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Mammalian fuel metabolic integration

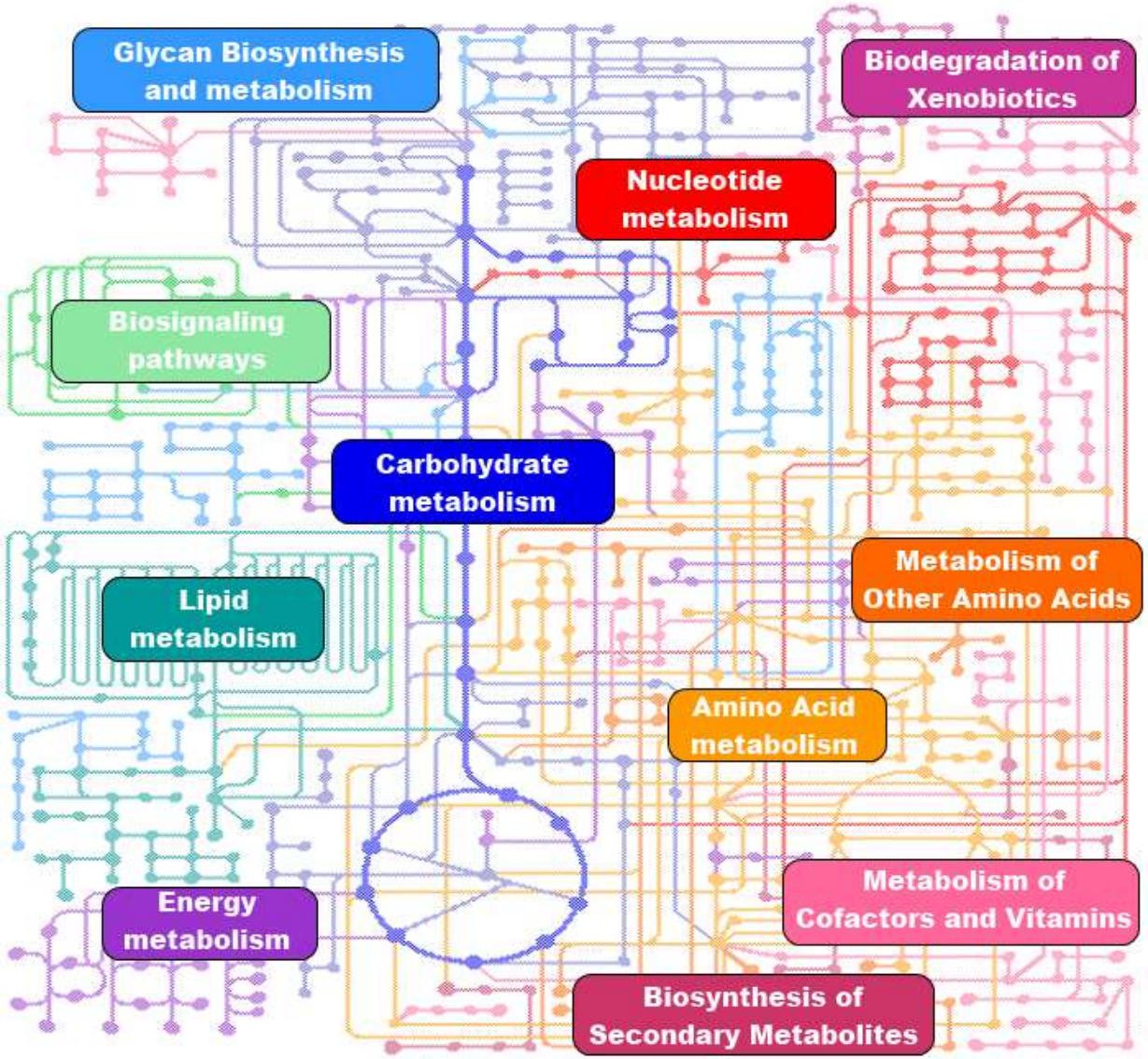
Shoba Ranganathan

Applied Biosciences

T: 02 9850 6262; E: shoba.ranganathan@mq.edu.au

Objectives

- Interorgan and Intracellular Coordination of Energy Metabolism in Vertebrates
  - Interdependence of the Major Organs in Vertebrate Fuel Metabolism
  - Hormonal Regulation of Fuel Metabolism
  - Responses to Metabolic Stress: Starvation, Diabetes
- Chapter 17



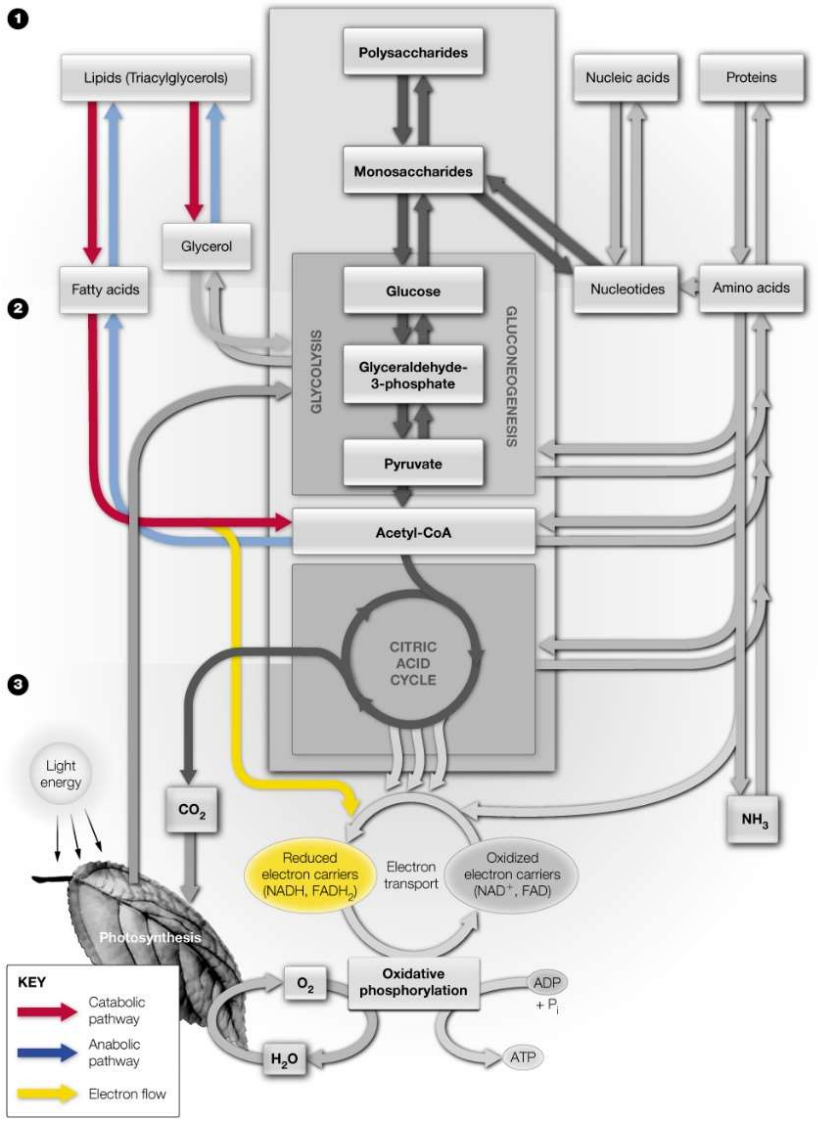
Questions

- How are metabolic processes coordinated so that opposing pathways do not operate simultaneously?
  - Adaptation to nutrient availability
  - Growth, repair and reproduction
  - Tissue specialisation
- Regulation between different tissues and organs?
- Overall effect of hormones
- What happens when things go wrong?

Major pathways in fuel metabolism in mammals

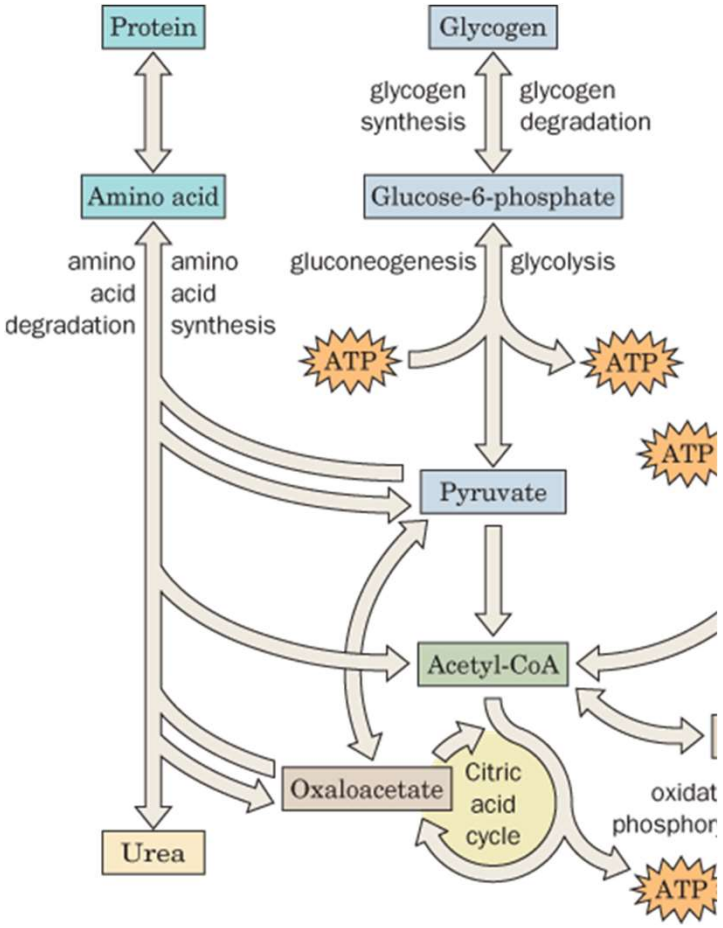
- Proteins, glycogen, and lipids are made from and broken into smaller units: amino acids, glucose-6-phosphate, and fatty acids.
- Oxidation of these fuels yields metabolic energy: ATP.
- Pyruvate (from glucose and amino acid degradation) and acetyl-CoA (from glucose, amino acid, and fatty acid degradation) are central.
  - ❖ Compounds producing pyruvate, e.g. oxaloacetate, can be used for gluconeogenesis
  - ❖ acetyl-CoA can give rise to ketone bodies but not glucose.

Not all the pathways occur in all cells or occur simultaneously in a given cell.



