Chapter 23
Homework Assignment
• The following problems will be due once we finish the chapter:
  4, 7, 8, 10, 12, 13
No Section 23.4

Integration of Regulation
The BIG Picture
• From Chapter 14 to 21, we have looked at various metabolic processes in both catabolic and anabolic pathways.
• For each, we talked about regulation for individual reactions and how that regulation can affect other pathways directly or indirectly.
• To fully appreciate the complexity and coolness of your ability to regulate yourself, we now want to look at metabolism from a higher perspective, the entire organism.
• We will look at how the body has developed specialized functions for specific tissues (Hello Liver!) and how hormonal signals integrate and coordinate the allocation of fuels and biosynthetic precursors.
• If you have been paying attention to early regulation information, this should be a snap.……

Chapter 23
Hormonal Regulation & Integration of Mammalian Metabolism

Integration of Regulation
Global Regulation Makes Sense

- Ample available energy (high ATP, NADH, etc)
- Lower available energy (high ADP, AMP, NAD⁺, etc)
Integration of Regulation
Examples of Reciprocal Regulation

- The fate of pyruvate is determined by the energy state of the cell, as is the efficiency of the TCA cycle:
  - Plentiful ATP sends pyruvate into gluconeogenesis for storage...
  - High ADP, AMP, or cAMP send it to TCA for oxidation for energy...
- The balance between glycolysis and gluconeogenesis is under both allosteric (intracellular) and hormonal (extracellular) control:
  - PFK1, FBPase1, pyruvate kinase and pyruvate carboxylase are all allosterically regulated by "energy" signals (ATP, AMP, etc.)
  - Low blood sugar results in glucagon release, which simultaneously shuts down glycolysis (PFK-1), while it stimulates gluconeogenesis (FBPase-1), via the control molecule F2,6BP (a nonmetabolite)
- Fatty acid oxidation and biosynthesis are reciprocally controlled by the levels of malonyl-CoA
- Also reciprocally regulated, the production and breakdown of Glycogen

The Players
Who (or What) Senses the Change

- The central nervous system (CNS) "reads" the body environment and transmits any changes to the hypothalamus
- The hypothalamus serves as the coordination center for the endocrine system, receiving, integrating and responding to messages from the CNS
Hormones

The Players

Hormones can be classified by how they get from their point of release to their target:

- **Endocrine** hormones are released into the blood and carried to their target cells (long range).
- **Paracrine** hormones are released into the extracellular space and diffuse to nearby target cells (short range).
- **Autocrine** hormones are released by and affect the same cell.

They occur as four major classes (and several minor ones):

- **Peptide hormones**: tiny "proteins" from 3-200 aa's, water-soluble, active only after cleavage of the targeting "pre-sequence" and the inactive "prohormone" (insulin, glucagon).
- **Catecholamine hormones**: derived from tyrosine, water-soluble, many are neurotransmitters (epinephrine).
- **Eicosanoids**: derived from arachidonate, minimally water-soluble, act locally (rather than through the bloodstream), mediate pain, inflammation, and smooth muscle contraction.
- **Steroid hormones**: derived from cholesterol, fat-soluble, are carried to targets by carrier proteins.

Hormones occur and function at very low concentrations – \(10^{-6}\) to \(10^{-12}\) M.

They are deliberately unstable – levels rise rapidly upon secretion, but fall fast when it stops.

The biochemical response may be very rapid, by altering existing enzyme activities, or slower, where gene expression levels change.

Can act through two receptor types: cell surface and nuclear.

Display remarkable specificity.

Operate through the "cascade" principle.

**Two Types of Hormone Receptor**

- Hormones are present at very low concentration, thus receptor affinity must be very tight.
- **Cell surface receptors** bind hormone outside – a conformational change transduces the signal to inside, resulting in a "second messenger" (e.g. cAMP).
- **Cytosolic/nuclear receptors** bind and retain hormone, migrating to the nucleus where, as a hormone-receptor complex, they alter gene transcription.
The Players
Some of our Favorites….

