ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

METABOLIC INTEGRATION

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METABOLIC INTEGRATION

Fed-fast cycle

- During *fasting*, *insulin* secretion *decreases* and *glucagon* secretion *increases*: there is a decrease in glycogen synthesis and an increase in glycogenolysis (liver switches from a *glucose-utilising* to a *glucose-producing* organ).
- A *steady state*, with hepatic glucose production equal to its peripheral uptake, is achieved after an overnight fast.
- The *liver* has a central role in the regulation of *systemic glucose* and *lipid* fluxes during feeding and fasting, and also relies on these substrates for its own energy needs.
- These parallel requirements are met by *coordinated control of carbohydrates and lipid fluxes* into and out of the Krebs cycle, which is highly dependent upon nutrient availability and heavily regulated by insulin and glucagon.

METABOLIC INTEGRATION

Fed-fast cycle

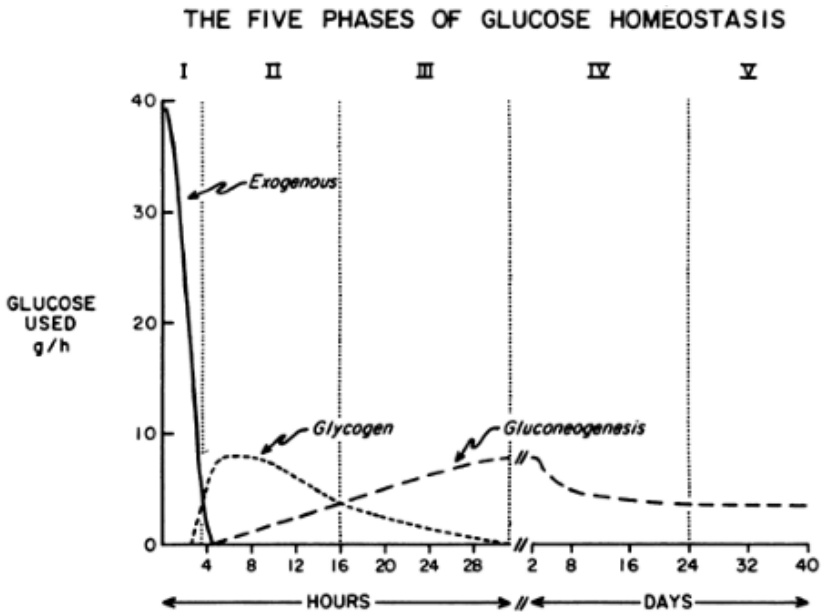
- In the *fasting* state, 80% of all glucose is taken up by *insulin-independent tissues (cornea, erythrocytes, brain, fetal tissues); of this,* 50% goes to the brain and 20% to the erythrocytes.
- *Insulin-dependent tissues* use relatively little glucose (muscle and adipose tissue together use only 20% of available glucose).
- After a 12 h fast, 65-75% of synthesised glucose is still derived from *glycogen*, the rest from gluconeogenesis.
- If fasting lasts longer, the contribution of *gluconeogenesis increases.*

METABOLIC INTEGRATION

Fed-fast cycle

Primary fuel of the brain during the 5 metabolic stages between the postabsorptive state and the near-steady state of prolonged starvation

- *I (up to 4 h)* – exogenous glucose
- *II (4-16 h)* – glucose (glycogen, hepatic gluconeogenesis)
- *III (16-36 h)* – glucose (hepatic gluconeogenesis, glycogen)
- *IV (2-24 days)* – glucose, ketone bodies (hepatic and renal gluconeogenesis)
- *V (after 24 days)* – ketone bodies, glucose (hepatic and renal gluconeogenesis)

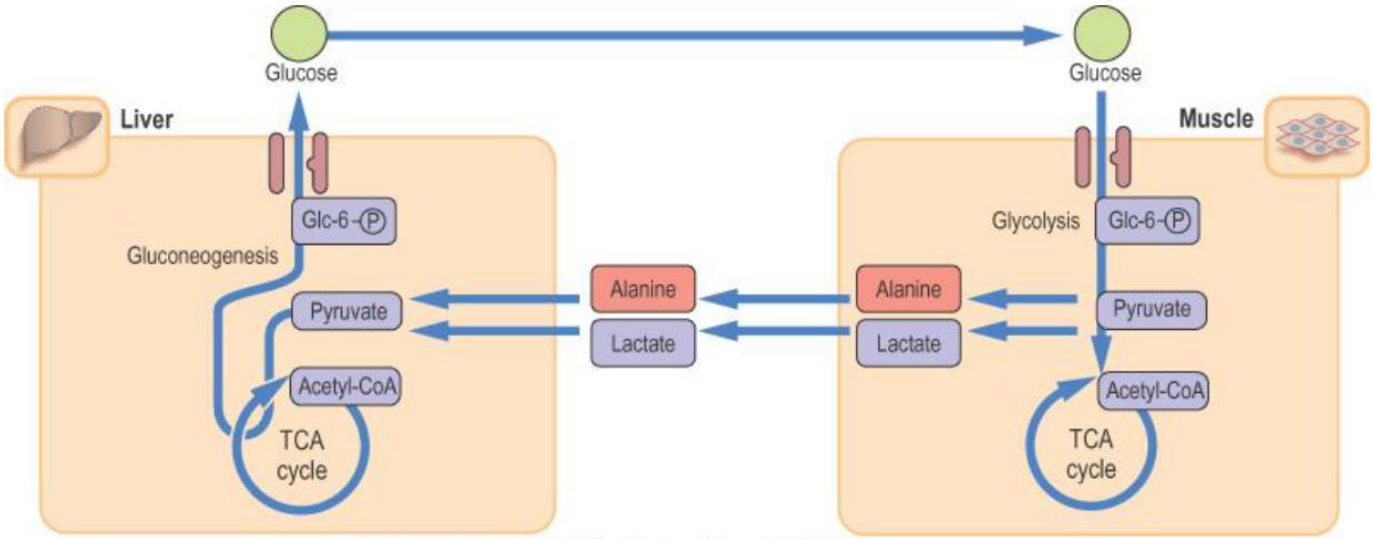


		(I)	(II)	(III)	(IV)	(V)
ORIGIN OF BLOOD GLUCOSE	:	Exogenous	Glycogen Hepatic gluconeogenesis	Hepatic gluconeogenesis Glycogen	Gluconeogenesis, hepatic and renal	Gluconeogenesis, hepatic and renal
TISSUES USING GLUCOSE	:	All	All except liver. Muscle and adipose tissue at diminished rates	All except liver. Muscle and adipose tissue at rates intermediate between II and IV	Brain, rbcs, renal medulla. Small amount by muscle	Brain at a diminished rate, rbcs, renal medulla
MAJOR FUEL OF BRAIN	:	Glucose	Glucose	Glucose	Glucose, ketone bodies	Ketone bodies, glucose

METABOLIC INTEGRATION

Fed-fast cycle

Cori cycle allows recycling of lactate back to glucose, but does not contribute to the *de novo* synthesis of glucose. Alanine is derived mainly from muscle proteolysis.



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Prolonged fasting - starvation

- Starvation is a chronic low-insulin, high-glucagon state.
- There is also a decrease in thyroid hormone concentration, which *decreases the metabolic rate*.
- *Free fatty acids* are now the primary source of energy
- Because gluconeogenesis uses oxaloacetate, the TCA cycle metabolite, its concentration in the mitochondria falls, limiting the activity of the TCA cycle.
- Slowing down of the cycle leads to the *accumulation of acetyl-CoA* from the β-oxidation of fatty acids.
- Acetyl-CoA is channelled into ketogenesis, and the concentration of *ketone bodies in plasma increases*.