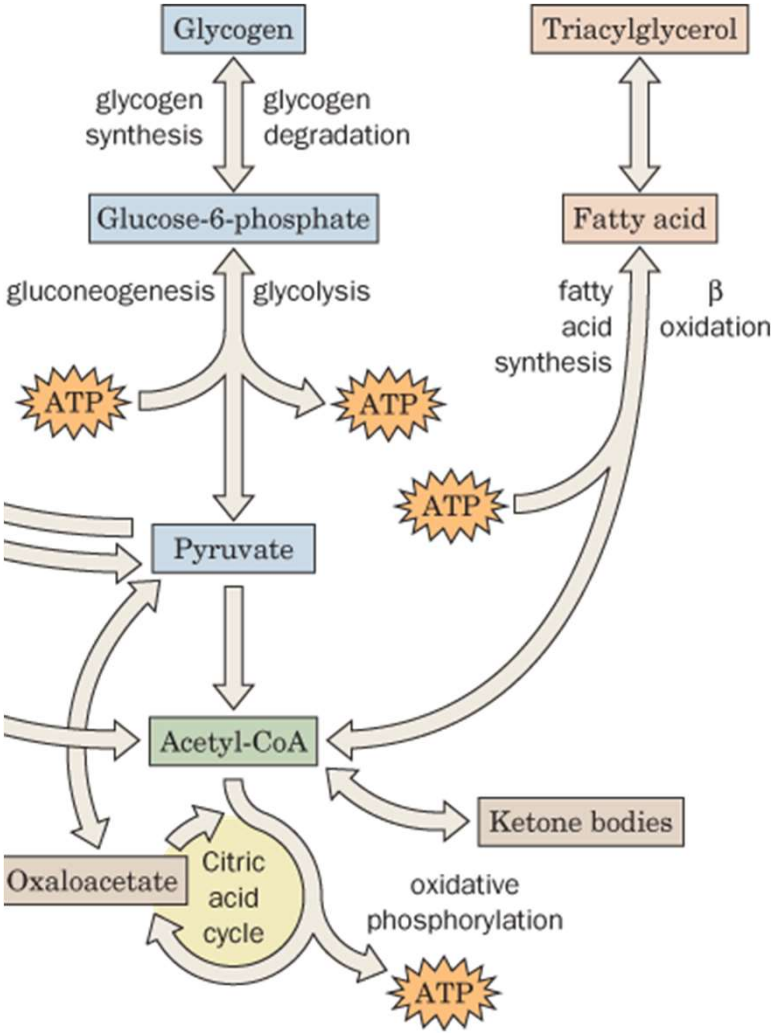
Major metabolic pathways

1. **Glycolysis:** The metabolic degradation of glucose begins with its conversion to two molecules of pyruvate with the net generation of two molecules of ATP.
2. **Gluconeogenesis:** Mammals synthesize glucose from a variety of precursors, such as pyruvate, *via* a series of reactions that largely reverse the path of glycolysis.
3. **Glycogen degradation and synthesis**. The opposing processes catalyzed by glycogen phosphorylase and glycogen synthase are regulated by hormones *via* phosphorylation and dephosphorylation.



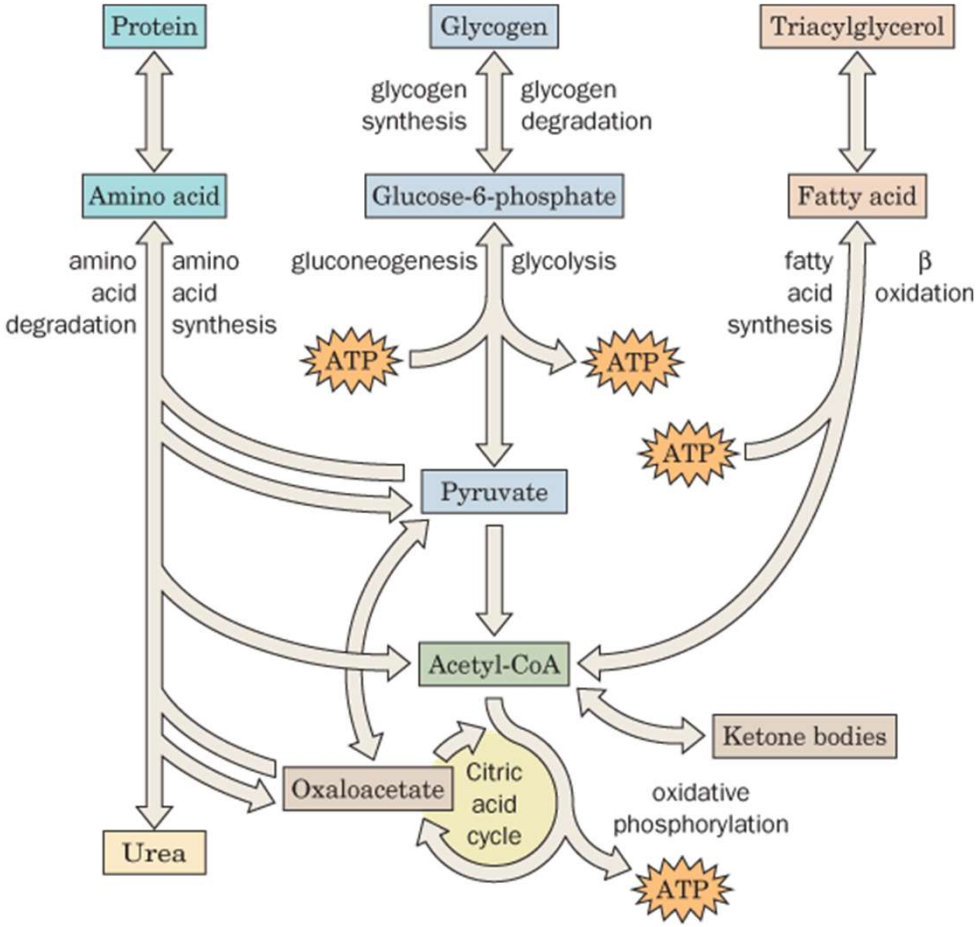
Major metabolic pathways

4. **Fatty acid metabolism**. Fatty acids are broken down through oxidation to form acetyl-CoA, which, through its conversion to malonyl-CoA, is also the substrate for fatty acid synthesis.
5. **The citric acid cycle**. CAC oxidizes acetyl-CoA to CO_2 and H_2O and reduced coenzymes, which drive ATP synthesis. Many glucogenic amino acids can be broken down into CAC metabolites, which then produce pyruvate and then acetyl-CoA, the cycle's only substrate.
6. **ETC and Oxidative phosphorylation**. This mitochondrial pathway oxidises NADH and $FADH_2$ from glycolysis and CAC to make ATP from ADP.



Major metabolic pathways

7. **Amino acid synthesis and degradation.** Excess amino acids are degraded to metabolic intermediates of glycolysis and the citric acid cycle.
   - The amino group is disposed of through urea synthesis.
- *Nonessential* amino acids are synthesized via pathways that begin with common metabolites.



At the crossroads: pyruvate and acetyl-CoA

- **Acetyl-CoA** is the common degradation product of **glucose, fatty acids, and ketogenic amino acids**.
  - Its acetyl group can be oxidized to CO_2 and H_2O via the citric acid cycle and oxidative phosphorylation or used to synthesize ketone bodies or fatty acids.
- **Pyruvate** is the product of **glycolysis** and the breakdown of **glucogenic amino acids**.
  - It can be oxidatively decarboxylated to yield acetyl-CoA, leading to further oxidation or to the biosynthesis of fatty acids.
  - Alternatively, pyruvate can be carboxylated via the pyruvate carboxylase reaction to form oxaloacetate, which can either make citric acid cycle intermediates or make glucose or certain amino acids.

Major Fuel-Metabolizing Organs

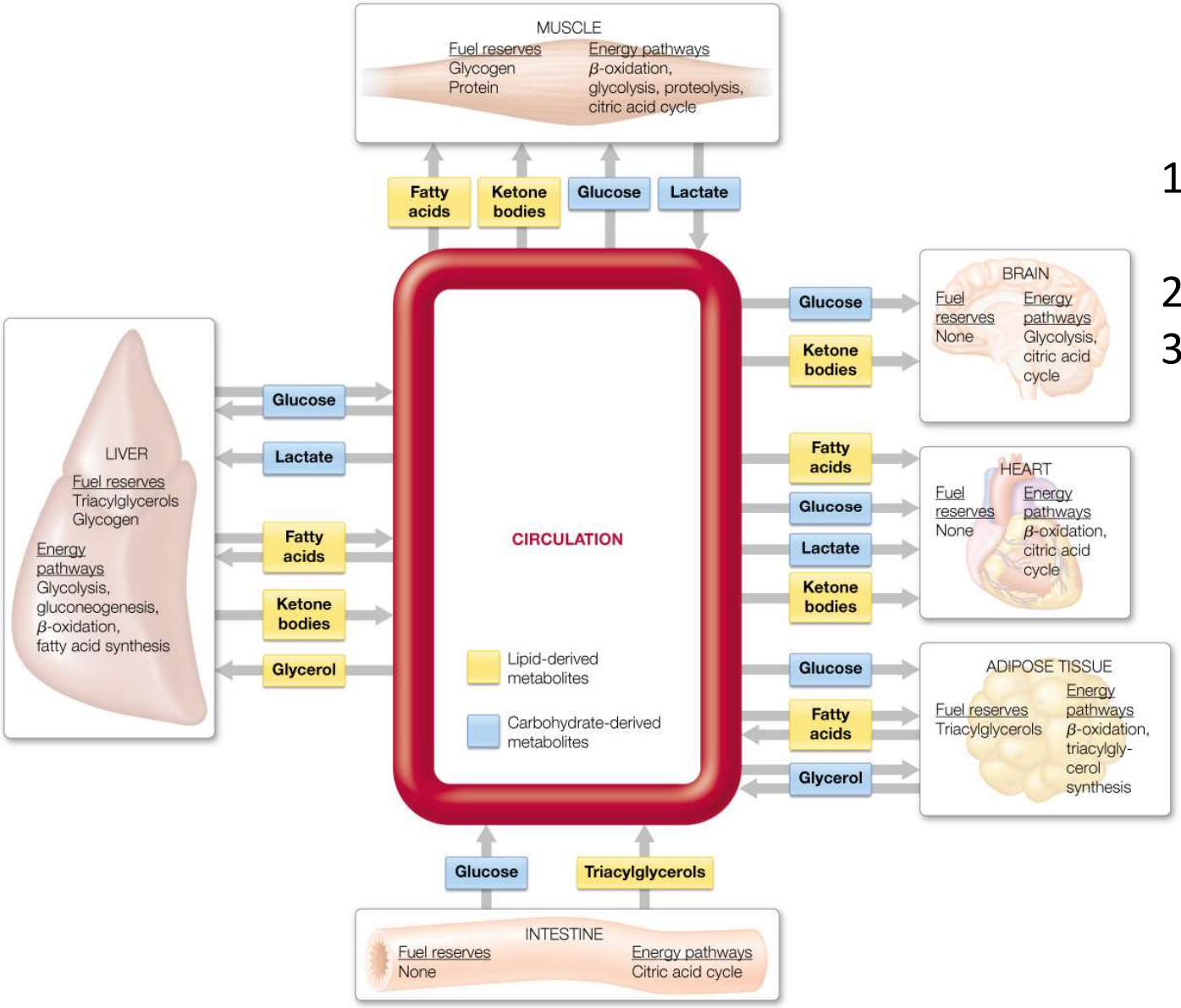
- Brain, muscle, heart, adipose tissue and liver are the major fuel-metabolizing organs
- **Triacylglycerols** (adipose tissue), **protein** (skeletal muscle), and **glycogen** (liver and muscle) are the **major fuel reserves**

TABLE 17.1 Profiles of the major vertebrate organs in fuel metabolism

Tissue	Fuel Reserves	Preferred Fuel	Fuel Sources Exported
Brain	None	Glucose (ketone bodies during starvation)	None
Skeletal muscle (resting)	Glycogen, protein	Fatty acids	None
Skeletal muscle (during exertion)	None	Glucose	Lactate
Heart muscle	None	Fatty acids	None
Adipose tissue	Triacylglycerols	Fatty acids	Fatty acids, glycerol
Liver	Glycogen, triacylglycerols	Glucose, fatty acids, amino acids	Fatty acids, glucose, ketone bodies

Organ specialisation (normal resting conditions)

- **Brain** uses glucose as the primary fuel.
- The **heart** prefers *aerobic energy pathways*.
- **Muscles** can generate ATP anaerobically and aerobically.
- **Adipose tissue** stores triacylglycerols and releases fatty acids as needed.
- ***The liver makes all types of fuel available to other tissues.***
- Some metabolic processes require cooperation among organs.
  - **Kidneys** filter out waste products and maintain blood pH
  - **Blood** provides the highway for metabolites, nutrients, waste products and hormones.



