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

II. CVD-Atherosclerosis Connections: Lecture 9 slides ≥ # 34

III. Endocrinology Overview  G&H ch 74+75, LS, Norris, Fox...
   A. Endocrine vignette: Cushing’s Syndrome LS
   B. What’s an endocrine? Hormone criteria & classifications?
   C. Mechanisms of hormonal action fig 74-6, 74-2, 74-7,...
   D. Endocrinology focuses on the relationship between the Hypothalamus - Controller → Pituitary - Subcontroller
   E. Endocrine organ & hormonal overview fig 74-1, tab 74-1
   F. Hypothalamus-Post & Ant Pituitary fig 75-9, 75-4, 75-2
   G. Anterior pituitary hormone functions tab 75-1, Fox + LS
   H. Negative feedback loops G&H p 885 + LS
   I. Growth Hormone (GH/STH) fig 75-5, 75-6, tab 75-3
       Body builder's dream or fountain of youth? Neither!

IV. Peripheral Endocrine Organs  G&H ch 76, 77, 78
   A. Pancreas: insulin vs. glucagon, diabetes, G&H ch 78 + Fox
   B. Thyroid: T3 & T4 G&H fig 76-2 thru fig 76-9 + DC
   C. Adrenal cortices G&H fig 77-1 & 77-2 + DC
**FIGURE 9-35**

Extent of myocardial damage as a function of the size of the occluded vessel
What is the **Ultimate Cause of Death?**

1. ↓ Q, CO or Cardiac Output
2. Pulmonary damming w/edema
3. Cardiac fibrillation
4. Thromboembolism
5. Cardiac rupture

G&H 2011 p 250
Systolic Stretch Due to Necrotic Tissue

- Normal Muscle
- Nonfunctional Muscle
- Systolic Stretch
G&H fig 21-8

Mild ischemia
Non-functional

Nonfunctional
Dead fibers

Dead fibers
Fibrous tissue
Treatment Triad

NB: Last blasted resort!!

Drugs/Surgery

Exercise

Dietary Modification
300/200

KA-BOOM!

Hg
An LDL to HDL ratio greater than 5 to 1 in men or 4.5 to 1 in women

Increased risk of heart disease
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 a/Lp_a, homocysteine metabolism enzymes N5,N10-methylene-tetrahydrofolate reductase, cystathione 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

Total Cholesterol Level

HDL = Drain
HDL - VLDL + LDL = Faucet

Atherogenic

Anti-Atherogenic

β

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

Bruce Kottke
Historical Hypotheses for Atherosclerosis Development

 Ross & Glomset

 Endothelial Injury
  ↓
 Platelet Adherence
  ↓
 PDGF Release
  ↓
 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 to 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.\(^{12}\)

“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
SOURCE: Lifeline Screening, 2007
Middle Cerebral Artery Branches


...Cerebral vasculature! Oh my!
Artery of Stroke

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.
CABG = Coronary Artery Bypass Graft

Double?
Triple?
Quadruple?
Quintuple?

SI Fox 2013 fig 14.19
Procedures and heart attack deaths

Per 10,000 population

As noninvasive techniques improve, the rate for bypass surgery goes down.

SOURCES: THOMAS THOM, NATIONAL HEART, LUNG, AND BLOOD INSTITUTE; CAUTAN GOWRISANKAR, WASHINGTON UNIVERSITY IN ST. LOUIS; SALIM YUSUF, McMASTER UNIVERSITY, THE INTERHEART STUDY
Healing the Heart
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)
Endocrine/Hormone?

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

**Exogenous**

**Endogenous**

[Diagram showing exogenous and endogenous hormone classifications with images of a pig and a cow.]
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
    - Thyroid
      - Cytoplasmic receptor
      - Hormone receptor complex
      - Nuclear receptor
  - DNA
    - Hormone response element
    - mRNA
  - Target cell
    - Proteins
      - Ribosome
    - mRNA
  - Extracellular fluid
  - Nuclear envelope
  - Nuclear pore

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

CAMP

ATP

Active cAMP-dependent protein kinase

Inactive cAMP-dependent protein kinase

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 74-2 Hormones That Use the Adenylyl Cyclase – Cyclic AMP Second Messenger System

<table>
<thead>
<tr>
<th>Hormone</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>

G&H 2011
Phospholipase C 2nd Messenger Mechanism
### Table 74-3 Hormones That Use the Phospholipase C Second Messenger System

- Angiotensin II (ANG II, vascular smooth muscle)
- Catecholamines (α receptors)
- Gonadotropin-releasing hormone (GnRH)
- Growth-hormone-releasing hormone (GHRH)
- Oxytoxin (OXY, hypothalamus production, posterior pituitary storage)
- Thyrotropin releasing hormone TRH)
- Vasopressin (ADH, VP, V₁ receptor, vascular smooth muscle)
Leptin: Enzyme-Linked Hormone Receptor

Janus-kinase 2 enzyme

Signal transducer & activator of transcription proteins (STAT)

transcription of target genes

Protein synthesis


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

Figure 74-1 Anatomical loci of the principal endocrine glands and tissues of the body.