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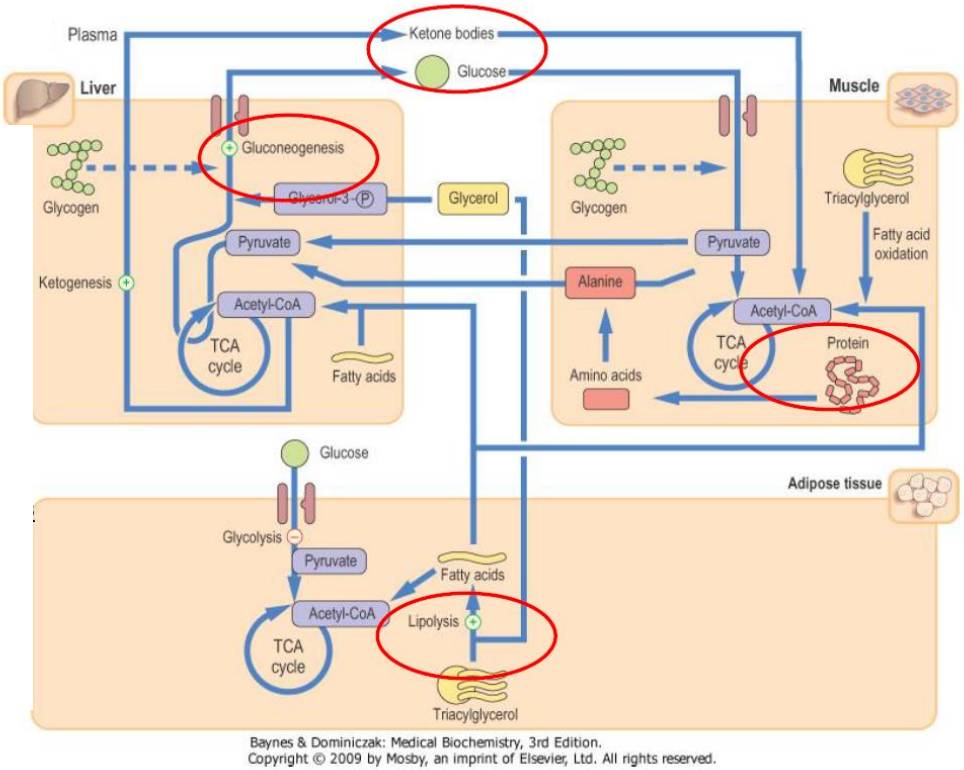
Prolonged fasting-starvation

- The direction of metabolism is similar to that during short-term fasting, with adaptive responses.
- *Glycogen stores* are depleted.
- The supply of fuels depends on *gluconeogenesis and lipolysis.*
- *Ketone bodies* become an important energy source for muscles, and the brain adapts to their use.
- A *decrease in the demand for glucose*, spares muscle proteins.



METABOLIC INTEGRATION

Prolonged fasting-starvation

- Under *fasting conditions*, triacylglycerols stored in adipocytes are hydrolyzed by hormone-sensitive lipase (lipolysis).
- Lipolysis is activated by *adrenaline* and *glucagon*, inhibited by *insulin*.
- Free *fatty acids* and *glycerol* are released in plasma.
- Free fatty acids are oxidised in tissues; in the liver, their oxidation produces ketone bodies.
- Glycerol is used in liver mainly for gluconeogenesis.

METABOLIC INTEGRATION

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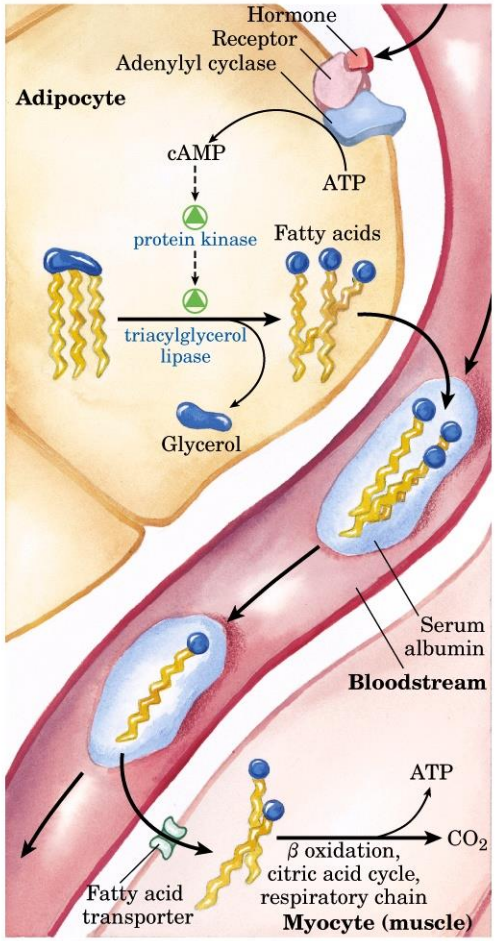

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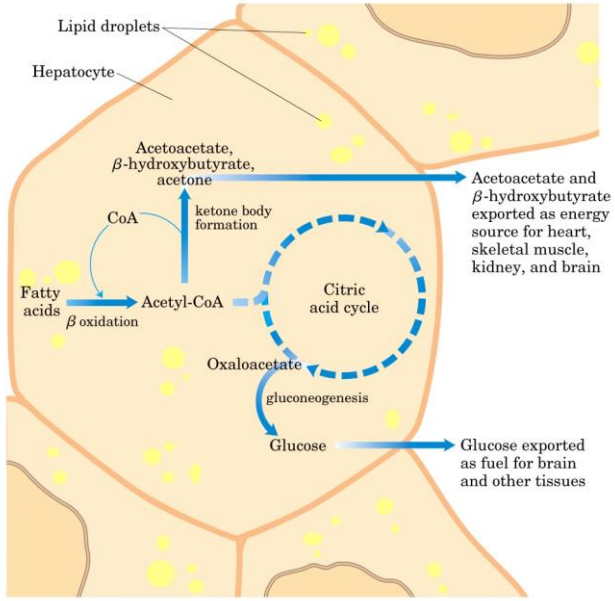
Ketogenesis

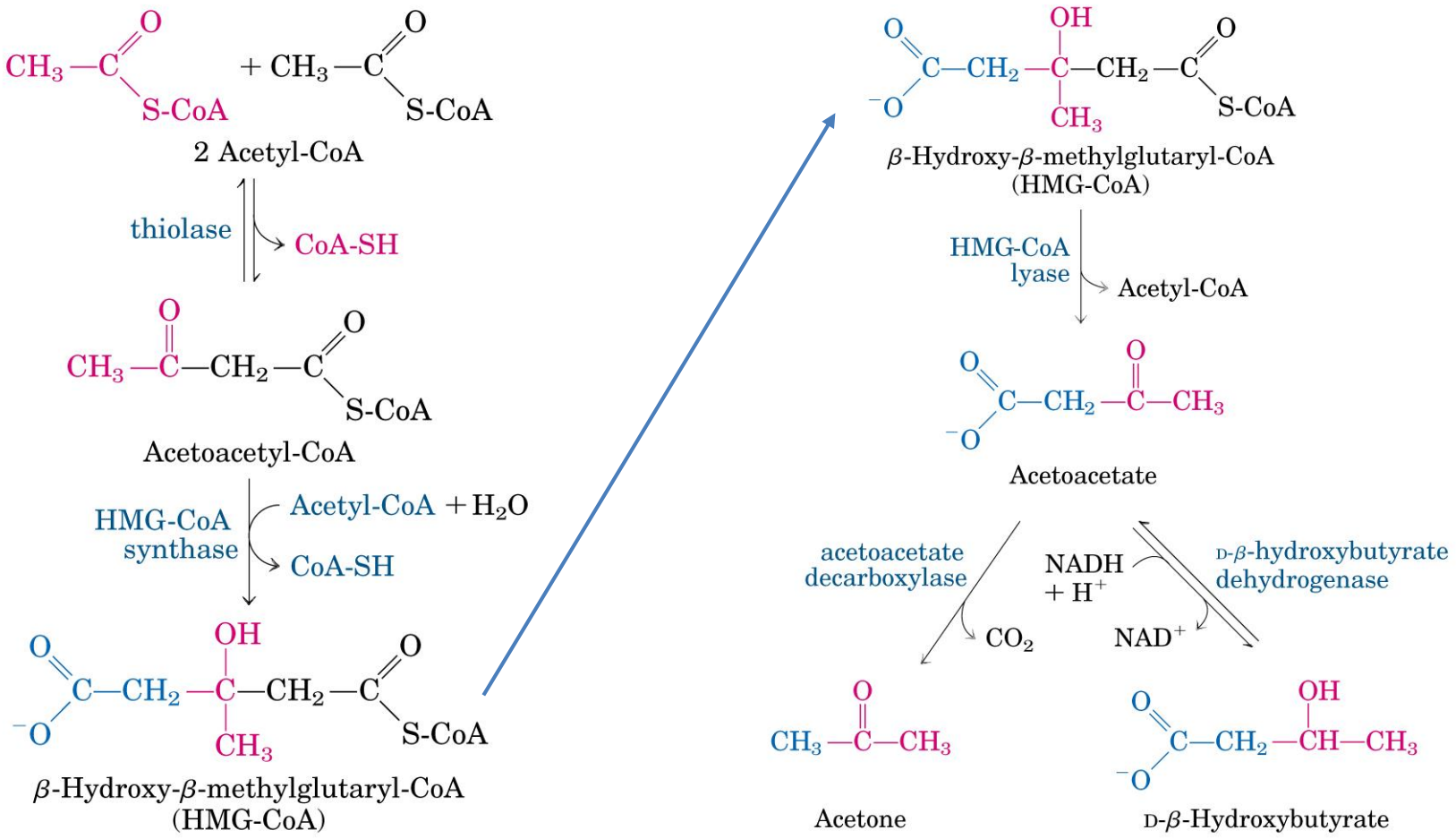
- Under *fasting conditions*, in *uncontrolled diabetes*, or the *ketogenic diet*, oxaloacetate is used to synthesise glucose in the liver (no TCA cycle) following this pathway:

