The Thyroid

Rho Chi Review Series
L-Thyroxine (T₄)

3,5,3′-Triiodo-L-thyronine (T₃)
Thyroid Hormone Structure

- Which amino acid is thyroid hormone synthesized from?
- What is the function of the two inner iodine molecules?
- Is the oxygen of the phenyl ether bond an essential molecule?
- Which thyroid hormone is usually ionized at body pH? Why?
- Which thyroid hormone is predominant in circulation? Why?
- Which thyroid hormone is the active form? Why?
Thyroid Hormone Structure

- Which amino acid is thyroid hormone synthesized from?
  - L-tyrosine

- What is the function of the two inner iodine molecules?
  - Create a skewed conformation needed for activity. Restricts movement around phenyl ether bond

- Is the oxygen of the phenyl ether bond an essential molecule?
  - No. Can replace with a sulfur or –CH2, as long as maintain the 120° angle so inner and outer ring are perpendicular to each other

- Which thyroid hormone is usually ionized at body pH? Why?
  - T4. Extra iodine increases electronegativity and the mesomeric effect. This increases acidity of the molecule, meaning it will be deprotonated (ionized) at lower pHs

- Which thyroid hormone is predominant in circulation? Why?
  - T4. Because it is ionized, it can form ionic bonds with protein carriers

- Which thyroid hormone is the active form? Why?
  - T3. It is not ionized at body pH, and can transport into the nucleus and bind to the thyroid hormone receptor using hydrogen bonding
Put the following steps of thyroid hormone synthesis in the correct order:

- A. Oxidized iodide (hypo-iodide intermediate) becomes bound to stored thyroglobulin, forming MIT and DIT.
- B. Conjugated DIT + MIT or DIT + DIT molecules are endocytosed from the follicular colloid into the follicular cell.
- C. Iodide in the blood is taken up into the thyroid follicular cell by a Na⁺/I⁻ symporter driven by a sodium gradient.
- D. Proteolysis releases T3 and T4 hormones and they’re transported from the follicular cell into the bloodstream.
- E. Iodide is oxidized by thyroid peroxidase at the apical membrane and transported into the follicular colloid.
- F. Thyroid peroxidase catalyzes the coupling of DIT and MIT molecules in a radical reaction.

The basal membrane is located between the follicular cell and the _______.

The apical membrane is located between the follicular cell and the _______.

Thyroglobulin is made up of _______ amino acids. It is synthesized in the _______ and stored in the ________.
Thyroid Hormone Synthesis

- Put the following steps of thyroid hormone synthesis in the correct order:
  - C. Iodide in the blood is taken up into the thyroid follicular cell by a Na\(^+\)/I\(^-\) symporter driven by a sodium gradient.
  - E. Iodide is oxidized by thyroid peroxidase at the apical membrane and transported into the follicular colloid.
  - A. Oxidized iodide (hypo-iodide intermediate) becomes bound to stored thyroglobulin, forming MIT and DIT.
  - F. Thyroid peroxidase catalyzes the coupling of DIT and MIT molecules in a radical reaction.
  - B. Conjugated DIT + MIT or DIT + DIT molecules are endocytosed from the follicular colloid into the follicular cell.
  - D. Proteolysis releases T3 and T4 hormones and they’re transported from the follicular cell into the bloodstream.

- The basal membrane is located between the follicular cell and the blood.
- The apical membrane is located between the follicular cell and the follicular colloid.
- Thyroglobulin is made up of tyrosine amino acids. It is synthesized in the endoplasmic reticulum and stored in the follicular colloid.
Thyroid Transportation and Activity

- Which carrier protein does the majority of thyroid hormone bind to in circulation?
- What is the half-life of thyroid hormone bound to this carrier protein?
- Which enzyme converts T4 to T3 in peripheral tissue? There are three types of this enzyme? What does each type do and where is each type located?
- Why is rT3 inactive?
- What cellular mechanism inactivates Type II enzymes?
- There are 5 mechanisms for how the body metabolizes T3 and T4 for elimination. What are they?
Thyroid Transportation and Activity

- Which carrier protein does the majority of thyroid hormone bind to in circulation? **Thyroxine binding globulin**

- What is the half-life of thyroid hormone bound to this carrier protein? 2-3 months