- **Insulin** (a 51 amino acid peptide hormone)
  - signals *satiation*: blood glucose levels are too high
- **Glucagon** (a 29 amino acid peptide hormone)
  - signals *starvation*: blood glucose levels are too low
- **Epinephrine** (an amine hormone derived from tyrosine)
  - signals *sudden stress*: “fight or flight” response

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The Players
Division of Labor – The Tissues

- Liver
  - Transports fluids and solutes to and from liver
  - Stores excess glycogen and glucose
  - Produces bile, which aids in digestion of fats
- Brain
  - Responds to changes in blood glucose levels
- Pancreas
  - Produces insulin and glucagon
  - Secretes hormones into blood stream
- Adipose tissue
  - Stores energy in form of fats
  - Converts glucose to fatty acids and glycerol
- Small intestine
  - Absorbs nutrients from digested food
  - Provides mechanical action

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The Players
The Pathways

What you should know now…

- G6P is “at the cross-roads” of carbohydrate metabolism
  1. If blood glucose is low (< 4 mM), it **must** be replenished (that hungry brain…)
  2. Otherwise, store it!
  3. Or oxidize it (but fats are better)
  4. Or convert into fats (Great.)
  5. As needed, make precursors

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The Liver
The Five-Fold Ways for Glucose

At the crossroads

1. If blood glucose is low (< 4 mM), it **must** be replenished (that hungry brain…)
2. Otherwise, store it!
3. Or oxidize it (but fats are better)
4. Or convert into fats (Great.)
5. As needed, make precursors
If you’re an AA, there must be 50 ways to leave your liver...

- Upon demand, AAs in the liver serve as a bio-synthetic pool
- If in excess, they are broken down to rid the body of ammonia
- Carbon skeletons are converted into TCA cycle intermediates
- These are either stored as glycogen or fatty acids
- Another option, oxidation to generate energy

The Liver

The Fates of Fats

- As needed, fat is the major oxidative fuel in liver
- In excess, stored as TAGs
- Exported in the blood to other tissues for storage (adipose) or fuel (serum albumin-bound) for heart and muscle
- Converted to cholesterol
- Shunted into ketone bodies (transport of acetyl groups)

The Adipocytes

Fat and Sassy

- Metabolically active storage cells for fat
- About 15% of body mass, roughly 2/3 TAGs, which aren’t made “in house”
- TAGs arrive in the blood, as VLDLs (what does that mean?) mostly from the liver and the GI tract
- TAG-lipase releases free fatty acids
- They respond quickly to hormonal stimuli:
  - **Epinephrine** stimulates TAG-lipase
  - **Insulin** suppresses its activity
- Specialized brown fat can keep you warm

The Myocytes

Lean and Mean

- Even resting, muscle accounts for 50% of our oxygen consumption
- Up to 90% during vigorous exertion – need lots of ATP!
- The fuel source depends on the energy demands
- Recall – when Glu-6-P from glycogen breakdown enters glycolysis, an extra ATP is generated (3, not 2/glucose)
- **Epinephrine** stimulates the breakdown of both liver and muscle glycogen (why are there different results?)
The Myocytes

Where Does Muscle Get Its ATP?

• 3 ATPs per glucose by fermentation from muscle glycogen
• 2 ATPs per glucose (~4.5 mM) from blood (liver)
• 1 ATP from phosphocreatine (stored at 10-30 mM – enough for several seconds of work!)
• Note: in recovery phase, both muscle glycogen and phosphocreatine are replenished
• Muscle can’t make its own glucose – why?

The Brain

Single-Minded in Its Energy Choices

• Needs ~ 120 gm/day of glucose, glucose, and glucose (except when it has to settle for ketone bodies… from body fat, sparing muscle protein)
• With a resting oxygen consumption of 20% of the body’s total – why does it need so much energy, and how is the Na⁺K⁺ transporter involved?
• But the brain has almost no glycogen, and can’t make its own glucose – why?

