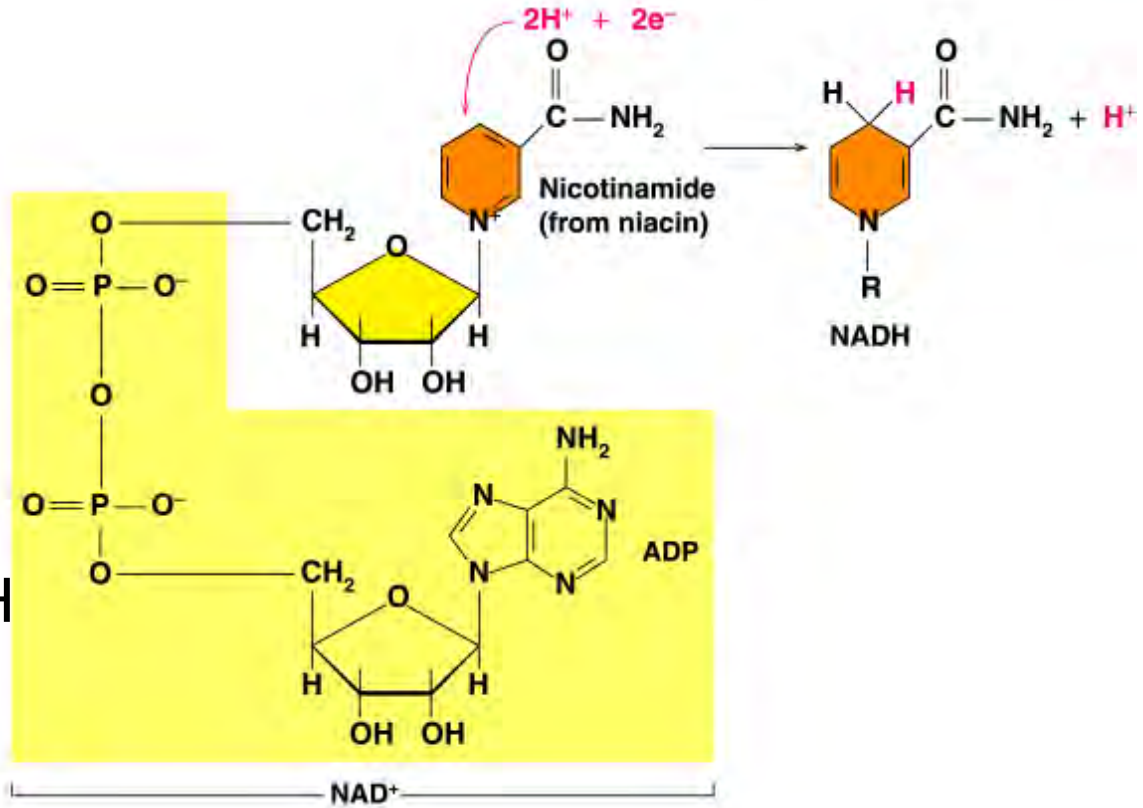
Reduction

$NAD^+ + 2H^+ + 2e^- \longrightarrow NADH + H^+$

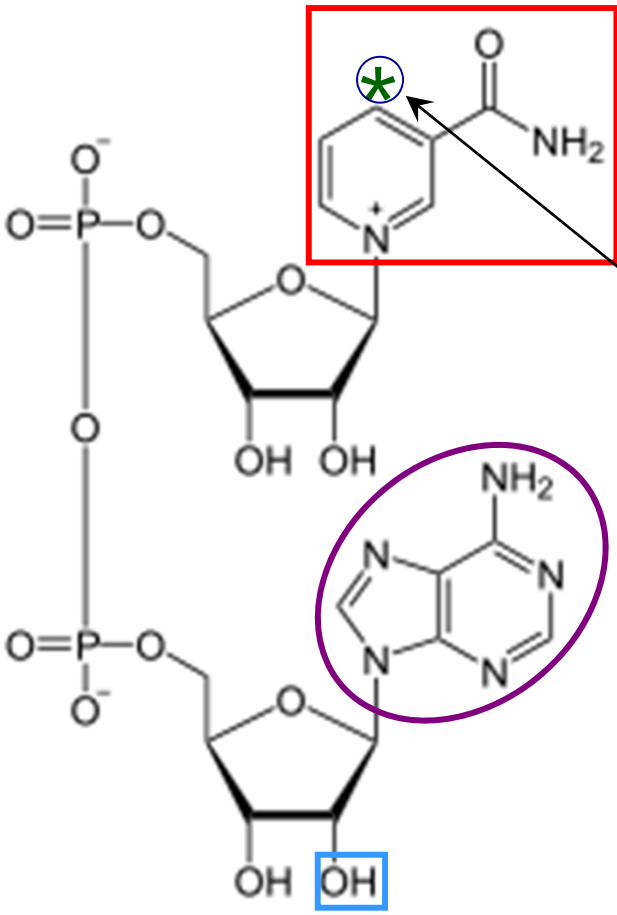
Structure of Coenzyme NAD^+

NAD^+

- Is nicotinamide adenine dinucleotide.
- Contains ADP, ribose, and nicotinamide.
- Reduces to NADH when the nicotinamide group accepts H^+ and $2e^-$.

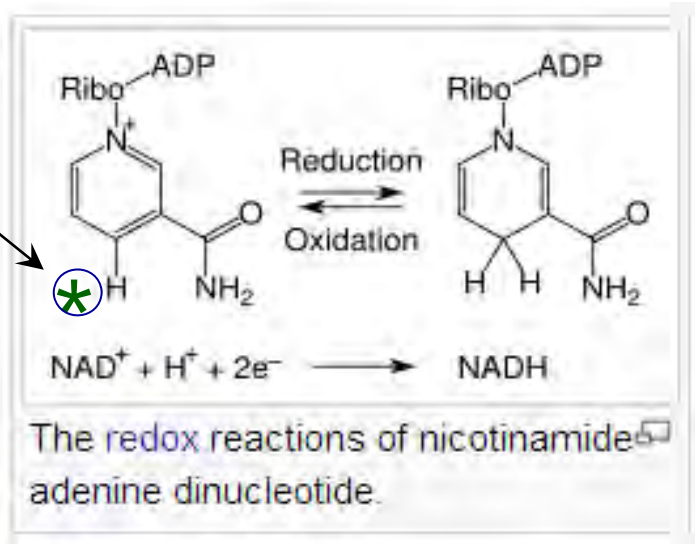


Niacin (B3). Biochemistry:



Nicotinic Acid	Nicotinamide

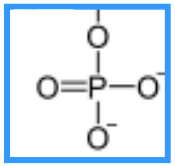
Niacin activity (pyridine derivatives)



The redox reactions of nicotinamide adenine dinucleotide.

Nicotinamide Coenzymes:

Nicotinamide
Adenine
Dinucleotide
(**P**hosphate)



NAD and NADP roles: **Redox Reactions**

1) Hydrogen acceptors in most dehydrogenations
2) Hydrogen donor in Electron Transport Chain
3) NADPH is a reducing agent in biosynthesis (ie. Fatty acids, cholesterol) & involved in protection against toxicity of ROS (ie. GSH from GSSG reduction by glutathione reductase)

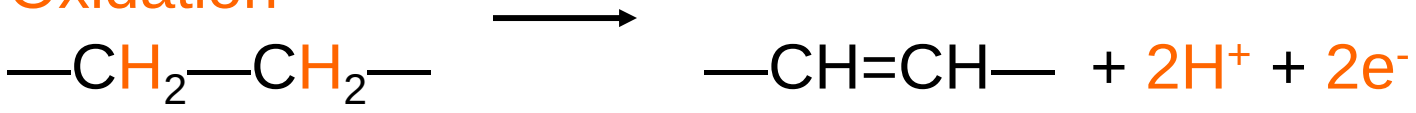
C. L. Krumdieck lecture notes & http://en.wikipedia.org

Coenzyme FAD

FAD (flavin adenine dinucleotide)

- Participates in reactions that produce a carbon-carbon double bond (C=C).
- Is reduced to $FADH_2$.

Oxidation

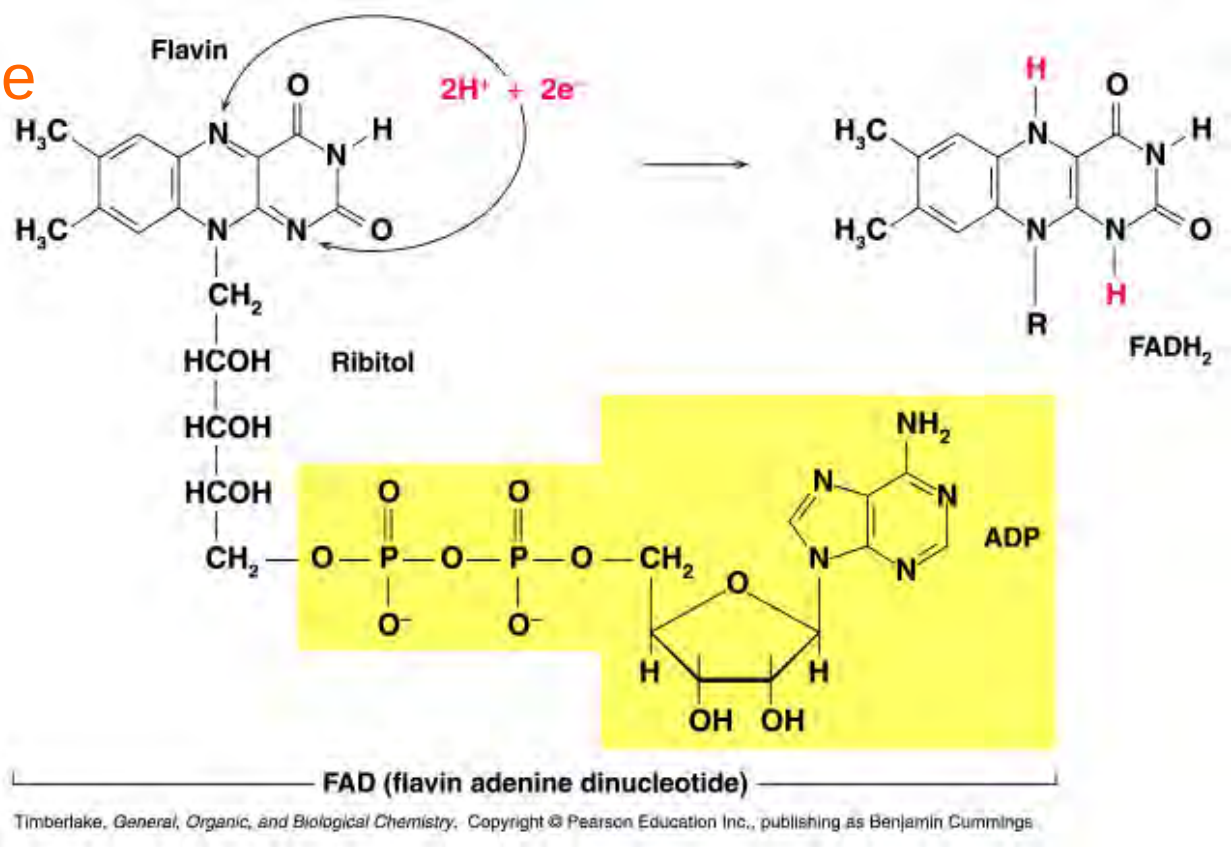


Reduction

Structure of Coenzyme FAD

FAD

- Is flavin adenine dinucleotide.
- Contains ADP and riboflavin (vitamin B_2).



Riboflavin (B2). Chemistry & Biochemistry:

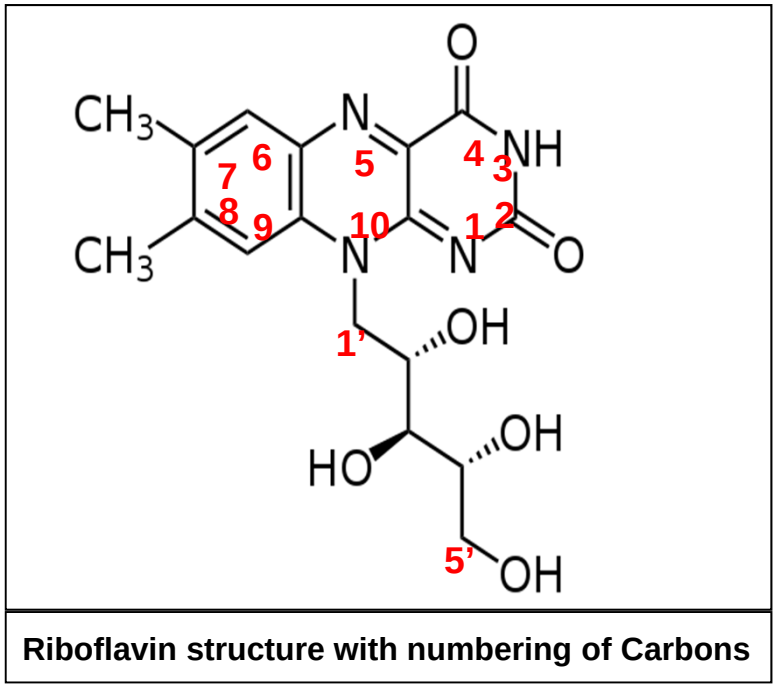
- Isoalloxazine (tricyclic ring) derivative:

7,8-di-methyl-10-(1'-D-ribityl)isoalloxazine

- "Ribo" refers to the ribityl side chain and "flavin" is now synoymous with any substituted isoalloxazine.

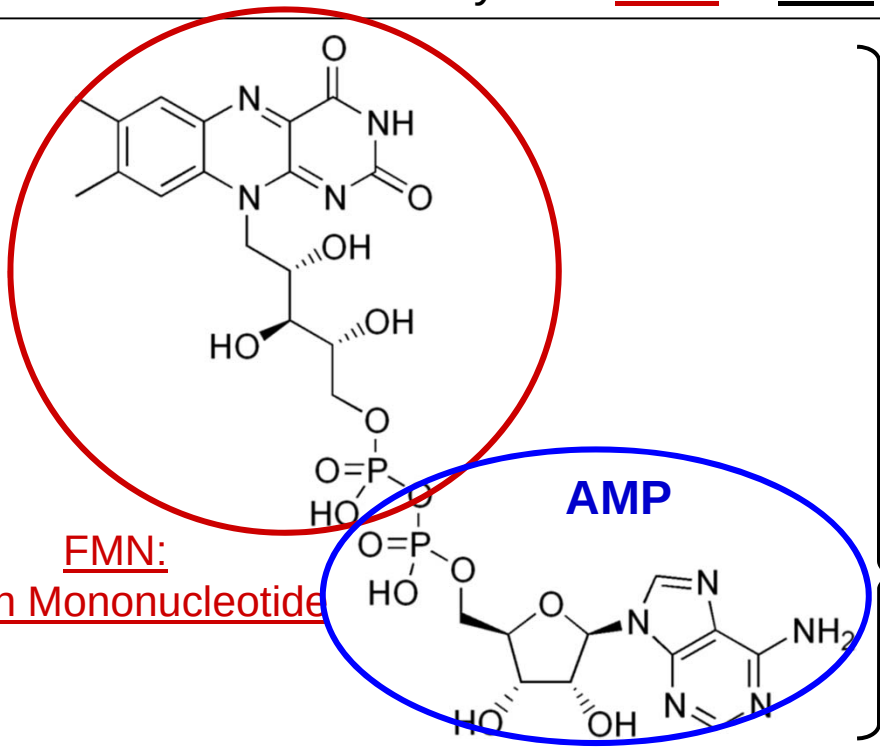
► bright yellow, fluorescent (UV), slightly water soluble

► decomposed by light but is heat stable



Riboflavin structure with numbering of Carbons

Converted to 2 Co-enzymes: **FMN** & **FAD**



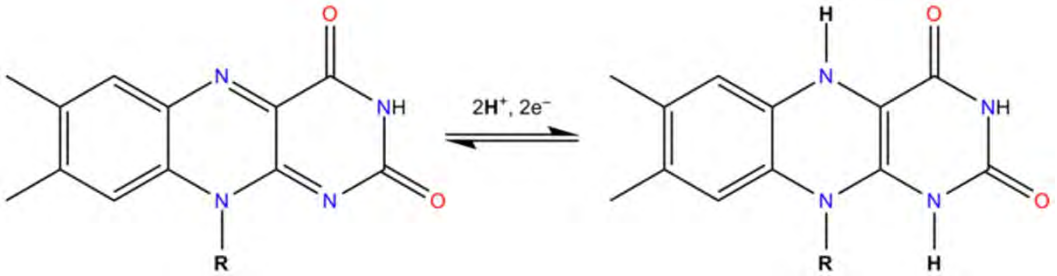
FMN:
Flavin Mononucleotide

FAD:
Flavin adenine dinucleotide


Riboflavin powder.

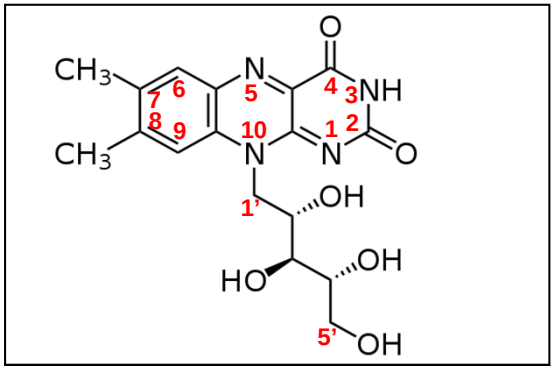

A riboflavin solution.

Riboflavin. Biochemistry: **Oxidation/Reduction Rxs**



FMN / FAD

FMNH2 / FADH2



Riboflavin structure with numbering of Carbons

FMN (riboflavin-5′-phosphate):

- produced from riboflavin by riboflavin kinase functions as prosthetic group of various oxidoreductases including NADH dehydrogenase.
- It is the principal form in which riboflavin is found in cells and tissues. It requires more energy to produce, but is more soluble than riboflavin.

FAD (flavin adenine dinucleotide):

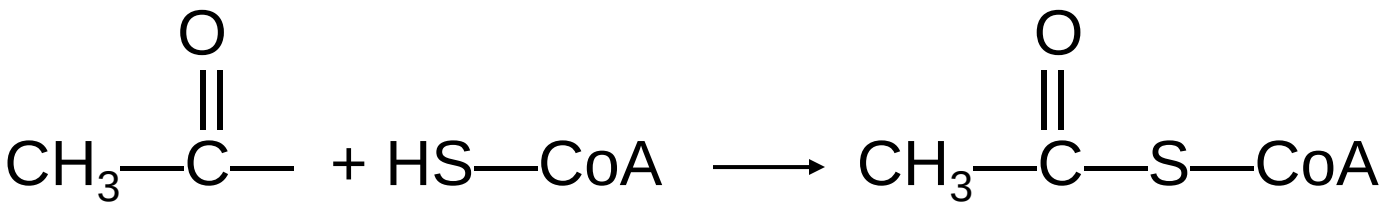
- derived from riboflavin bound to phosphate of ADP
- redox cofactor involved in metabolism.
- two different redox states that provide its function.
- FAD can be reduced to the FADH2, whereby it accepts two hydrogen atoms:
- Many oxidoreductases, called flavoenzymes or flavoproteins, require FAD as a prosthetic group which functions in electron transfers.
- reduced coenzyme FADH2 (energy-carrying), is a substrate for OxPhos in the mitochondria. FADH2 is reoxidized to FAD, generating proton gradient across the inner mitochondrial membrane for ATP synthase to produce 2.0 equivalents ATP.
- primary sources of reduced FAD in eukaryotic metabolism are the TCA (citric acid cycle). FAD is a prosthetic group in the enzyme succinate dehydrogenase → succinate to fumarate; whereas in beta oxidation - coenzyme in the reaction of acyl CoA dehydrogenase.

"Energy carriers"

Coenzyme A

Coenzyme A.