- Secretion of glucagon
- Lipolysis → NEFA
- β-oxidation in the liver
- Oxaloacetate is addressed in gluconeogenesis
- Acetyl-CoA cannot enter the TCA cycle
- Acetyl-CoA → ketone bodies



METABOLIC INTEGRATION

Ketogenesis



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Metabolism during stress and injury

- The insulin antagonist hormones drive the response to stress:

- «fight or flight reactions»
- trauma
- burns
- surgery
- infection

METABOLIC INTEGRATION

Metabolism during stress and injury

- Suppression of anabolic pathways (glycogen synthesis, lipogenesis).
- Increased insulin-dependent peripheral glucose intake.
- Early vasoconstriction, which limits possible blood loss.

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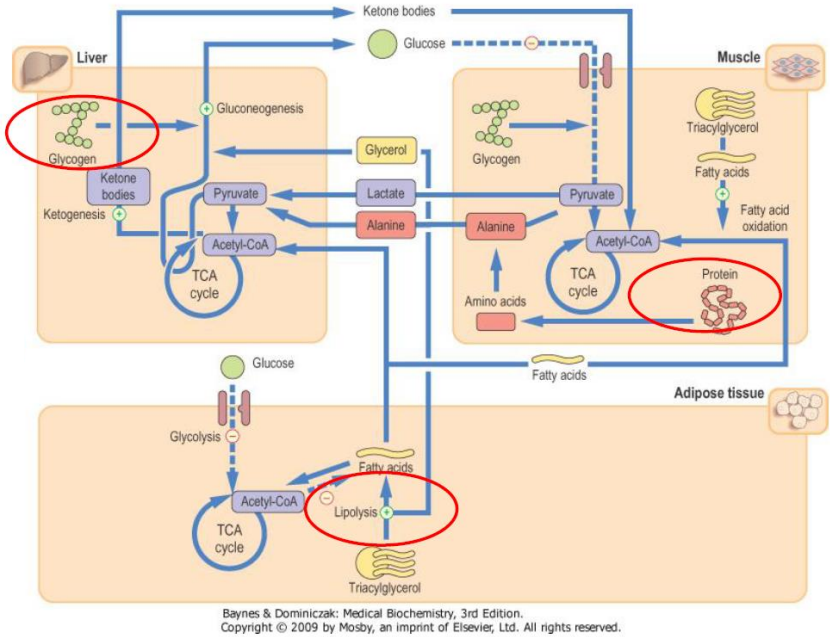
Metabolism during stress and injury

- The response to stress is catabolic, and broadly analogous to fasting.
- G*lucose* is mobilized from all available sources.
- E*pinephrine* plays a key role and, together with glucagon, inhibits insulin secretion.
- Stress induces peripheral *insulin resistance*, further sparing glucose.
- Energy is provided from *glucose*, *fatty acids* and *protein catabolism.*



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Metabolism during stress and injury

- Energy substrates are mobilized from all available sources.
- The priority is to provide *glucose for the brain*.
- Epinephrine and glucagon stimulate glycogenolysis and gluconeogenesis.
- Decreased peripheral uptake of glucose makes more glucose available to the brain.
- *Muscle proteins* supply amino acids for gluconeogenesis.
- This lead to a negative nitrogen balance within 2-3 days after injury.

METABOLIC INTEGRATION

Big picture: well fed state

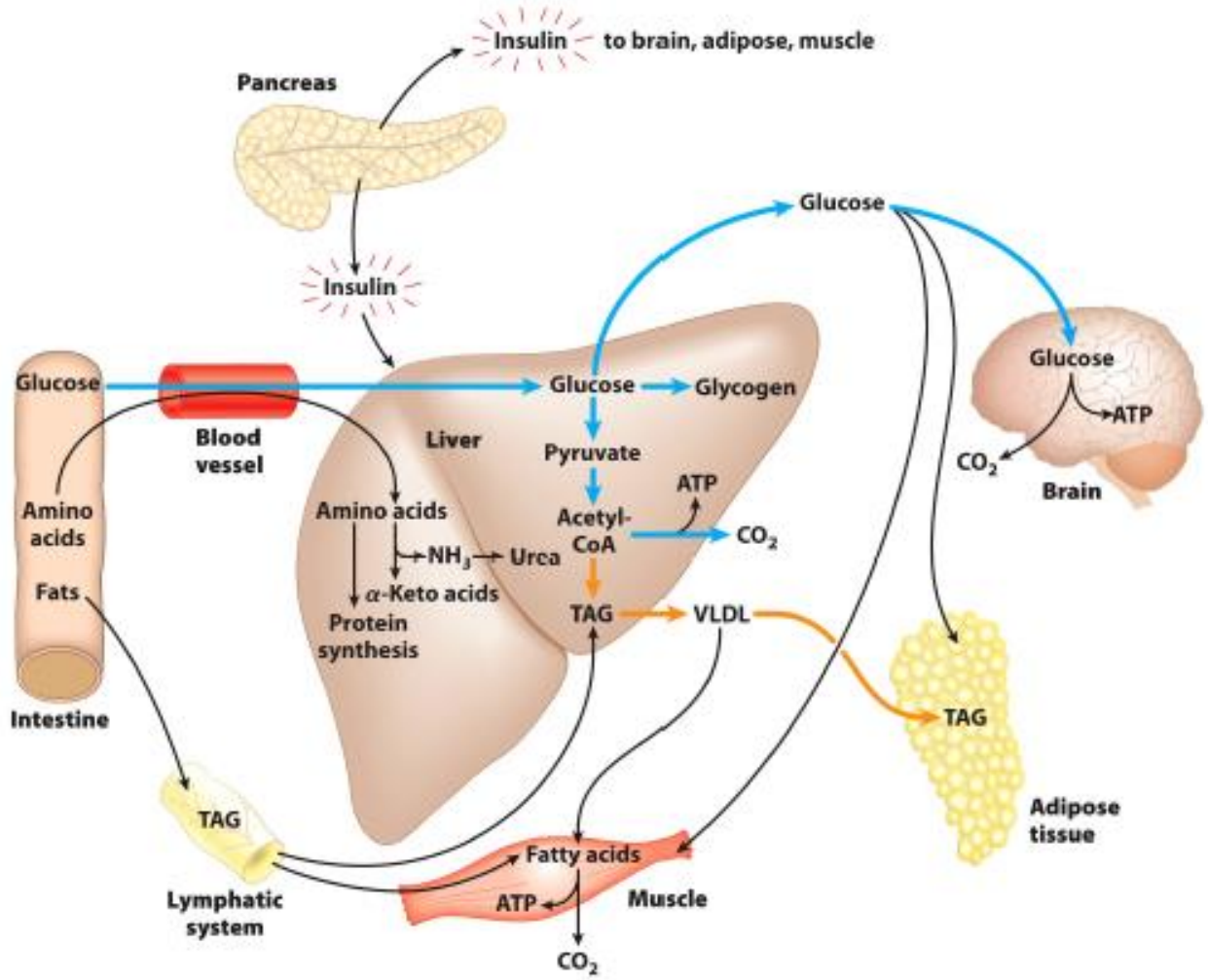

Figure 23-25
Lehninger Principles of Biochemistry, Sixth Edition
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METABOLIC INTEGRATION

