ENDOCRINOLOGY EXCERPTS

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

Adrenal Pathophysiology and Pharmacology

Part I of III

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

Positive CRH Releasing Factors
- Stress (via reticular formation): severe hypoglycemia; anxiety/fear (via Amygdaloid nucleus); increased ACh and serotonin; pain (via ascending pathways); circadian rhythms (via suprachiasmatic nucleus).

Negative CRH Releasing Factors
- Increased GABA
- Increased enkephalins
- Increased opioids

CRH via cAMP stimulates synthesis of POMC (Pro-opiomelanocortin) which splits into ACTH, MSH and endorphin.

STEROID BIOSYNTHETIC PATHWAYS IN ADRENAL GLAND

Cholesterol \(\rightarrow\) Desmolase \(\rightarrow\) Pregnenolone

Hydroxysteroid Dehydrogenase

Progesterone \(\rightarrow\) 17-hydroxylase \(\rightarrow\) 17-OH Progesterone

Androstenedione

Deoxytocorticosterone \(\rightarrow\) Deoxycortisol

11-hydroxylase

Corticosterone \(\rightarrow\) Aldosterone

17-hydroxylase

Deoxycorticosterone \(\rightarrow\) Deoxycortisol

17-OH Progesterone

Testosterone

Estradiol

Jahan Eftekari, Northwestern Medical Review, 2010
ACTH Effects on the Adrenal Gland
- ACTH acts on the adrenal cortex and causes hypertrophy of zona fasciculata and zona reticularis—sites of cortisol and androgen precursor’s synthesis.
- ACTH up-regulates ACTH receptors
- Increases cholesterol uptake via HDL/LDL receptors (increases adrenal free cytoplasmic cholesterol levels).
- Increases desmolase activity. Hence, increases cholesterol conversion to pregnenolone.
- Increases cytochrome P450 enzymes and causes an increased conversion of pregnenolone to cortisol and aldosterone.

Steroids
- Zona glomerulosa lacks 17 α-hydroxylase, and it is the only zone that contains aldosterone synthase
- Zona glomerulosa has no enzymatic pathway to synthesize cortisol, DHEA (dehydroepiandrosterone) and androstenedione
- Male and female gonads lack 11 and 21 α-hydroxylase. Thus, gonads cannot produce corticosterone, cortisol or aldosterone.
- DHEA and androstenedione can be converted to testosterone in gonads.
- Adrenal’s testosterone synthesis is insignificant
- Gonads only possess enzymes that are required for androgens (e.g. testosterone) and estrogen synthesis.

Zona Glomerulosa makes the hormones that act on the glomeruli—e.g. aldosterone!

Fasting drops blood sugar. Hence, zona fasciculata for blood-sugar-raising hormone, that is, cortisol!

In humans, sex starts with retinal stimulation! Hence, zona reticulosa for sex hormones!

Cortisol is the stress hormone. Its blood level rises just before waking up, and just before getting ready to confront everyday’s challenges!

Cortisol
- Binds to plasma proteins—Transcortin and albumin
- Plasma levels are high immediately prior to waking and lowest around mid-night
- Produced in Zona Fasciculata and Reticularis
- Release is stimulated by ACTH and epinephrine
- Signal transduction is via nuclear receptors (gene transcription).

Metabolic Effects of Cortisol
- Prepares body for stress by metabolizing fuels
- Catabolism of muscle protein to provide substrate for liver gluconeogenesis.
- Increases plasma glucose

Cortisol Effects on the Liver
- Increases amino acid (AA) uptake and gluconeogenesis. Increases glucose export (glucagon like!)
- Increases glycogen synthesis (insulin like!)
- Over all it has anabolic effect

Cortisol Effects on the Muscle
- Decreases glucose uptake, increases proteolysis and increases AA export (amino acids go to liver), decreases protein synthesis.
- Glucagon-like effect
- Catabolic role
Cortisol and the Adipose Tissues
- Decreases glucose uptake, increases lipolysis, increases free fatty acid (FFA) export (FFAs go to the liver and they are converted to acetylcholine, the precursor of ketone bodies) and increases plasma glycerol level.
- Catabolic role

Anti-Inflammatory Roles of Cortisol
- Strong inhibition of the entire inflammatory response
- Prevents transplant rejection
- Decreases neutrophil recruitment, and prostaglandin and leukotriene synthesis by inhibiting phospholipase A2
- Decreases T-cell count, and inhibits production of interleukin-2.
- Decreases capillary permeability, and inhibits histamine release from mast cells.
- Shrinks the lymphoid mass and drops the lymphocytic count. Hence, it is desirable in treatment of lymphomas.