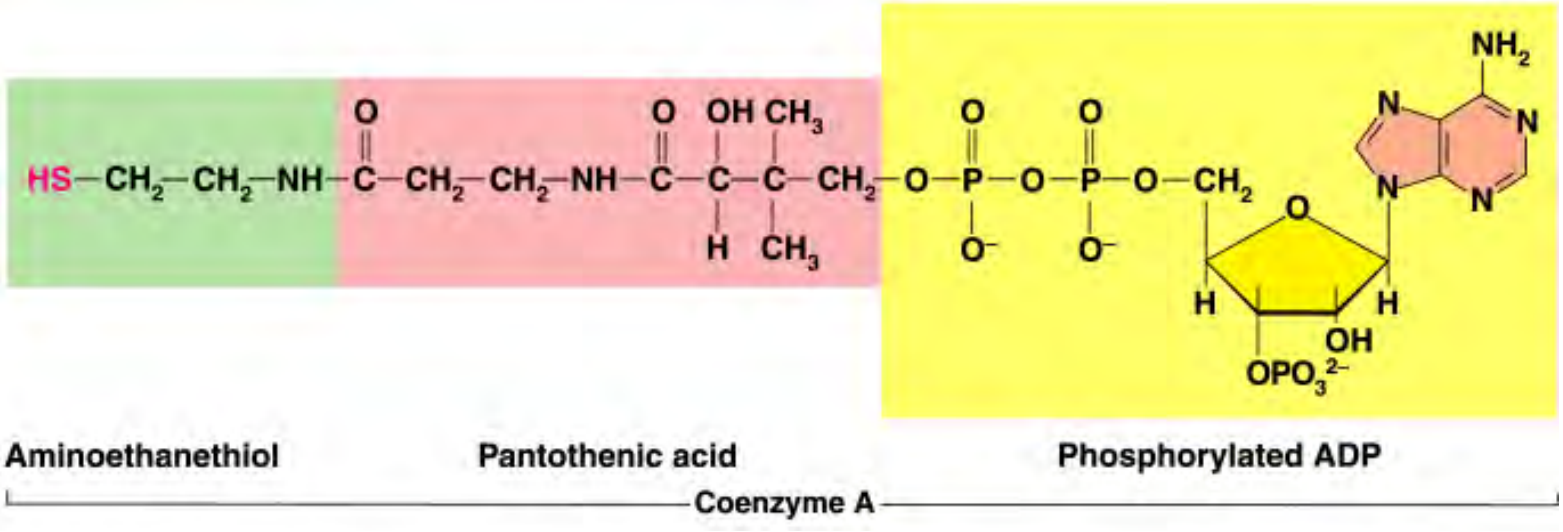
- Consists of vitamins B_3, pantothenic acid, and ADP.
- Activates acyl groups such as the two-carbon acetyl group for transfer.



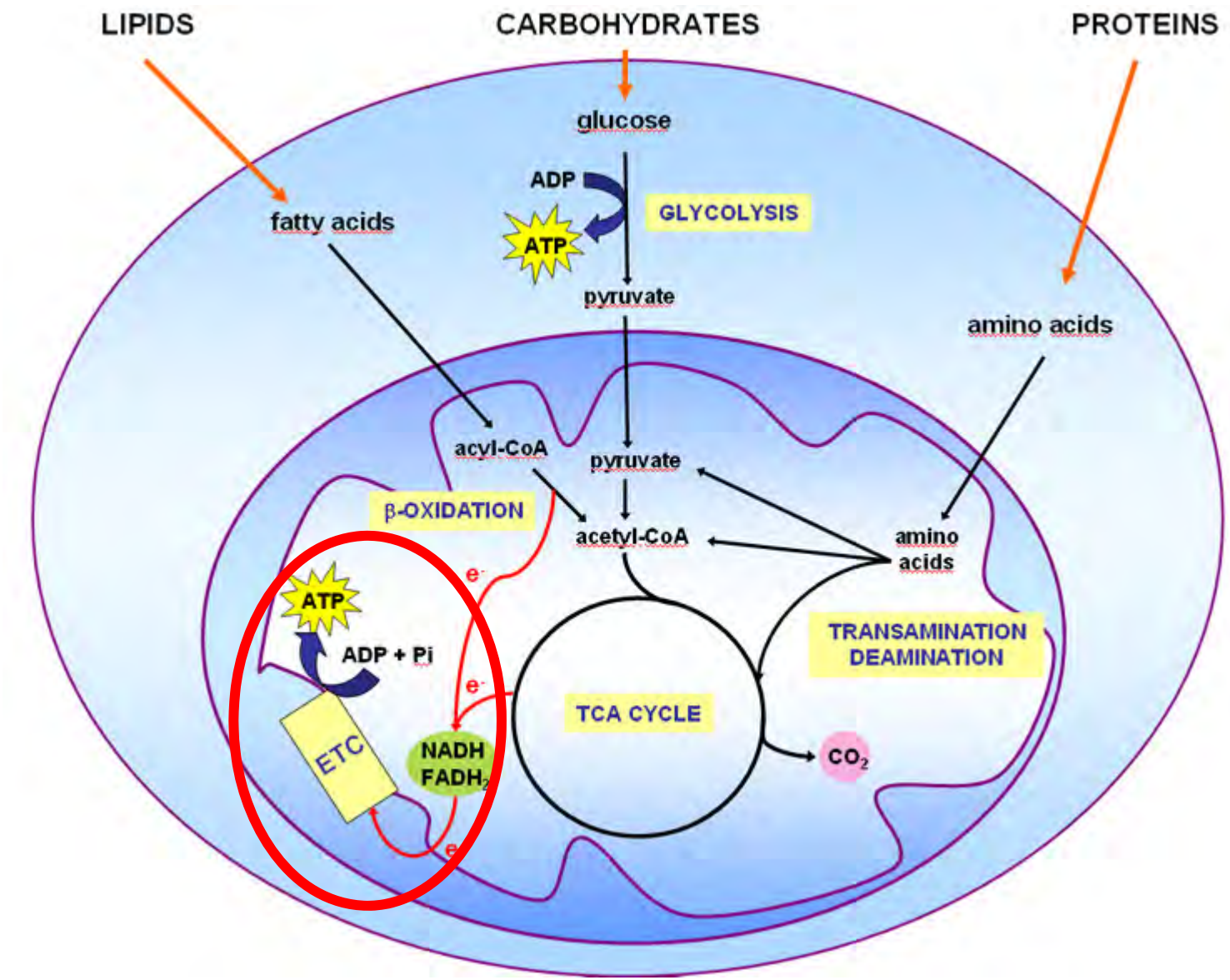
acetyl group

acetyl CoA

Structure of Coenzyme A



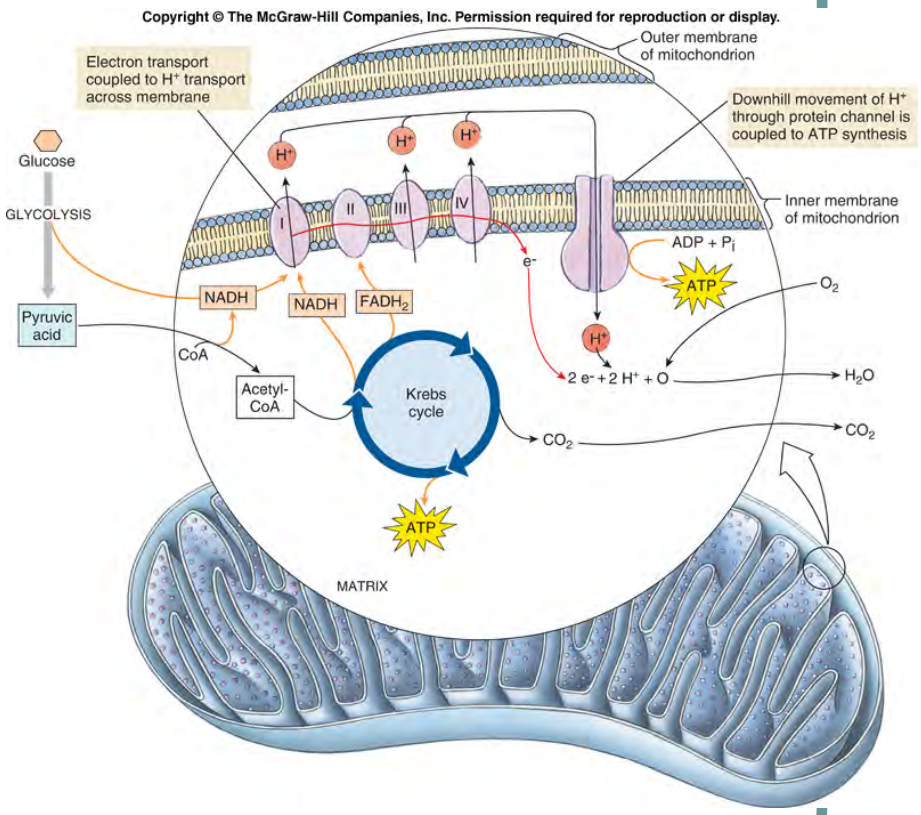
Fuel molecule entry points in Oxidative Metabolism



El Bacha, T., Luz, M. & Da Poian, A. (2010) Dynamic Adaptation of Nutrient Utilization in Humans. *Nature Education* 3(9):8

Using Electrons to Make ATP

- NADH & $FADH_2$ contain energized electrons.
- NADH molecules carry their electrons to the inner mitochondrial membrane where they transfer electrons to a series of membrane bound proteins – the **electron transport chain**.



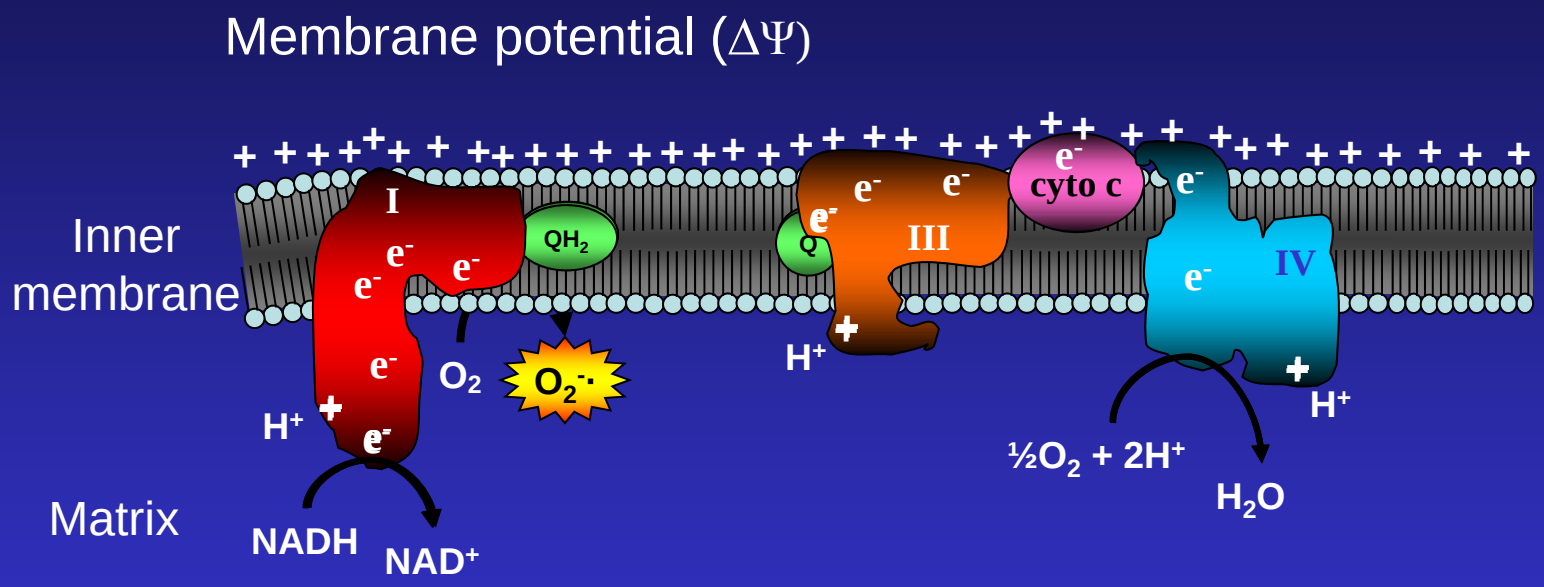
Building an Electrochemical Gradient

- In eukaryotes, aerobic metabolism takes place in the mitochondria in virtually all cells.
- The Krebs cycle occurs in the **matrix**, or internal compartment of the mitochondrion.
- Protons (H^+) are pumped out of the matrix into the **intermembrane space**.

Electron Transport Review

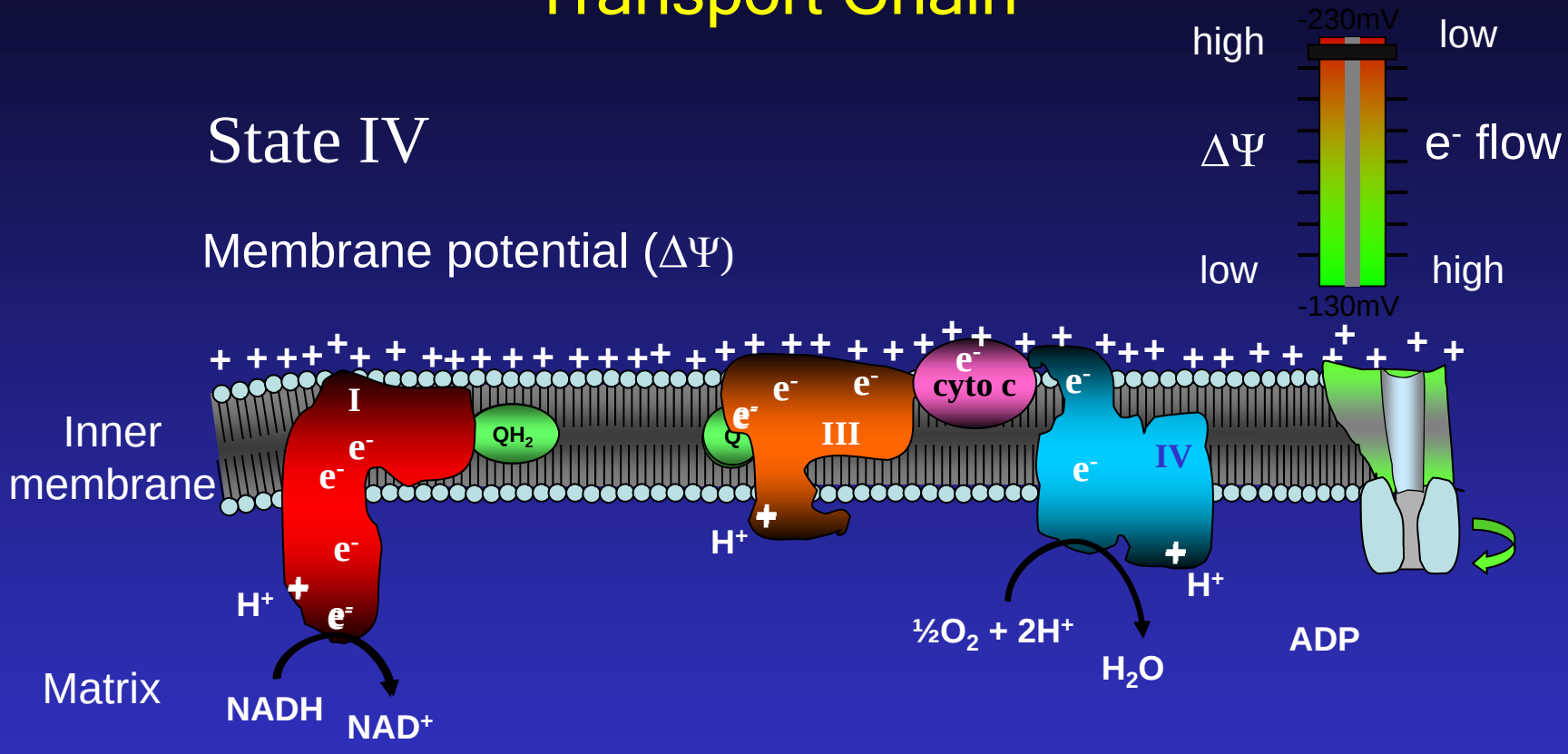
http://www.youtube.com/watch?v=kN5MtqAB_Yc&list=FL9N_Px072WuVorSwDfqf-9w&index=2&feature=plpp

Factors Governing Electron Flow Through the Transport Chain



Slide provided by Darrell Neufer, PhD; East Carolina University

Factors Governing Electron Flow Through the Transport Chain



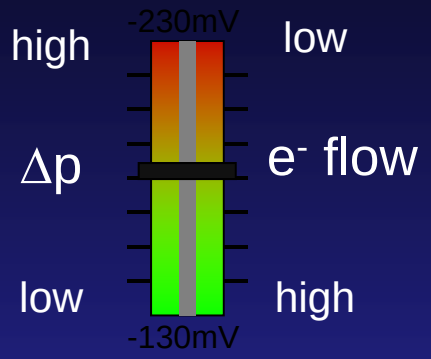
Point 1: The rate of respiration (electron flow) is determined by the rate at which protons enter back into the matrix

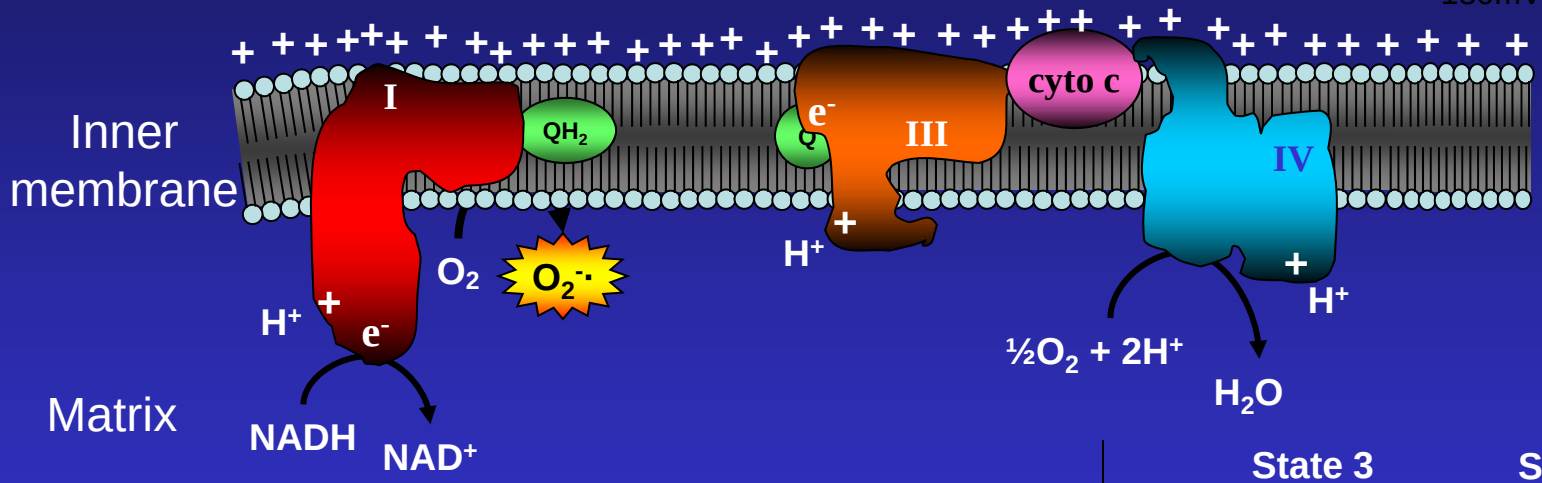
Slide provided by Darrell Neufer, PhD; East Carolina University

Factors Governing Electron Flow Through the Transport Chain

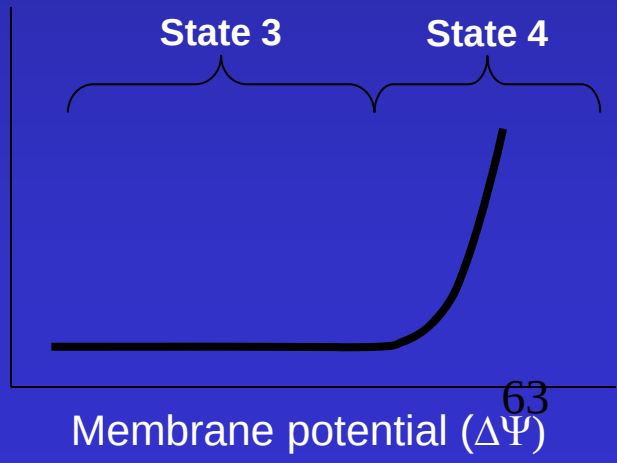
State IV

Membrane potential ($\Delta\Psi$)





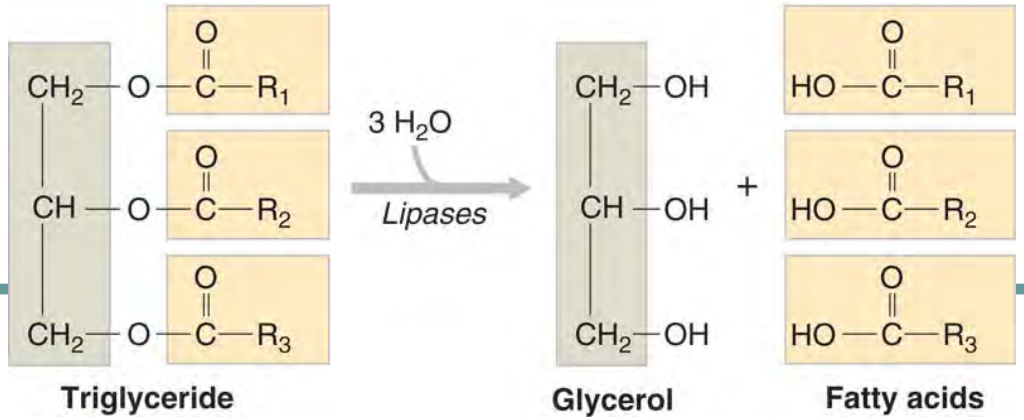
Point 2: Electron leak to oxygen is favored when membrane potential is high (i.e., state 4 conditions).