Big picture: prolonged fasting or uncontrolled diabetes

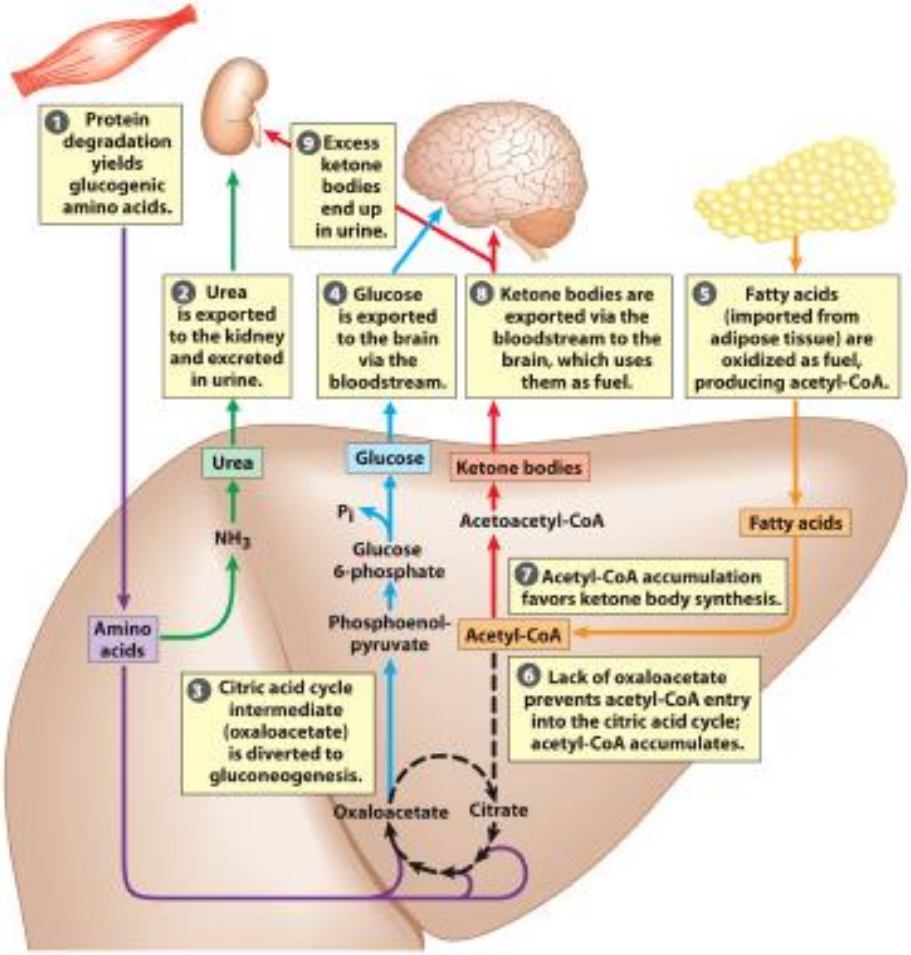

Figure 23-30
Lehninger Principles of Biochemistry, Sixth Edition

METABOLIC INTEGRATION

«ESSENTIAL» COMPOUNDS (that we must eat)

- *Water soluble vitamins* (thiamin, riboflavin, nicotinamide, pantothenic acid, pyridoxine, biotin, folic acid, Vitamin B12, ascorbic acid) → coenzymes
- *Lipid soluble vitamins* (A, D, E, K): coenzymes or signal molecules
- *Essential amino acids* (Arg, His, Ile, Leu, Lys, Met, Phe, Thr, Trp, Val, (Tyr))
- *Essential fatty acids* (precursors): 18:2 ω6, 18:3 ω3.

METABOLIC INTEGRATION

What can we make with dietary glucose?

- *Other monosaccharides* and derivatives (ribose, deoxyribose, fructose, galactose, glucosamine, glucuronic acid, sialic acid…); disaccharides, oligosaccharides (also bound to lipids and proteins), *polysaccharides* (glycogen, structural polysaccharides)
- Lipids: *fatty acids* (16:0, 18:0, 18:1), glycerol, triacylglycerols, phospholipids, glycolipids. *Cholesterol*, cholesterol esters. Steroids derived from cholesterol. Some *isoprenoid* compounds.
- *Non-essential aminoacids*; *purine and pyrimidine nucleotides*; porphyrins.

METABOLIC INTEGRATION

Metabolism of dietary fatty acids

Dietary fat → chylomicrons → lipoprotein lipase → fatty acids

- In *muscle*, *heart*: β-oxidation if energy needed
- *In adipose tissue*: resynthesis of lipids using dioxyacetone phosphate as source of glycerol-P.
- *CM remnants to liver*, some fatty acids re-used to make lipids together with biosynthetic fatty acids → VLDL
- *Fats in adipose tissue* (derived from both CM and VLDL) undergo lipolysis during fasting:

- Liver: β-oxidation and ketogenesis

- Peripheral tissues : β-oxidation and TCA cycle

: Complete oxidation of ketone bodies

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Biosynthetic functions of Krebs cycle

- Citrate → fatty acids, cholesterol
- α-Ketoglutarate → Glutamate, glutamine, proline, glucose
- Succinyl-CoA → Porphyrins, glucose
- Malate → Glucose
- Oxaloacetate → Aspartate, asparagine, glucose
- Pyruvate (3-P glycerate) → Alanine, Serine, Glycine, Cysteine

Indirectly: purines, pyrimidines, some phospholipids, sphingolipids.

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Amino acid derivatives

- **Glycine**: porphyrins, purine nucleotides, creatine, glutathione
- **Serine:** ethanolamine, choline and corresponding phospholipids, sphingomyelin, 1C units (purine, methyl group of thymine, methionine)
- **Glutamine**: amino groups in purine and pyrimidine nucleotides, amino sugar and their derivatives (polysaccharides etc)
- **Aspartate**: 2nd amino group in urea synthesis, N1 in IMP synthesis de novo, amino group in 6 of AMP; pyrimidine ring
- **Arginine**: nitric oxide. Through **ornithine**: putrescine, spermidine, spermine
- **Glutamate**: GABA
- **Phenylalanine**: dopamine, nor-adrenaline, adrenaline
- **Tryptophan**: serotonine
- **Methionine**: polyamines spermine and spermidine
- **Histidine**: histamine
- **Lysine**: carnitine

METABOLIC INTEGRATION

Examples of pathways

- **Glycerol to aspartate**

Glycerol → glycerol-.P → dioxyacetone-P → glyceraldehyde-3-P → pyruvate → oxaloacetate → aspartate

- **Lipogenesis from aminoacids: e.g. Aspartate to palmitate**

Aspartate → oxaloacetate → malate → pyruvate → acetyl-CoA → citrate *mito* → acetyl CoA *(cyt)* → palmitate

- **How can fatty acids feed brain during starvation?**

TGA in adipocytes → lipolysis → fatty acids to liver → β-oxidation → acetyl-CoA → ketone bodies → to brain

