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Adrenal Physiology & Steroid Pharmacology

Gary D. Hammer, M.D., Ph.D.
University of Michigan
Ann Arbor, Michigan  USA
Learning Objectives

After this lecture you should have an understanding of:

- The feedback loops regulating cortisol secretion.
- The physiologic actions of glucocorticoids (cortisol) + mineralocorticoids (aldosterone)
- The major pharmacologic uses of glucocorticoids.
- The major types of glucocorticoids.
- The major side effects of glucocorticoid therapy.
Anatomy of the adrenal glands
Histology of the Adrenal Gland

- adrenal cortex
- adrenal medulla

- z. glomerulosa
- z. fasciculata
- z. reticularis

Sources Undetermined
Adrenocortical Hormones = Steroids

GLUCOCORTICOID
Cortisol

MINERALOCORTICOID
Aldosterone

Adrenal
cortex
medulla
Steroidogenesis

Sources Undetermined
‘Roids: The Bottom Line

In the right amounts, steroids can be the body’s best friend….

or

in the wrong amounts, the body’s worst enemy….
Role of Glucocorticoids in Human Physiology

In the right amounts, glucocorticoids keep:

- Your blood pressure up (maintain cardiovascular stability).
- Your blood sugar up (maintain metabolic homeostasis).
- Your disposition sunny (maintain integrity of CNS function).
- Your temperament cool (regulate response to stress).
Adrenocortical Hormones = Steroids

GLUCOCORTICOID
Cortisol

MINERALOCORTICOID
Aldosterone

Adrenal

cortex
medulla
Regulation of ACTH Expression by CRH
Post-translational Processing of POMC in the Normal Pituitary

POMC = Pro-opiomelanocortin

MSH = Melanocyte stimulating hormone
ACTH and Steroid Biosynthesis

ACTH

CELL MEMBRANE

ADENYLATED CYCLASE

ATP

3',5' cAMP

PROTEIN KINASE

TRANSCRIPTION FACTORS

POLYSOME

transcription factors

ACTIVE

Transcription factors

CHOLESTEROL ESTER

CHOLESTEROL

STEROID BIOSYNTHESIS

G. Hammer
Circadian Rhythm of Cortisol Secretion

Plasma Cortisol µg/100 ml

- Highest in morning
- Lowest in evening

Source Undetermined
Corticosteroid Binding Globulin (CBG)

- Acidic glycoprotein MW 52,000
- Produced in liver, lung, kidney, testes
- Regulates delivery of cortisol to tissues
Secretion, Transport and Metabolism of Cortisol
Conditions that Affect Cortisol Metabolism

- **Increased Turnover:**
  - Thyroxine
  - Barbiturates
  - Phenytoin

- **Decreased Turnover:**
  - Liver disease

- **Increased Binding:**
  - Estrogens
Molecular Action of Glucocorticoids

Glucocorticoid receptors (GR) are transcriptional activators of a variety of gene products.
Metabolic Effects of Glucocorticoids

Prototypical Glucocorticoid = Cortisol

Glucocorticoids ≠ Insulin

Glucocorticoids effects are generally opposite those of insulin.
Glucocorticoids & Carbohydrate Metabolism

Glucocorticoids increase hepatic glucose output

Glucocorticoids decrease insulin sensitivity

Liver

GLUCOCORTICOIDs

Glucose

INSULIN

MUSCLE

FAT CELL

A. Kumagai
Glucocorticoid Effects on Protein Metabolism

**Insulin**
- Anabolism (storage) \(\uparrow\)
- Protein synthesis \(\uparrow\)
- Protein breakdown \(\downarrow\)
- Amino acid release \(\downarrow\)

**Glucocorticoids**
- Catabolism \(\uparrow\)
- Protein synthesis \(\downarrow\)
- Protein breakdown \(\uparrow\)
- Amino acid release \(\uparrow\)
Glucocorticoid Effects on Lipid Metabolism

**Insulin**
- ↑ Anabolism (storage)
- ↑ Lipid synthesis
- ↓ Lipolysis
- ↓ Fatty acid release

**Glucocorticoids**
- ↑ Catabolism
- ↓ Lipid synthesis
- ↑ Lipolysis
- ↑ Fatty acid release

Redistribution of fat

A. Kumagai
Glucocorticoid Effects on Inflammatory Mediators

Glucocorticoids INHIBIT inflammation.

*Inhibit:*

1) Arachidonic acid and its metabolites (prostaglandins; leukotrienes)
2) Platelet activating factor (PAF)
3) Tumor necrosis factor (TNF)
4) Interleukin-1 (IL-1)
5) Plasminogen activator
Sites of Action of Glucocorticoids in the Responses of Leukocytes During Antigenic Challenge/Inflammation
Clinical Uses of Glucocorticoids
Clinical Uses of Glucocorticoids

- Replacement therapy
- Anti-inflammatory effect
- Immunosuppression
- Androgen suppression
Steroid Therapy: Routes of Administration

- Systemic
  - Oral
  - Parenteral
- Topical
- Inhalation
Emily Janz, a 36-year old woman presents with a 3-year history of rheumatoid arthritis. The disease has been progressive with involvement of PIP joints in both hands, wrists, elbows and TM joints. Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) has not been successful.

Treatment with prednisone is begun using an alternate-day program.
A 25-year old man was walking through a field when he was stung by an insect. He developed generalized edema, dyspnea, wheezing and dizziness. He was rushed by a friend to the emergency room, where a diagnosis of anaphylactoid reaction to insect bite was made.