Organ specificity

1. Brain, heart, muscle, adipose tissue and liver
2. Connected by the bloodstream
3. Just after a meal, glucose, amino acids, and fatty acids are available from digestion.
4. When these fuels are exhausted, the liver supplies other tissues with glucose and ketone bodies
5. The adipose tissue provides other tissues with fatty acids.

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Fuel Characteristics of Major Organs

- Muscle:
  - uses glucose, fatty acids, ketone bodies
  - resting—fatty acids are primary fuel, exertion—stored glycogen is primary fuel (muscle also possesses creatine phosphate stores to regenerate ATP)
  - lacks glucose 6-phosphatase, so glucose released by glycogenolysis cannot be exported for use by other tissues
- Adipose tissue:
  - major fuel depot through stored TAGs (enough calories to supply the whole body for two months or more)
  - some glucose metabolism must occur for synthesis of glycerol-3-phosphate for TAG synthesis; when [glucose] falls, free fatty acids are released for use by other tissues

Fuel Characteristics of Major Organs - 2

- Liver:
  - synthesis of fuel components for other tissues: fatty acid synthesis and glucose synthesis, both from glycogen mobilization and gluconeogenesis
  - malonyl-CoA levels regulate fatty acid metabolism through inhibition of carnitine acyltransferase I, controlling fatty acid transport into mitochondria
  - buffers blood glucose partly through action of a high K_M hexokinase ("glucokinase") and partly through control of the intracellular location of glucose transporters
- Blood (connects organs):
  - vehicle of gas transport and metabolite transport
  - erythrocytes represent about half the total blood volume meet their energy needs primarily from glycolysis; no mitochondria in matured cells

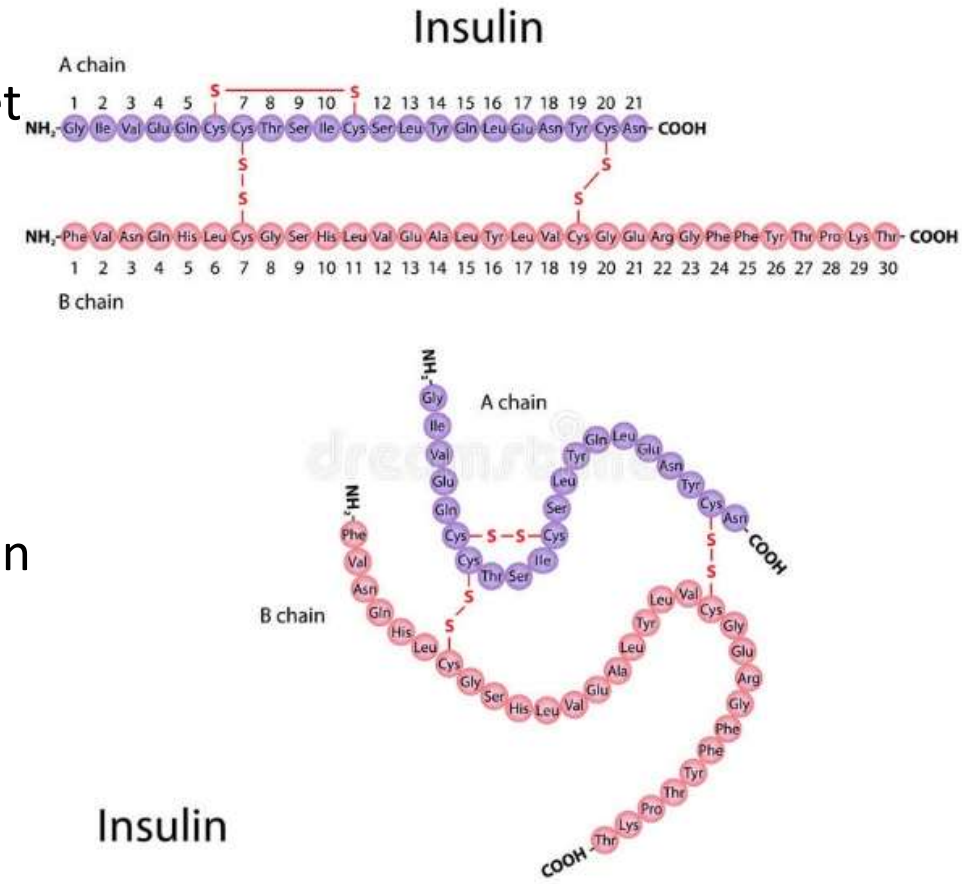
Pancreatic Islet Hormones Control Fuel Metabolism (recap)

3 polypeptide hormones released by the Islet cells

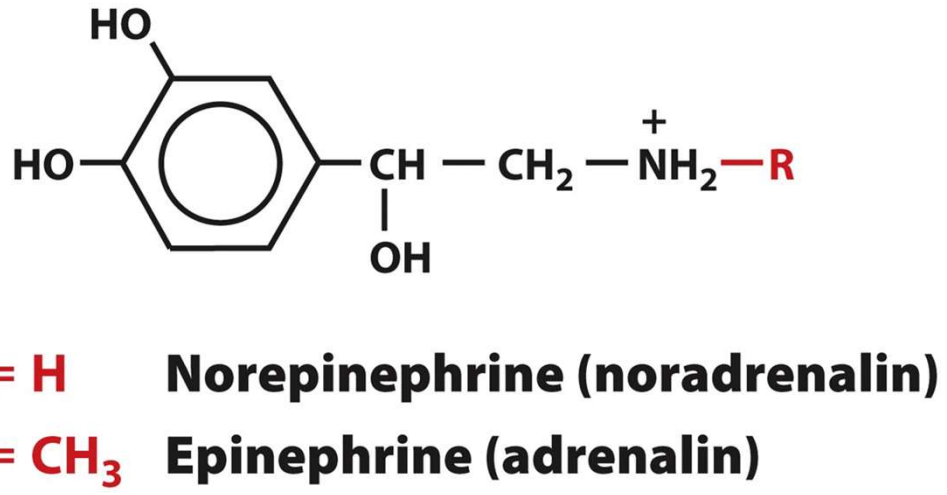
1. α cells: **glucagon** (29 residues)
2. β cells: **insulin** (51 residues)
3. δ cells: **somatostatin** (14 residues)

Glucagon and **insulin** have opposite effects on sugar metabolism (next slide).

Somatostatin inhibits the release of both glucagon and insulin, as well as other hormones such as growth hormones.



Epinephrine and Norepinephrine Prepare the Body for Action (recap)



- The **medulla** (core) of the **adrenal glands** makes two ***catecholamine hormones:***
  1. **norepinephrine (noradrenalin)** and
  2. its methyl derivative **epinephrine (adrenalin)**
- These bind to membrane-bound α- and β-adrenergic receptors on the different tissues, with different biological responses.
- The main function of these hormones is to overcome normal regulation for "flight-or-fight" responses.

Signal Pathways Involving the Insulin Receptor (recap)

- Leads to a huge amplification of the original signal
- Called a signalling cascade

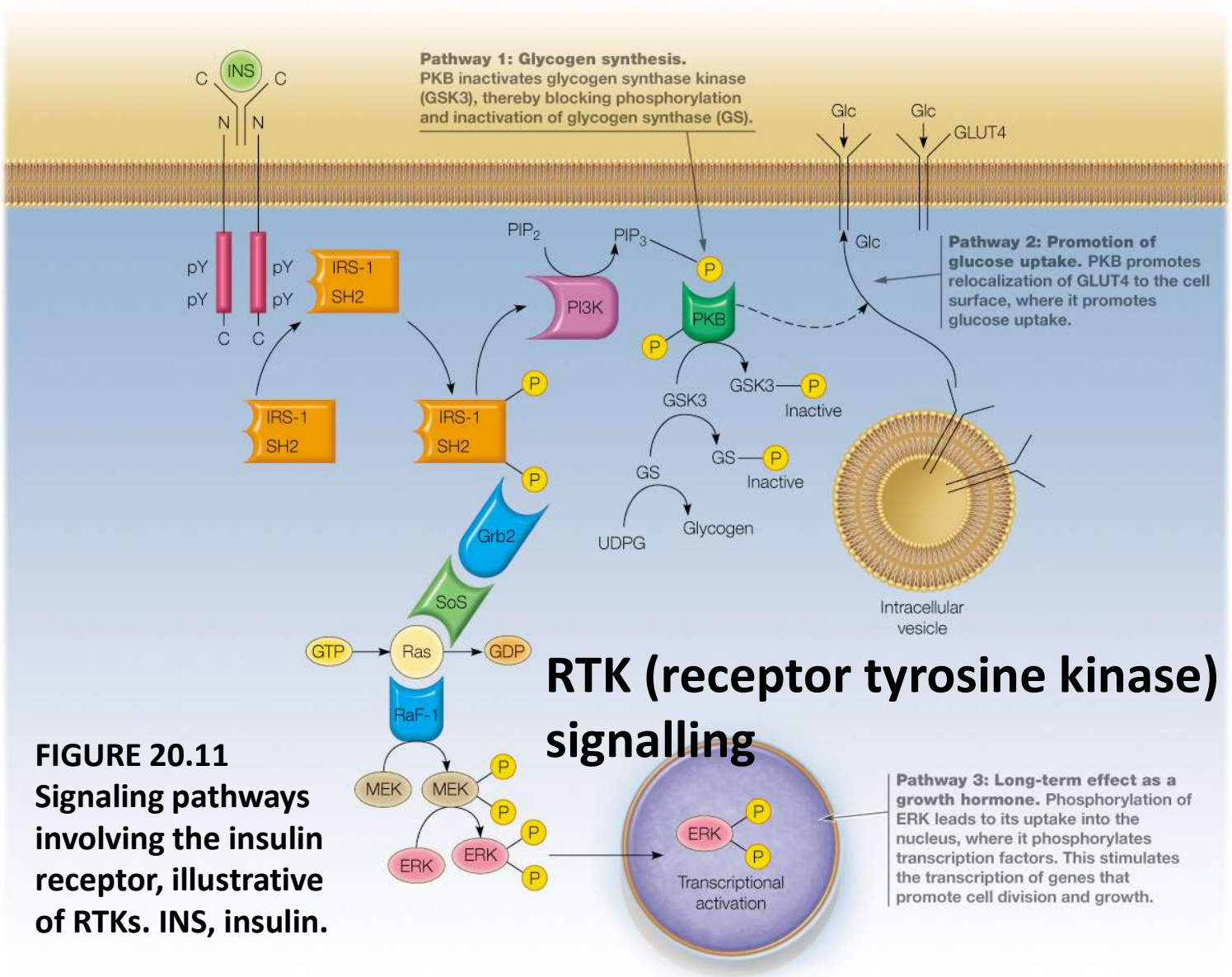


FIGURE 20.11
Signaling pathways involving the insulin receptor, illustrative of RTKs. INS, insulin.