Slide provided by Darrell Neufer, PhD; East Carolina University

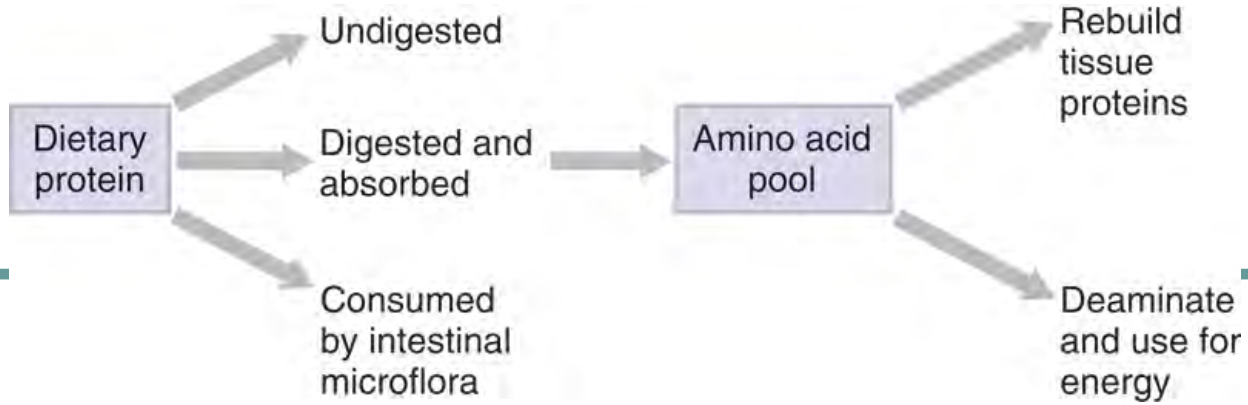
Metabolism of Lipids

- Triglycerides are broken down into glycerol and 3 fatty acid chains.
- Glycerol enters glycolysis.
- Fatty acids are oxidized and 2-C molecules break off as acetyl-CoA.
  - Oxidation of one 18-C stearic acid will net 146 ATP.
  - Oxidation of three glucose (18 Cs) nets 108 ATP.
  - Glycerol nets 22 ATP, so 1 triglyceride nets 462 ATP.



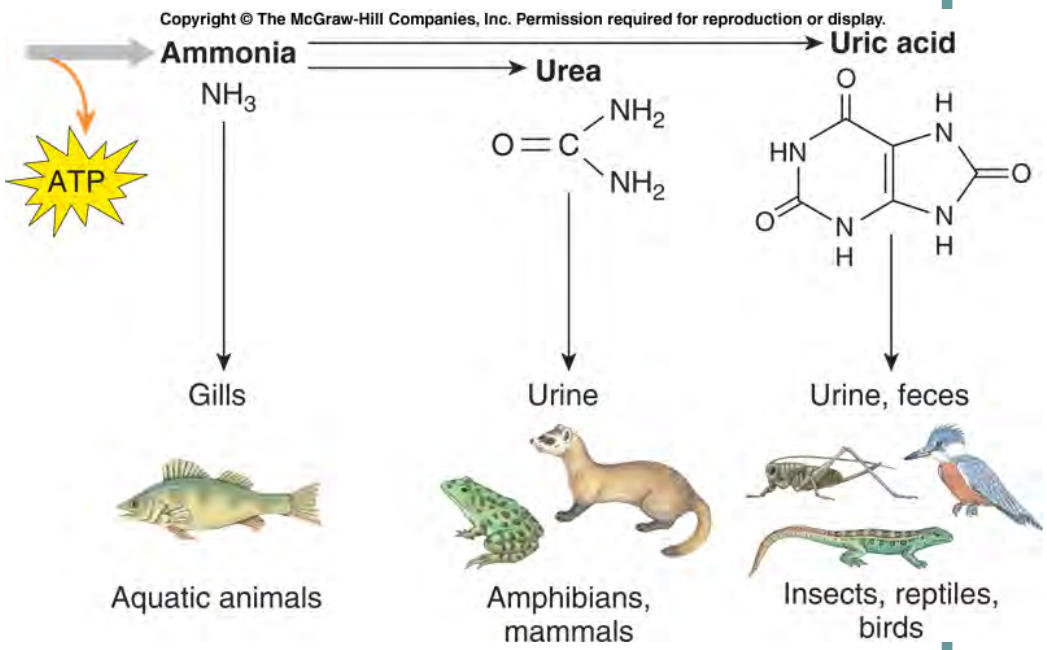
Metabolism of Proteins

- Proteins digested in the gut into amino acids which are then absorbed into blood and extracellular fluid.
- Excess proteins can serve as fuel like carbohydrates and fats.
  - Nitrogen is removed producing carbon skeletons and ammonia.
    - Carbon skeletons oxidized.



Metabolism of Proteins

- Ammonia is highly toxic, but soluble.
  - Can be excreted by aquatic organisms as ammonia.
- Terrestrial organisms must detoxify it first.

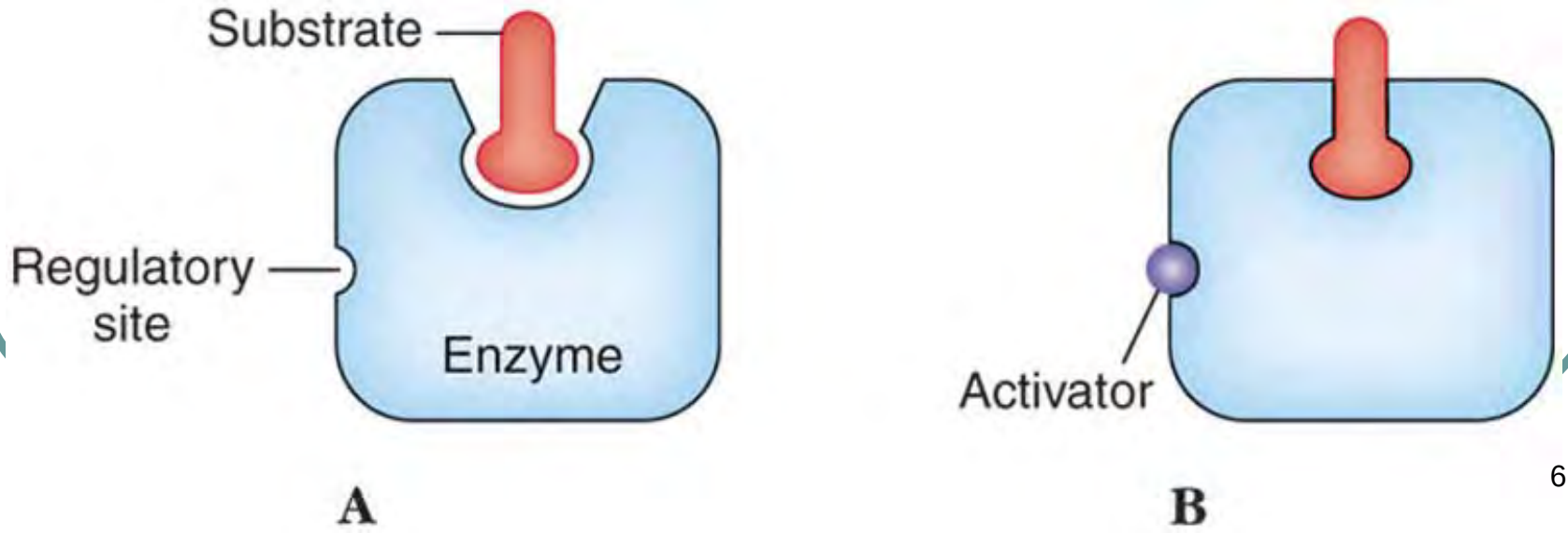


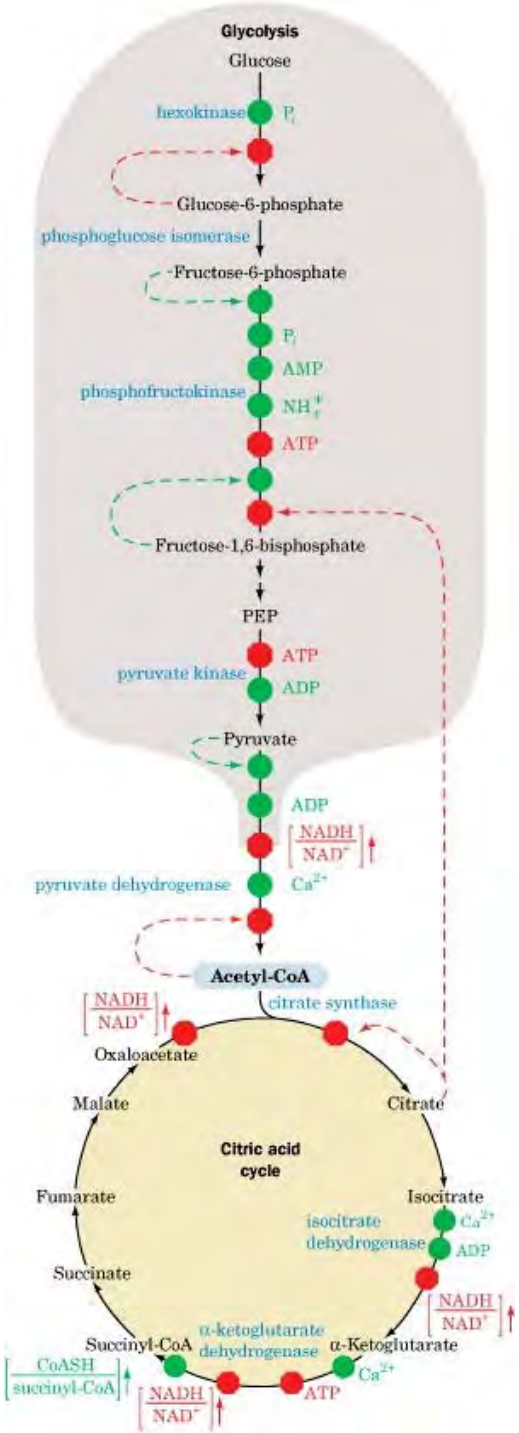
Regulating Cellular Respiration

- Rate of cellular respiration slows down when your cells have enough ATP.
- Enzymes that are important early in the process have an allosteric (regulating) site that will bind to ATP.
- When lots of ATP is present, it will bind to this site, changing the shape of the enzyme, halting cellular respiration.

Regulating Cellular Respiration

- Enzyme activity is controlled by presence or absence of metabolites that cause conformational changes in enzymes.
  - Improves or decreases effectiveness as catalyst.





Control of ATP production

Coordinated control of ATP production

- **Glycolysis, the citric acid cycle and the oxidative phosphorylation**
  Control of [NADH]/[NAD+]
- **Aerobic vs. anaerobic metabolism**
  Aerobic ATP production is far more efficient than anaerobic

- **Disease conditions:**

  Cancer: Coordinated controls broken down and increased ATP utilization

  Cardiovascular disease: oxygen deprivation, decreased O_2 supply to cells → reduced ATP synthesis, increased ROS production → cell damage.

Figure 22-48 Diagram depicting the coordinated control of glycolysis and the citric acid cycle by ATP, ADP, AMP, P_i, Ca^{2+}, and [NADH]/[NAD^+].

Regulation of blood glucose levels

Glucagon

- Catabolic, in response to hypoglycemia
- Liver
  - Activates glycogen degradation, gluconeogenesis
- Adipose
  - Stimulates lipolysis and release of fatty acids

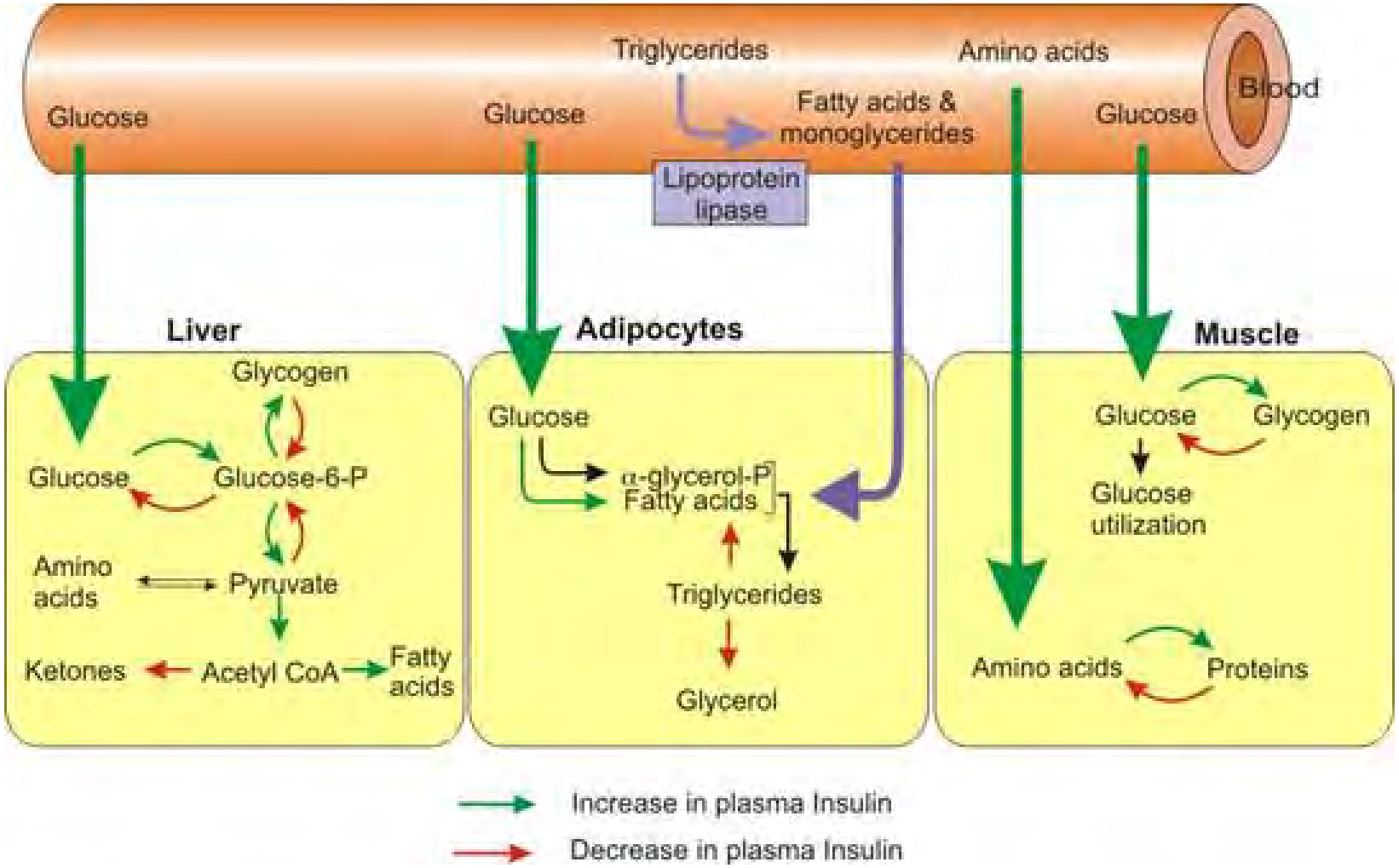
Regulation of blood glucose levels

Insulin

Anabolic in response to hyperglycemia

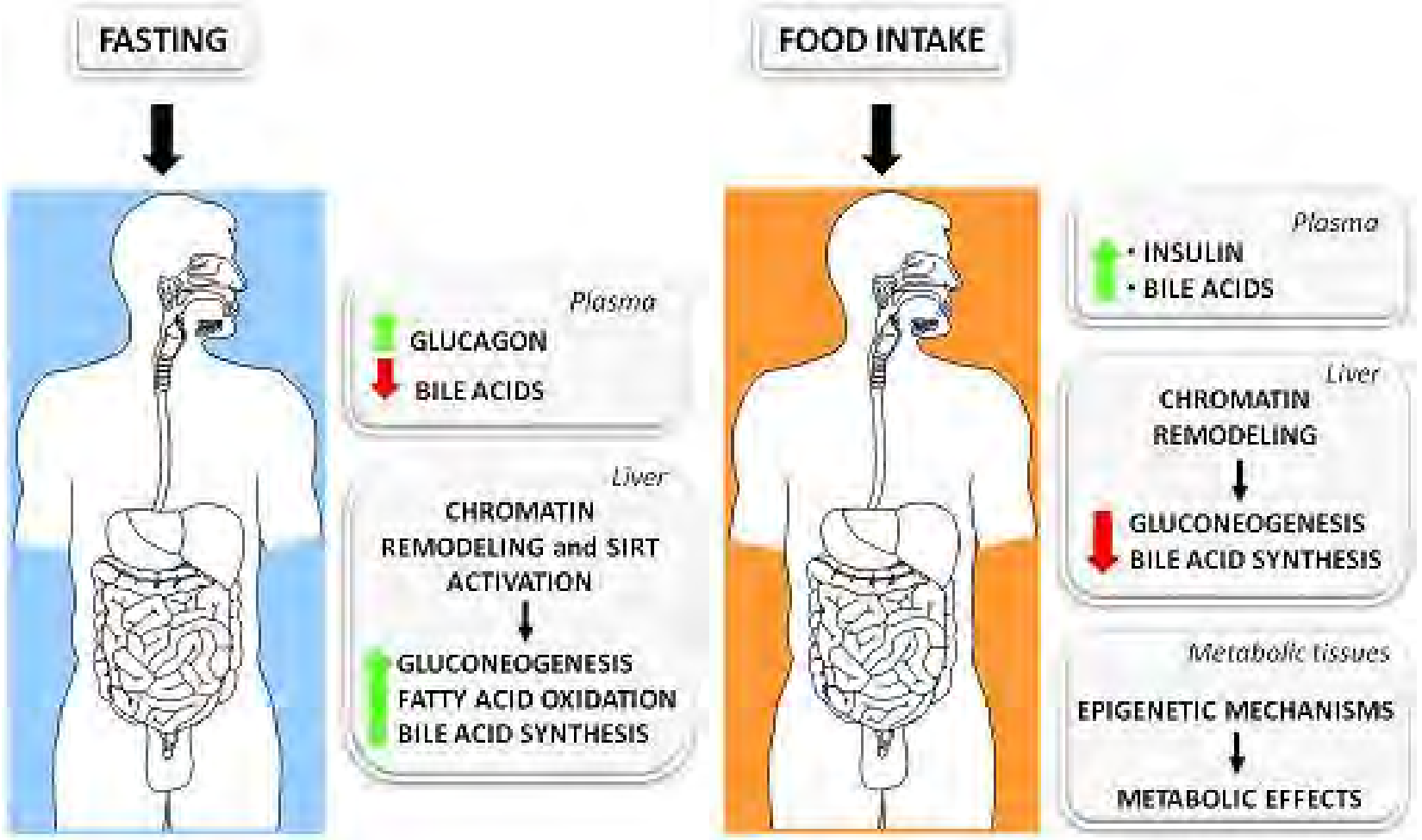
- Liver
  - Stimulates glycogen synthesis, glycolysis, and fatty acid synthesis
- Muscle
  - Stimulates glycogen synthesis
- Adipose
  - Stimulates lipoprotein lipase resulting in uptake of fatty acids from chylomicrons and VLDL
  - Stimulates glycolysis for glycerol phosphate synthesis (precurser to triglycerides)