He received a large dose of steroids parenterally and was subsequently advised on a program to taper the steroids over the next one week.
James Allen, a 55-year old man with a history of ischemic cardiomyopathy develops increasingly severe congestive heart failure. When he becomes totally incapacitated with a life-expectancy of less than 6 mo., he is placed on the cardiac transplantation list.

Two months later, he receives a heart and is subsequently placed on an immunosuppressive “cocktail” that includes prednisone, 5 mg daily.
Glucocorticoids: Use in Androgen Suppression

A 25-year old woman comes in for evaluation of hirsutism present over the past 3 years. The hirsutism is of the androgen type and is associated with acne and irregular menses. Diagnostic studies reveal elevated serum dehydroepiandrosterone (DHEA) and testosterone levels.

She receives Dexamethasone 2.0 mg daily, for seven days and serum DHEA and testosterone levels are measured the 8th day.
Steroidogenesis

- glomerulosa
- fasciculata
- reticularis

Sources Undetermined
Adrenocortical Hormones = Steroids

GLUCOCORTICOID
Cortisol

MINERALOCORTICOID
Aldosterone

Adrenal
cortex
medulla
Effects of Mineralocorticoid on Renal Tubule

Prototypical mineralocorticoid = Aldosterone

Aldosterone increases sodium resorption and potassium and hydrogen ion excretion.
Prototype of Steroid Compounds

CORTISOL (HYDROCORTISONE)

PRENISOLONE

METHYL PREDNISOLONE

CORTISONE

PREDNISONE

DEXAMETHASONE
A. Hydrocortisone  B. Prednisone  C. 9-α-Fluorocortisol

- Double-bond in 1,2 position increases glucocorticoid activity.
- Fluoro- group in 9-a position increases mineralocorticoid activity.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Anti-Inflam. potency</th>
<th>Na-Retain. potency</th>
<th>Duration of action</th>
<th>Equivalent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>1</td>
<td>1</td>
<td>Short</td>
<td>20 mg</td>
</tr>
<tr>
<td>Prednisone</td>
<td>4</td>
<td>0.8</td>
<td>Intermediate</td>
<td>5 mg</td>
</tr>
<tr>
<td>9-α-fluorocortisone</td>
<td>10</td>
<td>125</td>
<td>Short</td>
<td>*</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>25</td>
<td>0</td>
<td>Long</td>
<td>0.75 mg</td>
</tr>
</tbody>
</table>

Glucocorticoid effects:  
Dex > Prednisone > Cortisol

Mineralocorticoids: 9-α-fluorocortisone RULES
Glucocorticoid Therapy

Side Effects

Or

“Yes, Virginia, there can be at times ‘Too Much of a Good Thing...’”
Glucocorticoid Effects on Calcium & Bone

STEROIDS → “BRITTLE BONES”

↓ Osteoblastic activity
↓ Calcium absorption from gut.
↑ PTH secretion
↑ Osteoclastic activity
A 60 yo postmenopausal woman was seen in clinic with acute onset of mid-thoracic back pain. She had complained of back pain for the past 2 years and a 2” loss of height. She had been on Prednisone, 10-15 mg daily, for the past 5 years for chronic polymyositis. Radiographic exam of the spine shows compression deformities in several vertebral bodies.
Chronic glucocorticoid therapy may “unmask” diabetes in genetically susceptible individuals.
Glucocorticoid Effects on the Central Nervous System

- Neuronal death or atrophy
- Structures affected: Hippocampus, caudate
- Neuropsychiatric symptoms:
  - Cognitive- memory, learning
  - Mood- irritability, depression
  - Sleep- insomnia

[Image of brain with labels for hippocampus and caudate]
A 42-yo woman with an exacerbation of lupus nephritis was treated with high-dose prednisone for several days. Her nephritis improved markedly; however, she became increasingly euphoric and severely agitated with paranoid ideation and confusion.

Following tapering of the steroid, she returned to her “usual self.”
Glucocorticoid Effect on Gastric Function

- ↑ Secretion of HCl and pepsin
- ↓ Protective barrier in the gastric mucosa

Glucocorticoid therapy may increase risk of ulcers.
Complications of Chronic Exogenous Corticosteroid Use

CRH → ACTH → Cortisol → Adrenal Gland

Hypothalamus

Pituitary

Adrenal Gland

G. Hammer
Complications of Chronic Exogenous Corticosteroid Use

Exogenous glucocorticoids suppress ACTH-stimulated cortisol secretion.

- Exogenous Glucocorticoid
- CRH
- ACTH
- Hypothalamus
- Pituitary
- Adrenal Gland
- Cortisol

Exogenous glucocorticoids suppress ACTH-stimulated cortisol secretion.
Complications of Chronic Exogenous Corticosteroid Use

- Exogenous Glucocorticoid

CRH

ACTH (-)

Hypothalamus

Pituitary

↑↑ Cortisol

ACTH is normally a trophic factor for the adrenals

High-dose, long-term glucocorticoid use results in adrenal atrophy from ACTH suppression

Adrenal Gland

G. Hammer
Complications of Chronic Exogenous Corticosteroid Use

Exogenous Glucocorticoid

CRH

ACTH

↑↑ Cortisol

Hypothalamus

Pituitary

Adrenal Insufficiency

Adrenal Gland

(+)

G. Hammer
Complications with Prolonged Corticosteroid Therapy

- Retarded longitudinal growth in children*
- GI Bleeding
- Osteoporosis*
- Diabetes*
- Cushing’s Syndrome
- Steroid myopathy
- Hypertension
- Cataracts
- Psychiatric
- Adrenal suppression*

*Complications to remember
Full recovery of endogenous cortisol secretion may require up to 18 months following steroid withdrawal.
Case #1

A 45-year old woman present with a two-month history of anorexia, nausea, fatigue, dizziness when assuming the upright posture, and increased pigmentation of the skin.

