Endocrine Diseases

The Pathological Basis of Disease
- Graduate Course CMM5001

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Outline

- Endocrine System
- Adrenal Gland
  - Anatomy & Histology
  - Steroid Hormones
  - Addison’s Disease
  - Cushing Syndrome
  - Clinical Case Presentation
Endocrine Glands

- **Endocrine glands**
  - Pineal
  - Pituitary
  - Thyroid
  - Parathyroid
  - Adrenal

- **Neuroendocrine organ**
  - Hypothalamus

- **Exocrine & endocrine**
  - Pancreas, gonads, placenta

- **Other**
  - Thymus, heart, kidney etc.
Characteristics

- **Origin**
  all glands arise from the epithelium (all three germ layers)

- **Microscopic Structure**
  cords, clumps, hollow follicles & abundant capillaries

- **Merocrine Secretion**
Endocrine Function

➢ Controls & Integrates

- Growth and development
- Maintenance of electrolyte, water & nutrient balance of blood
- Regulation of cellular metabolism & energy balance
- Mobilization of body defenses
- Reproduction
Homeostasis

Hypothalamus connects nervous with endocrine via pituitary

Hypothalamic is controlled by

- neural connections
- negative feedback from hormones
Homeostatic Imbalance

- Increases risk of disease
- Causes changes associated with aging

*control systems less efficient*

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most disease seen as a disturbance of homeostasis (**homeostatic imbalance**)

*aging* associated with progressive decrease in our ability to maintain homeostasis (**greater risk for illness**)
# The Summary

## Hypothalamic Hormone

<table>
<thead>
<tr>
<th>Hypothalamic Hormone</th>
<th>Anterior Pituitary Hormone</th>
<th>Target Organ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyrotropin-Releasing Hormone (TRH)</td>
<td>Thyroid-Stimulating Hormone (TSH)</td>
<td>Thyroid Gland</td>
</tr>
<tr>
<td>Corticotropin-Releasing Hormone (CRH)</td>
<td>Adrenocorticoidtropic Hormone (ACTH)</td>
<td>Adrenal Glands</td>
</tr>
<tr>
<td>Gonadotropin-Releasing Hormone (GnRH)</td>
<td>Folicle-Stimulating Hormone (FSH)</td>
<td>Ovaries / Testes</td>
</tr>
<tr>
<td>Prolactin-Inhibiting Hormone (PIH, Dopamine)</td>
<td></td>
<td>Breast</td>
</tr>
<tr>
<td>Growth Hormone-Releasing Hormone (GHRH)</td>
<td>Growth Hormone</td>
<td>Liver</td>
</tr>
<tr>
<td>GHIH (Somatostatin)</td>
<td></td>
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</tr>
</tbody>
</table>

## Hypothalamic Neurons Synthesize

| Hypothalamic Neurons Synthesize | GHRH, GHIH, TRH, CRH, GnRH, PIH |

## Hypophyseal Portal System

- Primary capillary plexus
- Hypophyseal portal veins
- Secondary capillary plexus

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**Hypothalamus**

**Anterior lobe of pituitary**

**Superior hypophyseal artery**

**Hypophyseal portal system**

**GH, TSH, ACTH, FSH, LH, PRL**

**Anterior lobe of pituitary**
Adrenal Gland

- **Anatomy & Histology**
- **Steroid Hormones**
- **Addison’s Disease**
- **Cushing Syndrome**
- **Clinical Case Presentations**
Adrenal Gland (Suprarenal)
Adrenal Gland - *in situ*

Described as “accessory renal tissue”, “loose flesh” (left gland) by Claudius Galen (130-201)

Depicted in 1552 by Bartholomeaus Eustachius on copper plate

Reproduced by prints in 1563
Adrenal Gland - MRI

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Adrenal Gland – Cut Surface
Adrenal Gland – Cut Surface
Adrenal Gland - Cross Section

Cross Section through Suprarenal Gland

- Capsule
- Cortex
- Medulla
Adrenal Gland – Medulla

Chromaffin cells

Catecholamines
- epinephrine
- norepinephrine

Ganglion cells
Adrenal Gland

- Anatomy & Histology
- Steroid Hormones
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Adrenal Cortex

Three layers of cortex produce three corticosteroids

- **Zona glomerulosa** - mineralocorticoids
- **Zona fasciculata** - glucocorticoids
- **Zona reticularis** - gonadocorticoids
Adrenal Gland – Low Power

