I. **Announcements**  
Guest lectures all next week!  
Quiz after lecture in Discussion on Tuesday. Q?

II. **CVD-Atherosclerosis Connections**:  
Videos + …

III. **Endocrinology Overview**  
G&H ch 75 + 76, LS, Norris, Fox…

A. Endocrine vignette: Cushing’s Syndrome LS
B. What’s an endocrine? Hormone criteria & classifications?
C. Mechanisms of hormonal action fig 75-6, 75-2, 75-7,…
D. Endocrinology focuses on the relationship between the Hypothalamus - Controller ➔ Pituitary - Subcontroller
E. Endocrine organ & hormonal overview fig 76-1, tab 76-1
F. Hypothalamus-Post & Ant Pituitary fig 76-9, 76-4, 76-2
G. Anterior pituitary hormone functions tab 75-1, Fox + LS
H. Negative feedback loops G&H p 929-30 + LS

I. Growth Hormone (GH/STH) fig 76-5, 76-6, tab 76-3  
Body builder's dream or fountain of youth? Neither!

IV. **Peripheral Endocrine Organs**  
G&H ch 77, 78, 79
A. Pancreas: insulin vs. glucagon, diabetes, G&H ch 79 + Fox
B. Thyroid: T3 & T4 G&H fig 77-2 thru fig 77-9 + DC
C. Adrenal cortices G&H fig 78-1 & 78-2 + DC
Dr. Kraig’s lecture is on Tuesday!

Yes, Sherlock! Avian & human immune systems evolved from a common reptilian ancestor!!

Whoopee! For the birds??
Wear **Red** this Friday (Feb 5\(^{th}\)!) 
Help raise awareness about Women & \(\text{❤️}\) disease

http://www.goredforwomen.org/
https://www.goredforwomen.org/about-heart-disease/facts_about_heart_disease_in_women-sub-category/statistics-at-a-glance/
7 Resolutions to Improve ❤️ Health

• Quit smoking
• Avoid 2nd –hand smoke
• Know your numbers
• Process out processed foods
• Get moving
• Get your friends & family on board
• Spread awareness

[Link to website for more information]
Veins ➔ Atria ➔ Ventricles ➔ Arteries

http://www.nhlbi.nih.gov/health/health-topics/topics/hhw/contraction.html
A typical lipoprotein

Phospholipid
Cholesterol
Triglyceride
Protein
Selected Atherosclerotic Genetic Determinants – Ultra-short List!

Genes for HDL, LDL+ receptors, Apolipoproteins Apo B-100, Apo-E, Apo-M, lipoprotein α/Lpα, homocysteine metabolism enzymes N5,N10-methylene-tetrahydrofolate reductase, cystathionine beta-synthase, Type I antithrombin, mitochondrial haplogroup A, Protein tyrosine phosphate PTPN22 C/T single nucleotide polymorphism (SNP) @ +1858, HMG COA reductase, SNPs in TNF-alpha, IL-1beta & TGF-beta1, IL-6, IL-10, CD14, TLR-4 receptors, Human Leukocyte Antigens HLA-DRB1*01, HLA-B*07 + haplotype LTA+253a-LTA+633g-C4A3-C4B1, HDL-associated paraoxonase (PON1), lysosomal acid lipase (LAL), MEF2A protein affecting artery walls…
Bruce Kottke’s Bathtub Analogy

5 forms of cholesterol:
Chylomicrons, VLDL, LDL, IDL, HDL

Bruce Kottke

β

Atherogenic

Anti-Atherogenic

β-VLDL + LDL = Faucet

Total Cholesterol Level

HDL = Drain

Bathtub

“I don’t think the total cholesterol test by itself is worth a damn.”
—Eliot Corday

Biological Artifact!?
Historical Hypotheses for Atherosclerosis Development

Ross & Glomset

- Endothelial Injury
  - Platelet Adherence
    - PDGF Release
      - Other Growth Factors
        - Cell Proliferation
          - Advanced Lesion

Steinberg & Witztum

- High Plasma LDL
  - LDL Infiltration into Intima
    - Oxidized LDL + Macrophages
      - Foam Cells
        - Fatty Streak

Other Growth Factors

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2032127/
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC295745/
How Inflammation Attacks the Heart

1. **LDL Oxidized**
   - Oxidized LDL cholesterol creates the "injury" by burrowing into the artery wall. Cigarette smoking, high blood pressure, and high blood sugar make the injury worse.