Aren’t You Glad You Have a Heart?

• The engine that pumps your 5-6 liters of blood around
• Mediates the metabolic interactions between all tissues
  – Providing nutrients (recycled or ingested)
  – Removing waste products
  – Carrying oxygen and removing CO₂
  – Circulating hormonal signals
• Is totally aerobic – 50% mitochondria by volume
• Uses glucose, free fatty acids, and ketone bodies to derive its energy through oxidative phosphorylation

But why is your heart red?

And you won’t be a happy camper if your glucose gets too low…

…or if you don’t get much sleep – so don’t pull an all-nighter before the next Biochemistry exam!
The Organism

...so blood glucose levels are tightly regulated!

• The pancreatic hormones glucagon and insulin have opposite effects

• Glucagon, in response to low blood glucose, stimulates in the liver
  – Glycogen breakdown
  – Gluconeogenesis

• Insulin, in response to high blood glucose stimulates in the liver
  – Glycogen synthesis
  – Glycolysis

• You should know how glucagon’s effects are mediated by protein phosphorylation.

The Organism

High Glucose or Low, Your Body Knows What To Do...

• Note the participation of regulatory kinases and phosphatases

The Organism

What happens when you’re really starving

• The body does all it can to
  – Get more glucose!
  – Feed the brain!

• Appreciate the interplay among pathways...

The Organism

Tissue Specific Responses Make Sense

• Both hormones demand "more glucose!", but the liver makes it for export, and muscle uses it for energy
Hormone-Mediated TAG Mobilization

• In adipocytes, glucagon and epinephrine stimulate cAMP formation, activating PKA.
• PKA phosphorylates perilipin (allowing access to lipid droplets) and TAG lipase.
• The results in the release of glycerol (not shown) to enter glycolysis, and fatty acids for transport to muscle, heart and kidney.
• Where they are used as fuel.

Hormone-Mediated FA Metabolism

• Protein Kinase A phosphorylates acetyl-CoA carboxylase (ACC) to inactivate it when glucagon (or epinephrine) signals low blood sugar.

Tissue-Specific Control of Glycolysis

• The tissues
  – Liver
  – Adipose tissue
  – Muscle
• The fuels
  – Carbohydrates
  – Amino acids
  – Fats

The Situation

A Triple Trio Overview: 3 Tissues, 3 Fuels, 3 Hormones

• The tissues
  – Liver
  – Adipose tissue
  – Muscle
• The hormones
  – Insulin
  – Glucagon
  – Epinephrine
• The fuels
  – Carbohydrates
  – Amino acids
  – Fats
• Plus what happens in
  – Brain
  – Blood…
The Situation
Specialized Functions of Mammalian Tissues

Insulin – I am FULL!

• Where is insulin produced?
• When is insulin produced?
• What are the first order results of insulin production?
• What are the second order results of insulin production?
• How does the signaling actually occur?

The Situation
After a nice dinner, Insulin prevails...

Eliciting a variety of metabolic effects...

<table>
<thead>
<tr>
<th>TABLE 23-3</th>
<th>Effects of Insulin on Blood Glucose: Uptake of Glucose by Cells and Storage as Triacylglycerols and Glycogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic effect</td>
<td>Target enzyme</td>
</tr>
<tr>
<td>Glucose uptake (muscle, adipose)</td>
<td>Glucose transporter (GLUT4)</td>
</tr>
<tr>
<td>Glucose uptake (liver)</td>
<td>Gluconeokinase (inverted isomerase)</td>
</tr>
<tr>
<td>Glycogen synthesis (liver, muscle)</td>
<td>Glycogen synthase</td>
</tr>
<tr>
<td>Glycogen breakdown (liver, muscle)</td>
<td>Glycogen phosphatase</td>
</tr>
<tr>
<td>Glycolysis, acetyl-CoA production (liver, muscle)</td>
<td>PK-1 (by T PK-2)</td>
</tr>
<tr>
<td>Fatty acid synthesis (liver)</td>
<td>Pyruvate dehydrogenase complex</td>
</tr>
<tr>
<td>Triacylglycerol synthesis (adipose tissue)</td>
<td>Acetyl-CoA carboxylase</td>
</tr>
<tr>
<td>Lipoprotein lipase</td>
<td></td>
</tr>
</tbody>
</table>