RTK (receptor tyrosine kinase) signalling

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The adenylate cyclase signalling system of GPCRs (recap)

- **Glucagon** and **epinephrine** use the GPCR signalling system
- They bind to different GPCRs but both induce cAMP as second messenger
- **Glucagon** and **epinephrine counter the action of insulin**

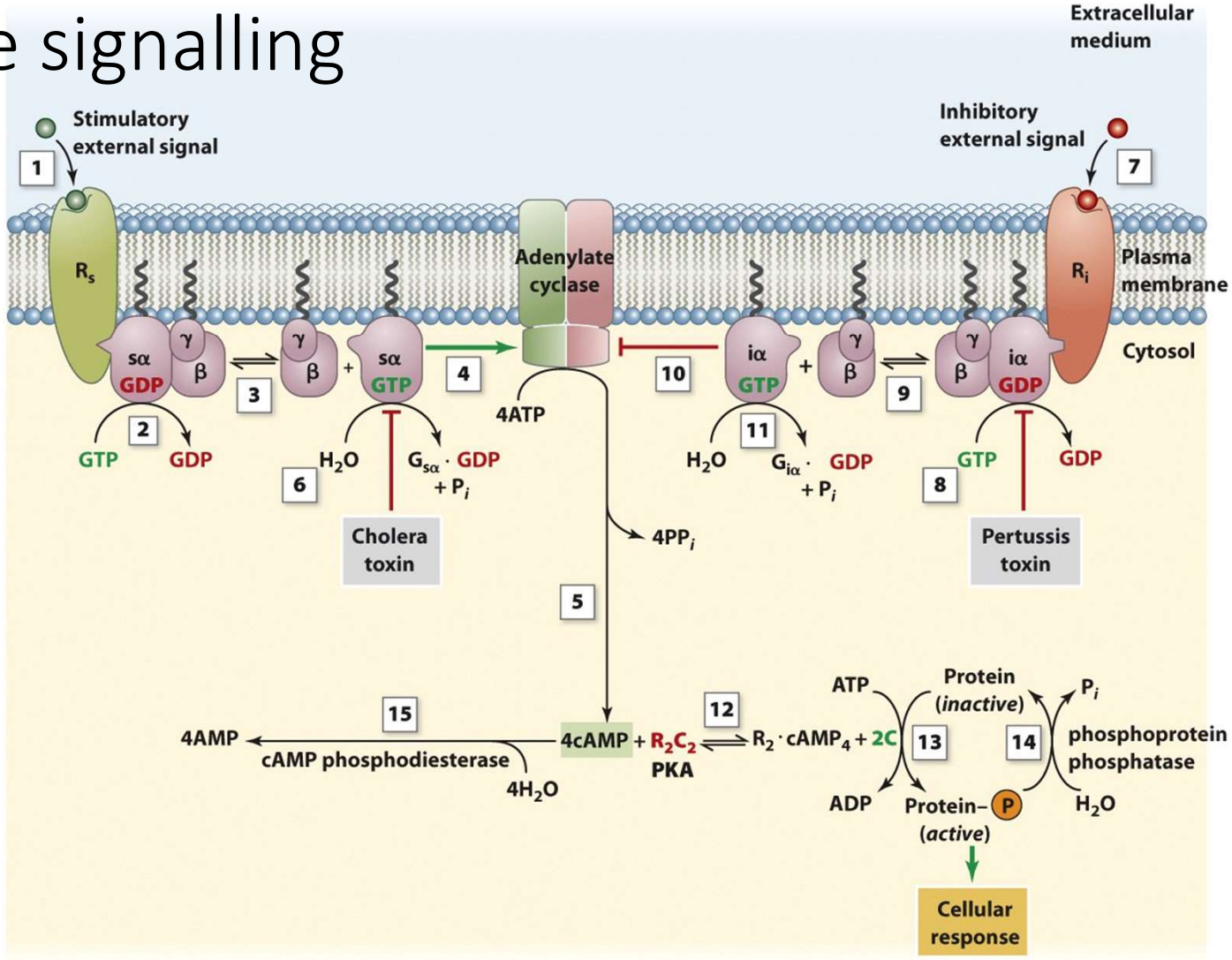
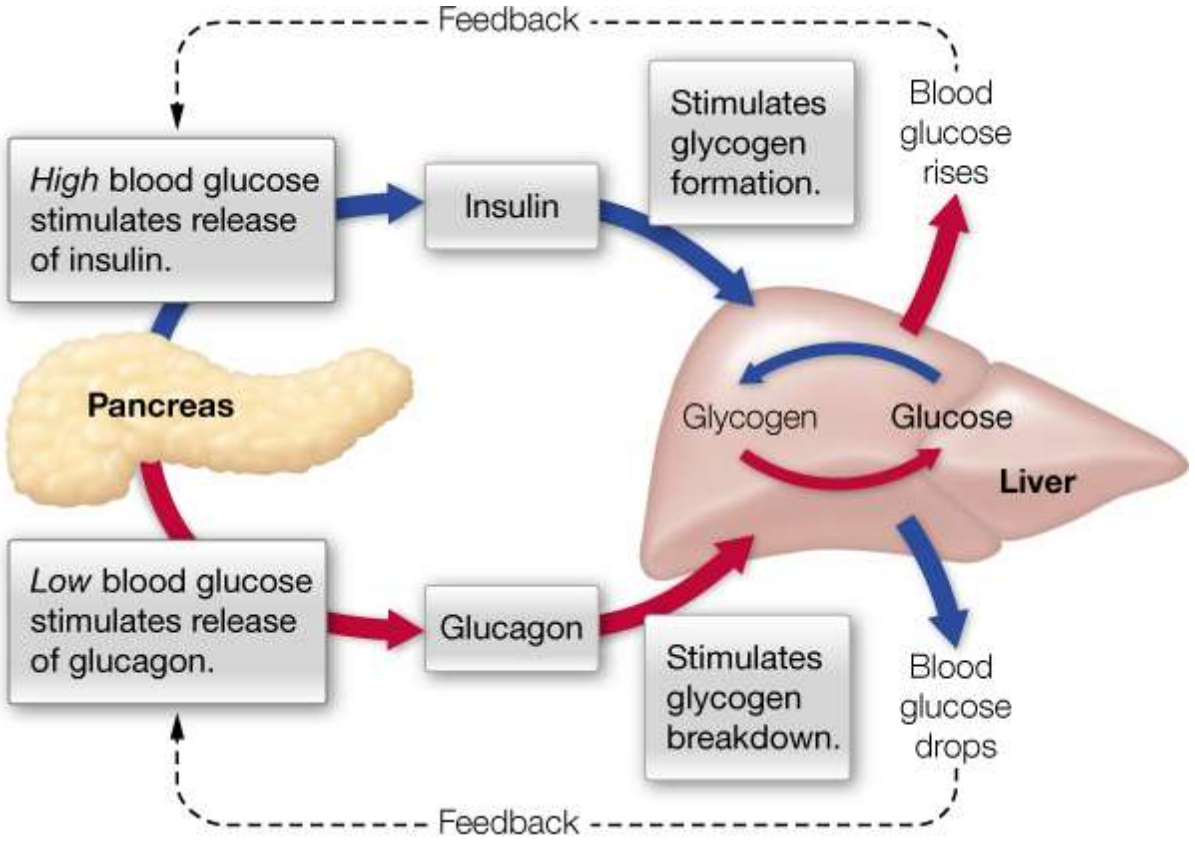


Figure 13-23

Control of Fuel Metabolism in Mammals (recap)

- Maintenance of blood glucose levels is particularly critical to brain function
- Major hormones:
  - insulin
  - glucagon
  - epinephrine



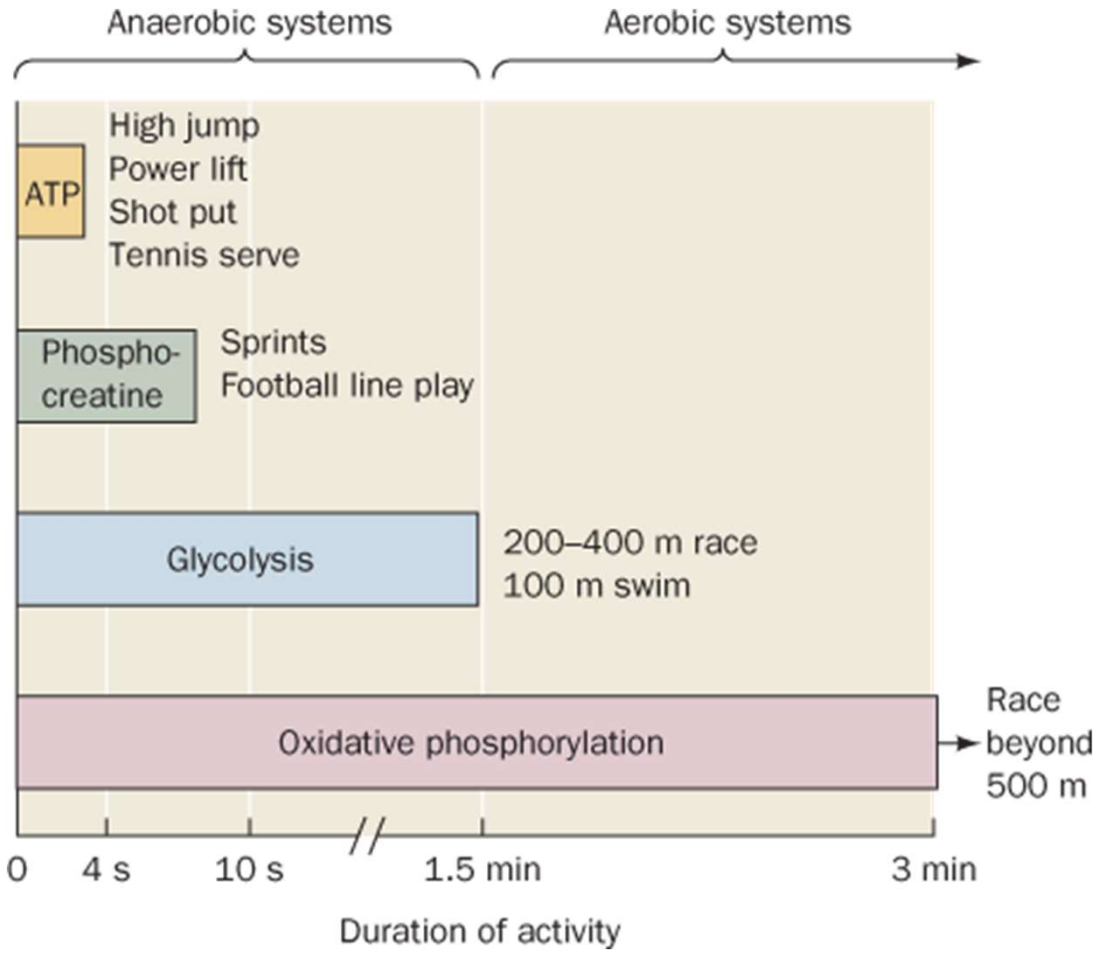
Increase of Blood Glucose Levels by Epinephrine

