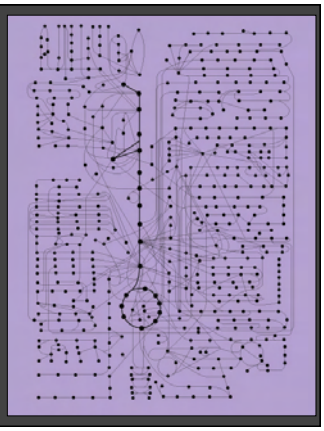
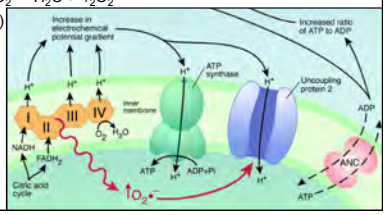
Regulation of Cellular Respiration & Metabolism in Humans

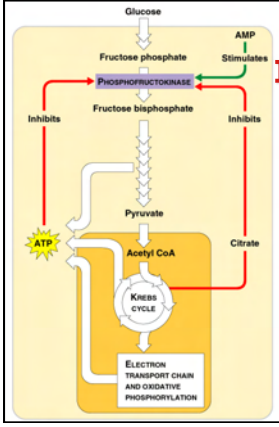


Uncoupling Proteins

Uncoupling proteins (UCP) in inner mitochondrial membrane of mammals

- Allow some H^+ leakage, bypassing ATP-synthase.
  - Burn fuel stores without generating ATP
  - May be important in regulating %body fat
  - May also be important in reducing formation of dangerous Reactive Oxygen Species (ROS)
    - H^+-leakage is activated by O_2^-.
    - $O_2^- + 2H^+ \rightarrow H_2O_2 \rightarrow H_2O + {}^1/_2O_2$
- In brown (thermogenic) fat, UCP1 causes heat generation by burning high-caloric lipid fuel without producing ATP





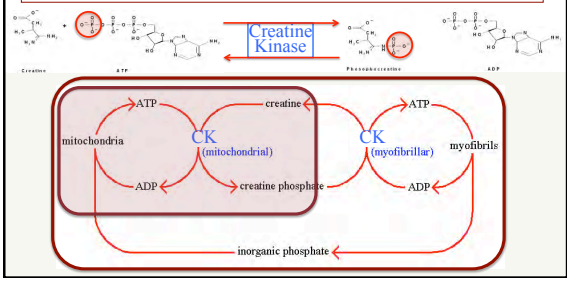
Feedback Inhibition Control of Respiration

⇑⇑ATP→ inhibits F-6-P-kinase
∴ F-6-P → back to G-6-P
→ alternate pathway → G-1-P
→ **glycogenesis**

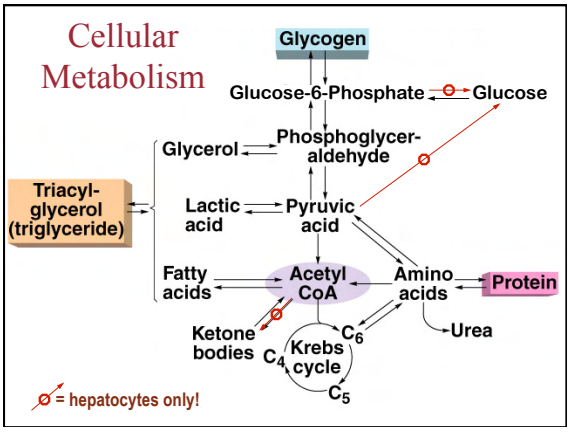
⇑⇑ATP→ inhibits Krebs Cycle enzymes
∴ acetyl-CoA → alternate pathway
→ fatty acid synthesis
→ **lipogenesis**

High activity tissues [skeletal muscle] have high ATP demand.
But since ⇧⇧[ATP] would inhibit ATP synthesis —
— cannot "store" excess ATP reserve.