Chapter 23
• Where is Glucagon produced?
• When is Glucagon produced?
• What are the first order results of Glucagon production?
• What are the second order results of Glucagon production?
• How does the signaling actually occur?

• Know the 3 types of fuel reserves
• Know the time course of fasting
• Know the liver’s main job when times are hard

- The released glucagon has the desired reciprocal effects on (a) glycogen synthesis and breakdown, and (b) gluconeogenesis and glycolysis, and (c) a stimulatory effect on fatty acid mobilization from storage

**You should learn this table...!**
If you continue fasting...

The Situation

<table>
<thead>
<tr>
<th>Type of fuel</th>
<th>Weight (g)</th>
<th>Estimated survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>141 (588)</td>
<td>3</td>
</tr>
<tr>
<td>Fasting, 100 kg man</td>
<td>80</td>
<td>762 (1.14)</td>
</tr>
</tbody>
</table>

A blood profile would show...

- Declining blood glucose, compensated for by a rise in ketone bodies (to feed the brain)
- TAGs become the main fuel for muscle and liver (but not the brain)
- Protein breakdown allows glucose synthesis in liver, but declines, to “spare” essential muscle loss as less glucose is required

How does this relate to diabetes?

What is Diabetes, Anyway?

- We know the role of insulin in metabolic regulation – but for now, just think of it as a signal that there is plenty of blood glucose
- As a hormone, its job is therefore to down-regulate those processes that are redundant if there is a lot of glucose around
- In diabetes (two major classes), the functioning of insulin is compromised (HOW? Two ways!) leading to problems with metabolic regulation
Type I Diabetes mellitus

- Occurs because of a defect or deficit of pancreatic β cells
- The body doesn’t know that it has plenty of glucose (even though it does), and thus
- It thinks that it is starving (even though it isn’t).
- This causes:
  - Buildup of very high blood glucose levels (mental confusion)
  - Excessive urination and dehydration (thirst)
  - Excretion of large amounts of glucose in the urine
  - Diversion of TCA cycle intermediates to gluconeogenesis (fatigue)
  - Excessive but incomplete fatty acid oxidation (ketosis from ketone body buildup)
  - Acidosis (from serum carboxylic acid buildup)

Type II Diabetes (Non-insulin Dependent)

- Occurs because of a defect in the regulatory activity of Insulin
- Again, the body doesn’t know that it has plenty of glucose (even though it does), and thus
- It thinks that it is starving (even though it isn’t).
- This causes:
  - Buildup of very high blood glucose levels (mental confusion)
  - Excessive urination and dehydration (thirst)
  - Excretion of large amounts of glucose in the urine
  - Diversion of TCA cycle intermediates to gluconeogenesis (fatigue)
  - Excessive but incomplete fatty acid oxidation (ketosis from ketone body buildup)
  - Acidosis (from serum carboxylic acid buildup)

Untreated Diabetics Can Smell of Acetone

<table>
<thead>
<tr>
<th>Ketone Body Accumulation in Diabetic Ketosis</th>
<th>Urinary excretion (mg/24 h)</th>
<th>Blood concentration (mg/100 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>≤ 125</td>
<td>&lt; 3</td>
</tr>
<tr>
<td>Extreme ketosis (untreated diabetes)</td>
<td>5,000</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>30 – 50x normal!</td>
<td></td>
</tr>
</tbody>
</table>
The Situation
There’s Lots More to Hormonal Regulation...

But that’s for another course…