A diagnosis of Addison’s disease (Cortisol and Aldosterone deficiency) is confirmed by appropriate testing.

Treatment is initiated with Cortef 25 mg. (10/10/5) and 9-α fluorocortisol 0.05 mg QD.
Corticosteroid Therapy Considerations

- How serious is the underlying disorder?
- How long is therapy required?
- What is the anticipated effective dose range?
- Is patient predisposed to complications?
- Which preparation to use?
- Alternate day vs every day therapy.
- Program for withdrawal.
Things to Remember if I put you to sleep and you’re just waking up…:

Understand:

• Feedback loops regulating cortisol secretion.

• The major physiologic actions of glucocorticoids (cortisol) and mineralocorticoids (aldosterone).

• The major pharmacologic uses of glucocorticoids.

• The major types of glucocorticoids—hydrocortisone, prednisone, dexamethasone, 9-a-fluorocortisol.

• The major side effects of glucocorticoid therapy.
Adrenal Steroid Physiology & Pharmacology

Questions?
Disorders of the Adrenal Cortex

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University of Michigan
Ann Arbor, Michigan  USA

Winter 2009
Goals/Objectives

- Remember the basic principles of the HPA axis: homeostatic control of plasma cortisol and aldosterone levels

- Remember the mechanism of action of glucocorticoids and mineralocorticoids

- Understand etiology, clinical features, differential diagnosis, evaluation and therapy of 3 classic adrenal disorders:
  - Adrenal Insufficiency
  - Cushing’s Syndrome
  - Primary Hyperaldosteronism
Which Twin is Sick????
Adrenal Glands in Medical History

Andreas Vesalius (1543) Book Five of De Corporis Humani Fabrica in 1543

Bartholomäus Eustachius (1564) glandulae quae renibus incumbunt" in 1564
History of Adrenal

- **1716**: Academie des Sciences of Bordeaux poses the question "Quel est l'usage des glandes surrenales?"

- **1845**: French thesis on organs of unknown function "The adrenal cease(s) to be a secreting gland."

- **1855**: Thomas Addison monograph
  "On the constitutional and local effects of disease of the supra-renal capsules," described 10 cases marked by "anemia . . . feebleness of the heart action . . . a peculiar change of color in the skin occurring in connection with a diseased condition of the ‘suprarenal capsules’.

- **In 1945 Nobel Prize**
  Kendall, Pfiffner, and Reichenstein first tested adrenal extracts on a patient with Addison's disease, and the response was prompt and striking.
Anatomy of the adrenal glands
Histology of the Adrenal Gland

adrenal cortex

adrenal medulla

z. glomerulosa

z. fasciculata

z. reticularis

Sources Undetermined
Adrenocortical Hormones = Steroids

GLUCOCORTICOID
Cortisol

MINERALOCORTICOID
Aldosterone

Adrenal
cortex
medulla
Definition of Adrenal Insufficiency

- “inappropriately low” adrenal steroid output
  - mineralocorticoids (aldosterone)
  - glucocorticoids (cortisol)
  - sex steroids (DHEAS)
How Frequent Is Adrenal Insufficiency?

- In general, about 40-60 per million individuals have adrenal insufficiency
- 30,000-34,000 people in U.S.
Types of Adrenal Insufficiency

- PRIMARY
- SECONDARY
- TERTIARY

CRH → ACTH → Hypothalamus → Pituitary → Cortisol → Adrenal Gland

CRH: (+) → ACTH: (-) → Hypothalamus: (-) → Pituitary: (-) → Cortisol: (+) → Adrenal Gland
Adrenal Insufficiency

1º adrenal insufficiency
- hypothalamic CRH
- pituitary ACTH
- adrenal cortisol
- adrenal aldosterone

2º adrenal insufficiency
- adrenal defect
- pituitary defect
- hypothalamic defect
Adrenal Insufficiency: Age Dependent Prevalence

mean age 40 yo (range 17-72 yo)
autoimmune adrenalitis most common in all age groups

children: consider PGA or genetic defect
young men: adrenoleukodystrophy
adults and elderly: glucocorticoids for non-adrenal diseases
PRIMARY Adrenal Insufficiency

Hypothalamus
- (-) (CRH)

Pituitary
- (-) (ACTH)

Cortisol

Adrenal Gland
(+)

PRIMARY
PRIMARY Adrenal Insufficiency

- Autoimmune adrenalitis (PGA I or II) 80%
- Infections: TB (20% - historically), CMV, fungal
- Vascular: hemorrhage, thrombosis, arteritis
- In cancer patients: metastatic cancer to adrenals
- In young men: adrenoleukodystrophy

IMPORTANT: In PRIMARY adrenal insufficiency, the adrenals are destroyed, and ALDOSTERONE is affected as well.
PRIMARY Adrenal Insufficiency

Autoimmune Adrenalitis

Adrenal atrophy

Normal adrenal

Adrenal Tuberculosis

Adrenal Hemorrhage

Sources Undetermined
Metastases in the Adrenal Gland

- Lung
- Kidney
- Ovaries
- Skin
- Chest
- Leukemia
- Lymphomas
Adrenoleukodystrophy/Adrenomyeloneuropathy

**X-LINKED - ONLY IN MALES**

**PRESENTATION**
- adrenal insufficiency (childhood)
- hypergonadotropic hypogonadism (puberty)
- spastic paraparesis/demyelination-AMN(20-30 yo) vs cerebral sclerosis-ALD (childhood)