- Which enzyme converts T4 to T3 in peripheral tissue? There are three types of this enzyme? What does each type do and where is each type located?
  - Iodothyronine deiodinases
  - 5'-deiodinases Type I – located in thyroid, kidney, and liver. Converts T4 to T3
  - 5'-deiodinases Type II – located in target tissues. Converts T4 to T3
  - 5-deiodinases Type III – located in all tissues. Converts T4 to rT3 and T3 to T2

- Why is rT3 inactive? **It has an anti-skewed conformation**

- What cellular mechanism inactivates Type II enzymes? **Ubiquitination**

- There are 5 mechanisms for how the body metabolizes T3 and T4 for elimination. What are they?
  - Transamination/deamination
  - Ether bond cleavage
  - Inner ring deiodination
  - Decarboxylation
  - Conjugation (w/ glutathione)
Thyroid Hormone Regulation

- Discuss the pathway of thyroid hormone release, starting at the hypothalamus and ending at the target cells. List positive and negative feedback mechanisms.

- Where is the thyrotropin releasing hormone (TRH) receptor located and what type of receptor is it? What is the main intracellular signaling mechanism?

- Where is the thyroid stimulating hormone (TSH) receptor located and what type of receptor is it? What is the main intracellular signaling mechanism?

- TRH is made of three amino acids. What are they and what two chemical groups protect this hormone from degradation?

- Which subunit of TSH gives this hormone specificity?
Thyroid Hormone Regulation

- Discuss the pathway of thyroid hormone release, starting at the hypothalamus and ending at the target cells. List positive and negative feedback mechanisms.
  - The hypothalamus releases TRH. TRH travels through the hypophyseal portal system to the pituitary gland and stimulates release of TSH. TSH travels through the bloodstream to the thyroid and stimulates release of thyroid hormone.
  - Thyroid hormones give negative feedback to the hypothalamus and pituitary glands.
  - Certain brain signals (triggered by various stimuli) act as positive feedback to the hypothalamus.

- Where is the thyrotropin releasing hormone (TRH) receptor located and what type of receptor is it? What is the main intracellular signaling mechanism?
  - Located on the pituitary gland (anterior). Is a G-protein coupled receptor. Signaling is driven by PKC and Ca2+.

- Where is the thyroid stimulating hormone (TSH) receptor located and what type of receptor is it? What is the main intracellular signaling mechanism?
  - Located on the thyroid (basal membrane). Is a G-protein coupled receptor. Signaling is driven by cAMP and PKA.

- TRH is made of three amino acids. What are they and what two chemical groups protect this hormone from degradation?
  - Histidine, Proline, Glutamate. Amide on C-terminus protect from carboxypeptidases and carboxy group on N-terminus protect from aminopeptidases.

- Which subunit of TSH gives this hormone specificity?
  - Beta subunit.
The Thyroid Receptor

- Where is the thyroid receptor located?
- How does thyroid hormone control gene transcription?
  - Where does it bind on DNA?
  - Which domain is homologous and which is tissue-dependent?
- What type of bonding occurs between thyroid hormone and the receptor?
The Thyroid Receptor

- Where is the thyroid receptor located?
  - Nucleus of target cells
- How does thyroid hormone control gene transcription?
  - Where does it bind on DNA?
    - Thyroid response elements on DNA
  - Which domain is homologous and which is tissue-dependent?
    - DNA binding domain is homologous and ligand binding domain is tissue-dependent
- What type of bonding occurs between thyroid hormone and the receptor?
  - Ionic (between carboxylate and arginine) and H-bonding (between phenol and histidine)
Hypothyroidism Therapeutics

- Name a common type of hypothyroidism (an autoimmune disorder)
  - Autoantigens develop against __________
  - Will see increase/decrease in TSH and increase/decrease in T3 levels

- What treatments are available for hypothyroidism?
Name a common type of hypothyroidism (an autoimmune disorder): **Hashimoto’s Disease**
- Autoantigens develop against **thyroglobulin**
- Will see **increase** in TSH and **decrease** in T3 levels

What treatments are available for hypothyroidism?
- Thyroid extract
- Synthetic T4: Levothyroxine
Name two causes for hyperthyroidism

In Grave’s Disease, TSH levels increase/decrease and T3 levels increase/decrease

What is radioactive iodine (I131) transformed to?
  - What particle is released from this reaction?
  - How does this particle directly and indirectly kill thyroid tissue?