Diagram of the action of insulin on liver, adipocyte and muscle cells



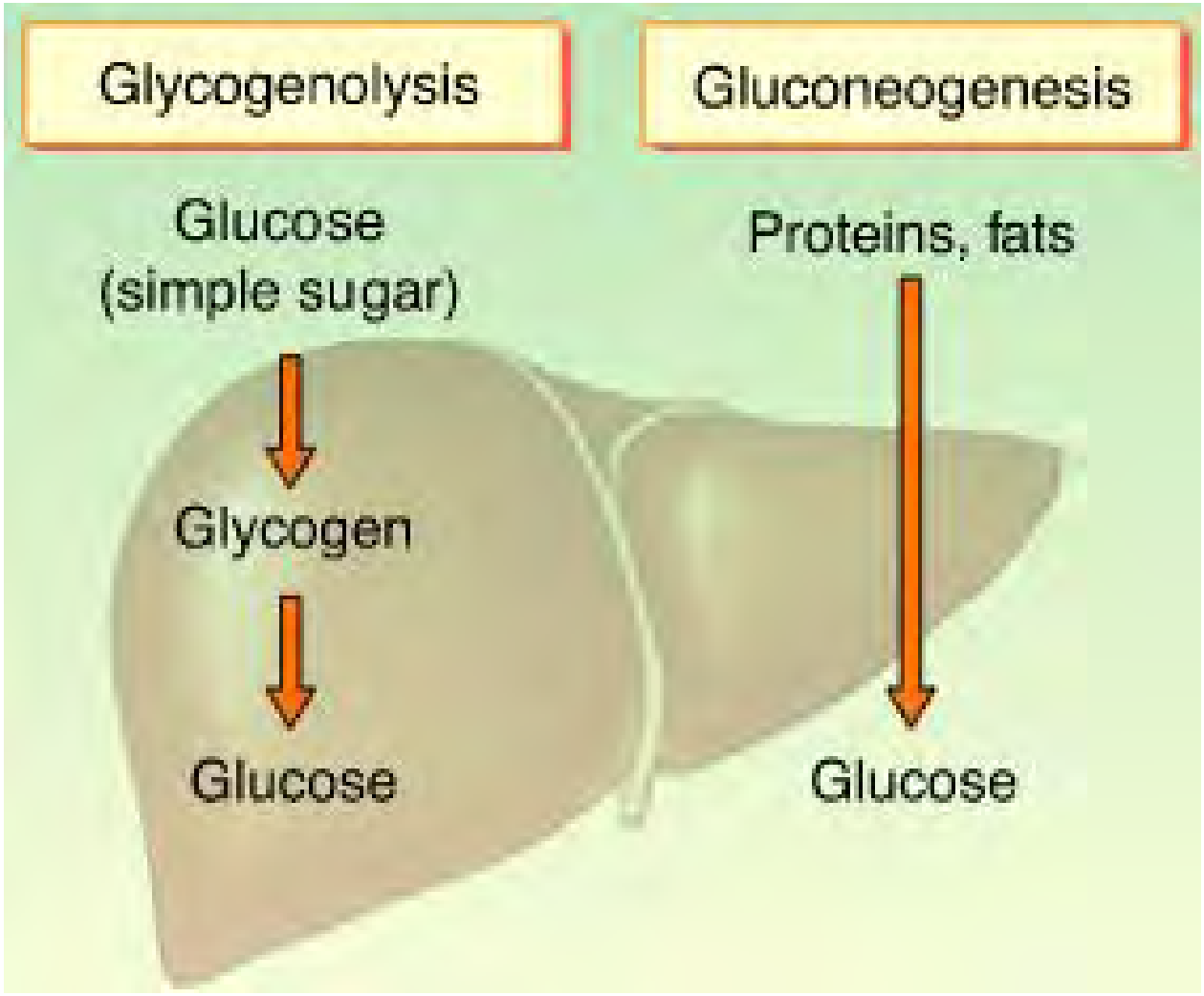
http://elearn.pharmacy.ac.uk/Diabetes/diabetes_07.htm

Metabolic changes occurring in the fasted-to-fed cycle



Review: **When Food Meets Man: the Contribution of Epigenetics to Health**
by Emma De Fabiani, Nico Mitro, Federica Gilardi, Andrea Galmozzi, Donatella Caruso and Maurizio Crestani.
Nutrients **2010**, *2*(5), 551-571; doi:10.3390/nu2050551

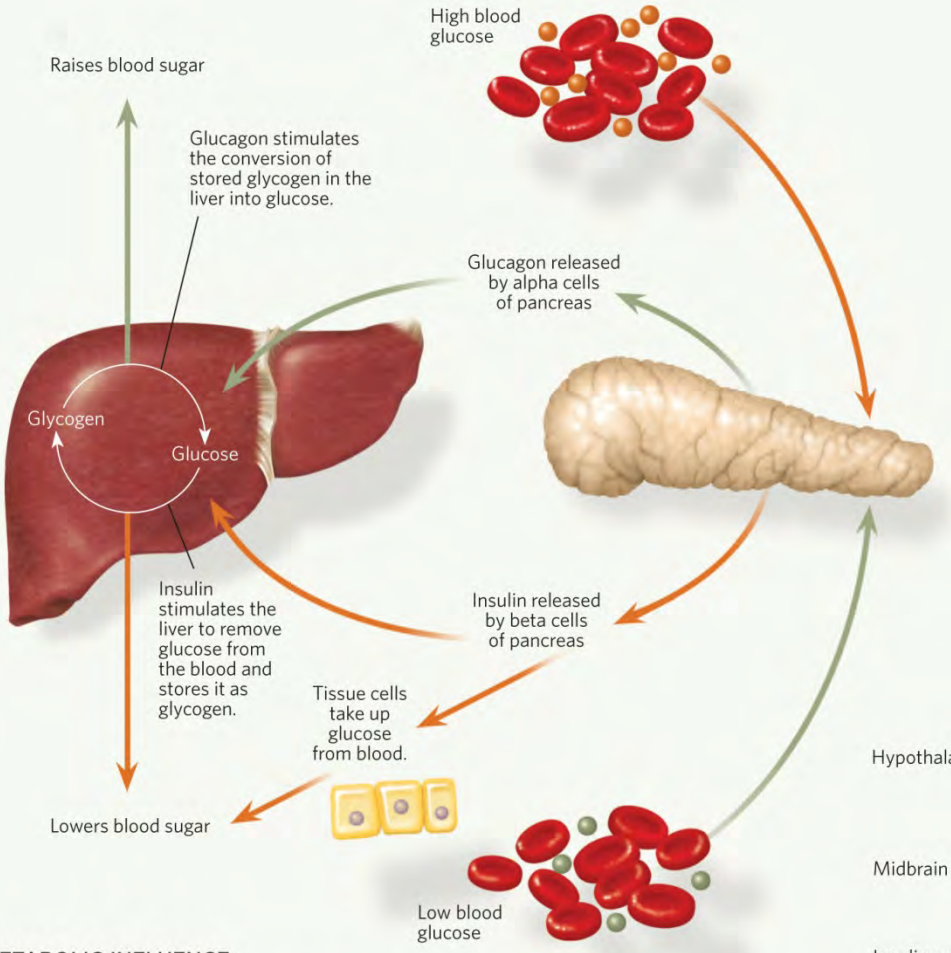
Fasted State



Insulin in Body and Brain

INSULIN'S ROLE IN BODY AND BRAIN

Insulin, long recognized as a primary regulator of blood glucose, is now also understood to play key roles in neuroplasticity, neuromodulation, and neurotrophism, the process of neuronal growth, stimulated by neuronal differentiation and survival.



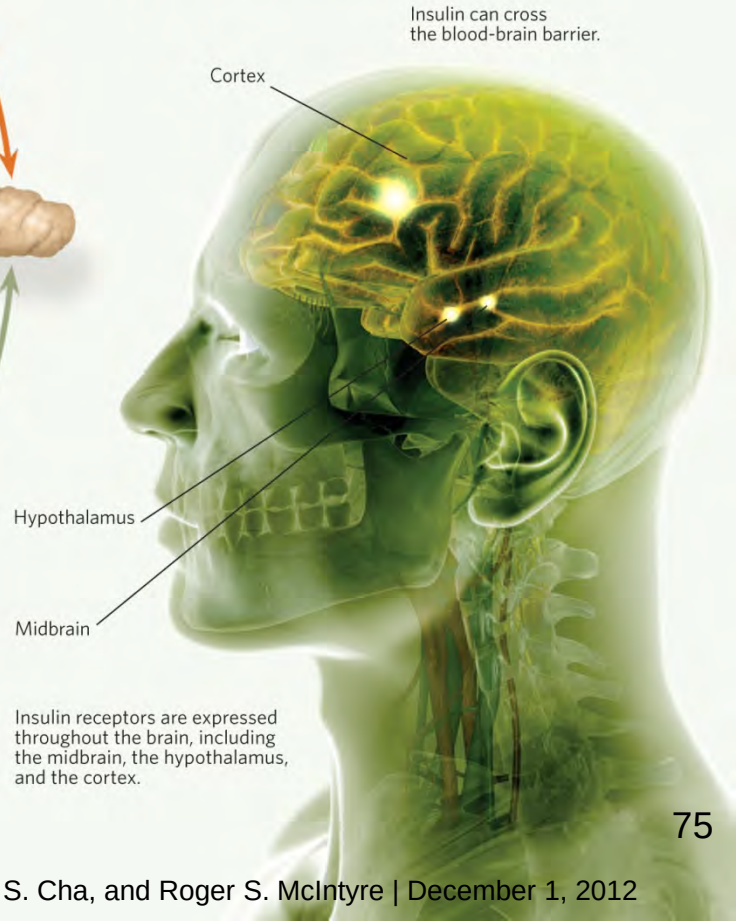
PRECISION GRAPHICS; HEAD © 3D4MEDICAL.COM/CORBIS

METABOLIC INFLUENCE

Insulin is one of the primary hormones involved in blood glucose regulation. Its dysregulation is associated with obesity and diabetes.

NEUROLOGIC INFLUENCE

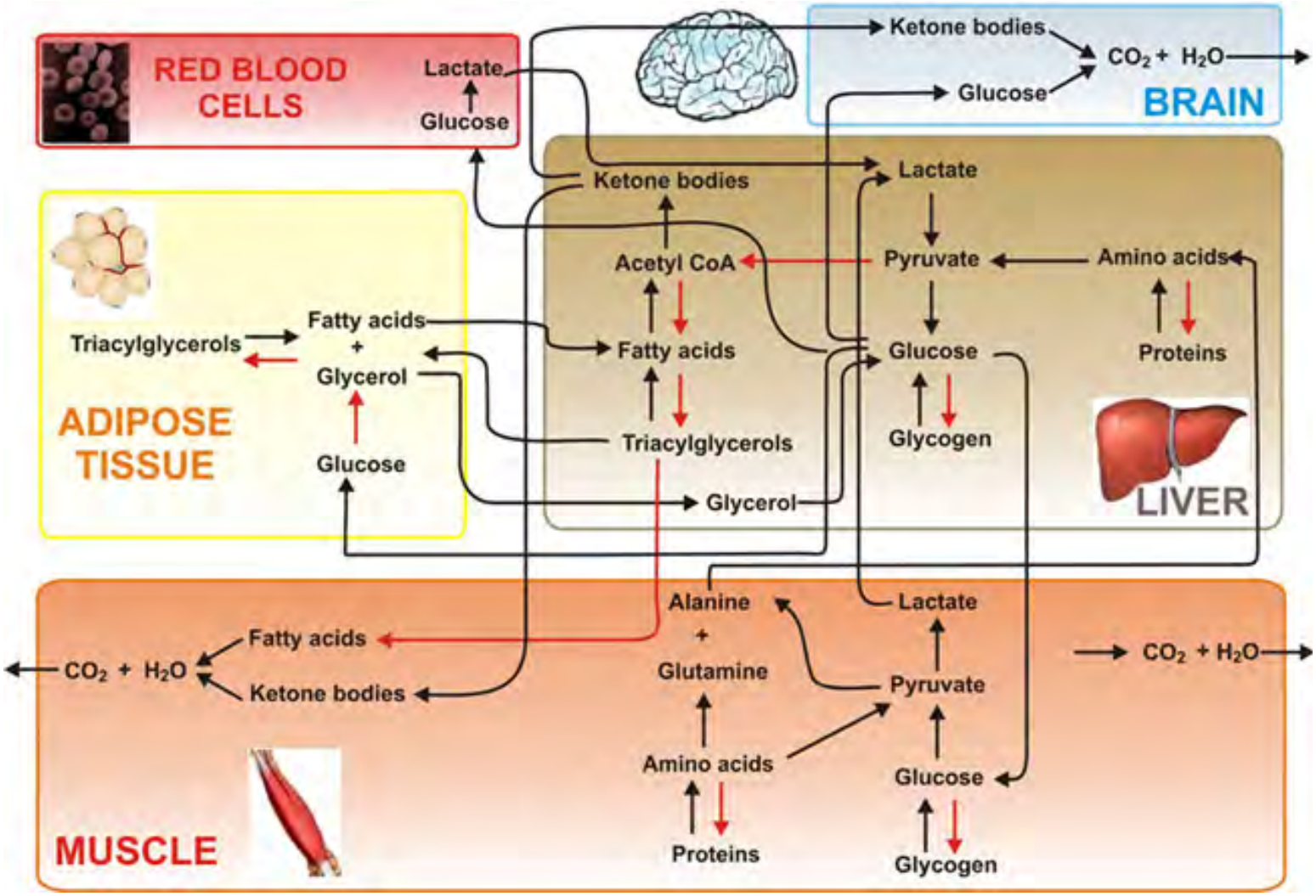
Insulin activates insulin receptors and downstream signaling molecules in the brain and spinal cord, as well as insulin-sensitive glucose transporters in the peripheral insulin-sensitive tissues (liver, muscle, fat). Through these mechanisms, insulin participates in feeding behavior, reward pathways, whole body metabolism, and normal emotional and cognitive brain functions. The dysregulation of insulin-mediated signaling pathways in the brain is implicated in neurodegenerative diseases such as Alzheimer's and psychiatric disorders such as schizophrenia.



Insulin receptors are expressed throughout the brain, including the midbrain, the hypothalamus, and the cortex.

*F1000 Biol Reports*2012, **4**:14; the-scientist.com; Oksana Kaidanovich-Beilin, Danielle S. Cha, and Roger S. McIntyre | December 1, 2012

Different Cell Types Require Different Fuel Molecules



El Bacha, T., Luz, M. & Da Poian, A. (2010) Dynamic Adaptation of Nutrient Utilization in Humans. *Nature Education* 3(9):8

Glycemic Index or Glycemic Load, are they the same?

Glycemic Index: David Jenkins, Thomas Wolever and colleagues 1981, University of Toronto – wanted a way to classify foods for diabetics,

- uses a scale from 0-100
- GI of 100 given to area under 2-hour blood glucose curve in response to oral intake of 50g of glucose.

How quickly carbohydrates enter the blood stream after intake *(proteins and fats are not on the glycemic index). Carbohydrates are chosen 1st for breakdown and metabolism over proteins and fats.

Original posited that 1) Starches produce a similar after meal blood glucose responses – Low AND ALL Sugars produce similar blood glucose responses – High – all based on chemical structures.

Low - 0-55; Moderate - 56-69; High - 70-100

Found: white bread (starch) = GI value of 69 = High
ice cream (w sugar) = GI value of 36 = Low

Use of GI: UK, Europe, Australia, USA, Canada, WHO, – all for Diabetes

www.EatGoodCarbs.com ; www.GlycemicIndex.com

Glycemic Index or Glycemic Load, are they the same?

High GI carbs – Gushers – quickly digested, rapid rise in blood glucose, GI = 70+
PROMOTE FAT STORAGE

Low GI carbs – Tricklers – slowly digested, slow/gradual rise in blood glucose, GI = 0-55
DISCOURAGES FAT STORAGE

QUALITY of carbohydrate = GI

Glycemic Load: BOTH the quality and quantity of the carbohydrate amount in 1 number

$$GL = \frac{\text{carbohydrate (grams/serving)} \times GI}{100}$$

Eg: GL of small versus large apple, since GI is the same

Apple Small	(13 grams x 38) / 100 = 5 grams
Apple Large	(26 grams x 38) / 100 = 10 grams

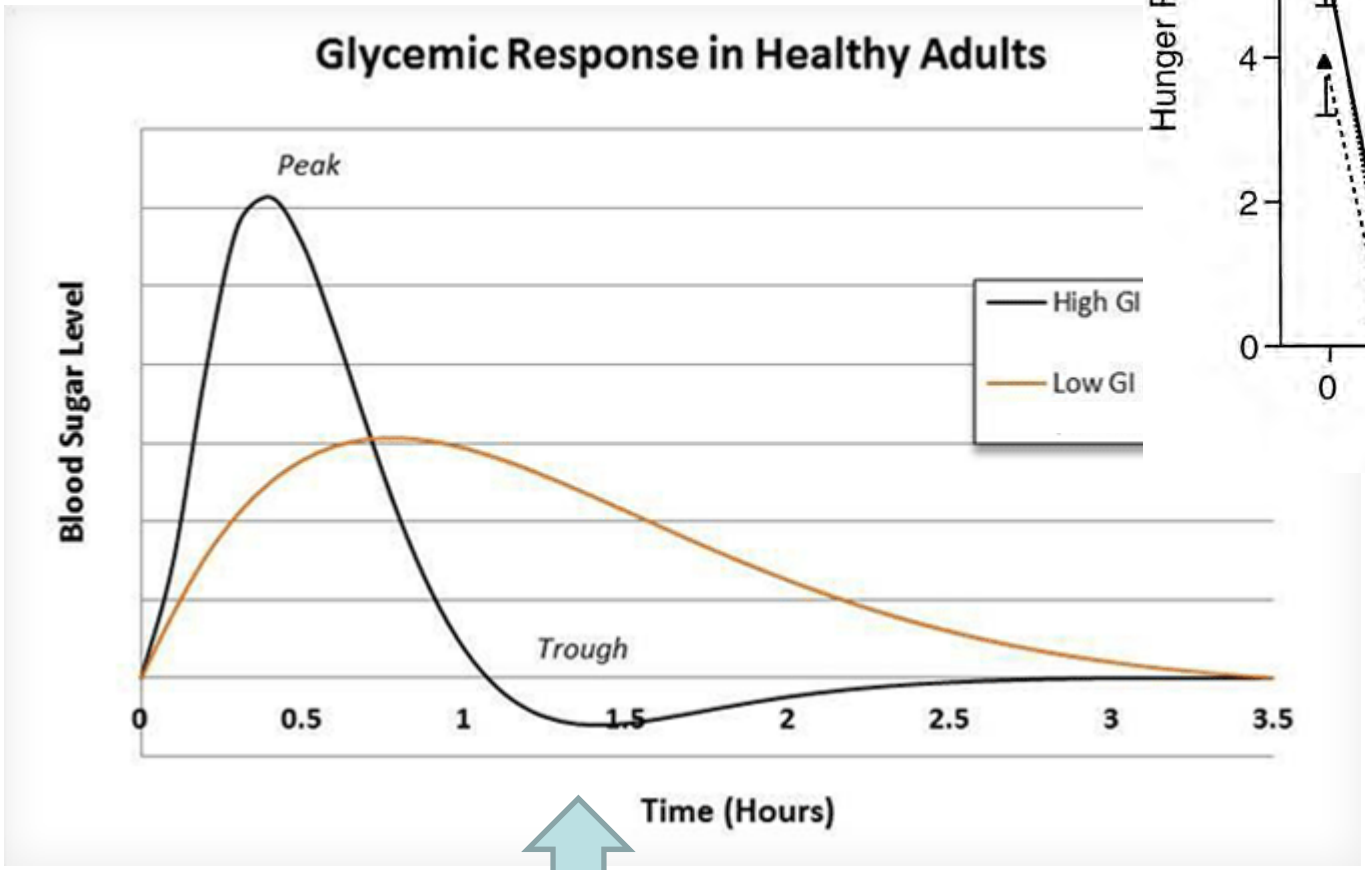
GL: how much insulin would need to be released by the pancreas into the blood stream to allow tissues to absorb that specific amount of that specific carbohydrate and reduce blood sugar levels effectively