**PATHOPHYSIOLOGY:** mutation in Adrenoleukodystrophy protein(ALPD)

**ALPD function** - pexoxisomal transport protein anchors very long chain AcylCoA synthetase

**DISEASE** - build up of chol. esters w unbranched saturated long chain FAs

**TREATMENT:** Cortisol replacement
Lorenzo’s Oil helps serum level of VLCFA - but no clinical benefit in 3 yr F/U

MUST BE INCLUDED IN w/u of AI in young men and in w/u AI or hypoglycemia in infants
Autoimmune adrenalitis results in **ADRENAL INSUFFICIENCY**

Autoimmune adrenalitis (and therefore its subsequent ADRENAL INSUFFICIENCY) can be found in specific genetic syndromes, **POLYGLANDULAR AUTOIMMUNE SYNDROMES**
Adrenal Insufficiency

2 of the following
- adrenal insufficiency (<15 yo)
- hypoparathyroidism (<10yo)
- chronic mucocutaneous candidiasis (<5 yo)

PLUS OFTEN
- dental enamel hypoplasia
- keratopathy/ectodermal dystrophy

PLUS OFTEN
- chronic active HepB
- malabsorption
- choleliathiosis
- juvenile onset pernicious anemia
- alopecia/vitiligo
- primary hypogonadism
- hypothyroidism
- diabetes mellitus

PGA I (Polyglandular Autoimmune Syndrome I)
autosomal recessive disease- Iranian Jewish heritage starting in childhood

APECED (Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy)
autosomal recessive-Finnish heritage starting in childhood

AIRE (AutoImmune REgulator) Nat Gen 17: 393398; 399-403
Which Twin is Sick????
Famous Names in Endocrinology

Addison’s Disease

John F. Kennedy
Cecil Stoughton, White House

Jane Austin (1775-1817)
Cassandra Austen (c. 1810)
Addison’s Disease & History

1960 Presidential Debate
John F. Kennedy vs. Richard M. Nixon
Chicago, Ill., September 21, 1960
Adrenal Insufficiency

Autoimmune adrenalitis

- PGA II
  - usually in middle age females
  - adrenal insufficiency
  - hyothyroidism or diabetes mellitus
  - *uncertain genetic component
  - autosomal dominant more likely
  - HAL-B8 chromosome 6

- PGA III
  - hypothyroidism
  - other autoimmune disorder (NOT adrenal insufficiency)
PRIMARY Adrenal Insufficiency

SYMPTOMS

Cortisol
- Fatigue
- Weakness & Malaise
- Anorexia
- Nausea and vomiting

Aldosterone
- Dizziness

SIGNS

- Proximal muscle weakness
- Orthostatic hypotension
- HYPERPIGMENTATION--Primary AI only
- HypoNa, HyperK—Primary AI only
Hypopaldosteronism

- Hypotension
- Hyperkalemia
- Hyponatremia

- Cholesterol
- pregnenolone
- progesterone
- 3βHSD
- DOCS
- CS
- Aldosterone
- p450c11B2 - 18βHSD
- p450c11B2 - 18OH
- p450scc
- STA
- p450c21

G. Hammer
So, with aldosterone deficiency:

- **Na**⁺ decreases
- **K**⁺ increases
- **Cl**⁻ decreases
- **HCO₃⁻** decreases
- **Glu** decreases
Glucocorticoid Deficiency

1. **cholesterol**
   - sTaR
   - p450scc

2. **pregnenolone**
   - 3βHSD
   - progesterone

3. **17OH-pregnenolone**
   - 3βHSD
   - **17OH-progesterone**
   - p450c21
   - DOC
   - cortisol

Symptoms:
- **fatigue**
- **hypotension**
- **hypoglycemia**
DHEAS Deficiency

Male: fatigue, △ mood
Female: fatigue, △ mood, libidinal dysfunction

Male: fatigue, △ mood
Female: fatigue, △ mood, libidinal dysfunction
Adrenal Insufficiency: Hyperpigmentation

T. Addison
"On the constitutional and local effects of disease of the suprarenal capsules" 1855

Hyperpigmentation of palmar creases

N Engl J Med
1997;337:1666.

Source Undetermined
SECONDARY Adrenal Insufficiency

CRH → Hypothalamus (−) → Pituitary (−) → Adrenal Gland (+) → Cortisol → Pituitary → CRH

Adrenal Gland
TERTIARY Adrenal Insufficiency

Hypothalamus

Pituitary

Cortisol

Adrenal Gland
SECONDARY and TERTIARY Adrenal Insufficiency

- Vascular: Postpartum necrosis (Sheehan’s)
- Lymphocytic hypophysitis
- Infiltrative diseases: Sarcoidosis, Histiocytosis X
- Tumor compression
- Following surgery or radiation

- Long term glucocorticoid treatment
  Pharmacologic Dose = more than physiologic replacement

Hypothalamus

CRH

Pituitary

ACTH

Cortisol

Adrenal Gland

G. Hammer
SECONDARY Adrenal Insufficiency

SYMPTOMS
• Mild malaise, fatigue
• Proximal muscle weakness

SIGNS
• NO hyperpigmentation
• NO orthostatic hypotension

SIGNS & SYMPTOMS are generally milder than with primary adrenal insufficiency due to cortisol deficiency ALONE (ie: NO ALDOSTERONE DEFICIENCY)
Adrenal Insufficiency