What are the three ways high dose iodine helps treat hyperthyroidism?
  - Why can this treatment only be used temporarily?

How do complex anions work?
  - Why does it take a while for the effect to be seen?
Hyperthyroidism Therapeutics

- Name two causes for hyperthyroidism
  - Autoimmune disorder (Grave’s disease) and adenoma releasing TSH
- In Grave’s Disease, TSH levels decrease and T3 levels increase
- What is radioactive iodine (I\(^{131}\)) transformed to? Xenon\(^{131}\)
  - What particle is released from this reaction? Beta particle
  - How does this particle directly and indirectly kill thyroid tissue?
    - Indirectly using hydroxyl radical to oxidatively damage DNA
    - Directly with electron cleaving the DNA
- What are the three ways high dose iodine helps treat hyperthyroidism? Inhibits Na\(^+\)/I\(^-\) symporter, inhibits TPO, inhibits thyroid hormone release
  - Why can this treatment only be used temporarily? Beneficial effects dissipate with time
- How do complex anions work? Competes with iodine for Na\(^+\)/I\(^-\) symporter
  - Why does it take a while for the effect to be seen? There are stores of thyroid hormone still available to be released
Thioamides: Name these two molecules
Thioamides: Name these two molecules

- Propylthiouracil
- Methimazole
Thioamides

- What is the mechanism of action for thioamides?
- Which thioamide also inhibits type 1 5’-deiodinase?
- Which two groups are required for propylthiouracil activity?
- What is one benefit of propylthiouracil?
- Which thioamide is more potent?
- Why do these drugs have a prolonged effect?
- Why does it take a while for the effect to be seen with these drugs?
What is the mechanism of action for thioamides?
- **Inhibits thyroid peroxidase**

Which thioamide also inhibits type 1 5’-deiodinase?
- Propylthiouracil

Which two groups are required for propylthiouracil activity?
- Thioketal/thioenal and propyl group

What is one benefit of propylthiouracil?
- **Can be used in pregnancy (1\textsuperscript{st} trimester)**

Which thioamide is more potent?
- Methimazole

Why do these drugs have a prolonged effect?
- Are concentrated at the thyroid

Why does it take a while for the effect to be seen with these drugs?
- **Has no effect on already stored thyroid hormone or it’s release**
Thyroid Disorders
▪ What are some conditions that may increase thyroid binding globulin? How would these impact free T4 levels and TSH?

▪ What are some conditions that may decrease thyroid binding globulin? How would these impact free T4 levels and TSH?

▪ What are the different markers that can be tested for to detect thyroid disorders?
What are some conditions that may increase thyroid binding globulin? How would these impact free T4 levels and TSH?
- Pregnancy, having HIV/hepatitis, being on oral contraceptives, others. Will decrease free T4 levels and increase TSH levels

What are some conditions that may decrease thyroid binding globulin? How would these impact free T4 levels and TSH?
- Corticosteroids, salicylates, systemic illnesses (liver disease). Will increase free T4 levels and decrease TSH levels

What are the different markers that can be tested for to detect thyroid disorders?
- TSH, free T4, free T3
- Radioactive iodine uptake
- Various antibodies (TSH, TPO, thyroglobulin)
Signs and Symptoms of Thyroid Disorders

- State if the following signs/symptoms are attributed to hypothyroidism or hyperthyroidism:
  - Increased HR and BP
  - Weight loss
  - Dry skin, brittle nails, dry hair
  - Constipation
  - Diarrhea
  - Fatigue
  - Heat intolerance
  - Weight gain
  - Decreased BP, HR, and edema
  - Tremor and insomnia
State if the following signs/symptoms are attributed to hypothyroidism or hyperthyroidism:

- Increased HR and BP → hyperthyroidism
- Weight loss → hyperthyroidism
- Dry skin, brittle nails, dry hair → hypothyroidism
- Constipation → hypothyroidism
- Diarrhea → hyperthyroidism
- Fatigue → hypothyroidism
- Heat intolerance → hyperthyroidism
- Weight gain → hypothyroidism
- Decreased BP, HR, and edema → hypothyroidism
- Tremor and insomnia → hyperthyroidism
# Thyroid Function Testing