Note: Patients with Cushing’s syndrome present with shrunken lymphoid mass. Prednisone (a glucocorticosteroid) is one of the commonly used drugs in treatment of Hodgkin’s lymphoma.

Potency of Various Steroids
- All steroids have both mineralo and glucocorticoid effects.
- Cortisol and cortisone have equal mineralo and glucocorticoid effects.
- Dexamethasone by far is the most potent glucocorticosteroid, and fluocortisone is the most selective mineralocorticoid.

Fluocortisone is Fluidocortisone!

Glucocorticoid (Cortisol) Side Effects
- Hypokalemic alkalosis
- Glycosuria
- Increased susceptibility to infection
- Peptic ulcers
- Myopathy
- Osteoporosis
- Cushing’s symptoms and hypertension
- ACTH suppression

2. The management of myasthenia gravis requires corticosteroid therapy. However, at times the patients are presented with worsening symptoms; why?

1. What non-steroid hormone has intra-nuclear transduction?

Please refer to chapter on eicosanoids and NSAIDs for more information on the above diagram.

Anti-steroids
- Aminoglutethimide
  - Inhibits P-450. In turn inhibits desmolase activity
  - It is used in (1) Cushing’s treatment and (2) to reduce estrogen level in breast cancer
- Ketoconazole: Desmolase inhibitor and antifungal. Reduces all steroids.
- Spironolactone: Diuretic used for treatment of hypertension and primary hyperaldosteronism.

Note: Aromatase converts androgens to estrogens and promotes estrogen formation.
Duration of Action of Glucocorticoids

<table>
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<tr>
<th>Short Acting Glucocorticoids</th>
<th>Duration of action: 8-12 hours</th>
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<td>Hydrocortisone and cortisone</td>
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<tr>
<th>Intermediate Acting Glucocorticoids</th>
<th>18 - 36 hours</th>
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<td>Prednisone, prednisolone, triamcinolone</td>
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<table>
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<tr>
<th>Long Acting Glucocorticoids</th>
<th>1 - 3 days hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betamethasone, dexamethasone, paramethasone</td>
<td></td>
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</tbody>
</table>

Potency of Various Steroids
- All steroids have both mineralocorticoid and glucocorticoid effects
- Cortisol has equal mineralo and glucocorticoid effects
- Dexamethasone is by far the most potent glucocorticoid, and fludrocortisone is the most selective mineralocorticoid.

3. Three steroids with noticeable mineral effects:

A __________________________
F __________________________
D __________________________

4. What are the top two side effects of mineralocorticoids?

_____________________________________
_____________________________________

5. Cushing’s and Addison’s disease have opposing effects on the level of eosinophils. Which one causes eosinophilia and which one causes eosinopenia?

_____________________________________

ADRENOCORTICAL DISEASES (PART I)

Case for the Next 3 Questions

A 17-year-old girl is being admitted to the OB/GY clinic for the complaint of amenorrhea. Examination reveals lack of development of secondary sex characteristics. Blood pressure is 180/110; result of funduscopy is normal; she has no lymphadenopathy or hepatosplenomegaly. Blood analysis indicates hypokalemia, hypernatremia, metabolic alkalosis, and suppressed renin. Urinary analysis confirms a high level of urinary gonadotropins.