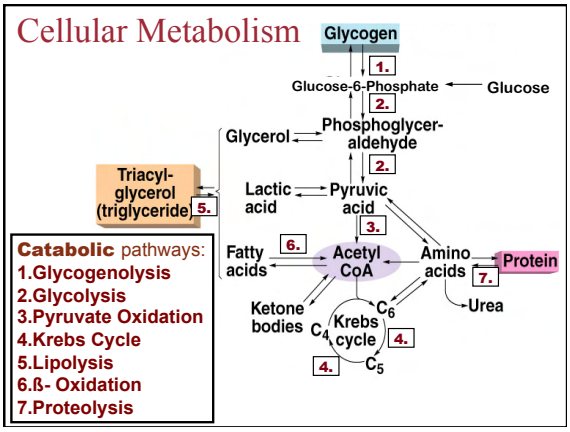
- Exchange –P of ATP to P–Creatine
- Exchange back to ATP from P–Cr at myofibrils



Cellular Metabolism

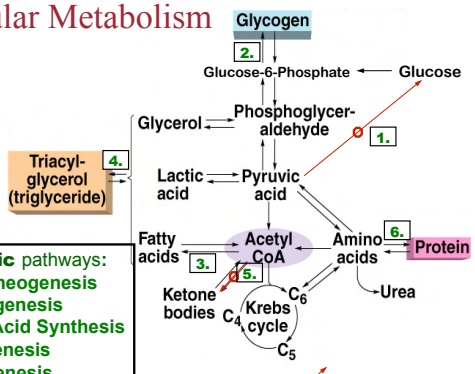


Cellular Metabolism



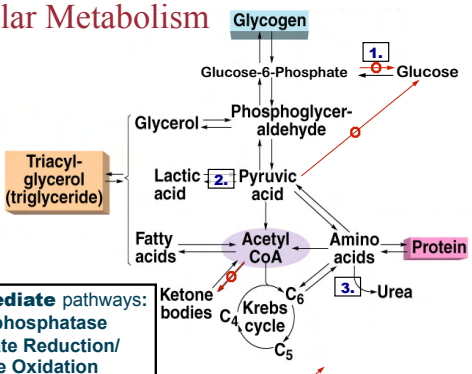
Catabolic pathways:
1.Glycogenolysis
2.Glycolysis
3.Pyruvate Oxidation
4.Krebs Cycle
5.Lipolysis
6.ß- Oxidation
7.Proteolysis

Cellular Metabolism



Anabolic pathways:
1. Gluconeogenesis
2. Glycogenesis
3. Fatty Acid Synthesis
4. Lipogenesis
5. Ketogenesis
6. Translation

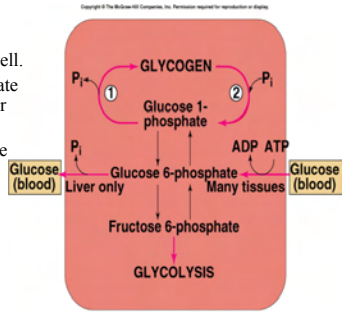
Cellular Metabolism



Intermediate pathways:
1. Glucophosphatase
2. Pyruvate Reduction/ Lactate Oxidation
3. Deamination

Glycogenesis and Glycogenolysis

- Glucose-6-phosphate cannot leak out of the cell.
- Skeletal muscles generate glucose-6-phosphate for own glycolytic needs.
- **Only Liver** contains the enzyme glucose-6-phosphatase that can remove the phosphate group and produce free glucose.

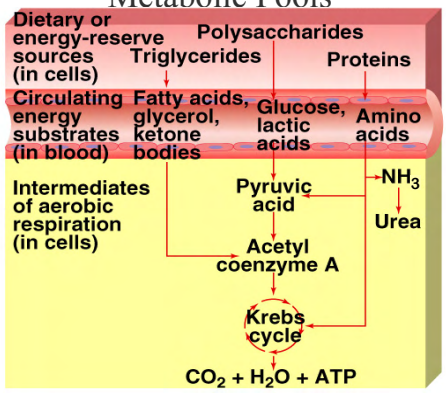


Uses of Different Energy Sources

Table 5.3 Relative Importance of Different Molecules in the Blood with Respect to the Energy Requirements of Different Organs

Organ	Glucose	Fatty Acids	Ketone Bodies	Lactic Acid
Brain	+++	–	+	–
Skeletal muscles (resting)	+	+++	+	–
Liver	+	+++	++	+
Heart	+	++	+	+

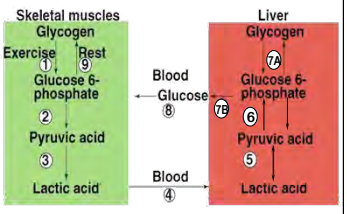
Metabolic Pools



Gluconeogenesis & the Cori Cycle

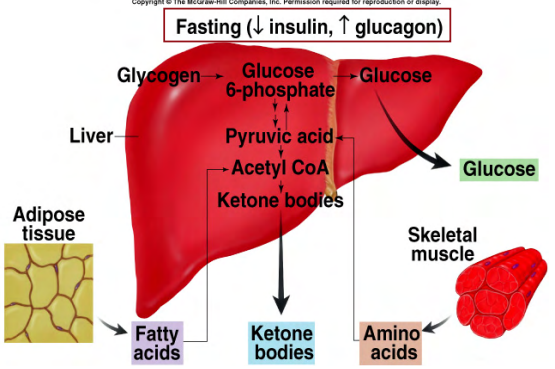
4) Lactic acid produced by anaerobic respiration in muscle is released into the bloodstream and delivered to the liver.
5) LDH converts lactic acid to pyruvic acid.
6) **Gluconeogenesis**: ("creating new glucose") Pyruvic acid converted to glucose-6-phosphate:

- G-6-P can be used either for **7A**- liver glycogenesis *or* **7B**- can be converted to free glucose and released into the bloodstream.



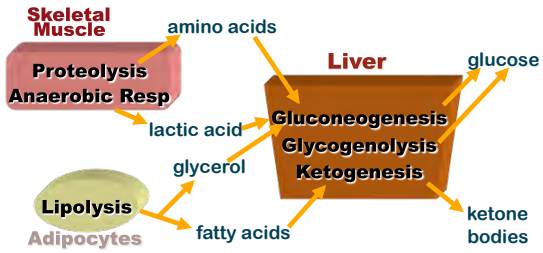
6 & 7B *only* occur in liver!

Interactions of Liver, Fat & Muscle



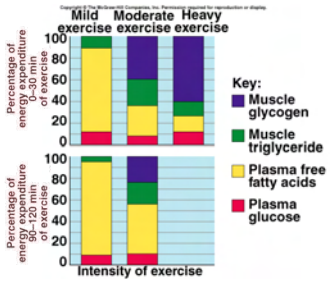
Maintenance of circulating energy substrates

- Fasting or low-carbohydrate diet



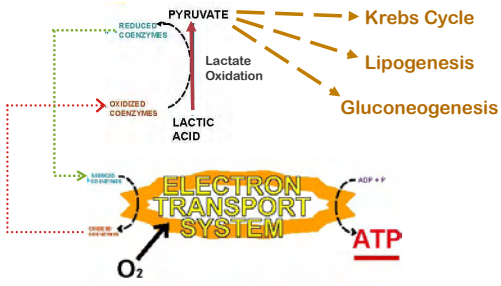
Muscle Fuel Consumption During Exercise

1. At rest: mostly from aerobic resp. of plama fatty acids.
2. Start exercise: anaerobic resp. of plasma glucose; start muscle glycogenolysis.
3. ↑ blood flow & O_2 delivery ➠ aerobic resp. of muscle triglycerides.
4. Gluconeogenesis
   ↑ plasma glucose from Cori Cycle.
5. Lipolysis in adipose tissue
   ↑ plama fatty acids for continued aerobic resp.



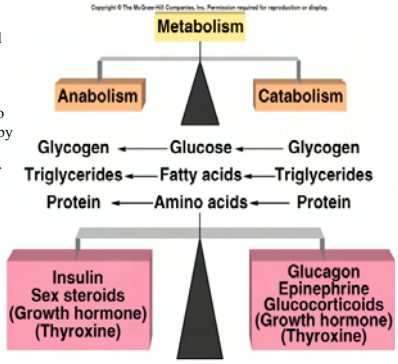
Oxygen Debt

Following anaerobic respiration, increased O_2 consumption continues to support aerobic oxidation of lactate back to pyruvate.
(Reverse of pyruvate reduction. — Uses same LDH enzyme.)

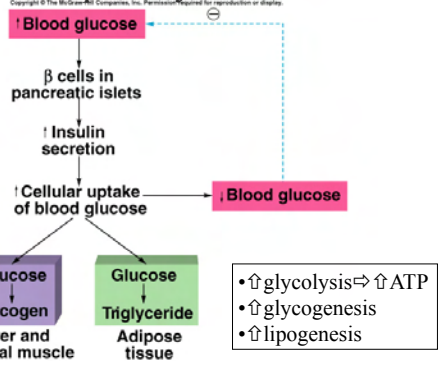


Balance Between Anabolism and Catabolism

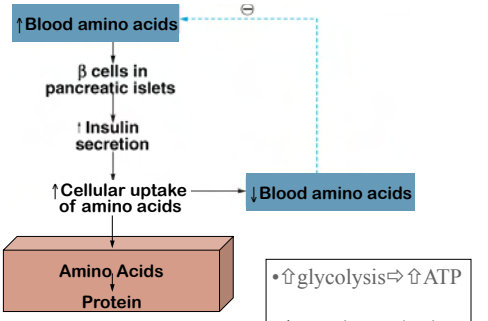
- The rate of deposit and withdrawal of energy substrates, and the conversion of one type of energy substrate into another; are regulated by hormones.
- Antagonistic effects of insulin, glucagon, GH, T_3, cortisol, and epinephrine balance anabolism and catabolism.