- Epinephrine is released by adrenal medulla in response to low blood glucose levels
- It reacts with second messenger systems:
  - Muscle – activates adenylate cyclase and glycogenolysis
  - Adipose tissue – simulates breakdown of TAG
  - Pancreas – inhibits insulin secretion, stimulates glucagon secretion
- Unlike glucagon, epinephrine effects are short-lived
- It also functions as a neurotransmitter

TABLE 17.2 Major hormones controlling fuel metabolism in mammals

Hormone	Biochemical Actions	Enzyme Target	Physiological Actions
Insulin	↑ Glucose uptake (muscle, adipose tissue)	GLUT4	Signals fed state:
	↑ Glycolysis (liver, muscle)	PFK-1 (via PFK-2/FBPase-2)	↓ Blood glucose level
	↑ Acetyl-CoA production (liver, muscle)	Pyruvate dehydrogenase complex	↑ Fuel storage
	↑ Glycogen synthesis (liver, muscle)	Glycogen synthase	↑ Cell growth and differentiation
	↑ Triacylglycerol synthesis (liver)	Acetyl-CoA carboxylase	
	↓ Gluconeogenesis (liver)	FBPase-1 (via PFK-2/FBPase-2)	
	↓ Lipolysis		
	↓ Protein degradation		
	↑ Protein, DNA, RNA synthesis		
Glucagon	↑ cAMP level (liver, adipose tissue)		Signals fasting state:
	↑ Glycogenolysis (liver)	Glycogen phosphorylase	↑ Glucose release from liver
	↓ Glycogen synthesis (liver)	Glycogen synthase	↑ Blood glucose level
	↑ Triacylglycerol hydrolysis and mobilization (adipose tissue)	Hormone-sensitive lipase, adipose triglyceride lipase	↑ Ketone bodies as alternative fuel for brain
	↑ Gluconeogenesis (liver)	FBPase-1 (via PFK-2/FBPase-2), pyruvate kinase, PEPCK	
	↓ Glycolysis (liver)	PFK-1 (via PFK-2/FBPase-2)	
	↑ Ketogenesis (liver)	Acetyl-CoA carboxylase	
Epinephrine	↑ cAMP level (muscle)		Signals stress:
	↑ Triacylglycerol mobilization (adipose tissue)	Hormone-sensitive lipase, adipose triglyceride lipase	
	↑ Glycogenolysis (liver, muscle)	Glycogen phosphorylase	↑ Glucose release from liver
	↓ Glycogen synthesis (liver, muscle)	Glycogen synthase	↑ Blood glucose level
	↑ Glycolysis (muscle)	Glycogen phosphorylase, providing increased glucose	

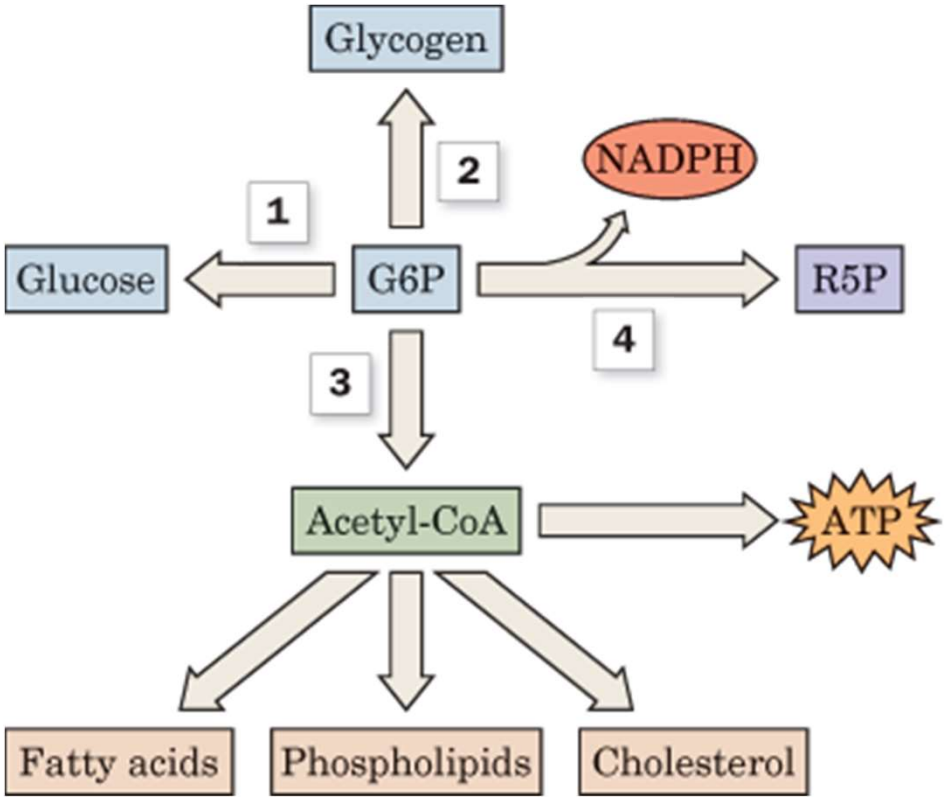
Control of Fuel Metabolism in Mammals



Muscles use up ATP progressively

1. Available ATP is used first
2. Phosphocreatine makes ATP from ADP.
3. Glycolysis is speeded up during exercise.
4. The shift from anaerobic to aerobic metabolism (oxidative phosphorylation) occurs after about 90 sec, or slightly later in trained athletes.

The liver can store glucose as G6P



- *Glucokinase* (the liver isozyme of hexokinase) is unaffected by G6P concentration.

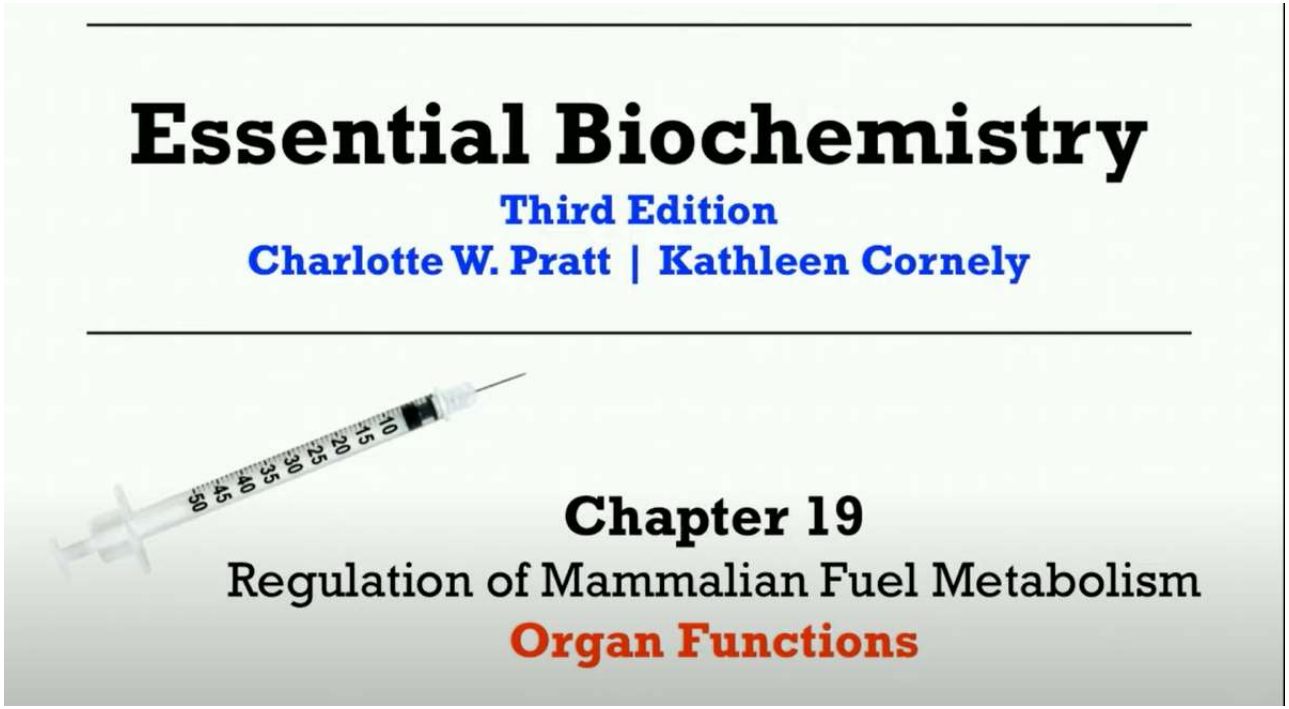
1. G6P back to glucose: when by blood [glucose] drops below 5mM and glucagon is secreted.
2. G6P to glycogen, when the demand for glucose is low.
3. G6P to acetyl-CoA via glycolysis and by pyruvate dehydrogenase. This can be used to synthesize fatty acids, phospholipids and cholesterol.
4. G6P can be degraded via the pentose phosphate pathway to generate the NADPH required for the biosynthesis of fatty acids and other compounds.

Summary of organ-specific pathways

- **Brain:** mainly **glycolysis**
- **Muscle**: breaks down **glucose** (from glycogen), **fatty acids**, and **ketone bodies**. Excess glucose stored as ***glycogen***.
- **Heart**: metabolizes fatty acids, ketone bodies, glucose, pyruvate, and lactate. Mostly **aerobic** – has lots of mitochondria.
- **Adipose tissue**: stores *triacylglycerols* and releases **fatty acids** and **glycerol**.
- **Liver:** metabolizes sugar, fats and amino acids. Also makes ketone bodies for other organs.