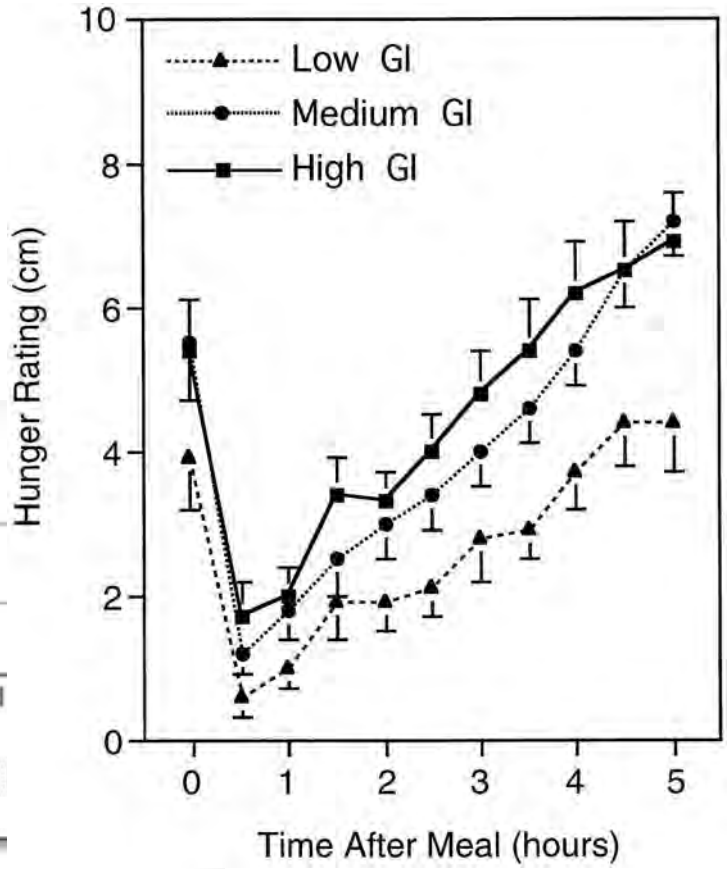
www.EatGoodCarbs.com ; www.GlycemicIndex.com

Walter Willett, Professor at Harvard School of Public Health

High GI vs Low GI Foods

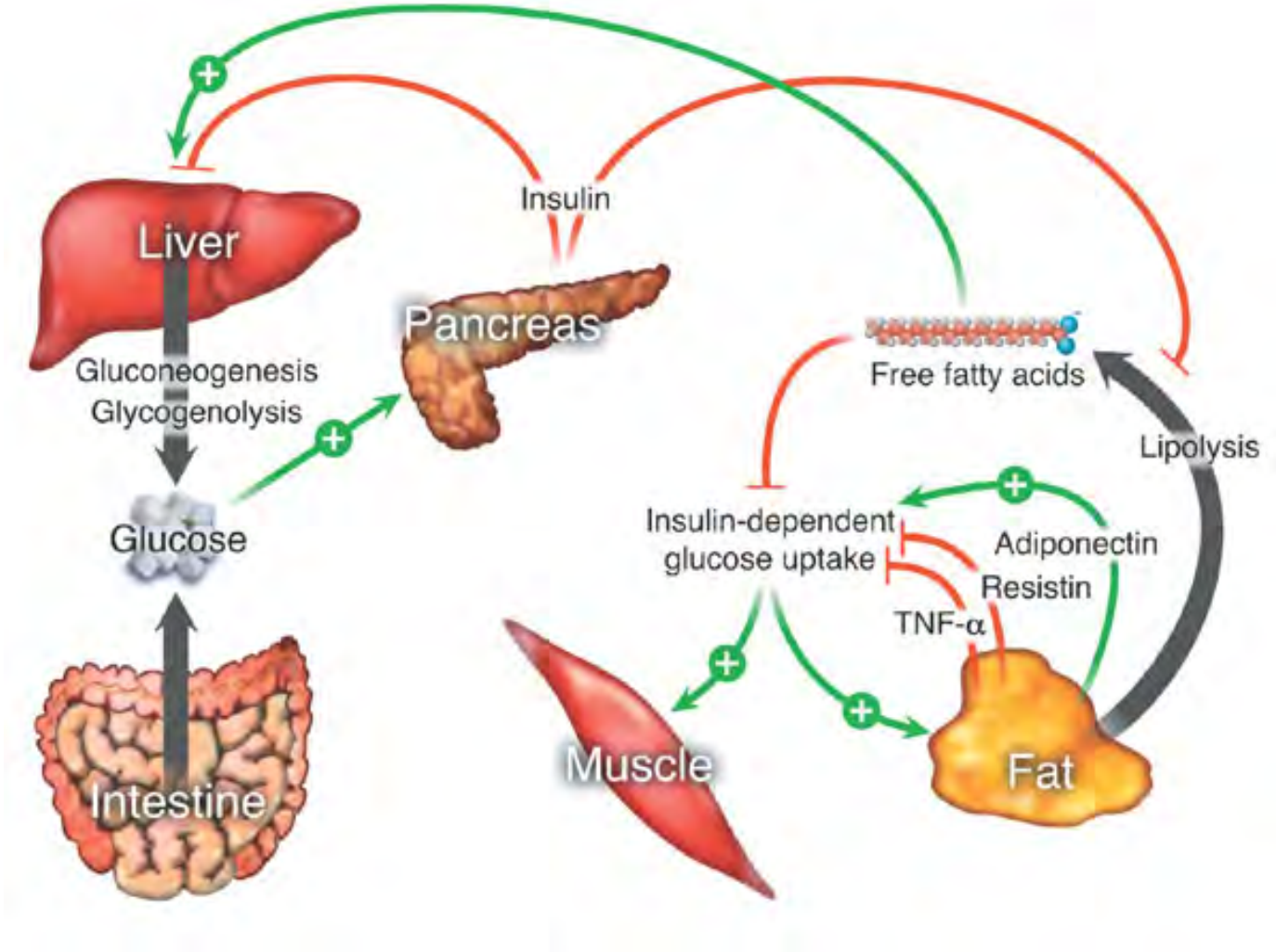
Graph adapted from: www.gisymbol.com (University of Sydney). Images from Microsoft Clipart.





Am J Clin Nutr **November 1991** vol. 54 no. 5 **846-854. Wolever TM, et. al.**

Tissue-tissue cross-talk in glucose and lipid homeostasis



Nature Medicine **10**, 355 - 361 (2004) **PPARs and the complex journey to obesity**
Ronald M Evans, Grant D Barish & Yong-Xu Wang

Diabetes Mellitus – Insulin Insufficiency

Characterized by: -> high blood-glucose level

-> Glucose overproduced by liver

-> glucose underutilized by other organs

-> shift in fuel usage from carbohydrates to fats -> keton bodies (shortage of oxaloacetate)

-> high level of keton bodies -> kidney cannot balance pH any more -> lowered pH in blood and dehydration -> coma

Type I diabetes: insulin-dependent diabetes (requires insulin to live)

caused by autoimmune destruction of β-cells

begins before age 20

-> insulin absent -> glycagon present

-> person in biochemical starvation mode + high blood-glucose level

-> entry of glucose into cells is blocked

-> glucose excreted into urine -> also water excreted -> feel hungry + thirsty

Type II diabetes: insulin-independent diabetes

have a normal-high level of insulin in blood -> unresponsive to hormone

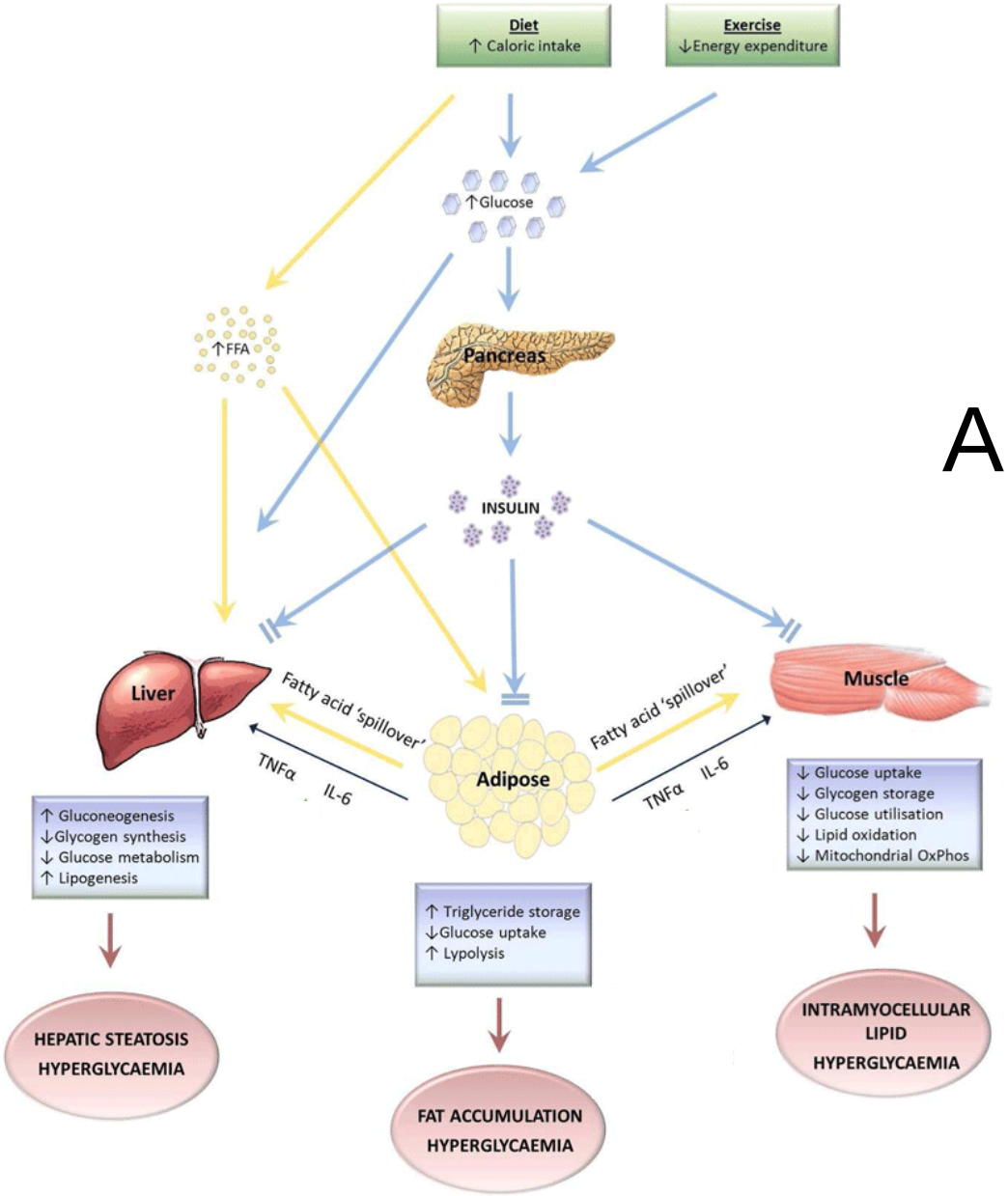
develops in middle-aged, obese people

Development of Systemic Insulin Resistance

Push

Food

Choice
Timing
Content
Water
Vitamins
Co-factors



Pull

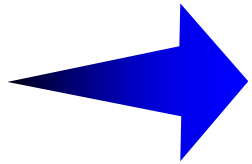
Activity

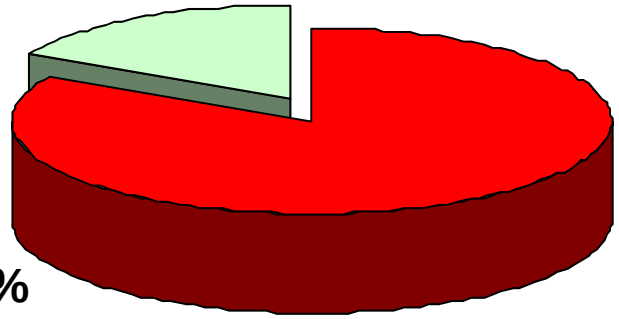
Choice
Duration
Intensity
Water
Vitamins
Co-factors

Modified from: http://michaelscally.blogspot.com/2013/02/obesity-induced-insulin-resistance.html

Metabolism: Standard Metabolic Rate

Energy Intake





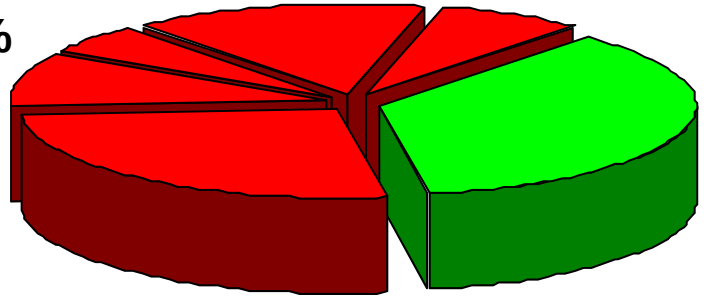
External Work 8%

Growth & Reproduction 15%

Thermogenesis 5%

Digestion 10%

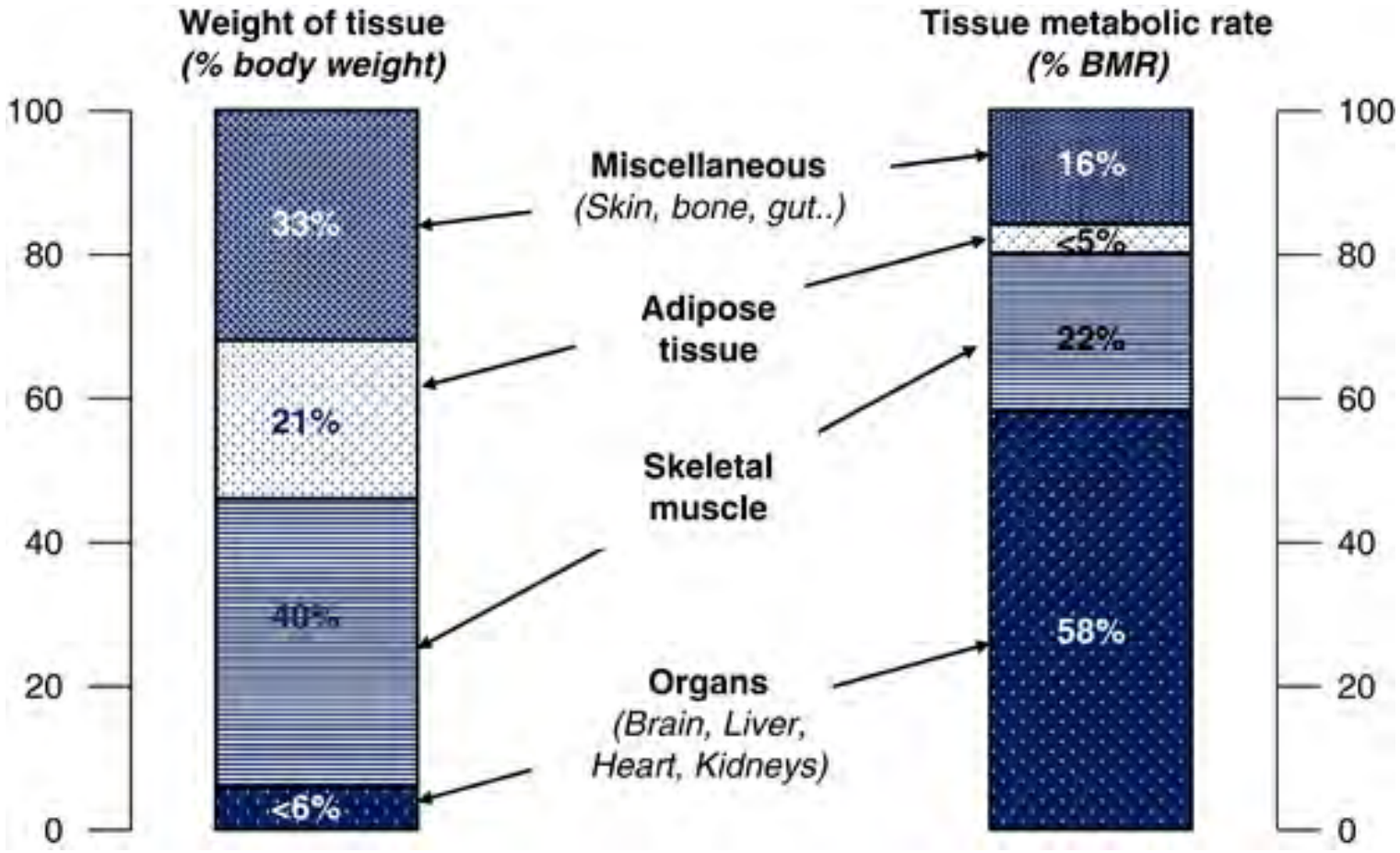
Muscle use 26%



SMR 36%

A significant proportion of standard metabolic rate is devoted to driving mitochondrial proton leak which is a futile cycle

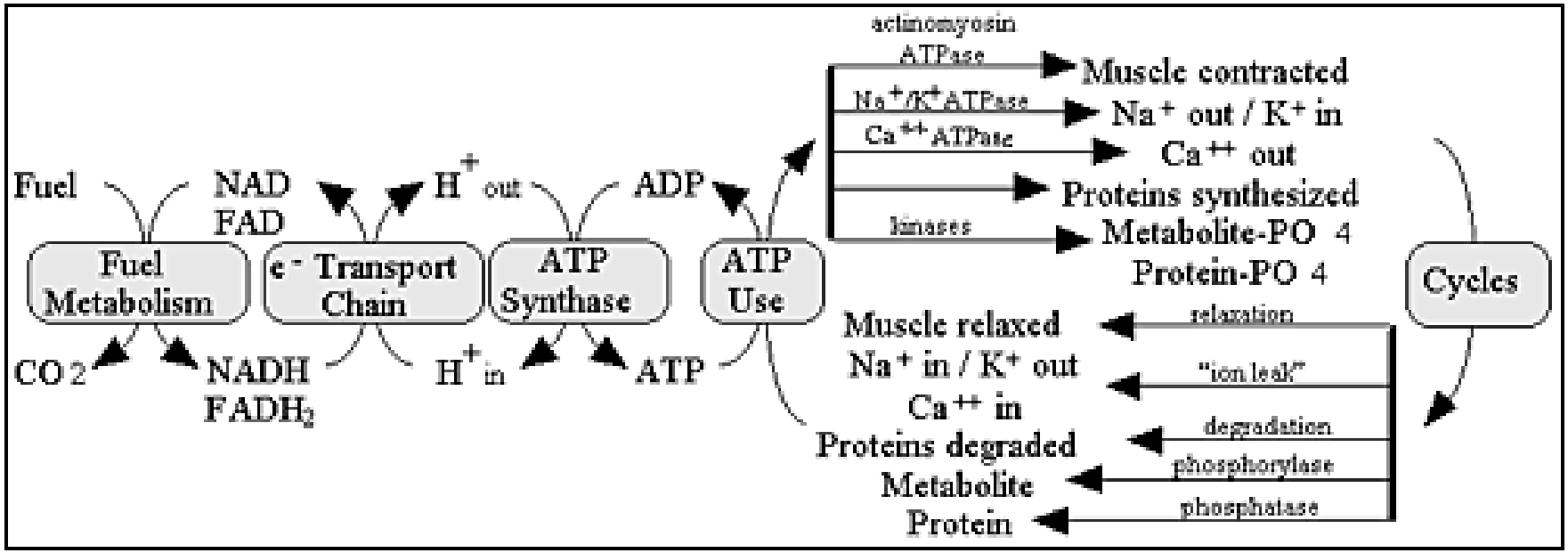
Contribution of organ/tissues to the basal metabolic rate (BMR) of a non-obese man



Note that organs contribute to <6% of body weight but that their contribution to basal metabolic rate (BMR) is disproportionately high (>50% BMR). Adapted from Elia. (Elia M. Organ and tissue contribution to metabolic rate. In: Kinney JM, Tucker HN (eds). *Energy metabolism: tissue determinants and cellular corollaries*. Raven Press Ltd: New York, NY, 1992. pp 61–79)

International Journal of Obesity (2010) **34,** S4–S17; doi:10.1038/ijo.2010.234

Coupling of reactions in energy metabolism and the operation of "futile cycles"