2. **Monocytes Migrate**
   - In response to the injury, the immune system sends in a team of inflammatory cells, including white blood cells called monocytes.

3. **Monocytes → Macrophages**
   - Monocytes migrate into the artery wall, where they turn into macrophages. The macrophages' job: gobble up the LDL cholesterol.

4. **Fatty Streak**
   - The macrophages, now stuffed with LDL cholesterol, form a "fatty streak" in the artery wall.

5. **Fibrous Plaque**
   - Over the decades, more cholesterol, connective and elastic tissue, calcium, and cell debris accumulate and turn the fatty streak into plaque. As the artery tries to heal itself, smooth muscle cells migrate in to cover the plaque, forming a fibrous cap around it.

6. **Cap Breakdown**
   - Macrophages kill the smooth muscle cells and release enzymes that break down the fibrous cap.

7. **Cap Rupture**
   - The cap ruptures.

8. **Clot Formation**
   - When a clot forms around the rupture, blood flow is blocked, which triggers a heart attack. (If the blocked artery feeds the brain, the blockage triggers a stroke.)

---

Coronary artery (supplies blood and oxygen to the heart muscle).
Brain Basics

Plaques and tangles. Those are the classic hallmarks of Alzheimer's disease.

The plaques are clumps of a protein fragment called beta-amyloid. The tangles are clusters of misshapen “tau” proteins that show up later in the disease.

But plaques and tangles alone don’t explain what happens to many aging brains. “Thirty percent of people over the age of 70 have elevated beta-amyloid and are cognitively normal,” says David Knopman, professor of neurology at the Mayo Clinic in Minnesota.

Scientists aren’t sure why. “The most prevalent idea is that amyloid deposits are only the initiating step often assume that it’s just Alzheimer’s,” notes Reed. “But it’s uncommon to find people with dementia who just have a single pathology. Very often, it’s mixed pathology.”

The most common other problem: damaged blood vessels in the brain.1,2

“The arteries become stiffened, narrowed, and sort of tortuous,” says Reed. “It’s much harder for the blood flow to occur normally.”

That can lead to a stroke that’s obvious, or to one that’s never noticed. “Around

In fact, some of the symptoms we think of as normal brain aging may be due to injury to the brain’s blood vessels,” he notes.

Researchers know the major threats. “The big risks for vascular brain injury are smoking, high blood pressure, and diabetes,” says Reed.

The causes of Alzheimer’s pathology are more murky. But new evidence suggests that insulin may play a role.

Here’s how to keep your brain in good working order.

1. Watch your blood pressure

“There’s a wealth of evidence that high blood pressure is a risk factor for late-life cognitive impairment,” says Knopman.
MRI Hyperintensities, Hypertension & Dementia
Middle Cerebral Artery Branches

Cerebral vasculature! Oh my!

The Window to the CV System?
Renal Vasculature

Figure 37-1 Devices for percutaneous transluminal coronary interventions. A, Coronary balloon. B, Rotational atherectomy burr (Rotablator). C, Coronary stent.
Balloon catheter approaching site of blockage

Guiding catheter in proper position

Balloon catheter advanced to middle of blockage...

balloon inflated...

then deflated; blockage reduced

BLOOD FLOW RESTORED

CABG = Coronary Artery Bypass Graft

Double?
Triple?
Quadruple?
Quintuple?

SI Fox 2013 fig 14.19
Procedures and heart attack deaths
Per 10,000 population

Sources: Thomas Thom, National Heart, Lung, and Blood Institute; Gautam Gowrisankaran, Washington University in St. Louis; Salim Yusuf, McMaster University; The INTERHEART Study
CardioWest artificial heart = $106,000!