REMEMBER TO DIFFERENCE BETWEEN PRIMARY AI AND SECONDARY AI

**PRIMARY ONLY**
- Hyperpigmentation (92-96%)
- Hyperkalemia (52-64%)
- Associated features (ie can see if PGA)
  - Vitiligo (4%)
  - Hypothyroidism (primary)
  - Hypogonadism (primary)

**SECONDARY ONLY**
- Associated features (ie can see if entire pit. involved)
  - Growth delay
  - HA
  - DI (if stalk involved)
  - Hypothyroidism (secondary)
  - Hypogonadism (secondary)
Adrenal Crisis

*hemorrhage
- thromboembolic disease
- Coagulopathy
- anticoagulant therapy
- Waterhouse-Friderichsen Syndrome
  - Neisseria meningitidis septicemia
  - Streptococcus pneumoniae,
  - Pseudomonas aeruginosa
  - Staphylococcus aureus
  - Escherichia coli
  - Haemophilus influenzae
- *drugs - increase metabolism GC
  - phenytoin, phenobarbitol, rifampin
- *drugs - decrease production GC
  - ketoconazole, AG, mitotane, metyrapone
- *withdrawal of exogenous glucocorticoids
If the diagnosis is missed, your patient will most likely die!

**Adrenal Crisis**

- **suspect in setting of:**
  - catecholamine resistant hypotension
  - hypotension with abd pain
  - must r/o adrenal hemorrhage

- **look for:**
  - hyperpigmentation/decreased pubic hair
  - hyperkalemia
  - hyponatremia
  - hypoglycemia

If the diagnosis is missed, your patient will most likely die.
SCREENING TEST:

AM CORTISOL: GOAL is to RULE OUT disease

Principle of test: Cortisol is highest in the AM allowing maximal chance of ruling out disease

- HI AM cortisol RULES OUT DISEASE
- BUT ONLY EXTREMELY LOW AM cortisol is DIAGNOSTIC

Most patients are neither EXTREMELY HI or EXTREMELY LOW and require DYNAMIC testing
DIAGNOSTIC TEST FOR PRIMARY ADRENAL INSUFFICIENCY:

ACTH STIMULATION TEST: GOAL is to RULE IN disease

Principle of test: ACTH stimulates steroidogenesis and secretion of cortisol - normal levels well documented

- Cortisol level after ACTH that is SUBNORMAL is DIAGNOSTIC of AI

- ACTH level that is EXTREMELY HI is CONSISTENT with diagnosis of PRIMARY AI but is NOT DIAGNOSTIC
The ACTH Stimulation Test

**NORMAL**

Hypothalamus → CRH → P Pituitary → ACTH → Adrenal Gland → Cortisol

**ADRENAL INSUFFICIENCY**

Hypothalamus → CRH → Pituitary → ACTH → Adrenal Gland → No or blunted increase in serum cortisol

Synthetic ACTH (Cosyntropin)
Adrenal Insufficiency Diagnostic

**DIAGNOSTIC TEST FOR SECONDARY ADRENAL INSUFFICIENCY:**

**INSULIN HYPOGLYCEMIA TEST:** GOAL is to RULE IN disease

Principle of test: Insulin results in hypoglycemia that is the strongest stimulus for activation of HPA axis at the level of CRH

- Cortisol level after IHT that is SUBNORMAL is DIAGNOSTIC of AI
- ACTH level after IHT that is SUBNORMAL is DIAGNOSTIC of SECONDARY AI
Diagnosis of Secondary/Tertiary Adrenal Insufficiency

The Insulin Tolerance Test

Insulin-induced hypoglycemia is a powerful stimulus of the HPA axis.
Therapy for Adrenal Insufficiency

(Left) Andreas Vesalius (1543) Book Five of De Corporis Humani Fabrica in 1543
(Center Images) Source Undetermined
(Right) Bartholomäus Eustachius (1564) glandulae quae renibus incumbent" in 1564
Guidelines for Management

GUIDING PRINCIPLE: The more severe the stress the more cortisol patient needs!

**Acute Therapy (significant ill or Adrenal Crisis)**
- IV fluids
- IV cortisol: HI DOSE
- glucose
- treat underlying precipitating events

**Maintenance Therapy**

**Gluocorticoids**
- **hydrocortisone ~ 15-25 mg/d**
  - titrate to a sense of well being and physical strength
  - avoid weight gain, hypertension, hyperglycemia and osteoporosis

**Mineralocorticoids**
- **fludrocortisone ~0.1 mg/d**
  - titrate to salt craving and postural hypotension
  - together with serum K and upper range renin

DHEA -

Do not wait for labs!!!!
### Guidelines for Management

**GUIDING PRINCIPLE:** The more severe the stress the more cortisol patient needs!

## Stress Dosing Glucocorticoids

<table>
<thead>
<tr>
<th>Level</th>
<th>Dosage</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal</td>
<td>no need for supplemental coverage</td>
<td></td>
</tr>
<tr>
<td></td>
<td>dental work</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mild or non-febrile illness</td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>25 mg hydrocortisone - <strong>day of procedure</strong> (or onset of fever)</td>
<td>hernia repair</td>
</tr>
<tr>
<td>Moderate</td>
<td>50-75 mg hydrocortisone - <strong>day of procedure</strong> (or onset of fever)</td>
<td>rapid taper in <strong>1-2 days</strong></td>
</tr>
<tr>
<td></td>
<td>hemicolectomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>significant febrile illness</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>100-150 mg hydrocortisone - <strong>day of procedure</strong> (or onset of fever)</td>
<td>rapid taper in <strong>1-2 days</strong></td>
</tr>
<tr>
<td></td>
<td>cardiac surgery</td>
<td></td>
</tr>
<tr>
<td>Critically ill</td>
<td>100 mg hydrocortisone i.v. bolus followed by -</td>
<td>sepsis</td>
</tr>
<tr>
<td></td>
<td>50-100 mg hydrocortisone i.v. q 6-8 hours (or 0.18 mg/kg/hr)</td>
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<tr>
<td></td>
<td>0.05 mg/d fludrocortisone until shock resolves (<strong>days to week</strong>)</td>
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Discontinuing Glucocorticoids Following Long Term Suppression