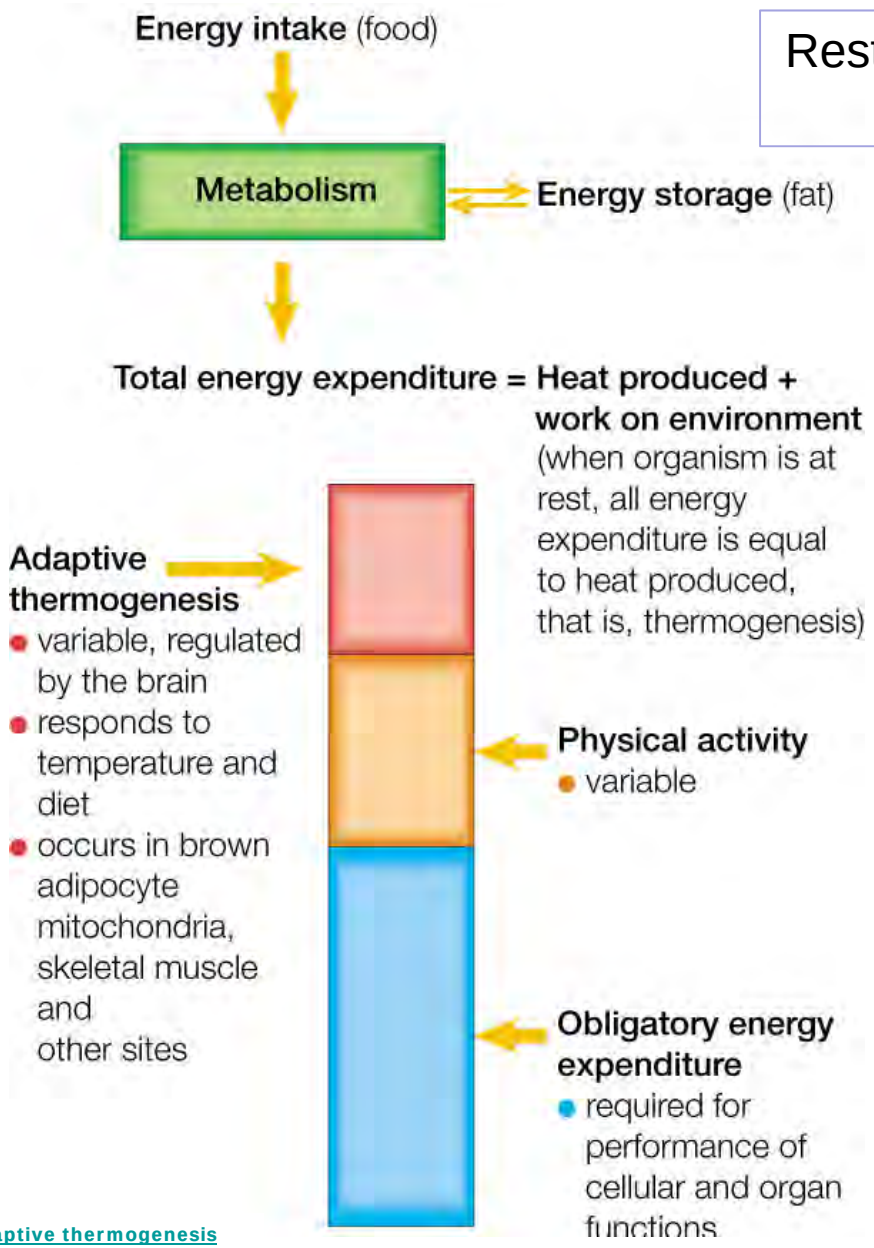


"Metabolism of fuel generates a stoichiometric amount of NADH and FADH2. Oxidation of NADH and FADH2 results in 10 and 6 protons, respectively, being pumped out of the mitochondrial matrix. Three protons enter via ATP synthase in order to synthesize one molecule of ATP from ADP and Pi. One additional proton enters the matrix as it is co-transported with Pi via the phosphate carrier. ATP is then utilized to perform a fixed amount of work. The major consumers of ATP are shown above. Muscle relaxation, ion leaks, protein degradation and dephosphorylation create the possibility for "futile cycles". See Rolfe and Brown (Rolfe, D. F. & Brown, G. C. Cellular energy utilization and molecular origin of standard metabolic rate in mammals. *Physiol. Rev.* **77**, 731–758 (1997)) for a complete analysis of the concept of coupling with respect to reactions in energy metabolism.

Towards a molecular understanding of adaptive thermogenesis
Bradford B. Lowell and Bruce M. Spiegelman
Nature **404**, 652-660(6 April 2000)
doi:10.1038/35007527

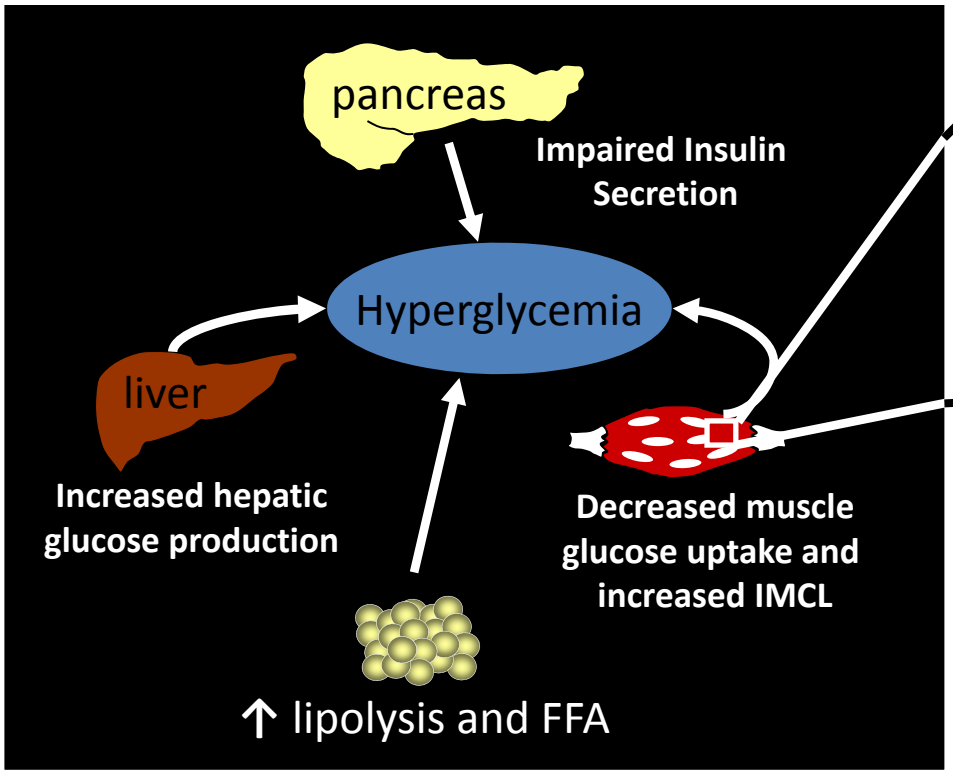
Thermodynamic perspective of energy expenditure

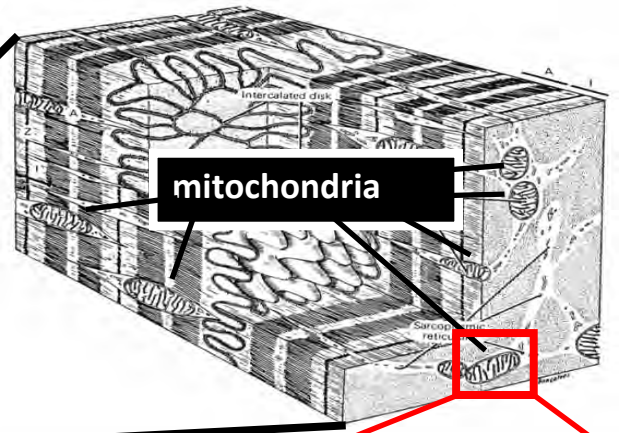
Resting Metabolic Rate and Energy Balance

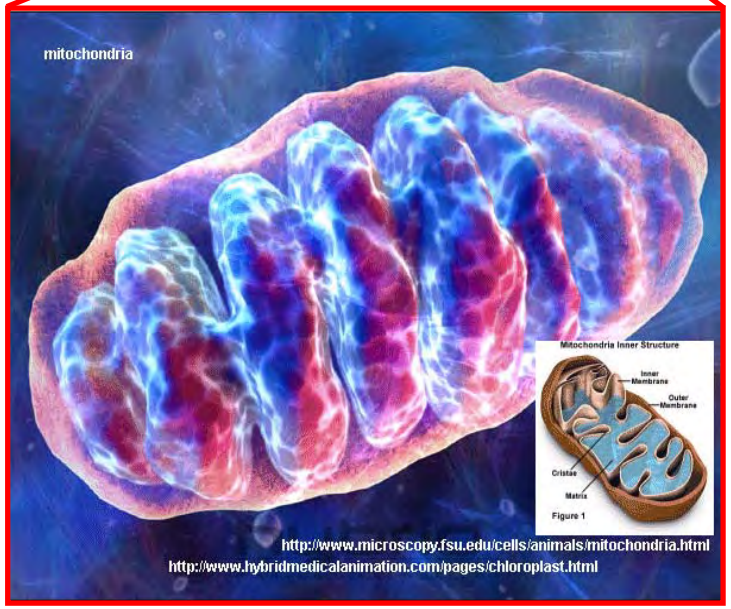


Towards a molecular understanding of adaptive thermogenesis
Bradford B. Lowell and Bruce M. Spiegelman
Nature **404**, 652-660(6 April 2000)
doi:10.1038/35007527

Potential Mechanisms of Obesity, IR, and T2DM







Identify molecular and functional changes in skeletal muscle and mitochondria which contribute to the development of obesity, insulin resistance, and diabetes

Human Oxidative Metabolism, IR and T2DM

J Appl Physiol. 1997 Jul;83(1):166-71.

Altered glycolytic and oxidative capacities of skeletal muscle contribute to insulin resistance in NIDDM.

Simoneau JA, Kelley DE.

Nature Genetics **34**, 267 - 273 (2003)
Published online: 15 June 2003; | doi:10.1038/ng1180

PGC-1α-responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes

Vamsi K Mootha[1, 2, 3, 10], Cecilia M Lindgren[1, 4, 10], Karl-Fredrik Eriksson[4], Aravind Subramanian[1], Smita Sihag[1], Joseph Lehar[1], Pere Puigserver[5], Emma Carlsson[4], Martin Ridderstråle[4], Esa Laurila[4], Nicholas Houstis[1], Mark J Daly[1], Nick Patterson[1], Jill P Mesirov[1], Todd R Golub[1, 5], Pablo Tamayo[1], Bruce Spiegelman[5], Eric S Lander[1, 6], Joel N Hirschhorn[1, 7, 8], David Altshuler[1, 2, 7, 9, 11] & Leif C Groop[4, 11]

Proc Natl Acad Sci U S A. 2003 Jul 8;100(14):8466-71. Epub 2003 Jun 27.

Coordinated reduction of genes of oxidative metabolism in humans with insulin resistance and diabetes: Potential role of PGC1 and NRF1.

Patti ME, Butte AJ, Crunkhorn S, Cusi K, Berria R, Kashyap S, Miyazaki Y, Kohane I, Costello M, Saccone R, Landaker EJ, Goldfine AB, Mun E, DeFronzo R, Finlayson J, Kahn CR, Mandarino LJ.

Diabetes. 2007 Mar;56(3):720-7.

Family history of diabetes links impaired substrate switching and reduced mitochondrial content in skeletal muscle.

Ukropcova B, Sereda O, de Jonge L, Bogacka I, Nguyen T, Xie H, Bray GA, Smith SR.

Science. 2005 Jan 21;307(5708):384-7.

Mitochondrial dysfunction and type 2 diabetes.

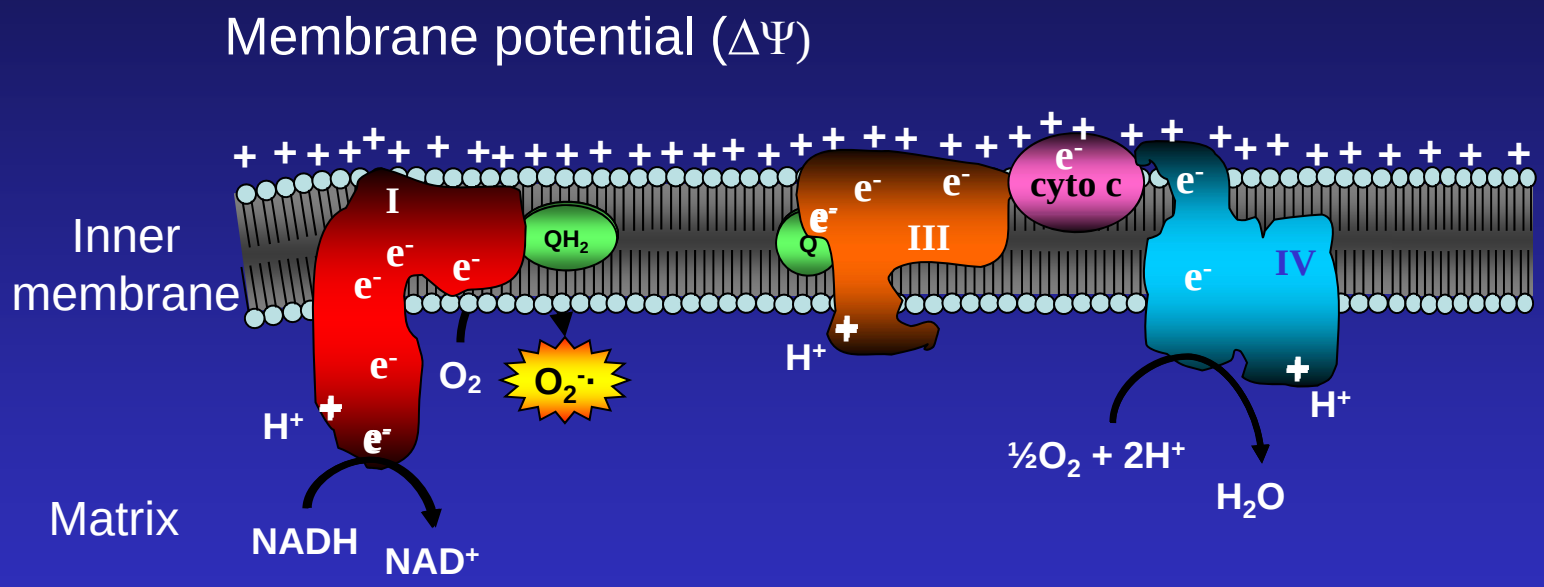
Lowell BB, Shulman GI.

Am J Clin Nutr. 2009 Jan;89(1):463S-6S. doi: 10.3945/ajcn.2008.26717C. Epub 2008 Dec 3.

Skeletal muscle "mitochondrial deficiency" does not mediate insulin resistance.

Holloszy JO.

Factors Governing Electron Flow Through the Transport Chain

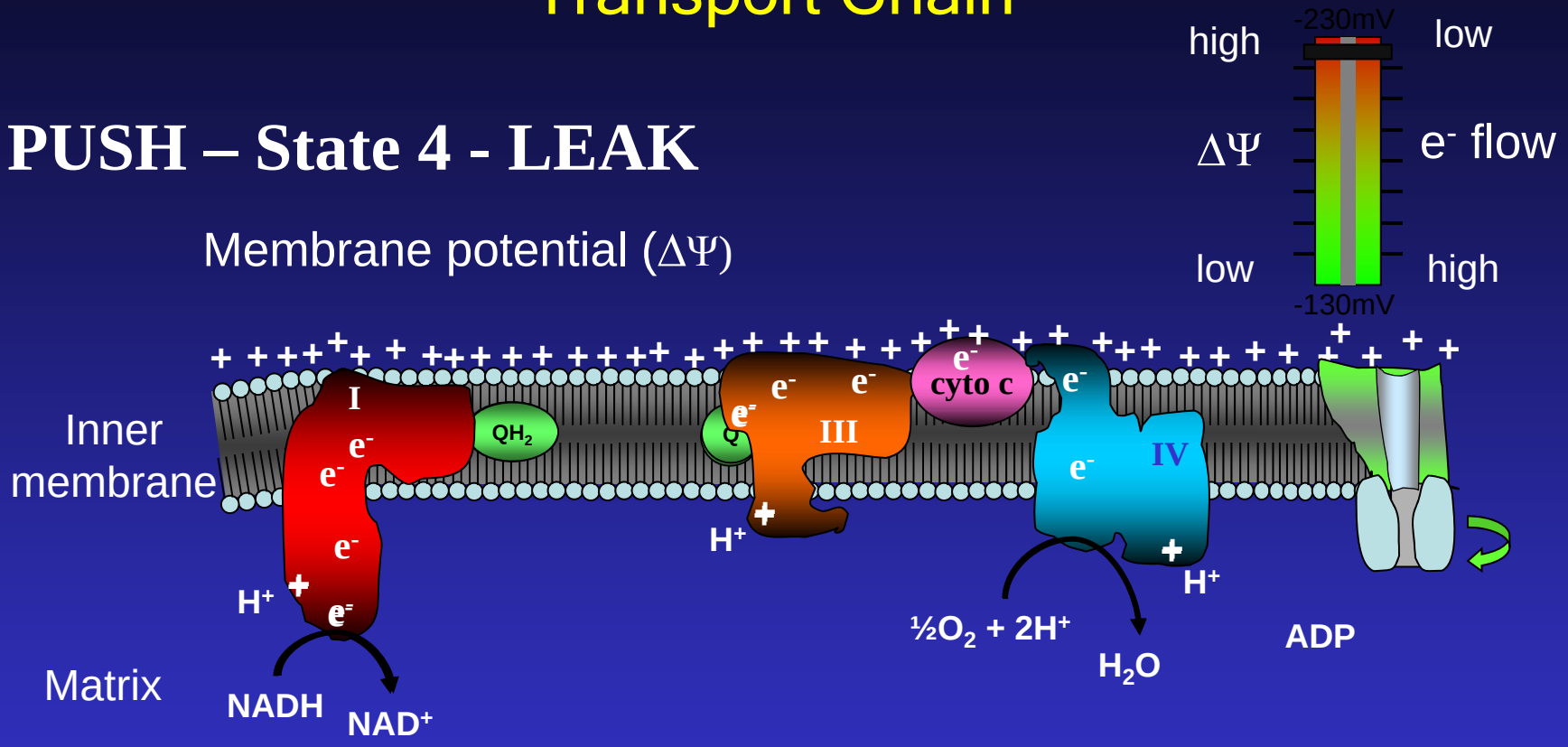


Linking mitochondrial bioenergetics to insulin resistance via redox biology.
Fisher-Wellman KH, **Neufer PD**.
Trends Endocrinol Metab. 2012 Mar;23(3):142-53. doi: 10.1016/j.tem.2011.12.008. Epub 2012 Feb 2. Review.