- Medulla
- Zona fasciculata
- Capsule
- Zona reticularis
- Zona glomerulosa
- Periadrenal fat
Adrenal Gland - Low & High Power
## Adrenal Cortex Steroids

<table>
<thead>
<tr>
<th>Zone</th>
<th>Class</th>
<th>Representative</th>
<th>Physiologic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>glomerulosa</td>
<td>mineralocorticoids</td>
<td>aldosterone</td>
<td>salt and water homeostasis</td>
</tr>
<tr>
<td>fasiculata</td>
<td>glucocorticoids</td>
<td>cortisol</td>
<td>carbohydrate metabolism</td>
</tr>
<tr>
<td>reticularis</td>
<td>sex steroids</td>
<td>androgens &amp; estrogen</td>
<td>minimal effects</td>
</tr>
</tbody>
</table>

![Chemical structures of adrenal steroids](image)
Adrenal Steroidogenesis

Mineralocorticoid pathway

Glucocorticoid pathway

Androgen pathway

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Glucocorticoids & the Receptor

- Cortisol (hydrocortisone)
  - the majority of glucocorticoid activity in most mammals
- 90% of circulating cortisol binds to cortisol binding globulin (CBG), for transportation, also limiting the rate of metabolic clearance & the concentration fluctuation
- Enter cells by passive diffusion
Effects & Usage of Glucocorticoids

- Carbohydrate, proteins and fat metabolism
  - gluconeogenesis
  - muscle breakdown
  - lipolysis

- Anti-inflammatory and immunosuppressive

- Medical Application:
  - arthritis, dermatitis
  - autoimmune diseases
  - fear phobic
Control of Cortisol Secretion

The Pituitary & Hypothalamus

HPA Axis

Hypothalamus

CRH

Anterior Pituitary

ACTH

Adrenal Cortex

Cortisol

Dr. Gary Farr
Research Milestones

* 1552: Bartholomaeus Eustachius
  - Depicted adrenal glands on copper plate
* 1656: Thomas Wharton
  - Adrenals took something from the nerves and secreted it into the circulation
* 1936: Edward Kendall and Tadeus Reichstein
  - Isolation and synthesis of cortisone
* 1949: Edward Kendall and Philip Hench
  - Effects of cortisone and ACTH on rheumatoid arthritis
* 1950: Nobel Prize to Kendall, Reichstein & Hench
  "for their discoveries relating to the hormones of the adrenal cortex, their structure and biological effects"
Adrenal Gland

- **Anatomy & Histology**
- **Steroid Hormones**
- **Addison’s Disease**
- **Cushing Syndrome**
- **Clinical Case Presentations**
Addison's Disease

- General languor and debility
- Remarkable feebleness of the heart's action
- Peculiar change in the color of the skin

Chronic adrenocortical insufficiency
progressive destruction of 90% of cortex

extreme weakness and fatigue
unintentional weight loss
loss of appetite
darkening of the skin
low blood pressure, dizziness or fainting
craving for salt
nausea, diarrhea, vomiting
irritability, depression

Thomas Addison 1855
Primary Adrenocortical Insufficiency

- **Primary Chronic Hypocortisolism**
  - Autoimmune adrenalitis 60-70%
  - Infections (TB, AIDS) TB 90%
  - Metastatic neoplasms
  - Genetic disorder (Addison’s disease)

- **Primary Acute Hypocortisolism**
  - Stress crisis (chronic AI)
  - Rapid Steroids withdraw
  - adrenal hemorrhage
Secondary Adrenocortical Insufficiency

- **Secondary Hypocortisolism**
  - *Hypothalamic pituitary disease*
  - *Hypothalamic pituitary suppression*
Managements

- Glucocorticoid replacement
- Mineralocorticoid replacement
- Prevent adrenal crisis
- Medic alert bracelet
Prognosis

For people with Addison’s Disease

- prior to 1930, 90% died within 5 years
- from 1930, much better prognosis
- since 1950, normal life span
Adrenal Gland

- Anatomy & Histology
- Steroid Hormones
- Addison’s Disease
- Cushing Syndrome
- Clinical Case Presentations
Causes of Cushing Syndrome

PITUITARY CUSHING SYNDROME
- Tumor in anterior pituitary
- ACTH
- Cortisol
- Adrenal hyperplasia

ADRENAL CUSHING SYNDROME
- Cortisol
- Tumor
- Nodular hyperplasia

PARANEoplastIC CUSHING SYNDROME
- Lung cancer (or other nonendocrine cancer)
- ACTH
- Cortisol
- Adrenal hyperplasia