- Fill in the following chart with “Low” “High” or “N/A”

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Free T4</th>
<th>TSH</th>
<th>Free T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hypothyroidism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary/Tertiary hypothyroidism</td>
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Hyperthyroidism

- Match the following lab results with the appropriate form of hyperthyroidism:

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<td>Goiter, (+) anti-TSH</td>
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Hyperthyroidism

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→ **Grave’s Disease**
→ **Toxic Multinodular Goiter**
→ **Toxic thyroid adenoma**
Using the word bank below, fill in the blanks:

- Grave’s Disease –
  - 1\textsuperscript{st} line treatment(s)
    _________________
  - 2\textsuperscript{nd} line treatment(s)
    _________________

- Toxic Multinodular Goiter –
  - 1\textsuperscript{st} line treatment(s)
    _________________
  - 2\textsuperscript{nd} line treatment(s)
    _________________

- Toxic Thyroid Adenoma –
  - 1\textsuperscript{st} line treatment(s)
    _________________
  - 2\textsuperscript{nd} line treatment(s)
    _________________

- Word Bank: thioamides, levothyroxine, radioactive iodine, thyroidectomy
Treatment of Hyperthyroidism

Using the word bank below, fill in the blanks:

- Grave’s Disease –
  - 1st line treatment(s) - thioamides
  - 2nd line treatment(s) – thyroidectomy, radioactive iodine

- Toxic Multinodular Goiter –
  - 1st line treatment(s) - thyroidectomy, radioactive iodine
  - 2nd line treatment(s) - thioamides

- Toxic Thyroid Adenoma –
  - 1st line treatment(s) - thyroidectomy, radioactive iodine
  - 2nd line treatment(s) – thioamides

- Word Bank: thioamides, levothyroxine, radioactive iodine, thyroidectomy
Pharmacology of Hyperthyroid Agents

- What is the purpose of using a β-blocker to treat hyperthyroidism?
- How often can you titrate the dose of a thioamide? What should you do when the patient has become euthyroid?
- What is the typical duration of therapy for thioamides? When would relapse most likely occur?
- List a few adverse effects of thioamides. Which two would be reason to stop therapy?
- Potassium Iodide is used as adjunctive therapy. What is a special precaution with this solution? (*hint* dosing)
- How long does it usually take a patient to become euthyroid when they are taking radioactive iodine? What can happen after a patient becomes euthyroid and stops treatment?
- Which treatment option is contraindicated in pregnancy?
- What are the risks of using methimazole during pregnancy? Propylthiouracil? What treatment is preferred in the 1st trimester? What about the 2nd/3rd trimester?
Pharmacology of Hyperthyroid Agents

- What is the purpose of using a β-blocker to treat hyperthyroidism? To treat palpitations, tremors, tachycardia.
- How often can you titrate the dose of a thioamide? What should you do when the patient has become euthyroid? **Every 2 weeks. Decrease dose by 20-30%**.
- What is the typical duration of therapy for thioamides? When would relapse most likely occur? **1-2 years. Within 6 months**.
- List a few adverse effects of thioamides. Which two would be reason to stop therapy?
- Potassium Iodide is used as adjunctive therapy. What is a special precaution with this solution? (*hint* dosing) There are two formulations for it, SSKI and Lugol’s, and one is 50 mg/drop (SSKI) while the other is 8 mg/drop (Lugol’s). Easy to mix up and over-underdose.
- How long does it usually take a patient to become euthyroid when they are taking radioactive iodine? What can happen after a patient becomes euthyroid and stops treatment? **6 months. They can relapse and get secondary hyperthyroidism (can happen to >50% patients)**.
- Which treatment option is contraindicated in pregnancy? **Radioactive iodine**.
- What are the risks of using methimazole during pregnancy? Propylthiouracil? What treatment is preferred in the 1st trimester? What about the 2nd/3rd trimester? **Aplasia cutis and choanal/esophageal atresia with methimazole; hepatotoxicity with propylthiouracil. Propylthiouracil preferred in 1st, methimazole in 2nd/3rd.**
Thyroid Storm

Be able to recognize some signs/symptoms

• Just think super severe form of hyperthyroidism: high fever, wt loss, tachycardia, cardio problems (CHF), shock
• Risk factors include vulnerable states: pregnancy, surgery, infection, trauma, metabolic disorders, untreated

What treatment options are available?
Thyroid Storm

Be able to recognize some signs/symptoms

• Just think super severe form of hyperthyroidism: high fever, wt loss, tachycardia, cardio problems (CHF), shock
• Risk factors include vulnerable states: pregnancy, surgery, infection, trauma, metabolic disorders, untreated

What treatment options are available?