GUIDING PRINCIPLE: The more glucocorticoid and the longer treated - the greater chance of long term suppression and atrophy of HPA axis

**risk of suppression**
- Low risk: Low dose, short duration or short “bursts” of glucocorticoid
- High dose and prolonged therapy (≥ 1-4 weeks) - risk is higher

**time course for recovery**
- Larger doses for prolonged periods (months - years) - recovery can take from 9 MONTHS up to 1-2 years

**need for taper**
- taper from pharmacologic to physiologic (determined by non-adrenal disease course)
- taper from physiologic to no treatment (determined by adrenal suppression)
DHEA: What is all the fuss?

- Marker of aging
  - Pharmacologic reversal of aging process?

- Predictor of morbidity/mortality

- Works wonders in rodents
  - CNS, obesity, diabetes, immunity

- Preliminary studies in humans
DHEA
what is it??

- Synthesized by adrenals only in humans and higher primates
  - obligate precursor of all sex steroids in humans

- More synthesized than all other steroids
  - up to 25 mg/day in adults
  - major secretion of fetal adrenal

- Most secreted as sulfate (DHEA-S)
  - sulfation is ONLY in ADRENAL (NOT GONAD)

- Inactive at androgen receptor
DHEA: How Does it Work?

- **Conversion to androgens**
  - 50 mg/d raises testosterone in females

- **Intrinsic activity of DHEA-S in brain**
  - trophic effects on cultured neurons
  - GABA, NMDA, sigma receptor-channels

- **Actions of weird metabolites**
  - concept of NEUROSTEROIDS
Case for DHEAS

**DHEA + DHEAS**

major secretory products of adrenal peak in fetal life and adrenarche

Decline throughout adult life to 20-20% by 70-80 yo

Advertisement as ANTI-AGING drug

In USA : FOOD SUPPLEMENT!!!!!

classic steroid converted to testosterone peripherally neurosteroid directly binding NMDA + GABA receptors
DHEA replacement in women with adrenal insufficiency improved overall well-being and mood, specifically depression, anxiety and both sexual interest and sexual satisfaction.

DHEA in men and women with primary adrenal insufficiency improves mood and well-being, irrespective of the patient's sex.
Guidelines for DHEA Treatment in Adrenal insufficiency

Adrenal Androgens

only in pts w AI who do NOT feel “normal on replacement GC and MC”

DHEA: 25 mg po q a.m.

-may increase to 50 mg
-dictated by response and androgenic side effects
-monitor labs

DHEAS, androstendione and free test
LFTS and lipids at 4 + 12 w
Watch Out for Supplements

Steroids are lipophilic
unknown dosing
unknown purity

Images of steroid supplements comparison removed
Adrenal Excess States
Congenital Adrenal Hyperplasia

- Genetic block in biosynthetic pathway for cortisol and aldosterone result in primary adrenal insufficiency.

- Decreased feedback on hypothalamus and pituitary increase CRH and ACTH.

- Increased ACTH further stimulates adrenals and results in shunting and production of precursors.

- ACTH stimulates growth (HYPERPLASIA) of adrenals.
Steroidogenesis

Sources Undetermined
Steroidogenesis

glomerulosa

fasciculata

reticularis

gonad periphery

Sources Undetermined
Steroidogenesis

glomerulosa
fasciculata
reticularis

gonad periphery

Sources Undetermined
SEVERE P45c21 Deficiency in FEMALE results in androgen excess in utero
MILD P45c21 Deficiency in FEMALE

results in androgen excess at puberty

Sources Undetermined
Congenital Adrenal Hyperplasia

Important things to remember:

• Loss of function of enzyme in steroidogenesis pathway

• "Block" in pathway leads to shunting down alternate paths and abnormal build-up of precursors before the block.

• Severe forms lead to virulization of females

• Milder forms ("non-classical") may lead to hirsuitism and menstrual abnormalities in women.

• Block in pathway may result in adrenal insufficiency during times of stress.
Causes of hypercortisolism

- **Physiological states**
  - Pregnancy
  - Stress
  - Chronic excessive exercise
  - Malnutrition

- **Pathologic states**
  - Cushing's syndrome
  - Diabetes mellitus
  - Hyperthyroidism
  - Severe chronic disease
  - Glucocorticoid resistance
  - Psychological states
  - Anorexia nervosa
  - Panic disorder
  - Melancholic depression
  - Obsessive-compulsive disorder

- **PHARMACOLOGIC USE OF GLUCOCORTICOIDs**
Cushing was the first to ascribe to pituitary malfunction a type of obesity of the face and trunk now known as Cushing's disease, or Cushing's syndrome.