Insulin: the primary anabolic hormone



Insulin: the primary anabolic hormone



Regulation of Insulin Action

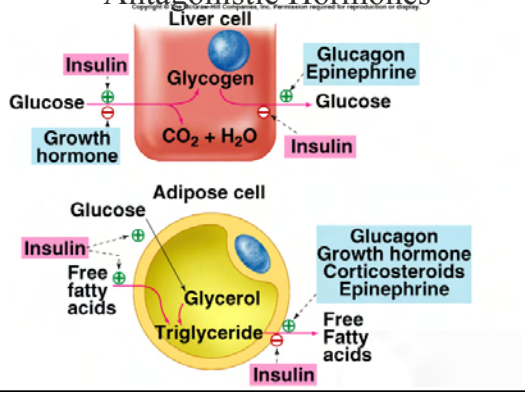
- ↑Blood glucose ⇒ ↑insulin
- ↑Blood amino acids ⇒ ↑insulin
  - If high protein/low carb diet ⇒ ↑blood amino acids/↓blood glucose; ⇒ both ↑insulin and ↑glucagon ⇒ ↓blood amino acids without ↓blood glucose
- Parasympathetic nervous system: rest-and-digest ⇒ ↑insulin
- Intestinal hormones
  - ↑Osm of chyme⇒ ↑GIP/GLP-1/CCK ⇒ ↑insulin
    - "anticipates" ↑blood glucose & amino acids
    - ↑insulin faster from ingested glucose than from intravenous glucose!
- Adipose hormones
  - Enlargement of fat cells ⇒ ↑insulin resistance factor [TNF_α] ⇒ ↓insulin sensitivity
    - Obesity aggravates diabetes
  - Atrophy of fat cells ⇒ ↓TNF_α⇒ ↑insulin sensitivity
    - Weight loss ⇒ more efficient lipogenesis ⇒ regain lost fat

The Catabolic Hormones — antagonistic to insulin action

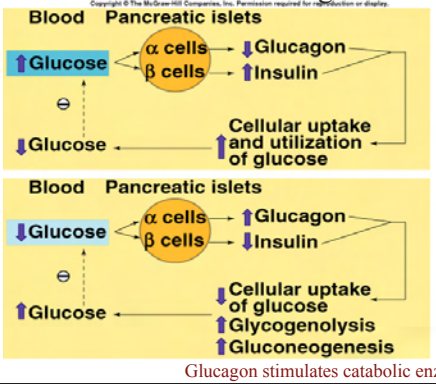
1. Glucagon: blood glucose homeostasis
2. Epinephrine: acute stress response
   - fight-or-flight
3. Cortisol [glucocorticoid]: chronic stress response
   - general adaptation syndrome [GAS]

i. Glucagon and Epinephrine bind to different receptors, but both receptors produce cAMP as a second messenger. Thus they activate the same catabolic enzymes producing the same response.
ii. Glucocorticoids bind to an intracellular DNA-binding receptor to activate genes for a long-term response.

Antagonistic Hormones

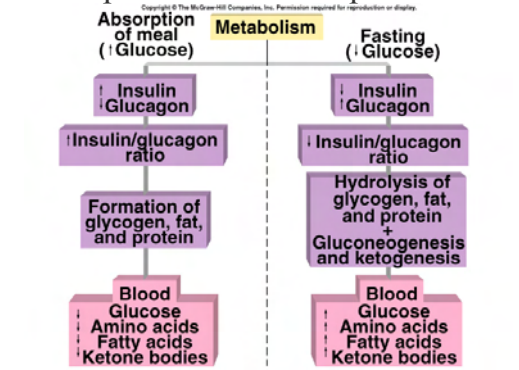


Regulation of Insulin and Glucagon Secretion

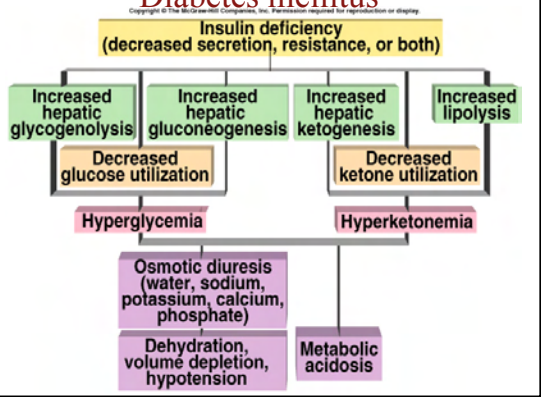


Glucagon stimulates catabolic enzymes.