6. Suppression of rennin in this patient is due to which of the following options?

(A) Negative aldosterone feedback
(B) Insensitivity of kidney to aldosterone
(C) Lack of adrenal development
(D) Lack of ACTH
(E) Insensitivity of JG cells

7. Which of the following hormones is expected to increase in this patient’s plasma?

(A) Deoxycortisol and cortisol
(B) Deoxycorticosterone and corticosterone
(C) Progesterone and deoxycortisol
(D) Androstenedione and corticosterone
(E) Aldosterone and cortisol

9. Which of the following deficiencies is the most likely cause of this patient’s problems?

(A) 11-hydroxylase
(B) 21-hydroxylase
(C) 17-hydroxylase
(D) Desmolase
(E) Hydroxysteroid dehydrogenase

Hydroxysteroid Dehydrogenase Deficiency
- Congenital adrenal hyperplasia
- Lack of steroids removes negative feedback over the pituitary and ACTH production stays uninhibited. Constant ACTH production causes hypertrophy of the adrenal cortex.
- Pregnenolone is not converted to all other subsequent steroids.
- All pathways; mineralocorticoids, corticosteroids and glucocorticoids are affected.
- The second most fatal steroid biosynthetic deficiency.
- Early death

Note: Desmolase deficiency is by far the most fatal steroid deficiency. Many patients die in early infancy.

17-Hydroxylase Deficiency
- Autosomal recessive defect
- Congenital adrenal hyperplasia
- Conversion of progesterone to subsequent sex hormones and glucocorticoids is affected.
- Female characteristics are preserved, but secondary developments are affected.
- Pathways are shunted to further mineralocorticoids production.
- Increased mineralocorticoids leads to sodium and water retention and hypertension
- Due to lack of androgens (i.e. development of zona reticularis) female phenotype is exaggerated. For instance males have shrunken external genitalia.

21-Hydroxylase Deficiency
- The most common deficiency.
- Congenital adrenal hyperplasia
- Deficiency of both mineralocorticoids and glucocorticoids.
- Due to lack of feedback over pituitary there is a high level of ACTH in the plasma.
- Pathways are shunted to sex steroid production
- There is a high level of androgens
- Adrenal virilism. Male phenotype exaggerated.
- Female patients present with masculine characteristics such as enlarged clitoris
- Salt loss and hypotension

11-Hydroxylase Deficiency
- Autosomal recessive deficiency that causes deficiency of corticosterone, aldosterone and cortisol.
- Increased level deoxycorticosterone leads to salt and fluid retention, and hypertension.
- Hypertension is due to accumulation of deoxycorticosterone that has a very strong mineralocorticoids effect.
- Like 21-α-hydroxylase leads to adrenal virilism (AKA. adrenogenital syndrome) and masculinization. More common in males.
- Less common than 21-hydroxylase deficiency
Androstenedione
Cholesterol
Progesterone
17-OH Progesterone
Testosterone
Estradiol
17-hydroxylase
Desmolase
Pregnenolone
11-hydroxylase deficiency
Zonal Glomerulosa  Zona Fasciculata  Zona Reticularis

Blackjack Makes You Happy (Hypotensive!)

About the Black Jack Mnemonic!
The top three tested congenital steroid deficiencies are 21, 17 and 11-hydroxylase deficiencies. All three conditions are associated with hypertrophy of the adrenals due to high levels of ACTH (lack of suppression).

The highest number among the three is 21. This number happens to be the highest and mostly desired number in black jack as well. It is the only number that if you get it in the game you would be happy (hypotensive). The other two numbers in the game, quite often will make the players hypertensive; especially if the dealer shows a 10 or 9 up!

In short, 11 and 17 hydroxylase deficiencies are associated with hypertension whereas 21-hydroxylase is associated with hypotension.

Important Note: Hypertension is the top most important distinguishing characteristic between 11 and 21-hydroxylase deficiencies. At the same time, the most common deficiency among all congenital adrenal deficiencies is the 21-hydroxylase deficiency. But the most commonly remembered one on the history of the exam (i.e. the most commonly tested one) has been the 17-hydroxylase deficiency!

Drill and Self-Study Questions

9. In the following two pedigree diagrams the solid squares and circles indicate genetically affected individuals. Which one of them is most likely affected with 17-hydroxylase deficiency?

A. A
B. B
C. C
D. A and B
E. B, C and D

10. A newborn presents with ambiguous external genitalia. The genitalia seem more like an enraged clitoris than penis. There is a scrotum-like structure that has resulted from labial fusion. Ultrasound confirms normal ovarian development and presence of bilaterally enlarged adrenal glands. Karyotyping indicates a 46 XX karyotype. Of the following conditions which one is the most likely cause of these findings?