Cushing HW. The basophil adenomas of the pituitary body and their clinical manifestations (pituitary basophilism). Bulletin of the Johns Hopkins Hospital. 1932;50:137-95

His research on the pituitary body gained him an international reputation.
Cushing‘s Syndrome

- All types of Cushing’s Syndrome
  - HI CORTISOL (urine and serum)
  - Absent circadian rhythm

- Adrenal Cushing’s syndrome is autonomous and therefore has LOW ACTH
- Only ACTH-dependent Cushing’s (by definition) has HI ACTH
Cushing’s Syndrome

ACTH independent Cushing’s
- hypothalamic CRH
- pituitary ACTH
+ adrenal cortisol

ACTH dependent Cushing’s

pituitary ACTH
+ adrenal cortisol

ectopic ACTH
+ adrenal cortisol

ectopic CRH
+ adrenal cortisol

Adrenal defect

Pituitary defect

Ectopic defect

Source Undetermined
Cushing’s Syndrome

Exogenous GC administration

Endogenous hypercortisolism

ACTH-dependent

ACTH-independent

Pituitary adenoma
Ectopic ACTH (CRH) syndrome
Adrenal adenoma
Adrenal carcinoma
Cushing’s Syndrome

- ACTH-dependent Cushing’s Syndrome
  - pituitary adenoma-ACTH (60%)
  - Ectopic hormone (10%)
    - ACTH
    - CRH

All result in bilateral adrenal hyperplasia
Types of Cushing's Syndrome

Cushing's Disease ("pituitary Cushings"): hypercortisolism from a pituitary adenoma
Normal Pituitary
Pituitary Cushing’s DISEASE

normal

Cushing’s disease
Hypercortisolism from Ectopic production of ACTH or CRH by tumor.

- Bronchial carcinoid
- Oat cell carcinoma
- Thymic carcinoid
- Pheochromocytoma
- Medullary thyroid ca

(Lungs) Source Undetermined

(Other images) G. Hammer
Cushing’s Syndrome

- ACTH-independent Cushing’s Syndrome
  - adrenal cortical neoplasm
    - adenoma
    - carcinoma
  - primary adrenal hyperplasia
Adrenal Cushing’s

Hypothalamus

CRH

ACTH

(-)

Pituitary

Cortisol

(+) Adrenal

Adrenal adenoma or carcinoma

Contralateral Adrenal

Adrenal Causes:
Hypercortisolism from a adrenal adenoma or carcinoma

Because ACTH is suppressed, the rest of the adrenal and contralateral gland are atrophied.
Cushing’s Syndrome

CLINICAL MANIFESTATIONS of CORTISOL EXCESS

- increased protein catabolism = striae, bruising, delayed wound healing, muscle wasting
- increased glucose production = DM
- redistribution of fat = truncal obesity
- bone breakdown = osteoporosis
- facilitation of catechol synthesis = hypertension
- anti-inflammatory = opportunistic infections
- Inhibition of HPG axis = amenorrhea, impotence
- CNS effects (limbic/hippocampus) = depression and memory difficulties

ACTH dependent ONLY
- Pigmentation (MSH)

ACTH dependent or Mixed Adrenal
- Androgen excess
  - Terminal hair hirsuitism
  - Acne
  - Irregular menses
  - balding
Cushing’s Syndrome

- Physical examination:
  - adiposity
  - moon face, plethora
  - (pseudo-) gynecomastia
  - striae
Redistribution of Fat in Glucocorticoid Excess

Central obesity seen in Cushing’s Syndrome (Glucocorticoid Excess)
Cushing’s Syndrome

- Acanthosis nigricans
- Purple striae
Cushing’s Syndrome

- Myopathy
  - Proximal muscle wasting
- Osteoporosis
- Oligo-Amenorrhea/Impotence
- Psychiatric Symptoms
  - depression, mania (Steroid psychoses)
ACTH-Dependent Pituitary Cushing's Disease

- Symptoms due to pituitary mass
  - bitemporal hemianopsia
  - pituitary insufficiency
  - HA

Source Undetermined
Cushing’s Syndrome: Diagnosis

- **Diagnosis**
  - First diagnose CORTISOL EXCESS
    - elevated 24 hr urine cortisol < 100 mg/24 hr
  - Then diagnose PATHOLOGIC CORTISOL EXCESS
    - r/o physiologic causes which suppress normally with low-dose DEX (Cort < 2 mg/dl)
  - ACTH dependent or NOT
    - Measure ACTH level
      - if DETECTABLE > 9 pg/ml - must be ACTH dependent
      - (if NOT DETECTABLE < 9 pg/ml - must be ACTH independent)
Cushing’s Syndrome: Low-dose DEX suppression

Low-dose Dex will suppress ACTH secretion in:
- normal patients
- physiologic hypercortisolism (stress)

Low-dose Dex will NOT suppress ACTH secretion in:
- ACTH dependent Cushing’s syndrome (pituitary adenoma or ectopic ACTH producing tumors)
- ACTH independent Cushing’s syndrome (adrenal tumors)
ACTH-DEPENDENT Cushing’s Syndrome

Is it pituitary or ectopic????

- High dose DEX SUPPRESSION TEST
  - Pituitary Cushing’s may suppress to high dose DEX
  - Ectopic NEVER suppresses to high dose DEX

- Inferior Petrosal sinus Sampling
  - Pituitary Cushing’s - find HI ACTH near pituitary and low in the periphery
  - Ectopic Cushing’s - find HI ACTH in the periphery and low near pituitary

- IMAGE the pituitary
Cushing’s Syndrome: High-dose DEX suppression

High-dose Dex will suppress ACTH secretion in:
- ACTH dependent Cushing’s syndrome (pituitary adenoma)

High-dose Dex will NOT suppress ACTH secretion in:
- ACTH dependent Cushing’s syndrome (ectopic tumors)

Most pituitary adenomas that secrete ACTH can still be inhibited by REALLY REALLY HIGH glucocorticoids (i.e., more that produced their diseased HPA axis).