METABOLIC INTEGRATION

Examples of pathways

Vitamins involved in complete oxidation of glucose to CO_2 and water

- *NAD* (from nicotinamide) in glyceraldehyde phosphate dehydrogenase
- *TPP* (thiamine), pantothenic acid (*CoA*), *FAD* (riboflavin), *NAD* (nicotinamide) in pyruvate oxidation
- *NAD* (nicotinamide), *FAD*, *FMN* (riboflavin), pantothenic acid (*CoA*) in Krebs cycle and respiratory chain
- *Biotin* in anaplerotic reaction to form oxaloacetate

METABOLIC INTEGRATION

LIVER

- Glucose and amino acids to *lipogenesis* (glycolysis, pyruvate oxidation, Krebs cycle, fatty acid biosynthesis, glycerol-P biosynthesis, synthesis of lipids and VLDL).
- Synthesis of *cholesterol* and bile acids
- *Gluconeogenesis*
- *Fatty acid oxidation* and *ketogenesis*
- Synthesis of *urea*
- Synthesis of *plasma proteins*
- *Detoxification reactions* (oxidation and conjugation of xenobiotics)
- *Bilirubin conjugation*
- Metabolism of *ethanol*

METABOLIC INTEGRATION

LIVER

Metabolism of ethanol

Alcohol dehydrogenase: $CH_3CH_2OH + NAD^+ \rightarrow CH_3CHO + NADH + H^+$

Catalase: $CH_3CH_2OH + H_2O_2 \rightarrow CH_3CHO + 2\ H_2O$

MEOS: $CH_3CH_2OH + O_2 + NADPH + H^+ \rightarrow CH_3CHO + NADP^+ + 2\ H_2O$

Acetaldehyde dehydrogenase: $CH_3CHO + NAD^+ \rightarrow CH_3COOH + NADH + H^+$

Acetyl thiokinase: $CH_3COOH + ATP + CoA\text{-}SH \rightarrow CH_3CO\text{-}SCoA + AMP + PP_i$

Ethanol toxicity:

- Accumulation of NADH increases reducing power for biosynthesis of fatty acids and cholesterol → liver steatosis → cirrhosis → carcinoma
- Accumulation of NADH increases the ratio lactate:pyruvate. Decrease of pyruvate blocks gluconeogenesis, with possible hypoglycemia
- Oxidative stress: Cytochrome P450 → ROS, acetaldehyde → altered respiratory chain ROS

METABOLIC INTEGRATION

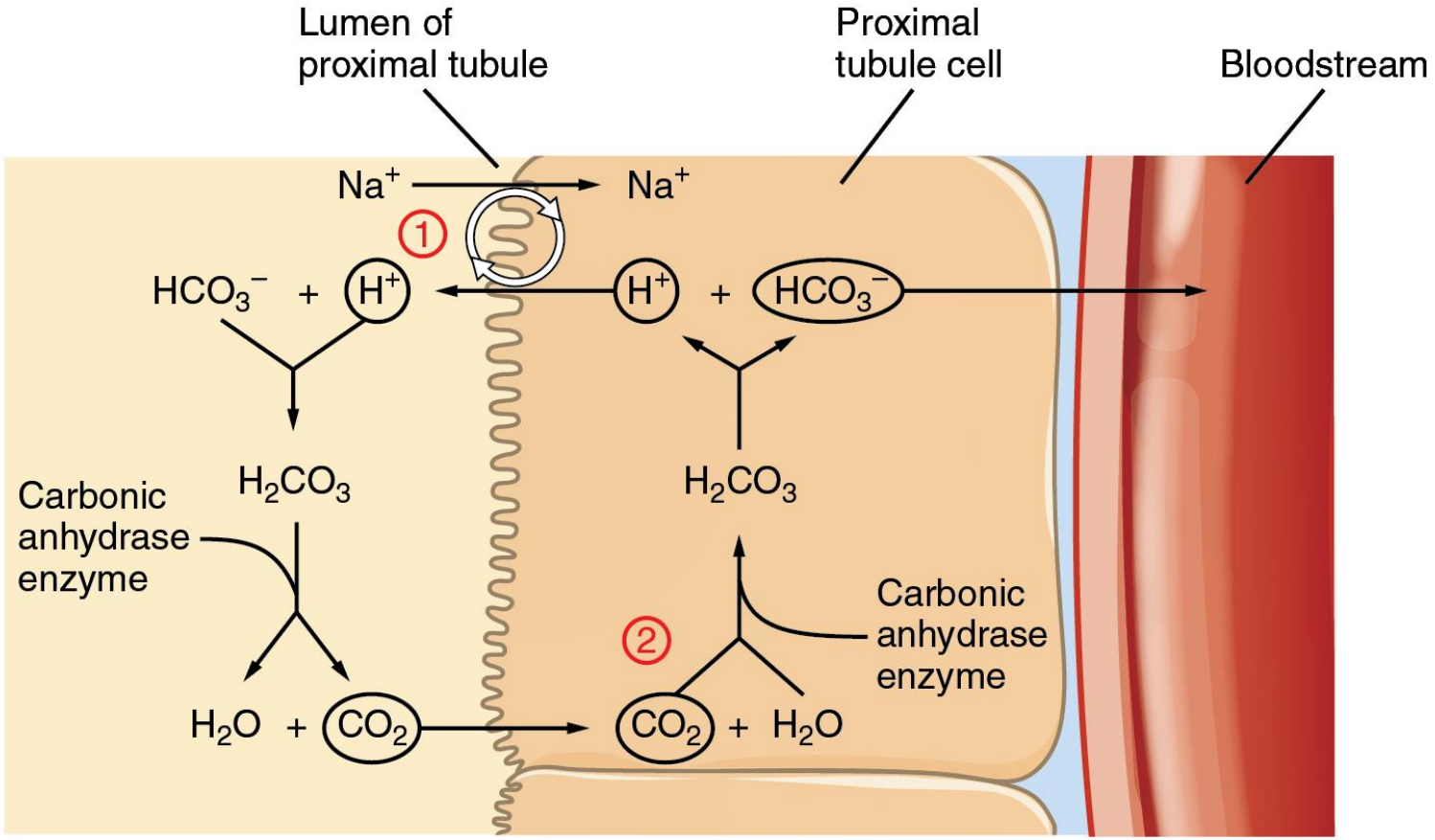
KIDNEY

- *Glucose oxidation* (mainly in medulla)
- *Fatty acid oxidation*, lactate oxidation (cortex)
- Very active *oxidative phosphorylation*
- *Gluconeogenesis*
- Secretion of NH_4^+
- *Transport systems* for re-absorption of metabolites and contribution to acid-base balance

  - Na^+/glucose, Na^+/aminoacids, Na^+/H^+ antiporter, HCO_3^-/Cl^- antiporter, Na^+ ,K^+-ATPase…
- Very active *carbonic anhydrase*