Summary of organ functions

https://www.youtube.com/watch?v=JiaA902gRec



Role of hormones

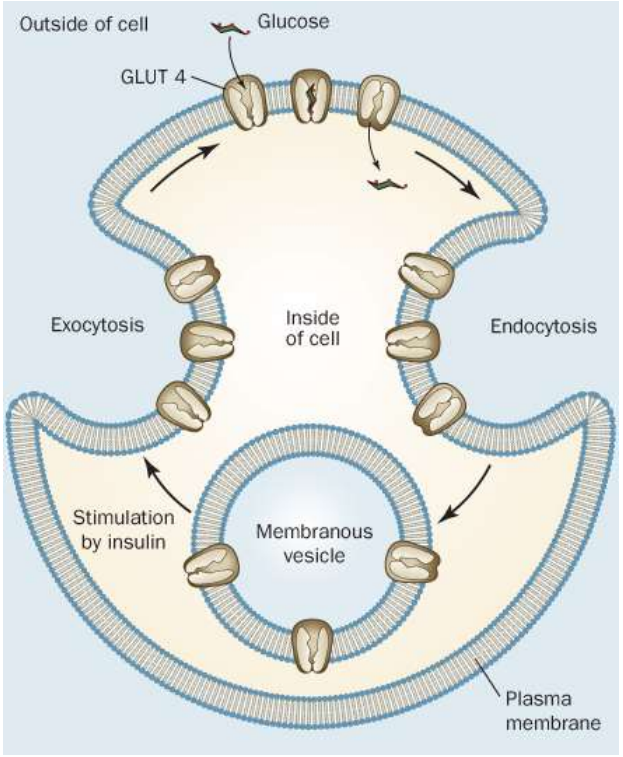
- Peptide hormones: insulin and glucagon
- Catecholamines: epinephrine (adrenalin) and norepinephrine
- Require cell-surface receptors (refer to biochemical signalling lectures)

1. maintain metabolic homeostasis (balance between energy inflow and output),
2. respond to external stimuli, and
3. follow various developmental programs.

- *Cells can react to discrete hormonal signals or combinations of signals with variations in the **magnitude** and **duration** of the cellular response*.

Insulin Release Is Triggered by Glucose

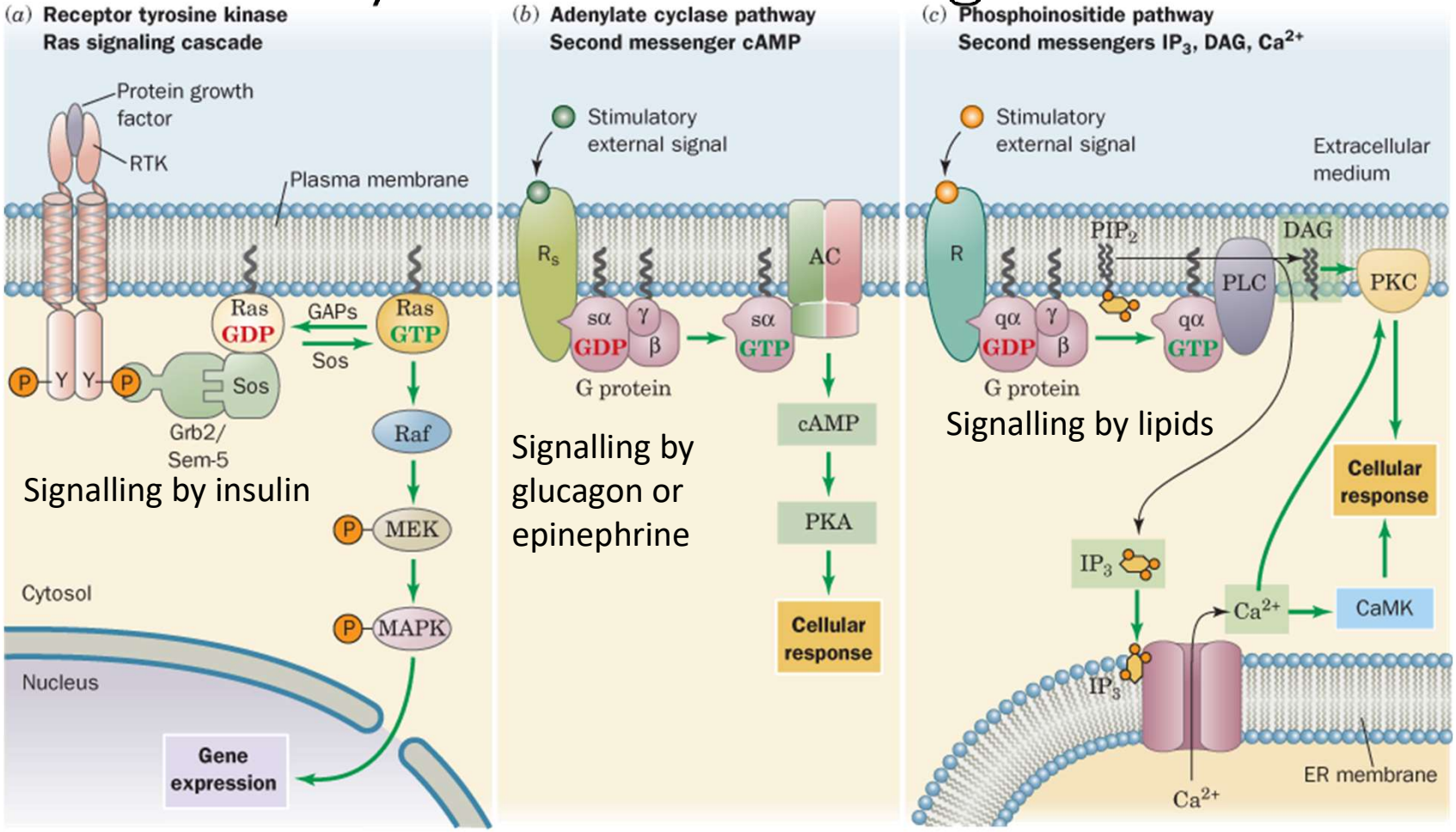
- Insulin promotes fuel storage in muscle and adipose tissue.
- After a meal, insulin-activated glucose transporters facilitate getting glucose into cells - fed state.
  - Glycogen or fatty acid synthesis
- ***Insulin blocks liver gluconeogenesis and glycogenolysis: signalling high [glucose].***



Glucagon and Catecholamines Counter the Effects of Insulin

- Glucagon leads to **glycogen breakdown** in the **liver** – fasting response. Also, mobilizes **fatty acids** from **adipose tissue**.
- Epinephrine and norepinephrine, which are released during times of stress, have a similar effect of muscles and adipose tissue. In the liver, these hormones support glucagon's actions, leading to **glucose mobilization**, as well as trigger **gluconeogenesis**.

Receptors and Biochemical Signalling Pathways in Metabolic Regulation



Hormone regulation summary

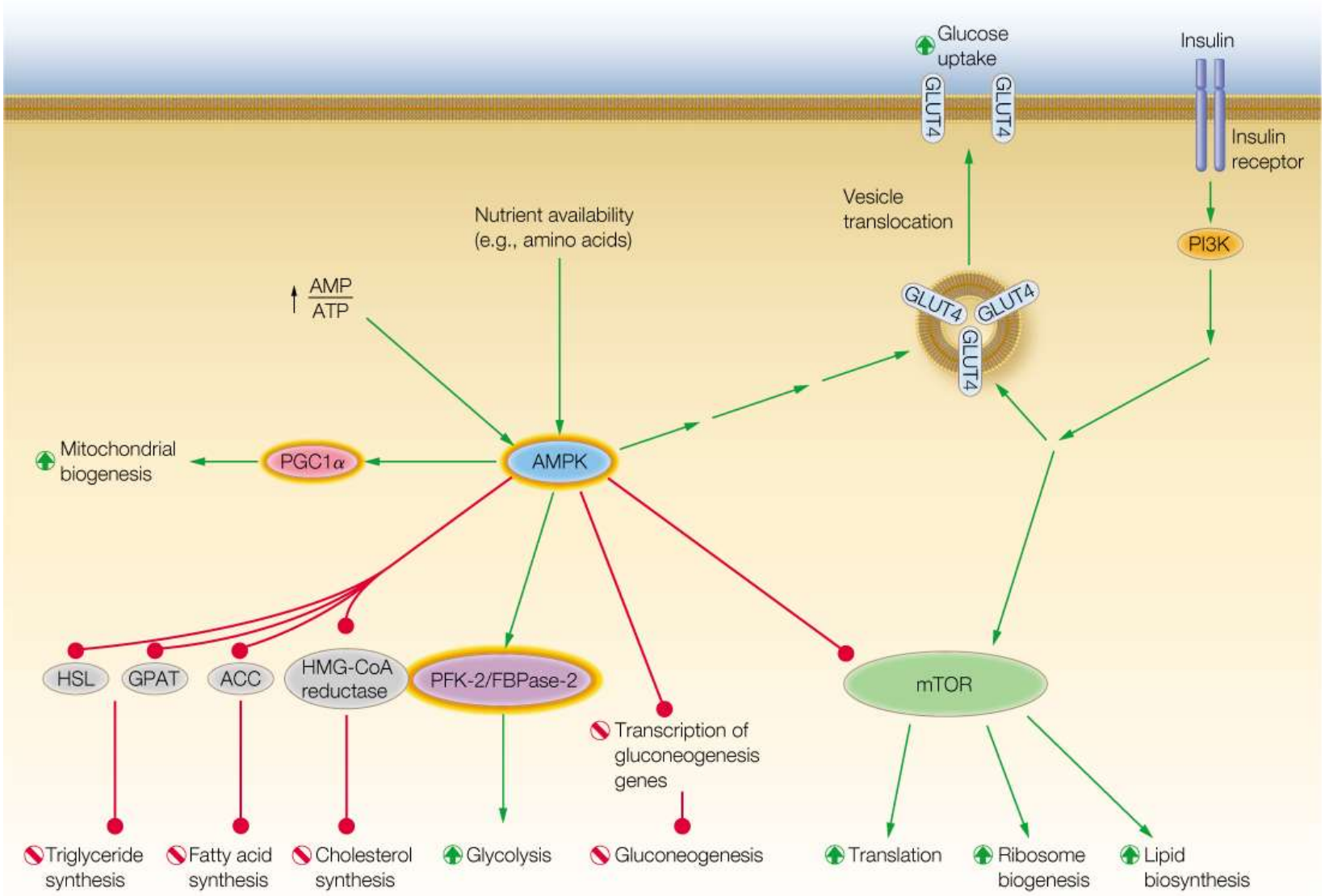
TABLE 22-1 Hormonal Effects on Fuel Metabolism

Tissue	Insulin	Glucagon	Epinephrine
Muscle	↑ Glucose uptake ↑ Glycogen synthesis	No effect	↑ Glycogenolysis
Adipose tissue	↑ Glucose uptake ↑ Lipogenesis ↓ Lipolysis	↑ Lipolysis	↑ Lipolysis
Liver	↑ Glycogen synthesis ↑ Lipogenesis ↓ Gluconeogenesis	↓ Glycogen synthesis ↑ Glycogenolysis	↓ Glycogen synthesis ↑ Glycogenolysis ↑ Gluconeogenesis

Metabolic Homeostasis: The Regulation of Energy Metabolism, Appetite, and Body Weight: AMPK/mTOR