IATROGENIC CUSHING SYNDROME
- Cortisol
- Steroids
- Cushing syndrome
- Adrenal atrophy
Cushing’s Disease

- Excessive Endogenous Cortisol
  - ACTH dependent:
    * Pituitary adenoma (70-80%)
    * Small cell carcinoma
  - ACTH independent
    * Cortical tumor
- Administration of Glucocorticoids
  - The most common cause
Ectopic ACTH Secretion

- Excessive Endogenous Cortisol
  - ACTH dependent:
    * Pituitary adenoma
    * Small cell carcinoma (10%)  
  - ACTH independent
    * Cortical tumor

- Administration of Glucocorticoids
  - The most common cause
Adrenal Defects

- Excessive Endogenous Cortisol
  - ACTH dependent:
    * Pituitary adenoma
    * Small cell carcinoma
  - ACTH independent
    * Cortical tumor (10-20%)

- Administration of Glucocorticoids
  - The most common cause
Exogenous CS

- Excessive Endogenous Cortisol
  - ACTH dependent:
    * Pituitary adenoma
    * Small cell carcinoma
  - ACTH independent
    * Cortical tumor

- Administration of Glucocorticoids
  - The most common cause
Cushing Syndrome

- Excessive Endogenous Cortisol
  - ACTH dependent:
    * Pituitary adenoma (Cushing’s Disease)
    * Small cell carcinoma
  - ACTH independent
    * Cortical tumor
- Administration of Glucocorticoids
  - The most common cause

Harvey Cushing 1912
Adrenal Gland - Gr / CS
Nodular Cortical Hyperplasia

Confluent Nodules
Adrenal Gland – Low Power

Nodular Cortical Hyperplasia

Nodule
Adrenal Gland – High Power
Nodular Cortical Hyperplasia
Adrenal Gland, cortical adenoma in Cushing Syndrome - Gr / CS
Adrenal Gland, cortical adenoma - LP
Adrenal Gland - Tumor
Adrenal Gland - Mass

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MRI: in-phase sequence
Clinical Manifestations

- Moodiness, depression  75-80%
- Moon face  85%
- Facial plethora  75%
- Osteoporosis  75%
- Truncal obesity *(buffalo hump)*  85-90%
- Skin striae *(abdomen)*  50%
- Menstrual abnormalities  70%
- Weakness and fatigability  85%
- Hirsutism  75%
- Hypertension  75%
- Glucose intolerance / diabetes  70 / 20%
Screening Tests

24-hour urine free cortisol level
am & pm cortisol level
* circadian rhythm, a *hall mark*
DST (Dex Suppression Test)

- Low-dose Dex suppression
  * identify Cushing Syndrome

- High-dose Dex suppression
  * identify Cushing’s Disease
Low Dose DST

Low-dose DST
Day 1: 1 mg of Dex at 11 pm
Day 2: blood cortisol at 8 am
    0.5 mg of Dex every 6 hrs for 48 hrs
    24-hr urinary cortisol for 3 days
    * identify Cushing Syndrome

High-dose DST
Day 1: a baseline cortisol at am
    8 mg of Dex at 11 pm
Day 2: blood cortisol at 8 am
    2 mg of Dex every 6 hrs for 48 hrs.
    24-hr urinary cortisol for 3 days
    * identify Cushing's Disease
High Dose DST

**Low-dose DST**
Day 1: 1 mg of Dex at 11 pm
Day 2: blood cortisol at 8 am
   0.5 mg of Dex every 6 hrs for 48 hrs
   24-hr urinary cortisol for 3 days
* identify Cushing Syndrome

**High-dose DST**
Day 1: a baseline cortisol at am
   8 mg of Dex at 11 pm
Day 2: blood cortisol at 8 am
   2 mg of Dex every 6 hrs for 48 hrs.
   24-hr urinary cortisol for 3 days
* identify Cushing’s Disease
Determining the Etiology

- Is ACTH dependent?
- If ACTH dependent
  - * pituitary or ectopic
- Source of overproduction
  - * MRI pituitary
  - * CT adrenals, chest, abdomen
Managements

- **Surgical Treatment**
  - laparoscopic adrenalectomy

- **Medical Treatment**
  - adrenal enzyme blockers
Adrenal Gland

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Adrenal Gland - Comparison
Resources

• *Pathologic Basis of Disease*
  *Robbins & Cotran 7th Edition*

• *Basic Pathology*
  *Robins 7th Edition*

• *Handbook of Clinical Pathology*
  *2nd Edition*