Absorptive & Postabsorptive States



Diabetes mellitus



Diabetes Mellitus:

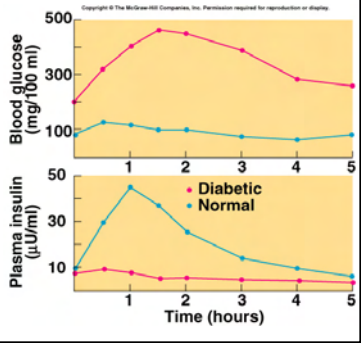
Type I: destruction of ß-islet cells ⇒ insulin deficiency
Type II: inactivation of insulin receptors ⇒ insulin resistance

Table 19.6 Comparison of Type 1 and Type 2 Diabetes Mellitus

Feature	Type 1	Type 2
Usual age at onset	Under 20 years	Over 40 years
Development of symptoms	Rapid	Slow
Percentage of diabetic population	About 10%	About 90%
Development of ketoacidosis	Common	Rare
Association with obesity	Rare	Common
Beta cells of islets (at onset of disease)	Destroyed	Not destroyed
Insulin secretion	Decreased	Normal or increased
Autoantibodies to islet cells	Present	Absent
Associated with particular MHC antigens*	Yes	Unclear
Treatment	Insulin injections	Diet and exercise; oral stimulators of insulin sensitivity

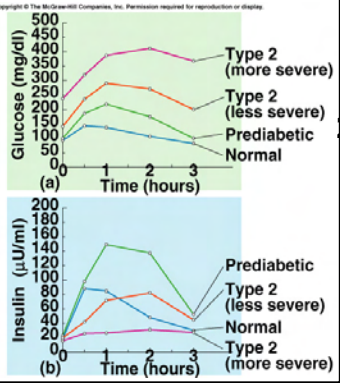
Oral Glucose Tolerance Test

- Measurement of the ability of β cells to secrete insulin.
- Ability of insulin to lower blood glucose.
- Normal person's rise in blood [glucose] after drinking solution is reversed to normal in 2 hrs.



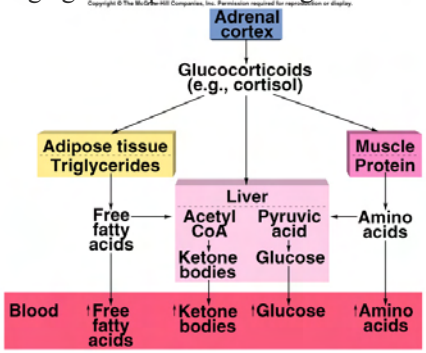
Type II Diabetes Mellitus

- Slow to develop.
- Genetic factors are significant.
- Occurs most often in people who are overweight.
- Decreased sensitivity to insulin or an insulin resistance.
  - Obesity.
- Do not usually develop ketoacidosis.
- May have high blood [insulin] or normal [insulin].



Glucocorticoids work via nuclear receptors:

change gene expression / long term effects



Synopsis of metabolic hormone action

Table 19.5 Endocrine Regulation of Metabolism

Hormone	Blood Glucose	Carbohydrate Metabolism	Protein Metabolism	Lipid Metabolism
Insulin	Decreased	↑ Glycogen formation ↓ Glycogenolysis ↓ Gluconeogenesis	↑ Protein synthesis	↑ Lipogenesis ↓ Lipolysis ↓ Ketogenesis
Glucagon	Increased	↓ Glycogen formation ↑ Glycogenolysis ↑ Gluconeogenesis	No direct effect	↑ Lipolysis ↑ Ketogenesis
Growth hormone	Increased	↑ Glycogenolysis ↑ Gluconeogenesis ↓ Glucose utilization	↑ Protein synthesis	↓ Lipogenesis ↑ Lipolysis ↑ Ketogenesis
Glucocorticoids (hydrocortisone)	Increased	↑ Glycogen formation ↑ Gluconeogenesis	↓ Protein synthesis	↓ Lipogenesis ↑ Lipolysis ↑ Ketogenesis
Epinephrine	Increased	↓ Glycogen formation ↑ Glycogenolysis ↑ Gluconeogenesis	No direct effect	↑ Lipolysis ↑ Ketogenesis
Thyroid hormones	No effect	↑ Glucose utilization	↑ Protein synthesis	No direct effect