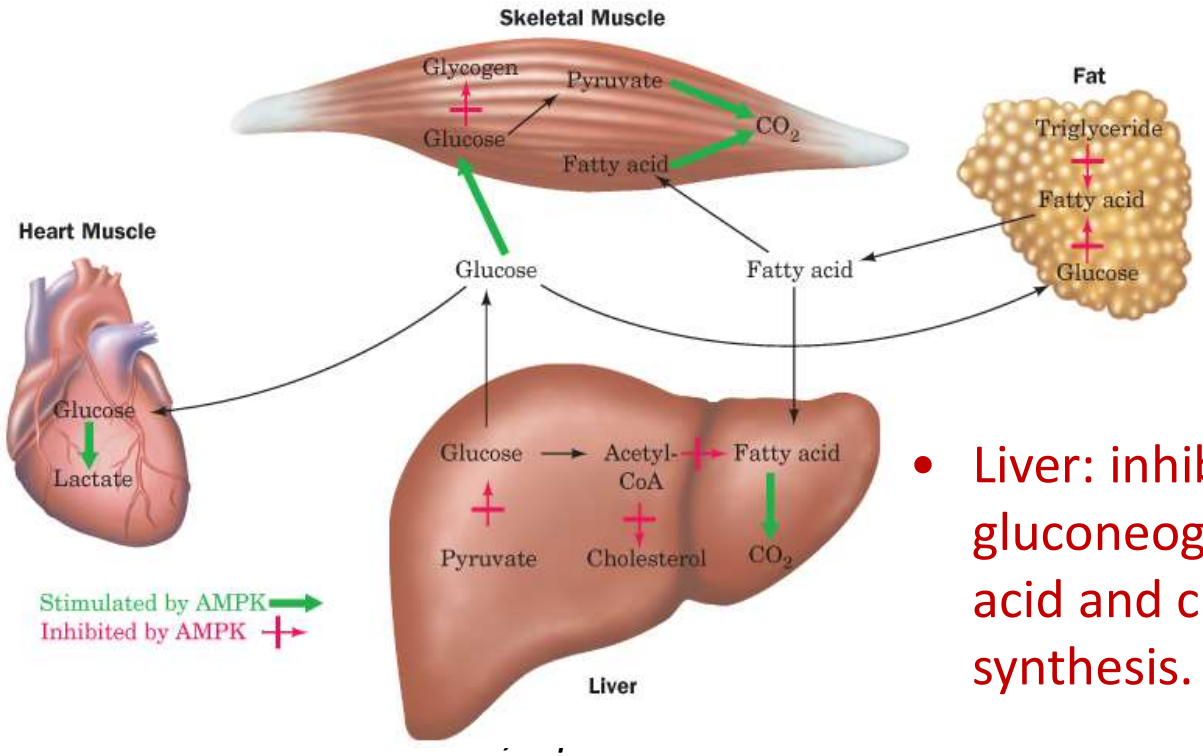
- AMP as a regulator, via **AMP kinase (AMPK)**
- Controlled release of fuels and appetite control
- What happens to excess energy?
- AMP-activated protein kinase (AMPK)
  - a serine/threonine kinase that is activated when energy charge is low (high AMP levels)
  - stimulates pathways that lead to ATP production, while inhibiting ATP-utilizing pathways
- Mammalian target of rapamycin (mTOR)
  - like AMPK, a protein serine/threonine kinase found in all eukaryotes
  - active only under nutrient-rich conditions
  - promotes anabolic processes – cell proliferation, protein synthesis, lipid biosynthesis
  - was discovered during studies on the action of rapamycin, an immunosuppressant

AMPK and mTOR signaling pathways



AMP-Dependent Protein Kinase (AMPK) controls fuel use: prevents build up of toxic levels of fats

- Muscle: promotes fatty acid oxidation and glucose uptake



- Adipose tissue: inhibits lipid breakdown
- Heart: promotes glycolysis
- Liver: inhibits gluconeogenesis and fatty acid and cholesterol synthesis.

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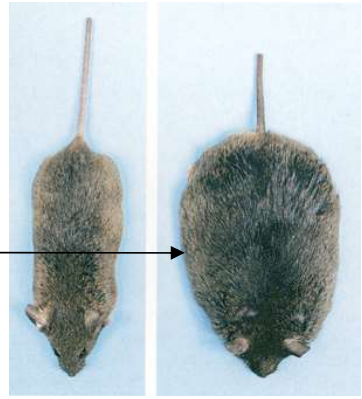
Adipose Tissue Hormone Summary

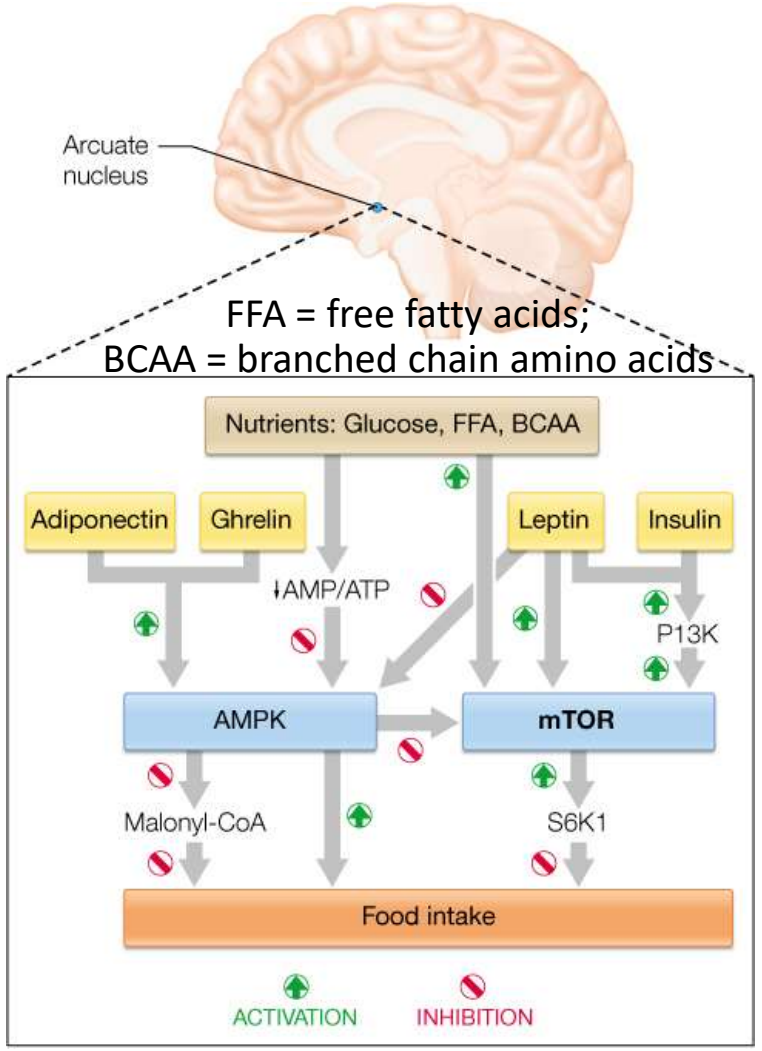
- **Adiponectin** (247-residue protein) regulates AMPK activity.
  - The binding of adiponectin to **adiponectin receptors**, which occur on the surfaces of both liver and muscle cells, acts to increase the phosphorylation and activity of AMPK.
- **Leptin** (146-residue polypeptide) is a satiety hormone: lack of leptin activity leads to obesity.
- **Ghrelin** is an appetite-stimulating peptide secreted by the empty stomach.



Overall, ghrelin stimulates appetite while leptin and insulin suppress appetite.

Fuel and Hormonal Control of Appetite

- In mammals, the brain coordinates whole-body energy homeostasis
- **AMPK** activation promotes food intake
- **Adiponectin** and **ghrelin** stimulate food intake via AMPK
- **Insulin** acts through PI3K (phosphoinositide 3-kinase) to inhibit food intake
- **Leptin** has direct and indirect effects (via PI3K and AMPK): inhibits feed intake



Disturbances in Fuel Metabolism

- As humans do not eat continuously, the use of dietary fuels and the mobilization of fuel stores changes sharply, during the few hours between meals.
- **Humans can survive fasts of even months by adjusting their fuel metabolism.**
- Metabolic flexibility therefore evolved before modern humans became used to three meals a day.

TABLE 22-2 Fuel Reserves for a Normal 70-kg Man

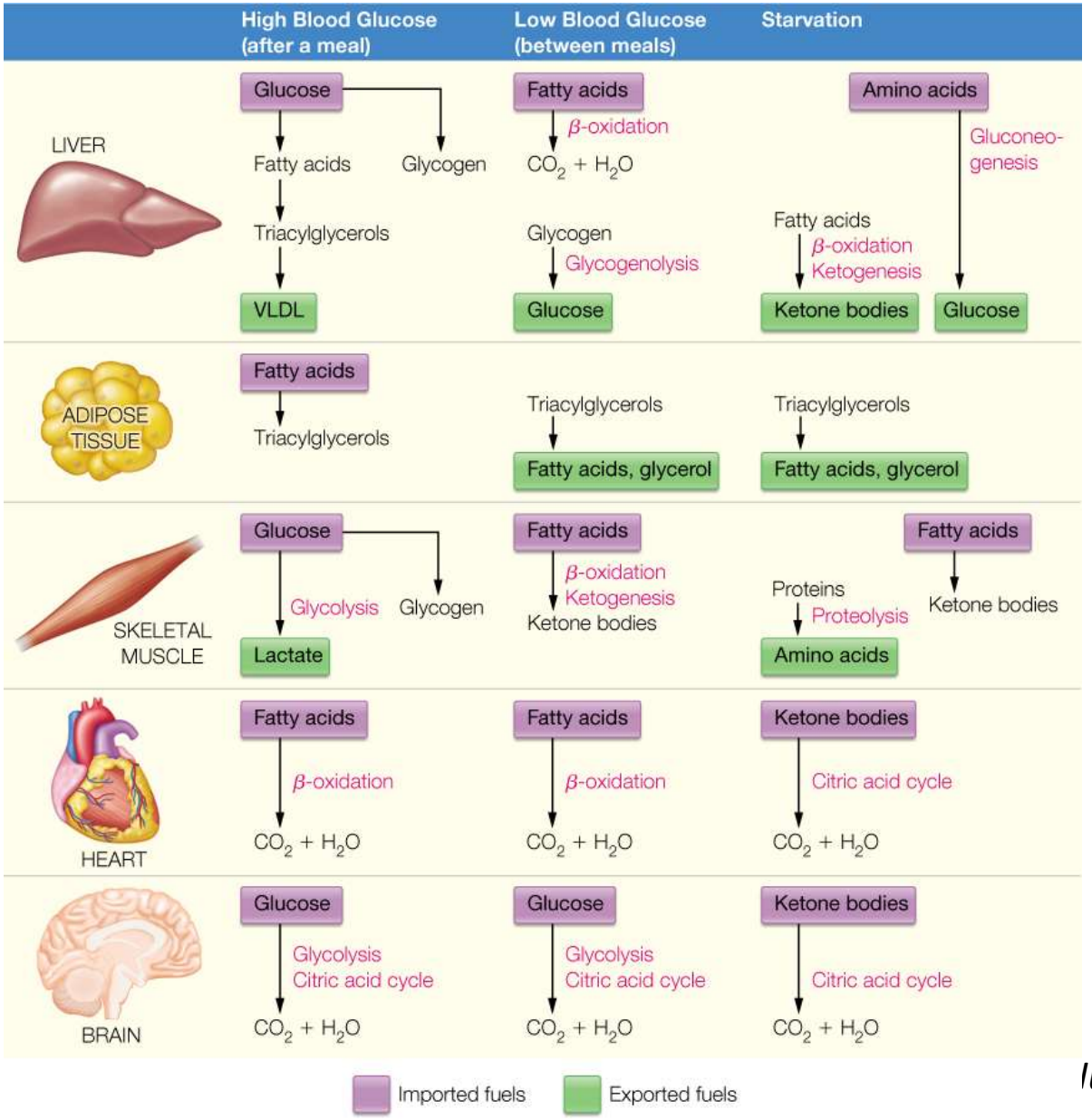
Fuel	Mass (kg)	Calories[a]
Tissues		
Fat (adipose triacylglycerols)	15	141,000
Protein (mainly muscle)	6	24,000
Glycogen (muscle)	0.150	600
Glycogen (liver)	0.075	300
Circulating fuels		
Glucose (extracellular fluid)	0.020	80
Free fatty acids (plasma)	0.0003	3
Triacylglycerols (plasma)	0.003	30
Total		**166,000**

Source: Cahill, G.E.,Jr., *New Engl. J. Med.* 282, 669 (1970).