Slide provided by Darrell Neufer, PhD; East Carolina Diabetes and Obesity Institute; ECU

Factors Governing Electron Flow Through the Transport Chain

PUSH – State 4 - LEAK



PULL - State III - Activity

The rate of respiration (electron flow) is determined by the rate at which protons enter back into the matrix

DRM Modified slide: original by Darrell Neufer, PhD; East Carolina Diabetes and Obesity Institute; ECU

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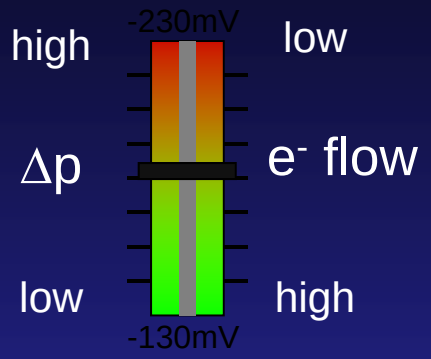
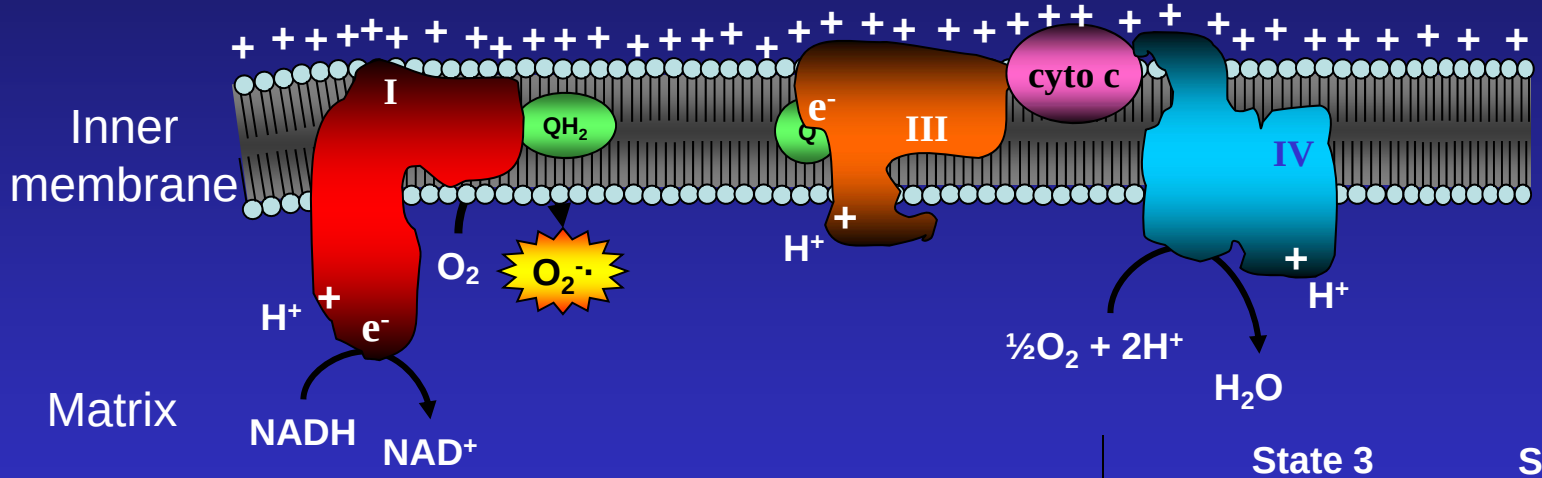
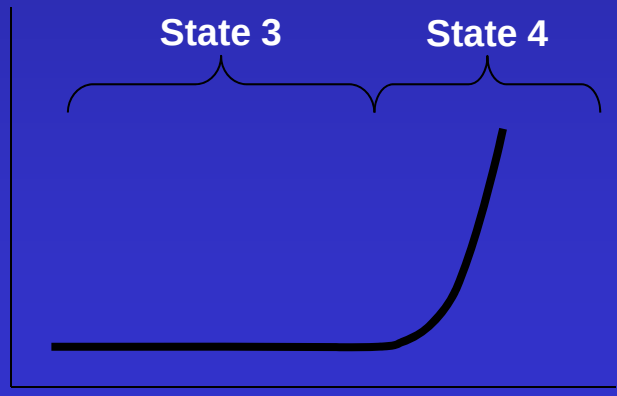
State IV - LEAK



Membrane potential ($\Delta\Psi$)

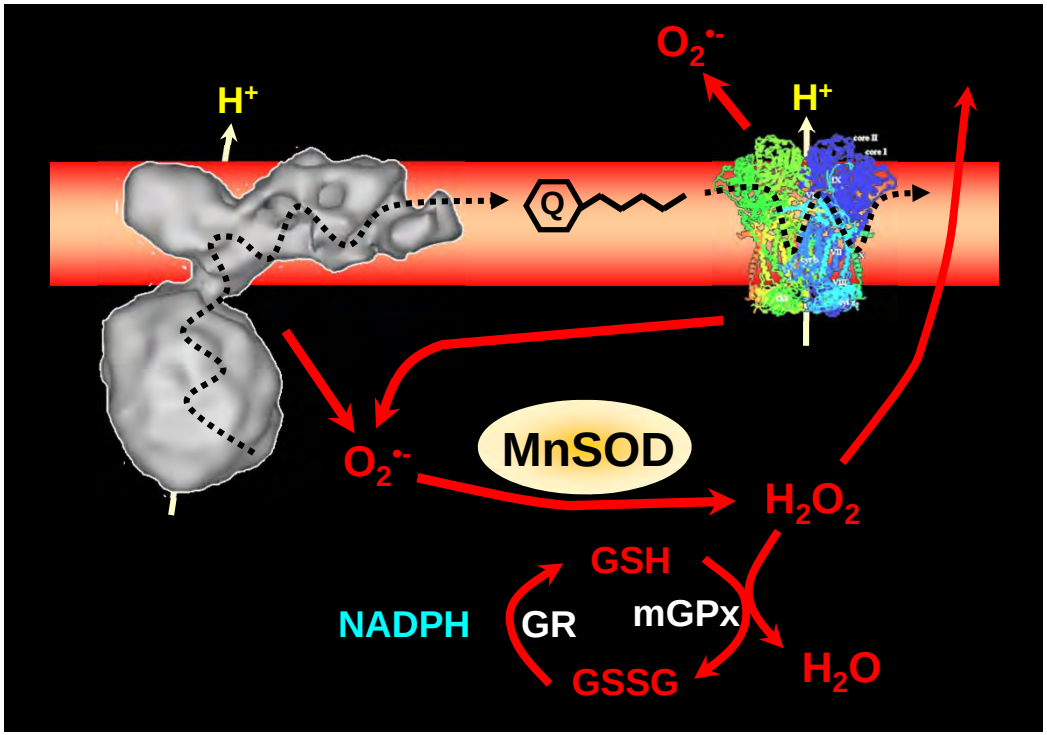


Electron leak to oxygen is favored when membrane potential is high (i.e., state 4 conditions).



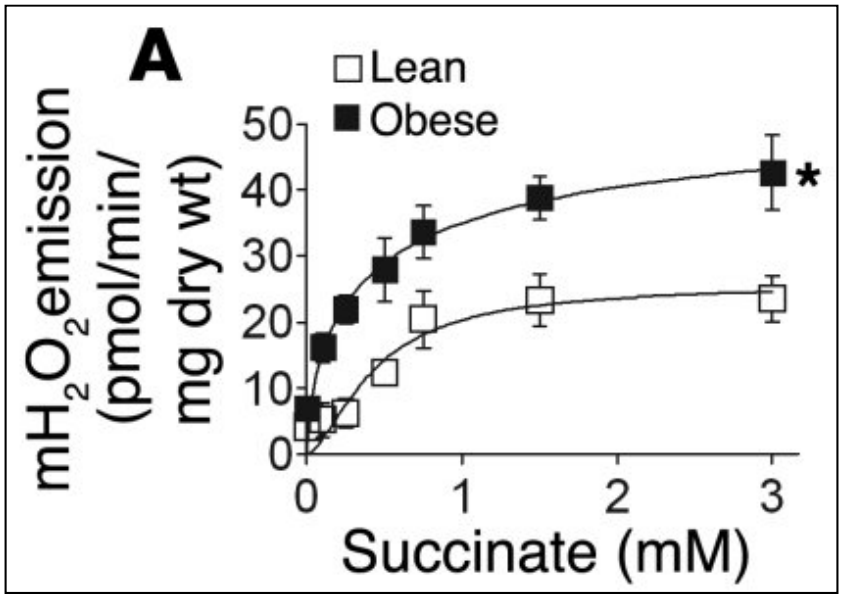
Slide provided by Darrell Neufer, PhD; East Carolina University

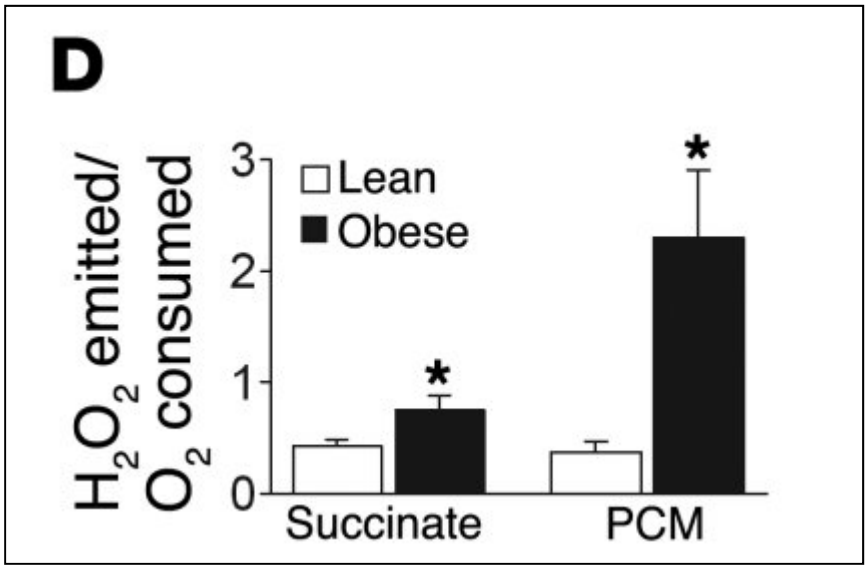
Mitochondria make "ROS"



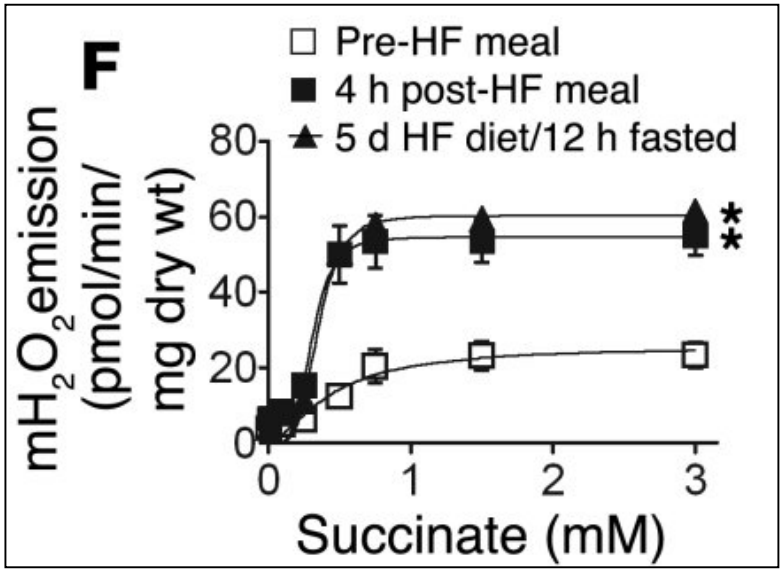
- ROS = Reactive oxygen species (a.k.a. free radicals)…
- Complex I → ROS from the FMN site, facing in.
- Complex III → ROS from semiquinone, on both sides of the membrane.
- Some debate as to whether $O_2^{\bullet-}$ or $HO_2^{\bullet}$ is formed.
- $O_2^{\bullet-}$ cannot leave mitochondrial matrix. H_2O_2 can freely diffuse out.
- Role in aging process (Harman theory) vs. role in cell signaling?
- mtDNA has no histones → greater mutation frequency than nDNA.

Mitochondrial H_2O_2 is Higher in Obese and HF-fed Lean males



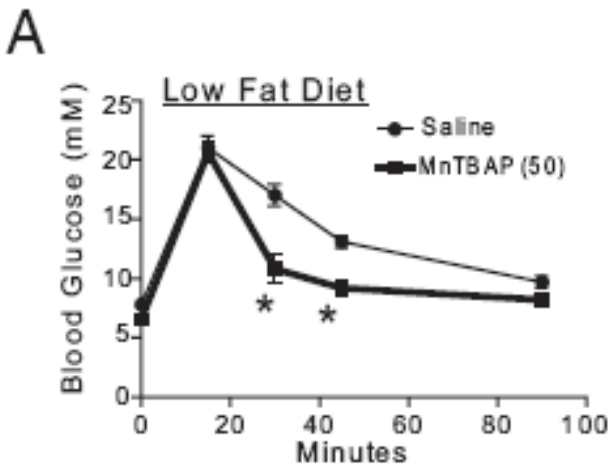


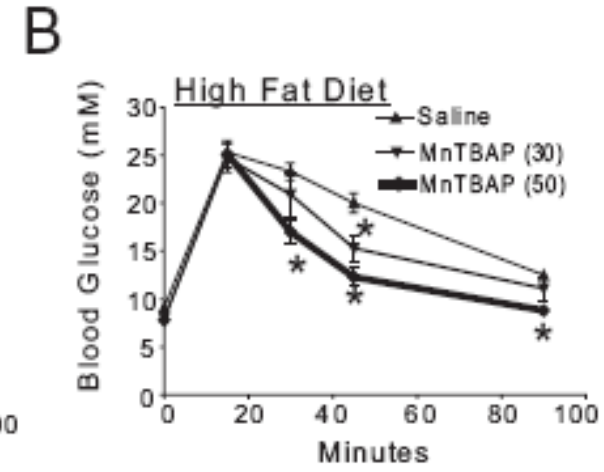
Lean Males



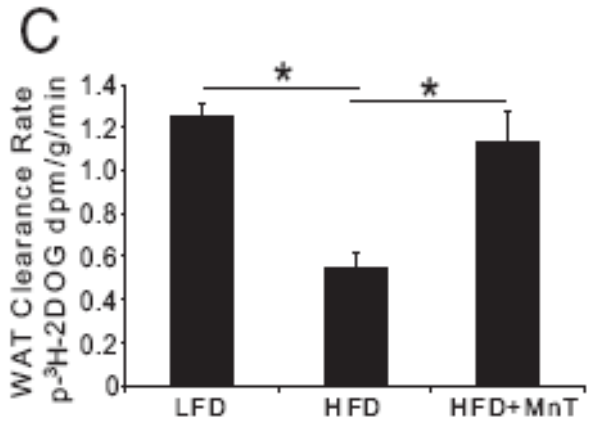
J Clin Invest. 2009; 119(3):573–581 doi:10.1172/JCI37048

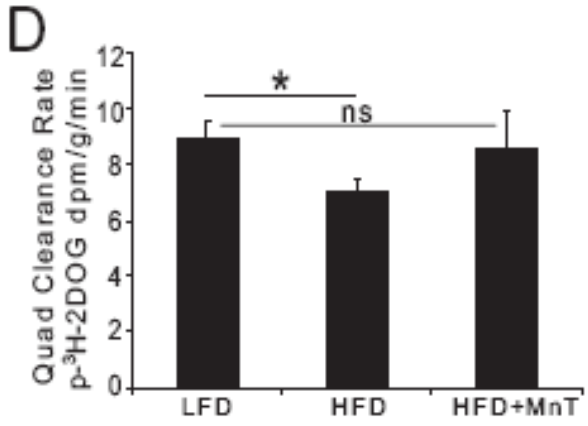
Mitochondrial superoxide regulates insulin sensitivity in vivo.





(A and B) Mice fed a standard lowfat (LFD, A) or high fat diet (HFD, B) ± 30 or 50 mg/kg MnTBAP 6h before i.p. injection of 1.5 g glucose/kg body weight. n≥8 mice per group.

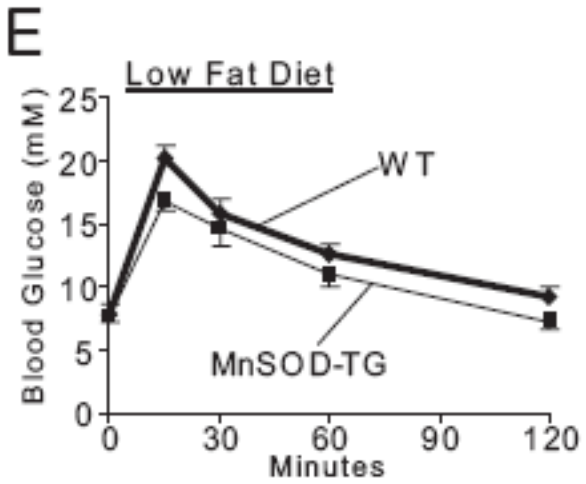


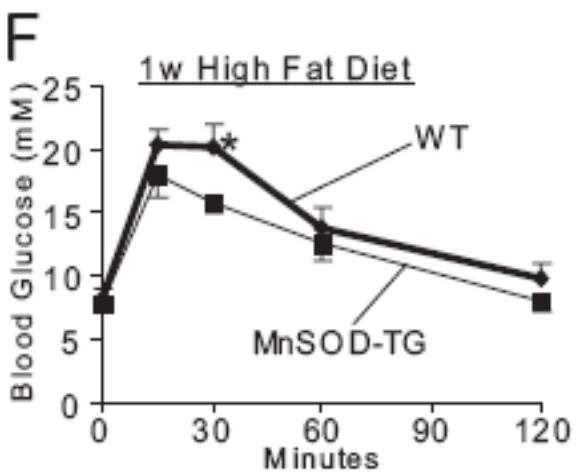


(C and D) Glucose disposal into muscle and gonadal adipose tissue was measured by GTT with 3H-2DOG tracer. Mice were fed LFD or 2 weeks HFD ± 50 mg/kg MnTBAP (HFD+MnT) 6 h before glucose tolerance testing. n = 5 mice per group.

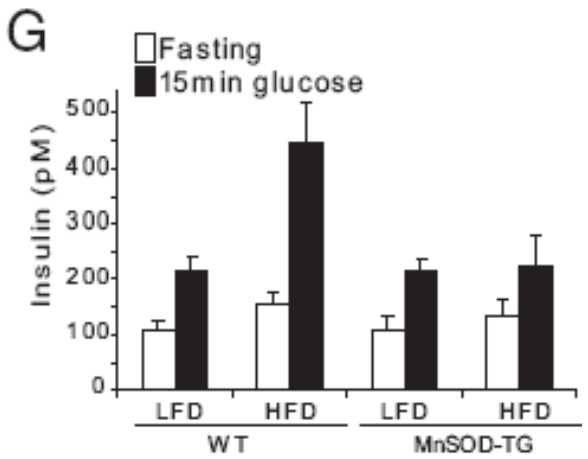
PNAS | October 20, 2009 | vol. 106 | no. 42 | 17787–17792

Mitochondrial superoxide regulates insulin sensitivity in vivo.

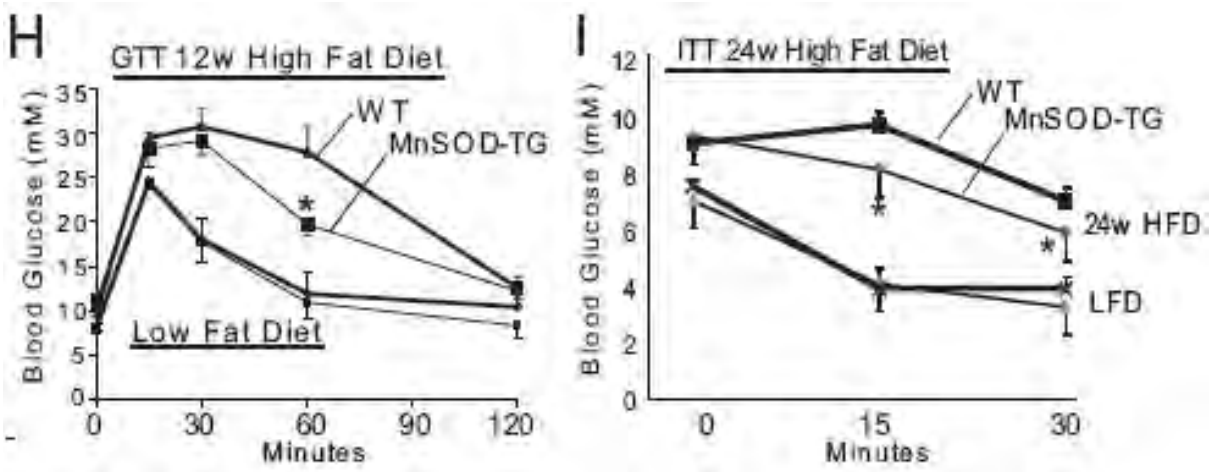




(E and F) GTTs (1.5 g glucose/kg body weight) were performed on MnSOD transgenic (MnSOD-TG) and age matched control (WT) mice fed a LFD then switched to HFD for 1 week. The same mice were used in both tests, n=7–8 mice.

