I. Announcements
Presentations Group I today!
Tight time-frame + immediate feedback? Q?

II. CVD-Atherosclerosis Connections:
Lecture 10 slides ≥ # 38

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
Bruce Kottke’s Bathtub Analogy

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

β

Atherogenic

Anti-Atherogenic

Bruce Kottke

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

β - VLDL

+ = Faucet

LDL

Total Cholesterol Level

HDL = Drain

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

3. **Monocytes \( \rightarrow \) Macrophages**
   - In response to the injury, the immune system sends in a team of inflammatory cells, including white blood cells called monocytes.

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).*

*NAHL Jan/Feb 2009, p 5*
**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.
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

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)
Endocrine/Hormone?

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

**Exogenous**

- Image of pigs with cucumbers
- Image of a box of Humulin NPH
- Image of a cow and a hat

**Endogenous**

- Diagram of hormone interaction with receptor and phosphorylation
- Molecular structures of T4 and T3 hormones
Steroid Hormone Structure: Cholesterol Backbone

Cortisol

Aldosterone

Testosterone

Estradiol

G&H 2011 fig 74-3; cf: fig 77-2
Lipophilic (Steroid+Thyroid) Hormone Mechanisms
Peptide Hormone Synthesis & Secretion
cAMP 2nd Messenger Mechanism

Extracellular fluid
Hormone
Cytoplasm

GTP
Adenylyl cyclase

Active cAMP-dependent protein kinase

Inactive cAMP-dependent protein kinase

Protein - PO4 + ADP

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>Hormone</th>
<th>Action/Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenocorticotrophic hormone (ACTH)</td>
<td></td>
</tr>
<tr>
<td>Angiotensin II (ANG II, epithelial cells)</td>
<td></td>
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<tr>
<td>Calcitonin</td>
<td></td>
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<tr>
<td>Catecholamines (β receptors)</td>
<td></td>
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<tr>
<td>Corticotropin-releasing hormone (CRH)</td>
<td></td>
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<tr>
<td>Follicle-stimulating hormone (FSH)</td>
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<tr>
<td>Glucagon</td>
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<tr>
<td>Human chorionic gonadotropin (hCG)</td>
<td></td>
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<tr>
<td>Luteinizing hormone (LH)</td>
<td></td>
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<td>Parathyroid hormone (PTH)</td>
<td></td>
</tr>
<tr>
<td>Secretin</td>
<td></td>
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<tr>
<td>Somatostatin (SS, GH RIH)</td>
<td></td>
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<tr>
<td>Thyroid-stimulating hormone (TSH)</td>
<td></td>
</tr>
<tr>
<td>Vasopressin (ADH, VP, V₂ receptor, epithelial cells)</td>
<td></td>
</tr>
</tbody>
</table>

Table 74-2 Hormones That Use the Adenylyl Cyclase – Cyclic AMP Second Messenger System
Phospholipase C 2nd Messenger Mechanism

1. Peptide hormone binds to the receptor.
2. Receptor activates the G protein.
3. G protein activates Phospholipase C.
4. Phospholipase C hydrolyzes PIP2 to DAG and IP3.
5. DAG and IP3 enter the cytoplasm.
6. DAG activates protein kinase C.
7. IP3 releases Ca++ from the endoplasmic reticulum.
8. Ca++ influx and protein kinase C activation lead to an increase in protein phosphorylation (Protein → Protein – PO4).

G&H 2011 fig 74-8
<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>Gonadotropin-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>

G&H 2011
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

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

Krieger & Hughes 1980
Hypothalamus – Posterior Pituitary Nervous Connection

ADH/VP → Supraoptic nucleus → Paraventricular nucleus → OXY

Optic chiasm → Mammillary body

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

Optic chiasm

Artery

Anterior pituitary

Hypothalamic-hypophysial portal vessels

Primary capillary plexus

Median eminence

Mammillary body

Posterior pituitary

Sinuses

1 of 6 Trophic/Nourishing Hormones

G&H 2011 fig 75-4
Capillary-Venule-Capillary Circulation

NB: Ensures RH/RIH super-concentrated upon arrival @ anterior pituitary!

Krieger & Hughes 1980
Long hypophyseal-portal veins

Infundibulum/stalk

Pituitary removed!

Krieger & Hughes
1980
<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>
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<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 (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>
Anterior Pituitary Metabolic Functions

Thyrotropin

Thyroid gland

Growth hormone

Anterior pituitary gland

Corticotropin

Adrenal cortex

Follicle stimulating

Luteinizing

Ovary

Prolactin

Mammary gland

Increases blood glucose level

Promotes secretion of insulin

Pancreas

G&H 2011 fig 75-2
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)

Strenuous exercise

Time of day

ng/ml = nanograms per milliliter

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.
Times of Plenty!!

NB: Diabetics have problems either here or here.
Diabetic & Normal Response to Glucose Load

Blood glucose level (mg/100 ml)

Diabetes
Normal

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
$I_2 + HO\text{-}CH_2\text{-}CHNH_2\text{-}COOH \xrightarrow{\text{Peroxidase}}$ 

**Tyrosine**

$HO\text{-}CH_2\text{-}CHNH_2\text{-}COOH +$ 

**Monoiodotyrosine**

$HO\text{-}CH_2\text{-}CHNH_2\text{-}COOH$ 

**Diiodotyrosine**

Monoiodotyrosine + Diiodotyrosine 

$HO\text{-}O\text{-}CH_2\text{-}CHNH_2\text{-}COOH$ 

**3,5,3'-Triiodothyronine (T₃)**

Diiodotyrosine + Diiodotyrosine 

$HO\text{-}O\text{-}CH_2\text{-}CHNH_2\text{-}COOH$ 

**3,3',5-Triiodothyronine (RT₃)**

Diiodotyrosine + Diiodotyrosine 

$HO\text{-}O\text{-}CH_2\text{-}CHNH_2\text{-}COOH$ 

**Thyroxine (T₄)**

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

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 and androgens
- **Zona reticularis**: Medulla (catecholamines)

Magnified section

Epi + NE during fight/flight

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