G&H 2011
Lateral View Showing Relationship of the Pituitary Gland to the Hypothalamus
Hypothalamus – Posterior Pituitary Nervous Connection

ADH/VP

Supraoptic nucleus

Paraventricular nucleus

Optic chiasm

H2O retention by kidneys

Contraction of sexual smooth m

Anterior pituitary

Posterior pituitary

Mammillary body

Hypothalamic-hypophysial tract

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

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

- Optic chiasm
- Artery
- Anterior pituitary
- Mammillary body
- Median eminence
- Primary capillary plexus
- Hypothalamic-hypophysial portal vessels
- Posterior pituitary
- Sinuses

**1 of 6 Trophic/Nourishing Hormones**

G&H 2011 fig 75-4
NB: Ensures RH/RIH super-concentrated upon arrival @ anterior pituitary!
Krieger & Hughes
1980

Long hypophyseal-portal veins

Infundibulum/stalk

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</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)</td>
<td>Inhibits release of growth hormone</td>
<td>Peptide</td>
</tr>
<tr>
<td></td>
<td>(somatostatin)</td>
<td></td>
<td></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>Inhibits release of prolactin</td>
<td></td>
</tr>
<tr>
<td>Anterior pituitary</td>
<td>Growth hormone</td>
<td>Stimulates protein synthesis and overall growth of most cells and tissues</td>
<td>Peptide</td>
</tr>
<tr>
<td>(Chapter 75)</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>
Anterior Pituitary Metabolic Functions

Thyrotropin

Growth hormone

Thyroid gland

Increases blood glucose level

Promotes secretion of insulin

Pancreas

Anterior pituitary gland

Corticotropin

Adrenal cortex

Follicle stimulating

Luteinizing

Ovary

Prolactin

Mammary gland

G&H 2011 fig 75-2
GH, a Protein Hormone (191 AA)

**Figure 75-5**

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!!

cf: G&H 2011 fig 75-6

Growth hormone (ng/ml plasma)

Time of day

0800 1200 1600 2400 0400 0800

ng/ml = nanograms per milliliter

Strenuous exercise

Sleep

cf: G&H 2011 fig 75-6
Proinsulin with C-Connecting Peptide

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.
Times of Plenty!!

NB: Diabetics have problems either here or here.

Fox 1987
Diabetic & Normal Response to Glucose Load

Blood glucose level (mg/100 ml)

Hours

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

Normal: 70-99
Pre-Diabetes: 100-125
Diabetes: ≥ 126 mg/dL
\[ I_2 + \text{Tyrosine} \rightarrow \text{Peroxidase} \]

- **Tyrosine**
- **Moniodotyrosine**
- **Diiodotyrosine**

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

- **3,5,3'-Triiodothyronine (T_3)**
- **3,3',5-Triiodothyronine (RT_3)**

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

- **Thyroxine (T_4)**

---

G&H 2011 fig 76-3
Basal metabolic rate vs. Days

Thyroxine injected
G&H 2011

Inadequate Iodine Promotes Goiter!

Figure 76-7  Regulation of thyroid secretion.

TRH

TSH ≡ Thyrotropin

Iodine present?

T₃ + T₄

Iodine

Hypothalamus

(Thyrotropin-releasing hormone)

Anterior pituitary

Thyroid-stimulating hormone

Thyroid

Hypertrophy

Increased secretion

Thyroxine

Increased metabolism

Cells

Inhibits

Iodine present?

G&H 2011
Near absence of thyroid-hormone function + myxedema
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 and androgens
- **Zona reticularis**: Medulla (catecholamines)

Epi + NE during fight/flight

Magnified section

G&H 2011 fig 77-1
Stress → Hypothalamus

CRH = ACTH-RH → Anterior Pituitary

Corticotropin = ACTH → Adrenal Cortices

Cortisol → Glucose, Amino Acids, Fatty Acids

Metabolic Fuels Building Blocks Relieve Stress

SOURCE: Modified after D Chiras 2003