3000 await transplants, but only 2100 donors are available...
Discussion

Comments

Q?
Cushing’s Syndrome = Hypersecretion of Cortisol: Hypothalamic (CRH), Pituitary (ACTH), or Adrenal (Cortisol)

\[ T = 0, \text{ near normal} \]

\[ T = 4 \text{ months later} \]
Endocrine/Hormone?

1. Made by gland?
2. Secreted into blood?
3. Acts on target?
Hormone/Endocrine Classifications

**Exogenous**
- Cartoon of pigs eating cucumbers
- Image of Humulin NPH package

**Endogenous**
- Diagram of hormone-receptor interaction
- Molecular structures of T3, T4, and T5 hormones
- Process of gene expression and protein synthesis

Exogenous hormones are produced outside the body, often by plants or animals. Endogenous hormones are produced internally by the body.
Steroid Hormone Structure: Cholesterol Backbone

- Cortisol
- Aldosterone
- Testosterone
- Estradiol

G&H 2011 fig 74-3; cf: fig 77-2
Lipophilic (Steroid+Thyroid) Hormone Mechanisms

- Lipophilic hormone
  - Diffusion
  - Steroid
    - Cytoplasmic receptor
    - Hormone receptor complex
  - Thyroid
    - Nuclear receptor
  - DNA
    - Hormone response element
  - mRNA
    - Nuclear envelope
    - Nuclear pore

Target cell

Extracellular fluid

Proteins

Ribosome

mRNA

G&H 2011 fig 74-6
Peptide Hormone Synthesis & Secretion

G&H 2011 fig 74-2
cAMP 2nd Messenger Mechanism

Extracellular fluid

Hormone

Cytoplasm

GTP

Adenylyl cyclase

α

β

γ

Active cAMP-dependent protein kinase

Inactive cAMP-dependent protein kinase

cAMP

ATP

Protein - PO4 + ADP

Protein + ATP

Cell’s response

G&H 2011 fig 74-7
G-Protein Coupled Receptor (blue) sits within lipid bilayer (green) to respond to hormone (yellow)

Robert Lefkowitz, MD
Duke University Cardiologist
2012 Nobel Prize in Chemistry

http://www.hhmi.org/bulletin/winter2013/features/index.html
Image by Wayne Decatur
<table>
<thead>
<tr>
<th>Hormones That Use the Adenylyl Cyclase – Cyclic AMP Second Messenger System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenocorticotropic hormone (ACTH)</td>
</tr>
<tr>
<td>Angiotensin II (ANG II, epithelial cells)</td>
</tr>
<tr>
<td>Calcitonin</td>
</tr>
<tr>
<td>Catecholamines (β receptors)</td>
</tr>
<tr>
<td>Corticotropin-releasing hormone (CRH)</td>
</tr>
<tr>
<td>Follicle-stimulating hormone (FSH)</td>
</tr>
<tr>
<td>Glucagon</td>
</tr>
<tr>
<td>Human chorionic gonadotropin (hCG)</td>
</tr>
<tr>
<td>Luteinizing hormone (LH)</td>
</tr>
<tr>
<td>Parathyroid hormone (PTH)</td>
</tr>
<tr>
<td>Secretin</td>
</tr>
<tr>
<td>Somatostatin (SS, GH RIH)</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone (TSH)</td>
</tr>
<tr>
<td>Vasopressin (ADH, VP, V₂ receptor, epithelial cells)</td>
</tr>
</tbody>
</table>
Phospholipase C 2nd Messenger Mechanism

[Diagram showing the mechanism of peptide hormone binding to a receptor, activation of a G protein, and subsequent activation of phospholipase C. The diagram illustrates the involvement of DAG, IP3, and PIP2 in the process, leading to the activation of protein kinase C and the release of Ca++.]