• Thioamide, beta blocker, potassium iodine, corticosteroid
Using the word bank below, fill in the blanks:

- **Primary hypothyroidism:**
  - ____________: an autoimmune disease with antibodies against the thyroid
  - ____________: KILL the thyroid with surgery, radioiodine, or antithyroid drugs

- **Secondary hypothyroidism:**
  ____________

- **Tertiary hypothyroidism:**
  ____________

- **Word Bank:** Pituitary insufficiency, Thyroid ablation, Grave’s disease, Hypothalamic insufficiency, Hashimoto’s disease, Iatrogenic induced
Using the word bank below, fill in the blanks:

- Primary hypothyroidism:
  - **Hashimoto’s disease**: an autoimmune disease with antibodies against the thyroid
  - **Iatrogenic induced**: KILL the thyroid with surgery, radioiodine, or antithyroid drugs

- Secondary hypothyroidism: **Pituitary insufficiency**

- Tertiary hypothyroidism: **Hypothalamic insufficiency**

**Word Bank**: Pituitary insufficiency, Thyroid ablation, Grave’s disease, Hypothalamic insufficiency, Hashimoto’s disease, Iatrogenic induced
Pharmacotherapy of Hypothyroid Agents

- Which thyroid hormone form is levothyroxine comprised of?
- Why would someone be initiated at a lower starting dose? How often can the dose be titrated in these patients?
- How often can doses of levothyroxine be adjusted? Dose adjustments are based off of which lab value?
- For which group of patients is dessicated thyroid (Armour Thyroid) indicated?
- Why is liothyronine sodium not as useful as levothyroxine?
- How long may it take to see improvements in lab values? How about symptoms?
- How should patients be counseled to take levothyroxine in relation to their other medications?
- What dose adjustment of levothyroxine needs to occur for pregnant women?
Pharmacotherapy of Hypothyroid Agents

- Which thyroid hormone form is levothyroxine comprised of? **T4**

- Why would someone be initiated at a lower starting dose? How often can the dose be titrated in these patients? **Elderly patients, patients with pre-existing coronary artery disease. Every 6-8 weeks**

- How often can doses of levothyroxine be adjusted? Dose adjustments are based off of which lab value? **Every 4-6 weeks. TSH**

- For which group of patients is dessicated thyroid (Armour Thyroid) indicated? **Patient’s who were already on it and are stable on it**

- Why is liothyronine sodium not as useful as levothyroxine? **Much shorter t½ levothyroxine. Needs more frequent dosing and adherence becomes an issue**

- How long may it take to see improvements in lab values? How about symptoms? **TSH levels may not improve for 6 months. Can see improvements in symptoms as soon as 2 weeks.**

- How should patients be counseled to take levothyroxine in relation to their other medications? **Try and separate from other meds (many meds impact levothyroxine absorption)**

- What dose adjustment of levothyroxine needs to occur for pregnant women? **They need a higher dose**
The Adrenal Gland
What are the three zones of the adrenal gland and what hormones do they secrete?
▪ Zona reticularis – secretes androgens
▪ Zona fasciculata – secretes glucocorticoids
▪ Zona glomerulosa – secretes mineralocorticoids
Fill in the blank:
- Mineralocorticoids work in the ______ to increase reabsorption of the electrolyte ________
- Glucocorticoids increase/decrease (choose) gluconeogenesis and glycogen synthesis
- In children, glucocorticoids can decrease ________________
- Moon facies and buffalo hump are due to ________________ with glucocorticoids
- Glucocorticoids have a(n) stimulatory/inhibitory effect on the immune system
- For the cardiovascular system, glucocorticoids have a beneficial/detrimental (choose) effect
- Weakening of skeletal muscle due to glucocorticoids is know as ________________
- Glucocorticoids improve/reduce (choose) wound healing
- In the central nervous system, glucocorticoids can cause ________________
Adrenal Hormone Activity