A. 11 alpha-hydroxylase deficiency
B. 17 alpha-hydroxylase deficiency
C. 21 alpha-hydroxylase deficiency
D. Desmolase deficiency
E. Turner’s syndrome
11. At age 10 the patient is admitted to the hospital for complete physical evaluation. Which of the following lab findings would be the most remarkable finding in the patient?

A. High level of cortisol  
B. Low level of ketosteroids  
C. Low blood pressure  
D. Low level of rennin  
E. Low level of ACTH

12. Addison’s disease causes eosinophilia and darkened mucosa. What are the major causes of eosinophilia?

13. Wegener’s Granulomatosis also causes eosinophilia. What are some of the main characteristics of this disease?

14. What is the name of the condition that is associated with eosinophilia, fibrotic thickening of heart valves and restrictive cardiomyopathy?

**Answers**

1. The only other hormone other than steroids with intracellular transduction is thyroxine.

2. Steroid-induced myopathy is the problem associated with myasthenia treatment. Despite this finding corticosteroids are the mainline medications.

   **Note:** MG is an autoimmune disease and often is associated with thymoma.

3. The 3 steroids that have mineralocorticoid effect are: aldosterone, fludrocortisone and deoxycorticosterone.

4. Side effects of mineralocorticoids are hypokalemia and congestive heart failure (CHF) due to volume overload!

5. Cushing’s (hypocortisolism) depresses immune functions and causes eosinopenia. Addison (lack of steroids) does the opposite (eosinophilia).

6. Option [A] is correct.

7. Option [B] is correct.

8. Option [C] is correct.

9. The correct answer is [A]. 11, 21 and 17 alpha-hydroxylase deficiencies are all autosomal recessive conditions. Only the pedigree I is illustrative of autosomal recessive conditions. Hence, the female person marked “A” is the one who is affected with the deficiency.

   Note that the pedigree II is illustrative of dominant genetic conditions. The person “B” in this pedigree has randomly acquired a mutated dominant gene.

10. The correct answer is [C]. Patients with 21 hydroxylase deficiency characteristically are hypertensive as a result of lack of development of zona glomerulosa or production of mineralo-corticoids. Note that as result of low aldosterone and blood volume and pressure, the rennin level is going to be high in these patients. Also as a result of lack of cortisol, the level of ACTH is also high in the patient. Also note that ketosteroids are the byproducts of metabolism of androgens such as testosterone or dihydrotestosterone. The patients with 21-hydroxylase deficiency have a very high level of androgens that raises the levels of ketosteroids in their serum and urine.

11. Option [C] is the correct answer. The karyotype of 46XX indicates that the patient has acquired congenital adrenal virilism (masculinization) as a result of too much androgens or over activity of zona reticularis. Note, that the option “A” may also cause the very same symptoms. But by far 21-hydroxylase deficiency is the most common cause of congenital adrenal hyperplasia, and between the two options it seems to be the more probable answer.

12. “NAACP “ is the mnemonic for major causes of eosinophilia!
Causes of Eosinophilia

- Neoplasms (Hodgkin’s & leukemia)
- Allergy (rhinitis, asthma & eczema)
- Addison’s
- Collagen diseases (Wegener’s granulomatosis, arteritis nodosa, pemphigus vulgaris)
- Parasites (pulmonary eosinophilia)

Note: Eosinophilia is often associated with skin hypersensitivity reactions that color the skin. In Addison's, ACTH is high and as such MSH is high.

13. About Wegener’s Granulomatosis...
   (Please review the chapter on vascular pathology for more information)
   - Granulomatous inflammation of arterioles, capillaries and venules.
   - Triad of Wegener’s: (1) Focal lung vasculitis; (2) Necrotizing pulmonary granuloma; and (3) Necrotizing glomerulitis.
   - Fifth decade onset. 80% of patients die in year one if not treated
   - Immunosuppression (with cyclophosphamide) has saved more than 90% of the victims.
   - C-ANCA (antineutrophilic cytoplasmic autoantibodies) is present in more than 90% of patients. It is a good disease marker.

14. Loeffler’s endocarditis (A.K.A. endomyocardial fibrosis)
   (Please review Bare Minimum Pathology Book for more information)

**End of Adrenal Endocrinology Part I**