G&H 2011 fig 74-8
Table 74-3 Hormones That Use the Phospholipase C Second Messenger System

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin II (ANG II, vascular smooth muscle)</td>
<td></td>
</tr>
<tr>
<td>Catecholamines (α receptors)</td>
<td></td>
</tr>
<tr>
<td>Gonatotropin-releasing hormone (GnRH)</td>
<td></td>
</tr>
<tr>
<td>Growth-hormone-releasing hormone (GHRH)</td>
<td></td>
</tr>
<tr>
<td>Oxytoxin (OXY, hypothalamus production, posterior pituitary storage)</td>
<td></td>
</tr>
<tr>
<td>Thyrotropin releasing hormone TRH)</td>
<td></td>
</tr>
<tr>
<td>Vasopressin (ADH, VP, V₁ receptor, vascular smooth muscle)</td>
<td></td>
</tr>
</tbody>
</table>
Leptin: Enzyme-Linked Hormone Receptor

Homodimer receptor

Janus-kinase 2 enzyme

Signal transducer & activator of transcription proteins (STAT)

transcription of target genes

Protein synthesis

Activation of enzymes

Physiological effects

Translation

mRNA

Target gene


G&H 2011 fig 74-5
ANP = Atrial Natriuretic Polypeptide

Vasodilation

Figure 74-1 Anatomical loci of the principal endocrine glands and tissues of the body.
Lateral View Showing Relationship of the Pituitary Gland to the Hypothalamus

Third Ventricle
Pineal Body
Anterior Commissure
Mamillary Body
Optic Chiasm
Median Eminence Area

Hypothalamus

Krieger & Hughes 1980
Hypothalamus – Posterior Pituitary Nervous Connection

ADH/VP

Supraoptic nucleus

Paraventricular nucleus

Optic chiasm

Mammillary body

Hypothalamic-hypophysial tract

Anterior pituitary

Posterior pituitary

OXY

H₂O retention by kidneys

Contraction of sexual smooth m

G&H 2011 fig 75-9
Hypothalamus – Anterior Pituitary Vascular Connection

Releasing (RH)/Release-Inhibiting (RIH) Hormones

1 of 6 Trophic/Nourishing Hormones

G&H 2011 fig 75-4
NB: Ensures RH/RIH super-concentrated upon arrival @ anterior pituitary!
Infinidibulum/stalk

Long hypophyseal-portal veins

Pituitary removed!
<table>
<thead>
<tr>
<th>Gland/Tissue</th>
<th>Hormones</th>
<th>Major Functions</th>
<th>Chemical Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothalamus (Chapter 75)</td>
<td>Thyrotropin-releasing hormone (TRH)</td>
<td>Stimulates secretion of thyroid-stimulating hormone (TSH) and prolactin</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>Corticotropin-releasing hormone (CRH)</td>
<td>Causes release of adrenocorticotropic hormone (ACTH)</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>Growth hormone–releasing hormone (GHRH)</td>
<td>Causes release of growth hormone</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>Growth hormone inhibitory hormone (GHIH) (somatostatin)</td>
<td>Inhibits release of growth hormone</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>Gonadotropin-releasing hormone (GnRH)</td>
<td>Causes release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH)</td>
<td>Amine</td>
</tr>
<tr>
<td></td>
<td>Dopamine or prolactin-inhibiting factor (PIF)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior pituitary (Chapter 75)</td>
<td>Growth hormone</td>
<td>Stimulates protein synthesis and overall growth of most cells and tissues</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>TSH</td>
<td>Stimulates synthesis and secretion of thyroid hormones (thyroxine and triiodothyronine)</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>ACTH</td>
<td>Stimulates synthesis and secretion of adrenocortical hormones (cortisol, androgens, and aldosterone)</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>Prolactin</td>
<td>Promotes development of the female breasts and secretion of milk</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>FSH</td>
<td>Causes growth of follicles in the ovaries and sperm maturation in Sertoli cells of testes</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>LH</td>
<td>Stimulates testosterone synthesis in Leydig cells of testes; stimulates ovulation, formation of corpus luteum, and estrogen and progesterone synthesis in ovaries</td>
<td>Peptide</td>
</tr>
</tbody>
</table>
Hypothalamus

Hormone 1

Anterior pituitary

Hormone 2

Target endocrine gland

Hormone 3

Target cells

Negative feedback
Comparison of weight gain of a rat injected daily with growth hormone with that of a normal littermate.
Progression & Development of Acromegaly
Growth Hormone ≡ Somatotrophic Hormone
Body Builder’s Dream?
GH/STH Effects: Insulin Resistance/Type II Diabetes?