METABOLIC INTEGRATION

KIDNEY



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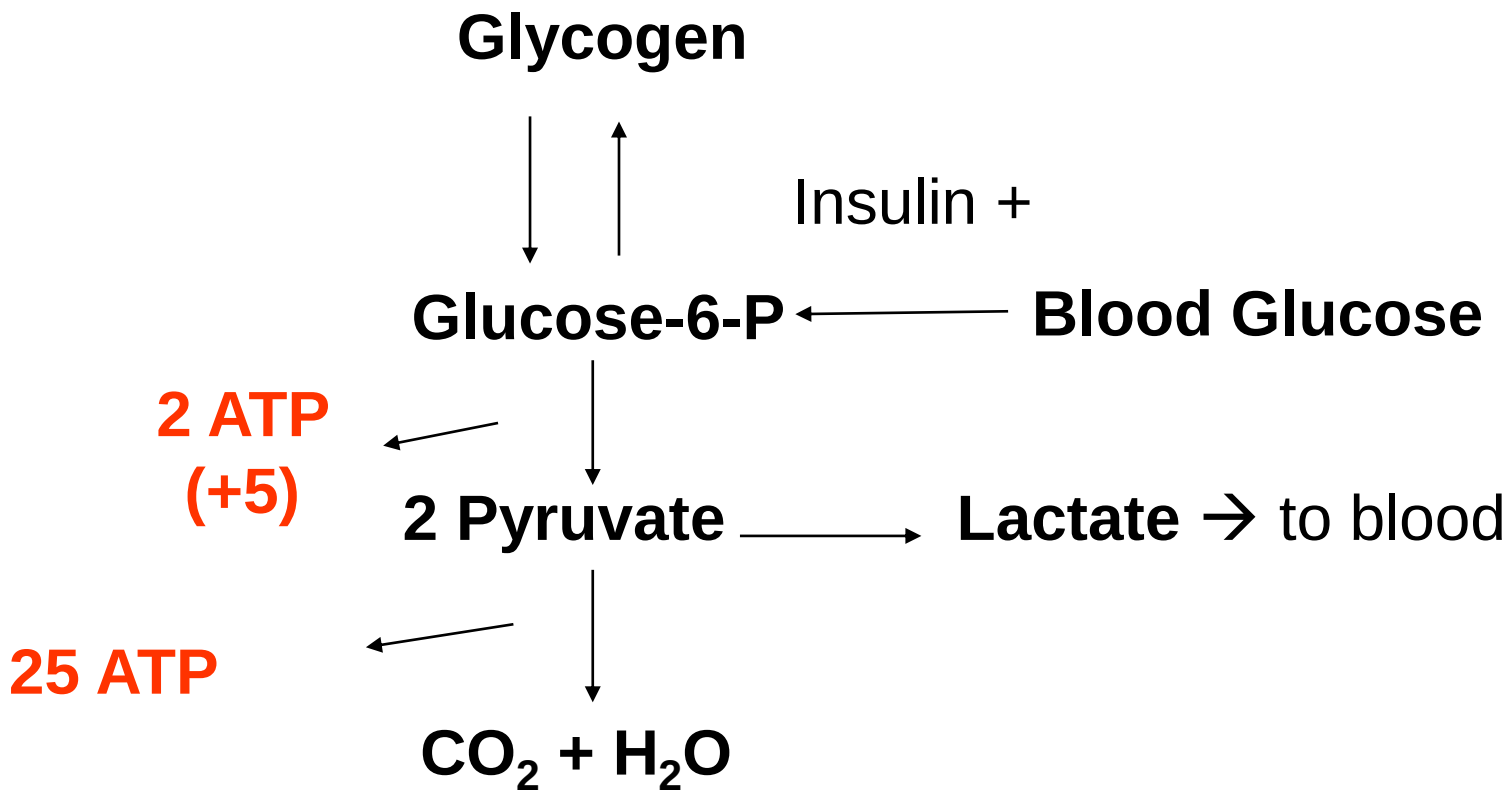
SKELETAL MUSCLE

- *Insulin-dependent* glucose transporter
- *Glycogen synthesis* and *glycogenolysis*
- *Glycolysis*
- In *white muscle*: glycolysis leads to lactate
- In *red muscle*: glycolysis and pyruvate oxidation
- *Fatty acid oxidation*
- *Ketone bodies* oxidation
- *Amino acid* oxidation
- *Oxidative phosphorylation*
- *Nucleotide metabolism*
- *Protein synthesis*

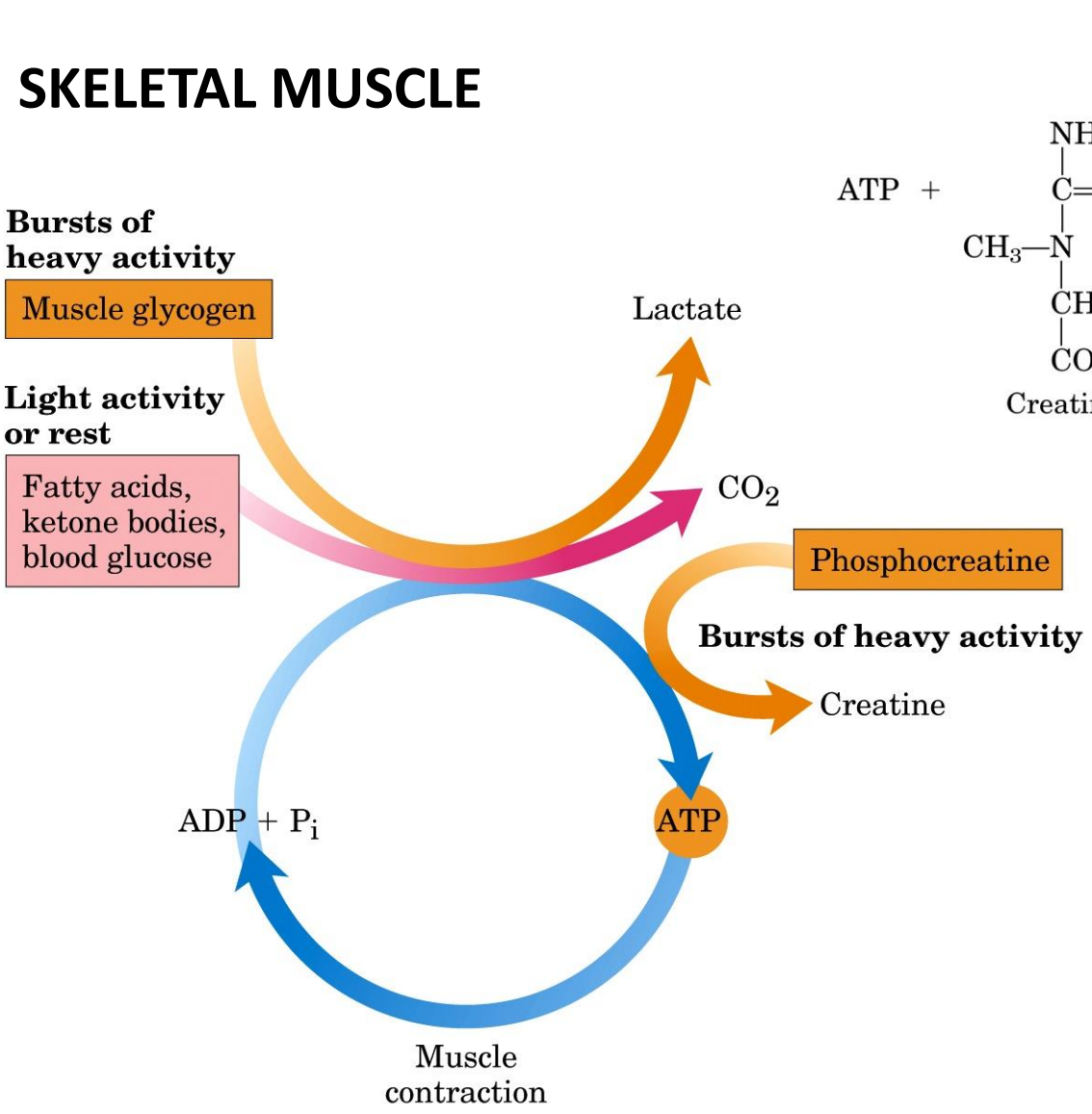
METABOLIC INTEGRATION

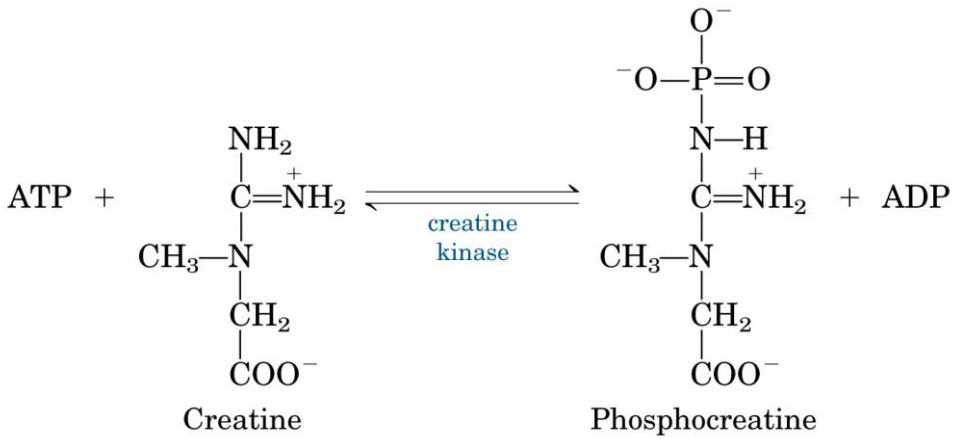
SKELETAL MUSCLE



METABOLIC INTEGRATION

SKELETAL MUSCLE





METABOLIC INTEGRATION

NERVOUS TISSUE

- *Aerobic glucose oxidation* and *oxidative phosphorylation*
- No fatty acid oxidation
- Oxidation of *ketone bodies*
- Synthesis of *glutamine*
- Protein and lipid biosynthesis
- Specific metabolism of *neurotransmitters* (acetylcholine, catechiolamines, serotonin, GABA, glutamate).