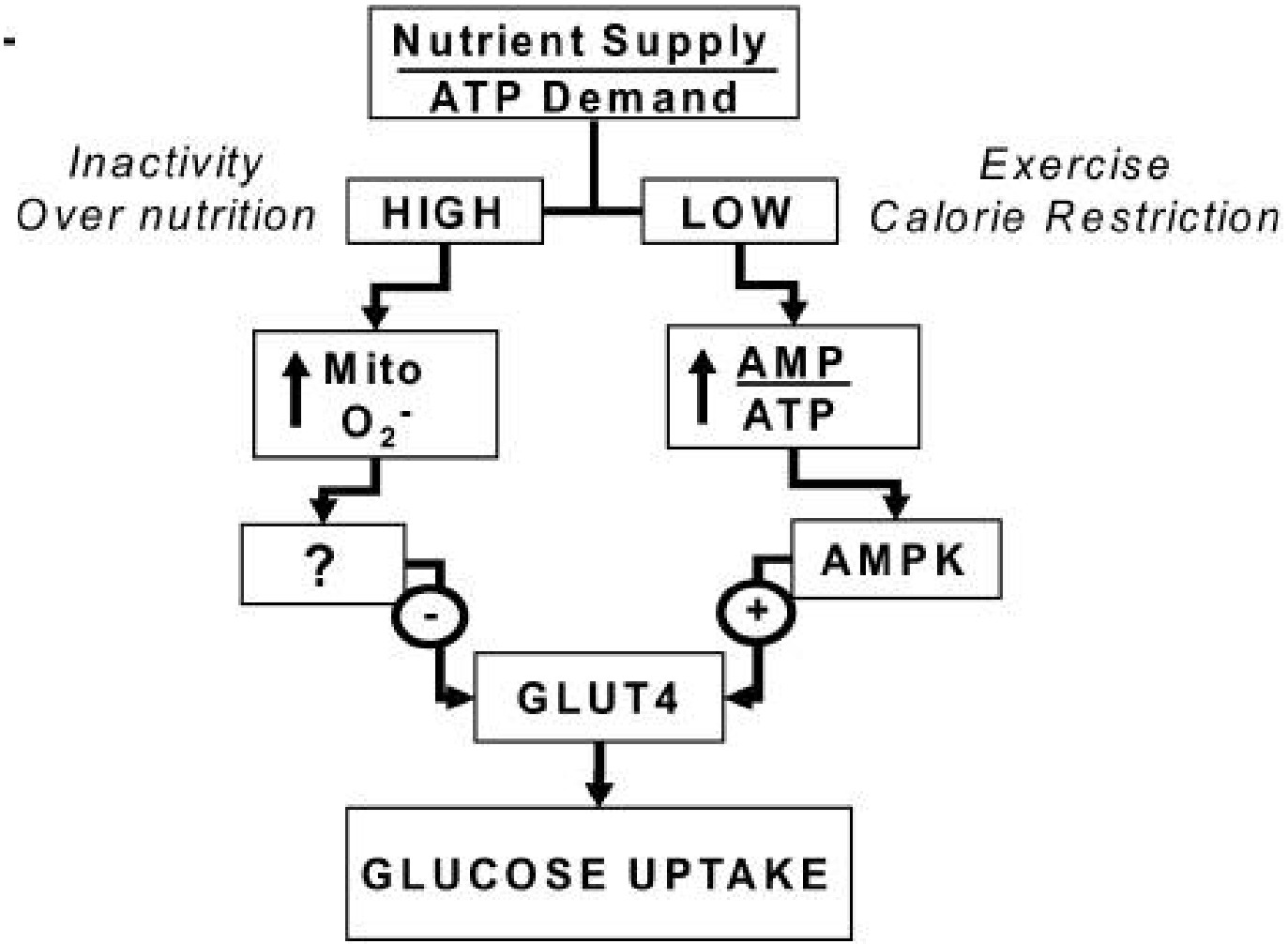


(G) For the experiment in E-F above, insulin levels were measured after 6 h fasting and 15 min after glucose injection. N=7.



(H) GTT of MnSOD-TG and age matched WT mice fed a LFD or HFD for 12 weeks. n = 3–4 for LFD and 5–6 for HFD.
(I) Insulin tolerance test (ITT) of MnSOD-TG and age matched WT mice fed a LFD or HFD for 24 weeks. n = 7–8 in each group.

Insulin Resistance as a Cellular Antioxidant Defense



Proc Natl Acad Sci U S A. 2009 Oct 20;106(42):17787-92. doi: 10.1073/pnas.0902380106. Epub 2009 Sep 30.

Insulin resistance is a cellular antioxidant defense mechanism.

Hoehn KL, Salmon AB, Hohnen-Behrens C, Turner N, Hoy AJ, Maghzal GJ, Stocker R, Van Remmen H, Kraegen EW, Cooney GJ, Richardson AR, James DE.

Metabolic Syndrome

WHO

•High Insulin Fasting/postpr

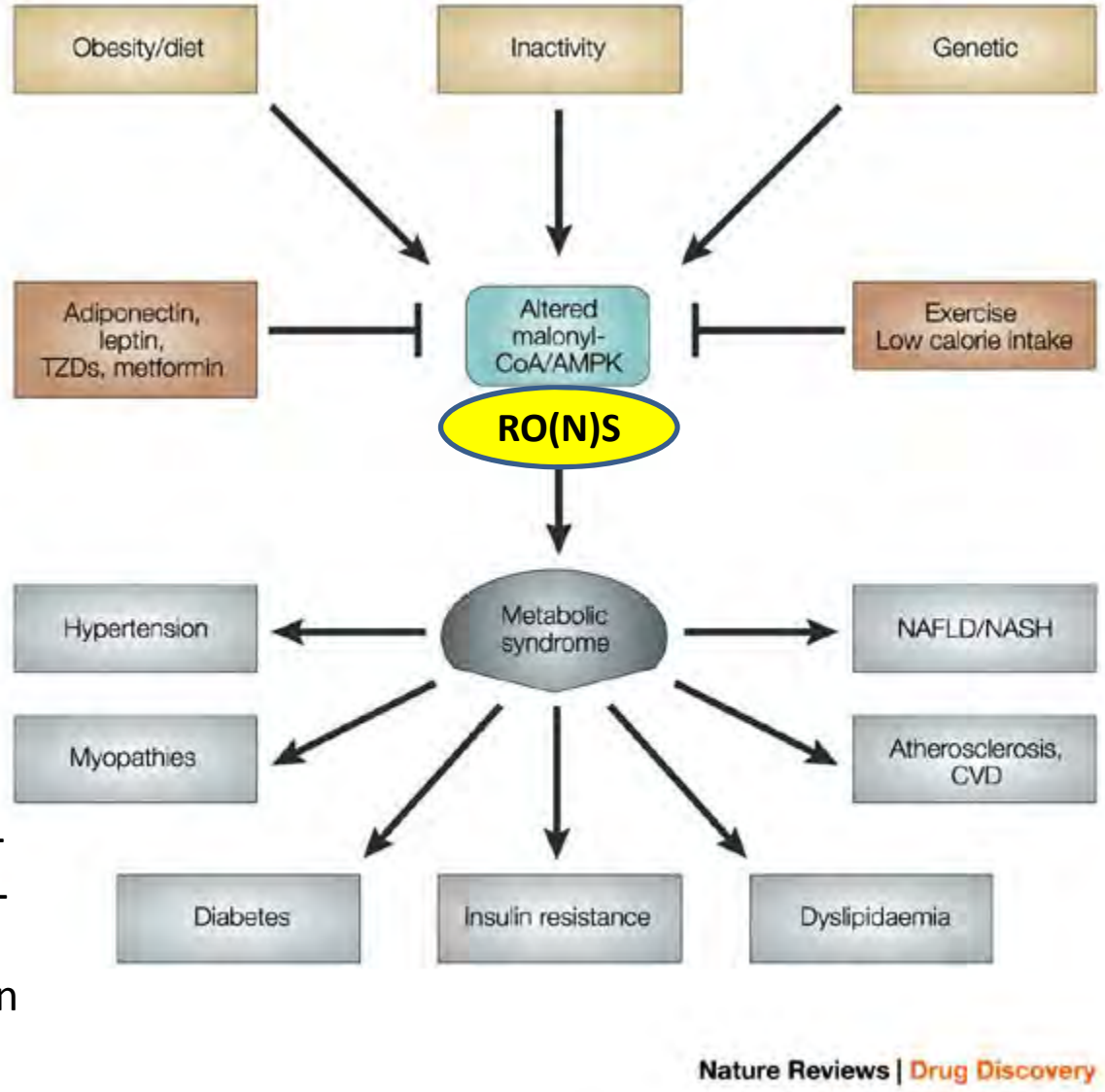
+

(any 2 below)

- Wst/Hip > 0.9
- BMI ≥ 30kg/m²
- Waist > 37in

- TG ≥ 150mg/dL
- HDL < 40mg/dL

•BP –Trtment Htn or ≥ 140/90



2001 ATP III

(any 3 below)

Men:

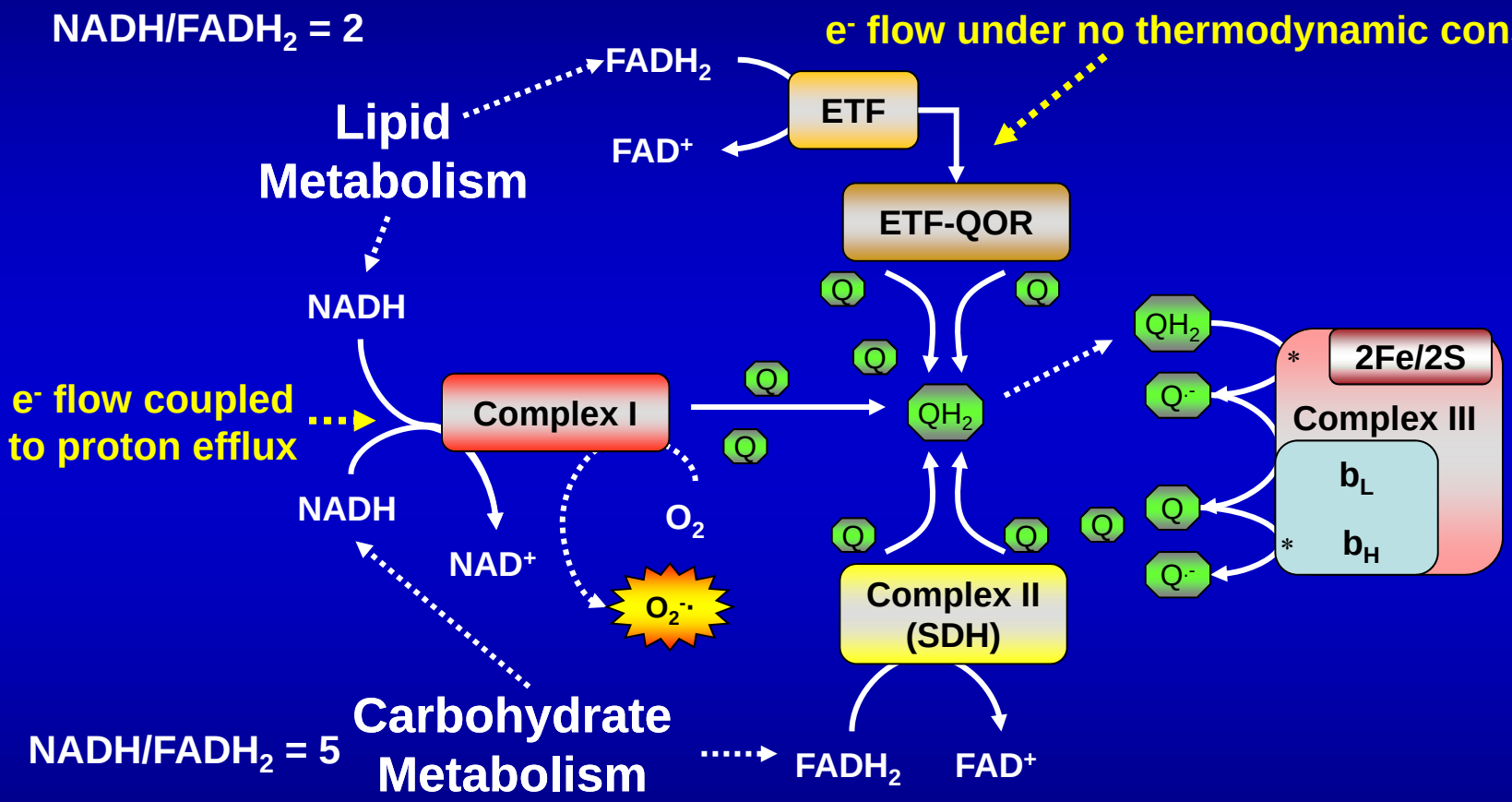
Waist ≥ 40in
TG ≥ 150mg/dL
HDL < 40mg/dL
BP ≥ 130/85 mm Hg
FBG ≥ 100mg/dL

Women:

Waist > 35in
TG ≥ 150mg/dL
HDL < 50mg/dL
BP >130/85 mm Hg
FBG > 100 mg/dL

Source of Oxidative Stress [RO(N)s] include fat overloaded adipose cells in viscera (VAT), liver and muscle: 'metabolically triggered inflammation - meta-inflammation'.

Proposed Regulation of Superoxide Production in Skeletal Muscle



The greater the rate of entry of e^- from ETF, the greater the competition for oxidized Q → increased rate of superoxide production at complex I

Slide provided by Darrell Neufer; Trends in Endo. & Metab. 23(3), 2012, 142–153 & Int. J. Obesity Suppl., 2,S31-S36, 2012

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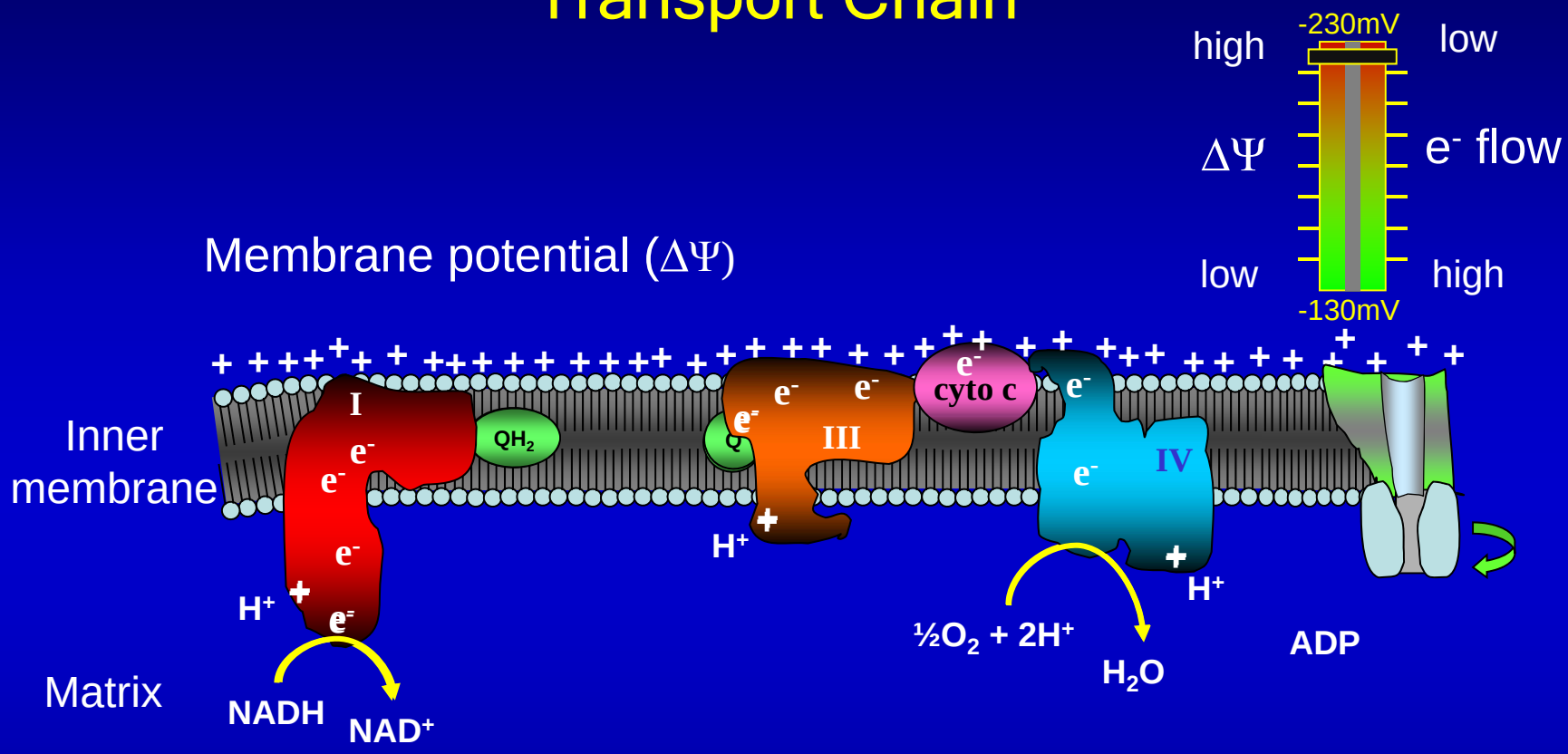
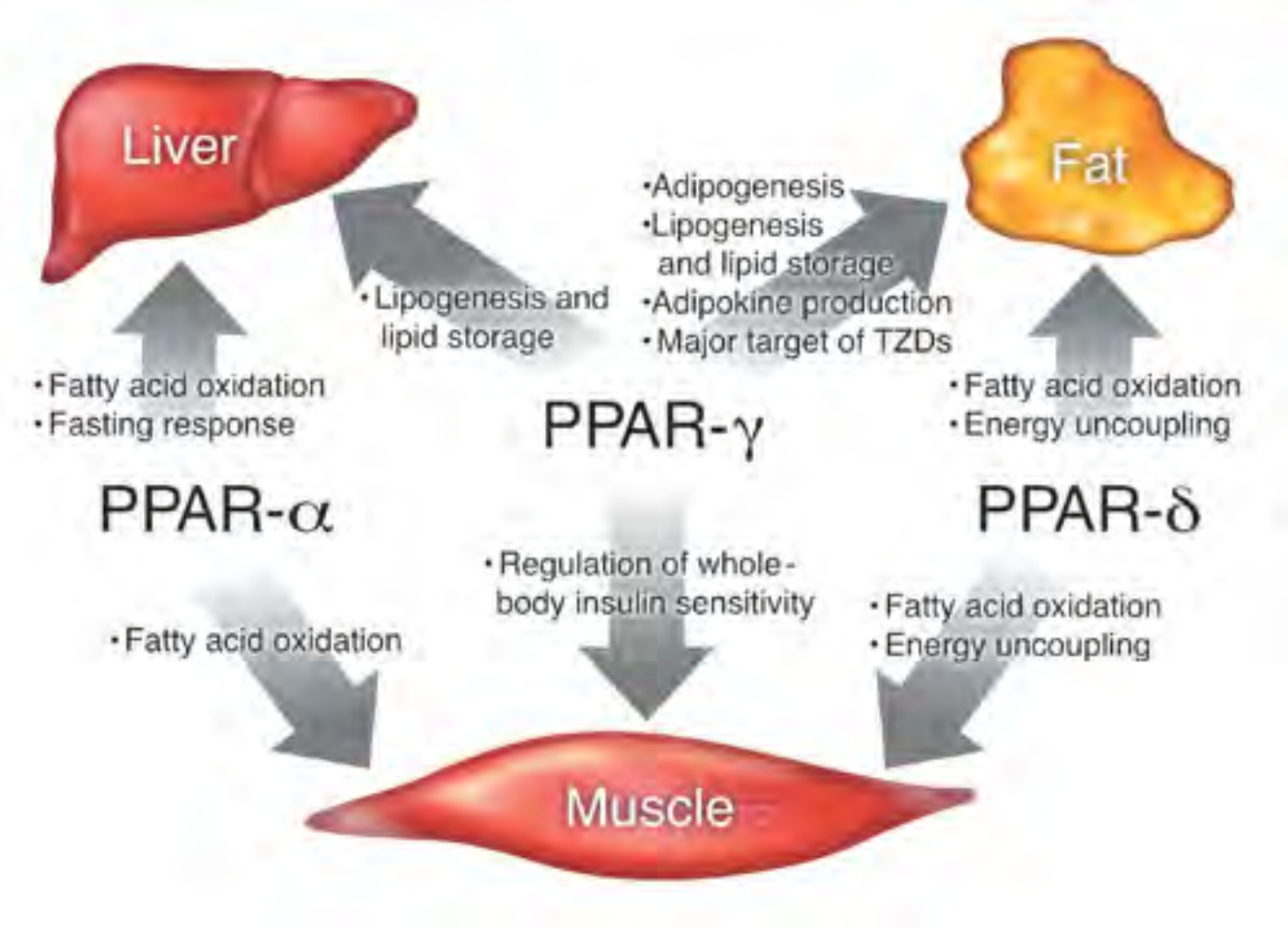


Expend energy

Slide courtesy of Darrell Neufer modified DRM

Metabolic integration by PPARs.



Nature Medicine **10**, 355 - 361 (2004) **PPARs and the complex journey to obesity**
Ronald M Evans, Grant D Barish & Yong-Xu Wang

The End
and
Thank you for your attention.

Now onto:
Mitochondria in Sickness and in Health