↑ Amino acid uptake & protein synthesis
↑ Lipolysis & fatty acid mobilization
↓ Glucose uptake (skeletal muscle & adipocytes)
↑ Glucose production (liver glycogenolysis)
↑ Insulin secretion
Increase GH naturally with exercise & sleep!!

Growth hormone (ng/ml plasma)

Time of day

ng/ml = nanograms per milliliter

Sleep

Strenuous exercise

cf: G&H 2011 fig 75-6
FIG. 10-4. Amino acid sequence of a mammalian proinsulin molecule. Note how the insulin molecule can be formed by cleaving this polypeptide chain at two locations to liberate the C peptide.
Diabetics have problems either here or here.
Diabetic & Normal Response to Glucose Load

Blood glucose level (mg/100 ml) vs. Hours

- **Diabetes**
- **Normal**

G&H 2000 cf: G&H 2011 fig 78-12
Glucose: Sugar in Blood

- **Normal:** 70-99 mg/dL
- **Pre-Diabetes:** 100-125 mg/dL
- **Diabetes:** ≥ 126 mg/dL
\[
\text{I}_2 + \text{HO-CH}_2-\text{CHNH}_2-\text{COOH} \rightarrow \text{Peroxidase}
\]

\text{Tyrosine}

\[
\text{HO-CH}_2-\text{CHNH}_2-\text{COOH} + \quad \text{Monoiodotyrosine}
\]

\[
\text{HO-CH}_2-\text{CHNH}_2-\text{COOH} \quad \text{Diiodotyrosine}
\]

\[
\text{Monoiodotyrosine} + \text{Diiodotyrosine} \rightarrow
\]

\[
\text{HO-}\text{O-CH}_2-\text{CHNH}_2-\text{COOH} \quad \text{3,5,3'-Triiodothyronine (T}_3\text{)}
\]

\[
\text{Diiodotyrosine} + \text{Diiodotyrosine} \rightarrow
\]

\[
\text{HO-}\text{O-CH}_2-\text{CHNH}_2-\text{COOH} \quad \text{3,3',5-Triiodothyronine (RT}_3\text{)}
\]

\[
\text{Diiodotyrosine} + \text{Diiodotyrosine} \rightarrow
\]

\[
\text{HO-}\text{O-CH}_2-\text{CHNH}_2-\text{COOH} \quad \text{Thyroxine (T}_4\text{)}
\]

G&H 2011 fig 76-3
Inadequate Iodine Promotes Goiter!

Hypothalamus (↑ increased temperature)
(Thyrotropin-releasing hormone)

Anterior pituitary

Thyroid-stimulating hormone

Inhibits

Cells

Increased metabolism

Thyroxine

Hypertrophy

Increased secretion

Thyroid

T3 + T4

TRH

TSH ≡ Thyrotropin

Iodine present?

Iodine

Figure 76-7 Regulation of thyroid secretion.
Near absence of thyroid-hormone function + myxedema

Figure 76-8. Patient with myxedema. (Courtesy of Dr. Herbert Langford.)
FIGURE 13-12
Adrenal Gland  The adrenal glands sit atop the kidney and consist of an outer zone of cells, the adrenal cortex, which produces a variety of steroid hormones, and an inner zone, the adrenal medulla. The adrenal medulla produces adrenalin and noradrenalin.
Adrenal Cortex Zones

- **Zona glomerulosa**
  - aldosterone

- **Zona fasciculata**
  - Cortisol
  - androgens

- **Zona reticularis**

- Medulla
  - (catecholamines)

- Cortex

- Magnified section

**Epi + NE during fight/flight**

G&H 2011 fig 77-1
Stress → Hypothalamus → Anterior Pituitary → Adrenal Cortices → Cortisol

- Metabolic Fuels
- Building Blocks
- Relieve Stress

CRH = ACTH-RH

Corticotropin = ACTH

Glucose, Amino Acids, Fatty Acids

SOURCE: Modified after D Chiras 2003