[a] 1 (dieter's) Calorie = 1 kcal = 4.184 kJ.

Adaptive Strategies in Fuel Metabolism

- *Absorbed fuels are allocated immediately.*
- *Blood glucose remains nearly constant.*
- *Gluconeogenesis supplies glucose during starvation.*
- *Ketone Bodies Become a Major Energy Source during Starvation.*
  - The survival time of a starving individual therefore depends much more on the size of fat reserves than on muscle mass.
- *Caloric restriction may increase longevity.*



Responses to Metabolic Stress:

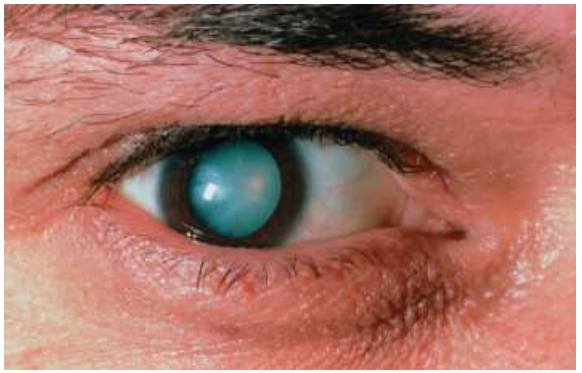
Major Events in the Storage and Use of Fuels in the Fed State, Unfed State, and Early Starvation

Diseases of plenty

- ***Diabetes mellitus*** is characterized by high blood glucose levels
  - ➢is a family of diseases resulting from insulin deficiency or defects in insulin response
  - ➢The biochemical response to starvation is similar to the response to diabetes mellitus, in that alternative fuel sources must be found because there is essentially a glucose deficiency
- Two types of diabetes
  1. Insulin-dependent or juvenile-onset diabetes mellitus, which most often strikes suddenly in childhood.
  2. Non-insulin-dependent or maturity-onset diabetes mellitus, which usually develops gradually after the age of 40, but is becoming more common in younger adults.

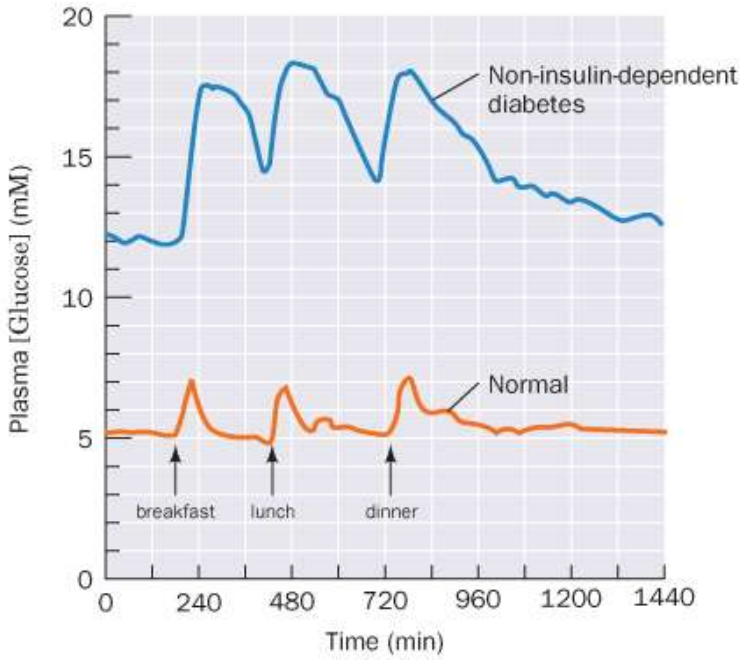
Type 1 or Juvenile Diabetes

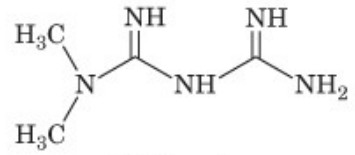
- Insulin-dependent diabetes is caused by a deficiency of pancreatic β cells
  - ➢ Due to an autoimmune response (e.g., autoimmune destruction of pancreas β cells, mutation in insulin receptor, etc.)
  - ➢ Type 1 diabetes can be treated with (injections of) insulin
  - ❖ Decreased life span?
  - ❖ Hyperglycemia (high blood [glucose]) of diabetes mellitus also leads to blindness
  - ❖ β-cell transplant: is a possible cure!



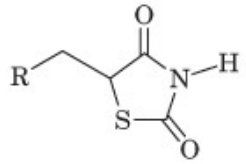
Type 2 or Non-Insulin-Dependent Diabetes

- Over 90% of cases: particularly >65 years of age
- Caused by a deficiency of insulin receptors or insulin signal transduction
- Treatment is by way of drugs that either suppress glucose release by the liver (metformin) or promote insulin-stimulated glucose disposal in muscle (TZDs).



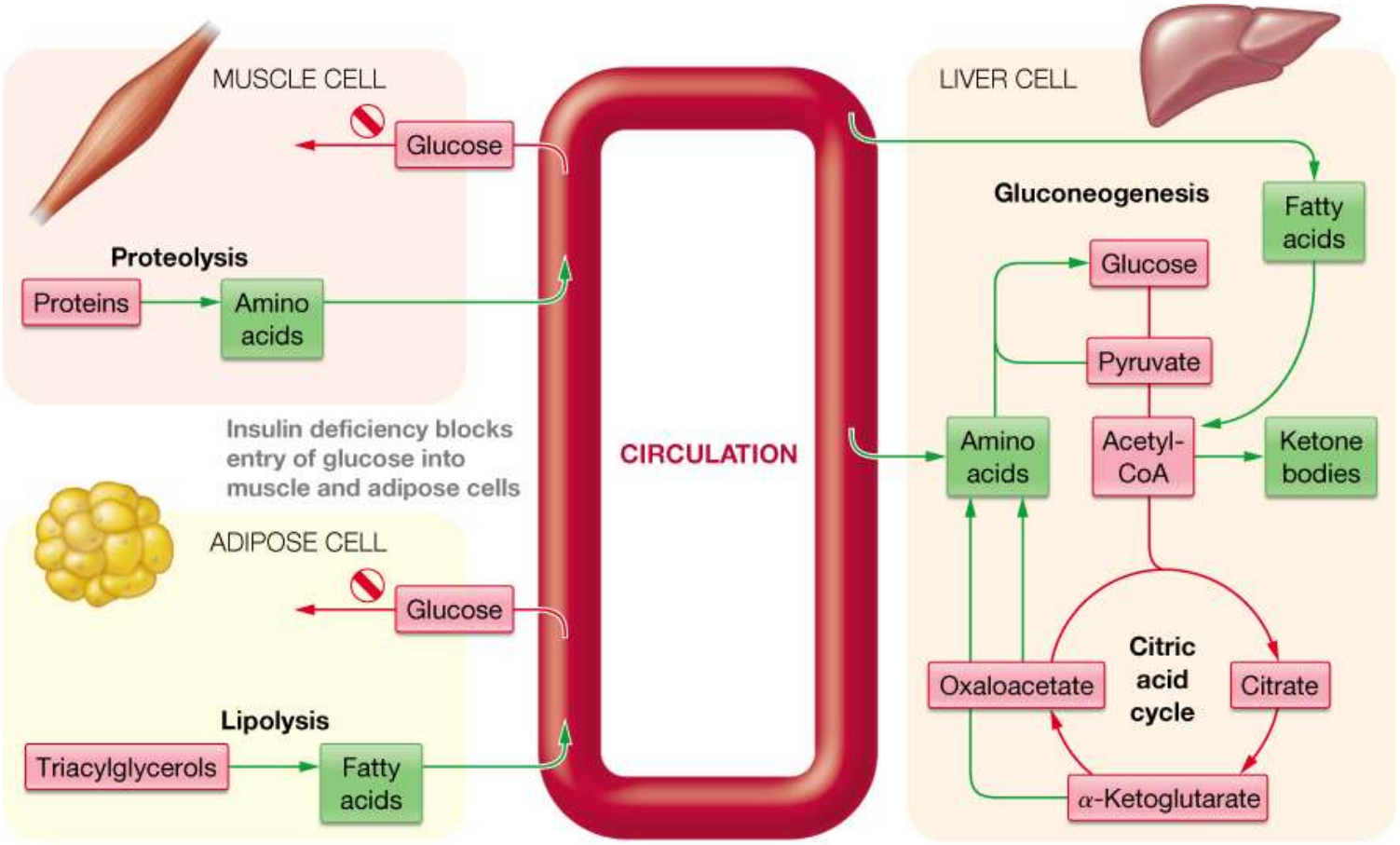


Metformin



A thiazolidinedione (TZD)

Metabolic Abnormalities in Diabetes



Metabolic disturbances: summary

- During starvation, the body makes metabolic changes to maintain blood glucose levels.
- Diabetes may be caused by:
  - either insufficient production of insulin (type 1) or
  - an insensitivity to its presence (type 2).
- Obesity may result from improper regulation of appetite or energy expenditure.

Chapter 17 Summary

- Each organ or tissue of a multicellular organism has a distinctive profile of metabolic activities that allows it to serve its specialized functions
- However, these tissues and organs must remain in constant communication to maintain homeostasis with respect to levels of nutrients (glucose), energy (ATP) and other factors
- Glucose homeostasis is mainly controlled by the actions of three hormones – insulin, glucagon, and epinephrine
- Two protein kinases, AMPK and mTOR, play central roles in orchestrating the metabolic activities of mammalian cells important for energy homeostasis by responding to AMP/ATP ratios, nutrient-poor/rich conditions, etc.