METABOLIC INTEGRATION

NERVOUS TISSUE

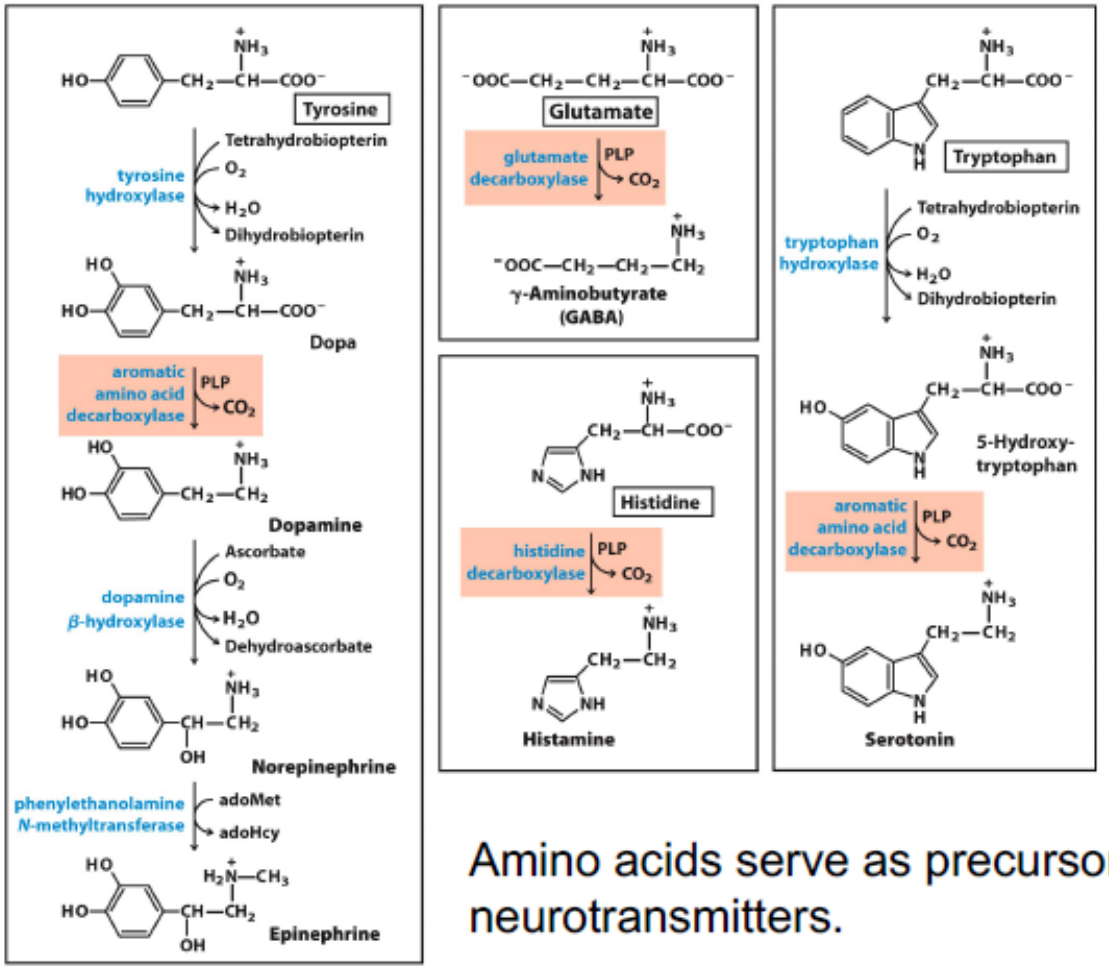


Figure 22-31
Lehninger Principles of Biochemistry, Sixth Edition

Amino acids serve as precursors for neurotransmitters.

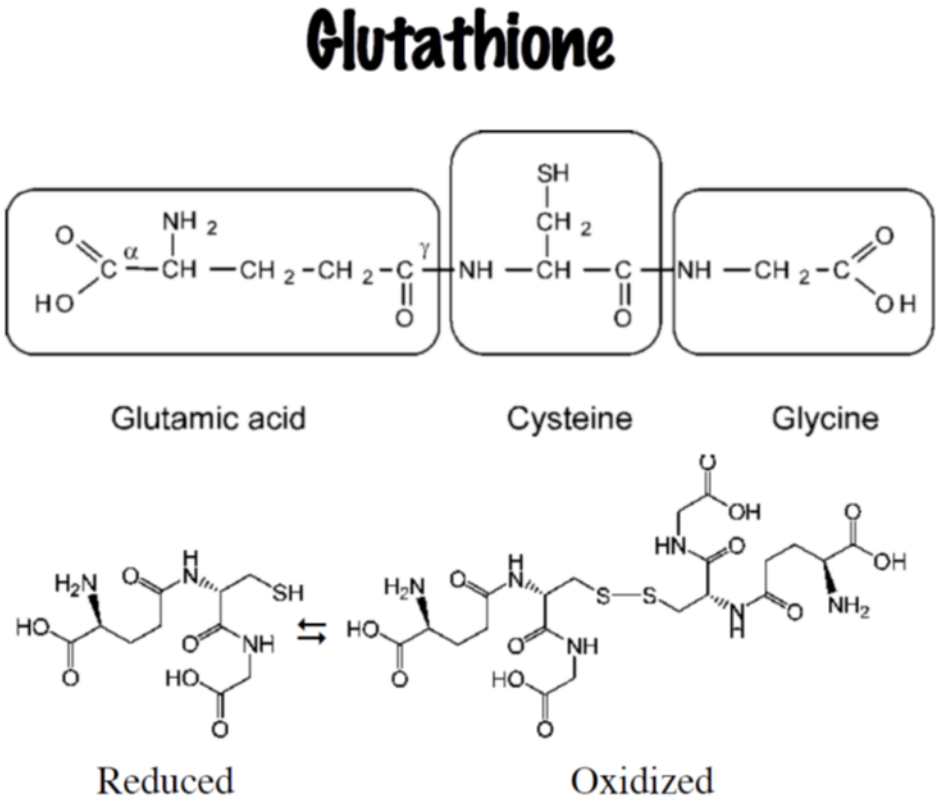
METABOLIC INTEGRATION

RED BLOOD CELLS

- *Glycolysis* to lactate
- Synthesis of 2,3-BPG
- *Pentose phosphate shunt*
- *Purine* metabolism
- Metabolism of *glutathione*