Therefore, high-dose dexamethasone will NOT suppress ACTH from ectopic tumors.

G. Hammer
Most ectopic ACTH-producing tumors secrete ACTH independently from regulation by glucocorticoids. Therefore, high-dose dexamethasone will NOT suppress ACTH from ectopic tumors.

High-dose Dex will suppress ACTH secretion in:
- ACTH dependent Cushing’s syndrome (pituitary adenoma)

High-dose Dex will NOT suppress ACTH secretion in:
- ACTH dependent Cushing’s syndrome (ectopic tumors)
Imaging in Cushing Syndrome

- **ADRENAL CT findings**
  - adrenals small = ?
  - one adrenal large and 1 small = ?
  - Both adrenals large = ?

- **Pit MRI findings**
  - Mass or no mass
    (some pituitary corticotrope tumors are too small to be seen on MRI)

- **Search for ectopic ACTH or CRH producing tumor**
  - Lung: Bronchial Carcinoid and SCC 50%
  - Thymic Carcinoid (epithelial thymoma) 10%
  - Pancreatic Islet Cell Tumor 10%
  - Pleochromocytoma 10%
  - Abdominal Carcinoids 5%
  - Medullary Thyroid Carcinoma 5%
Cushing’s Syndrome Treatment

- adrenal adenoma
  - resection
  - cortisol replacement
  - if not curative
    - XRT
    - bilateral adrenalectomy
    - adrenolytic therapy
      - mitotane
      - ketoconazole

- pituitary adenoma
  - transphenoidal resection (TSR)
  - cortisol replacement
  - if not curative
    - XRT
    - bilateral adrenalectomy
    - adrenolytic therapy
      - mitotane
      - ketoconazole

- Ectopic ACTH or CRH
  - Find the tumor!!!!!!!!!!!
  - if not curative
    - bilateral adrenalectomy
    - adrenolytic therapy
      - mitotane
      - ketoconazole
Cushing’s Syndrome

before treatment

after treatment

Sources Undetermined
Cushing's Syndrome

ferrets
dogs
horses
Conn JW. Primary aldosteronism, a new clinical syndrome. J Lab Clin Med. 1955;45:3-17
Primary Aldosteronism

- Clinical Presentation
  - Manifestations of HYPOKALEMIA and HTN
    - LOW K
      - neuromuscular
        - paresthesias
        - weakness
        - tetany
    - Renal
      - Polyuria
    - Carbohydrate
      - abnormal GTT
    - HTN usually not malignant
      - early in disease may have HTN with NORMAL K
Causes of Hyperaldosteronism

Definition: syndrome of inappropriate excessive secretion of aldosterone by adrenal gland

An increase in aldosterone ACTION can theoretically result from ANY defect in RAA pathway

- LOW IVV (real or perceived by kidney in renal artery stenosis)
- JGA renin tumor
- ACE polymorphisms
- overproduction of All by renal tumors
- ADRENAL overproduction of ALDO
- constitutive MR or Na channel
Primary Aldosteronism

primary hyperaldosteronism  (HI ALDO/LOW RENIN)
- ZG Aldo tumor  70%
- ZG Aldo hyperplasia  30%

rare/rare/rare
- Congenital adrenal hyperplasia  <1%
  (p450c11ß, p450c17)
- ACE polymorphisms  <1%
- All overproduction  <1%

secondary hyperaldosteronism  (HI ALDO/HI RENIN)
- JGA renin tumor  <1%
- renal artery stenosis  <1%

apparent mineralocorticoid excess  (LOW ALDO/LOW RENIN)  (downstream of ALDO)
- constitutively active MR  <1%
- Na/K/H channel  <1%
- licorice  <1%
Primary Aldosteronism

Consider in patients with:

- New HTN
- HTN with LOW K

EVEN THOUGH it only accounts for 0.5% of all HTN

BECAUSE - IF YOU NEVER THINK OF THIS-----YOU WILL NEVER FIND IT!!!
Primary Aldosteronism

- **Work-Up**
  - R/O other causes of LOW K
    - LOW intake (diet)
    - HI output
      - N/V/D
      - Diuretic use with loops + thiazides
  - 24 h Urine ALDO
    - If LOW- pt does not have PRIMARY ALDO
    - IF HI (>10 ug/day)
      - check RENIN level (suppressed < 1 ng/ml/hr)
        - If RENIN HI ----JGA renin tumor or RAS
        - If RENIN LOW---- PRIMARY HYPERALDO

- IF NECESSARY (ie AMBIGUOUS) Volume expand to see if can suppress RAA
  - If can suppress --essential HTN
Adrenal Zona Glomerulosa Adenoma
Primary Aldosteronism

- IMAGING and TREATMENT
  - CT scan
    - Adenoma
      - unilateral ADX
    - NO adenoma
      - selective venous cath to measure ALDO rt vs lt
        - If unilateral elevation-small adenoma
        - If no lateralization-bilateral hyperplasia
    - Medical trt with spironolactone or amiloride
    - bilateral ADX
Adrenocortical Carcinoma

- Larger adrenal mass
  - High probability NOT benign if >5 cm in diameter
  - Development of Cushingoid features usually very rapid (several months rather than years)
  - Often associated with elevated DHEA-sulfate and virulization
Endocrine disorders are NOT diagnosed by means of imagining studies. Biochemical confirmation must come first before imagining is performed.
“Even our destiny is determined by our endocrine glands.”

Albert Einstein
Additional Source Information

for more information see: http://open.umich.edu/wiki/CitationPolicy

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