METABOLIC INTEGRATION

RED BLOOD CELLS



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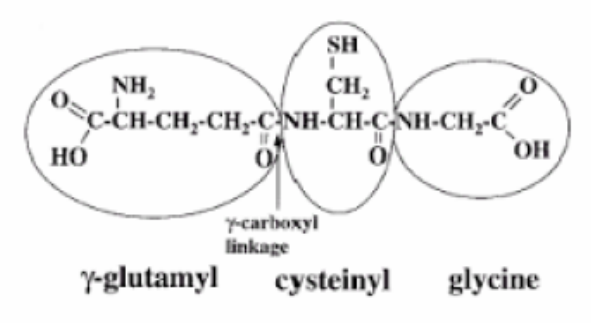
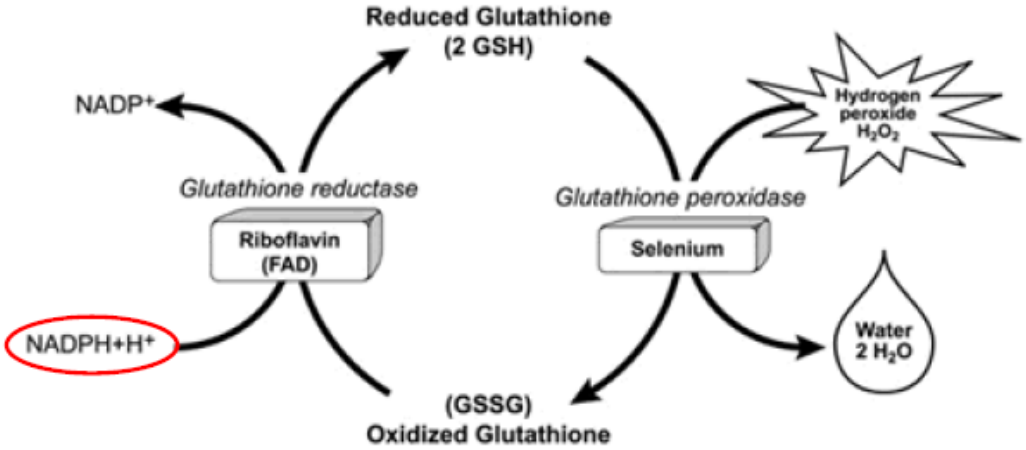
RED BLOOD CELLS





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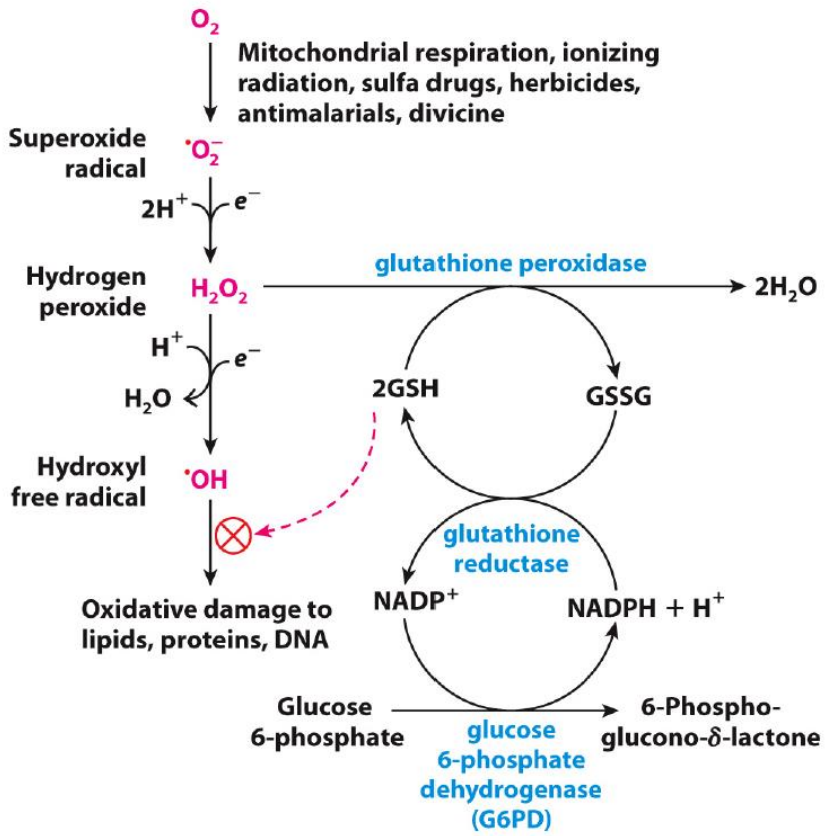
RED BLOOD CELLS

NADPH and Glutathione

Especially important in erythrocytes And brain

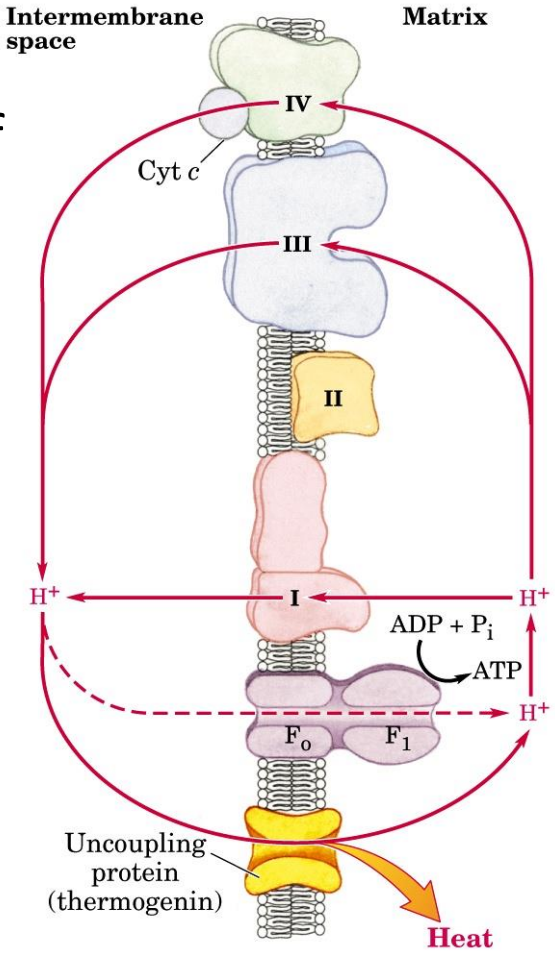


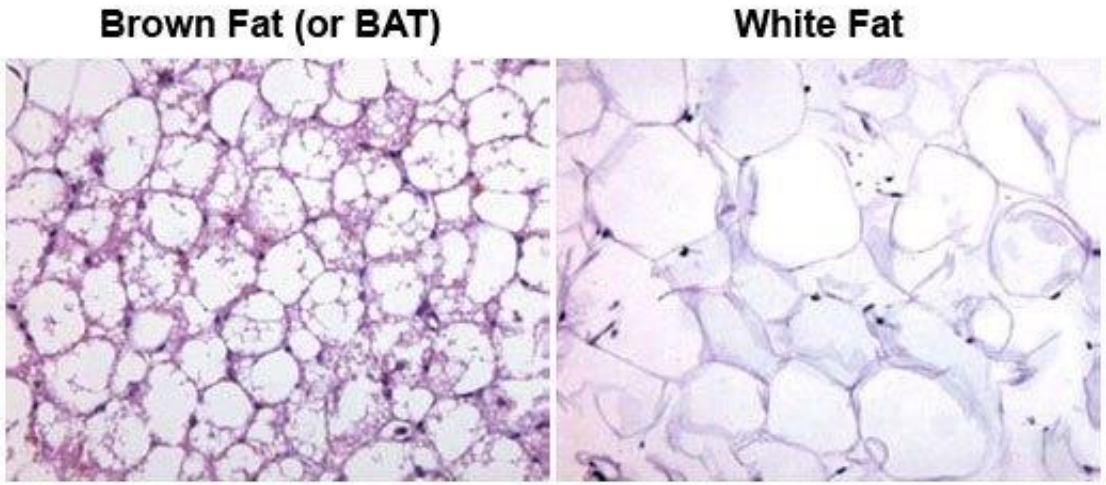
Box 14-4 Figure 1
Lehninger Principles of Biochemistry, Seventh Edition

METABOLIC INTEGRATION

ADIPOSE TISSUE

- Extracellular *hydrolysis of triacylglycerols* of chylomicrons and VLDL
- *Lipid* (triacylglycerol) *biosynthesis*: fatty acid biosynthesis, synthesis of glycerol-P.
- *Glycolysis* and *glycerogenesis*
- *Lipolysis*
- Brown adipose tissue: UCP and thermogenesis





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