- Fill in the blank:
  - Mineralocorticoids work in the **kidney** to increase reabsorption of the electrolyte **sodium**
  - Glucocorticoids **increase** gluconeogenesis and glycogen synthesis
  - In children, glucocorticoids can decrease **skeletal growth**
  - Moon facies and buffalo hump are due to **lipid redistribution** with glucocorticoids
  - Glucocorticoids have an **inhibitory** effect on the immune system
  - For the cardiovascular system, glucocorticoids have a **detrimental** effect
  - Weakening of skeletal muscle due to glucocorticoids is know as **steroid myopathy**
  - Glucocorticoids **reduce** wound healing
  - In the central nervous system, glucocorticoids can cause **agitation and psychosis**
- Describe the HPA axis. What acts as positive and negative feedback?
- What time of day are cortisol levels highest? Lowest?
- What is a major trigger for rises in cortisol levels?
- Cortisol is highly/minimally (choose) protein bound. The two proteins that bind cortisol are called what?
- Name some conditions that cause an increase in cortisol secretion. Name some conditions that cause an increase in binding protein concentration.
- In regards to blood pressure, sodium levels, and nervous system stimulation, what stimulates and inhibits aldosterone release?
Describe the HPA axis. What acts as positive and negative feedback?
- **HPA includes hypothalamus, pituitary gland, and adrenal gland.** Hypothalamus releases corticotropin releasing hormone, which stimulates pituitary gland to release adrenocorticotropin, which travels to the adrenal gland and stimulates adrenal hormone secretion. Corticosteroids act as negative feedback.

What time of day are cortisol levels highest? Lowest?
- **Highest in morning, lowest while sleeping**

What is a major trigger for rises in cortisol levels?
- **STRESS**

Cortisol is highly protein bound. The two proteins that bind cortisol are called what?
- **Corticosteroid binding globulin and albumin**

Name some conditions that cause an increase in cortisol secretion. Name some conditions that cause an increase in binding protein concentration
- Increase cortisol secretion: exercise, stress, anxiety
- Increase protein level: pregnancy, diabetes, hypothyroidism, hematologic disorders

In regards to blood pressure, sodium levels, and nervous system stimulation, what stimulates and inhibits aldosterone release?
- **High BP, high sodium inhibits release. Low BP, low sodium, beta-adrenergic stimulation will stimulate release**
Where are substituents 18, 19, and 20 located?
Where are substituents 18, 19, and 20 located?
Name the following structures
Name the following structures

5α-estrane
5α-androstane
5α-pregnane

5α-androstane is precursor to androgens and 5α-pregnane is precursor to mineralocorticoids and cortisol
▪ Which enzyme is missing in the zona glomerulosa, which commits to formation of mineralocorticoids only?

▪ In the P450c17 enzyme, which activity of this enzyme is impaired in the zona fasciculata, making androgen synthesis very minor?

▪ Which enzyme is missing in the zona fasciculata, which prevents formation of mineralocorticoids?

▪ Which enzyme is greatly diminished in the zona reticularis, preventing formation of mineralocorticoids and cortisol?
Reactions in the mitochondria:

1. **Cholesterol** → **Pregnenolone**
   - **P450**ccc (CYP11A1)

2. **17α-Hydroxylase** → **17α-Hydroxyprogrenolone**
   - **P450**b17 (CYP17)

3. **17α,20β-Lyase** → **Dehydroepiandrosterone (DHEA)**

4. **3β-Hydroxysteroid dehydrogenase** → **Progesterone**
   - **21-Hydroxylase** (CYP21A2)

5. **17α-Hydroxyprogesterone** → **Androstenedione**

6. **21-Hydroxylase** (CYP21A2) → **21-Hydroxyprogesterone or Deoxycorticosterone**

7. **11β-Hydroxylase** (CYP11B1) → **11-Deoxycorticosterone**

8. **11β-Hydroxylase** (CYP11B1) → **Deoxycorticosterone**

Reactions in the endoplasmic reticulum:

1. **Androstenedione** → **DHEA**
2. **DHEA** → **Progesterone**
3. **Progesterone** → **17α-Hydroxyprogesterone**
4. **17α-Hydroxyprogesterone** → **Androstenedione**
5. **Androstenedione** → **Aldosterone synthesis (CYP11B2)**
6. **Aldosterone** → **Cortisol (hydrocortisone)**
7. **Cortisol (hydrocortisone)** → **Aldosterone**
▪ Which enzyme is missing in the zona glomerulosa, which commits to formation of mineralocorticoids only? P450c17

▪ In the P450c17 enzyme, which activity of this enzyme is impaired in the zona fasciculata, making androgen synthesis very minor? 17,20-Lyase activity

▪ Which enzyme is missing in the zona fasciculata, which prevents formation of mineralocorticoids? Aldosterone synthase

▪ Which enzyme is greatly diminished in the zona reticularis, preventing formation of mineralocorticoids and cortisol? 21-hydroxylase
Match the drug with what enzyme it inhibits

- Aminoglutethimide
- Trilostane
- Ketoconazole
- Metyrapone

- A. 3β-hydroxysteroid dehydrogenase
- B. 11β-hydroxylase
- C. 17α-hydroxylase
- D. 17,20-lyase
- E. P450scc
Match the drug with what enzyme it inhibits

- Aminoglutethimide - E
- Trilostane - A
- Ketoconazole – B, C, D
- Metyrapone - B

- A. 3β-hydroxysteroid dehydrogenase
- B. 11β-hydroxylase
- C. 17α-hydroxylase
- D. 17,20-lyase
- E. P450scc
- Aminoglutethimide inhibits synthesis of which adrenal hormone(s)?
- Trilostane inhibits synthesis of which adrenal hormone(s)?
- Ketoconazole inhibits synthesis of which adrenal hormone(s)?
  - What is the mechanism of action of this drug?
- Metyrapone inhibits synthesis of which adrenal hormone(s)?
- Aminoglutethimide inhibits synthesis of which adrenal hormone(s)?
  - Androgens, glucocorticoids, mineralocorticoids

- Trilostane inhibits synthesis of which adrenal hormone(s)?
  - Androgens, glucocorticoids, mineralocorticoids

- Ketoconazole inhibits synthesis of which adrenal hormone(s)?
  - Androgens, glucocorticoids

- What is the mechanism of action of this drug? Inhibits biosynthesis of ergosterol in fungi

- Metyrapone inhibits synthesis of which adrenal hormone(s)?
  - Glucocorticoids
Name these two hormones
Name these two hormones

- Spironolactone
- Eplerenone
Which metabolic pathways are reversible and which are irreversible?
Which metabolic pathways are reversible and which are irreversible?
Corticosteroid Receptor

- Where are the receptors located in the cell? Where do they go when activated?
- Which region of the nuclear binding domain is highly homologous between the various steroid receptors? Which is the more variable region?
- True or False? Cortisol can only bind to the glucocorticoid receptor.
- Cortisol is converted to cortisone by 11β-hydroxylase. Cortisone cannot bind to the mineralocorticoid receptor. This process is reversible/irreversible (choose) in the liver and reversible/irreversible (choose) in the kidney.
Corticosteroid Receptor

- Where are the receptors located in the cell? Where do they go when activated? **Cytosol, moves to nucleus**

- Which region of the nuclear binding domain is highly homologous between the various steroid receptors? Which is the more variable region?
  - DNA-binding region is homologous. Ligand-binding region is more variable

- True or False? Cortisol can only bind to the glucocorticoid receptor. **False, can bind to the mineralocorticoid receptor as well**

- Cortisol is converted to cortisone by 11β-hydroxylase. Cortisone cannot bind to the mineralocorticoid receptor. This process is reversible in the liver and irreversible in the kidney
• Adding a substituent to the 16C and 6C positions in the α/β (choose) conformation, decreases mineralocorticoid activity
• Adding a fluoride or chloride at the 9C position in the α/β (choose) conformation increases mineralocorticoid and glucocorticoid activity
• Adding a double bond to the ________ position increases mineralocorticoid and glucocorticoid activity
• Adding a 16-OH or 16-methyl increases ________ activity
• Having a double bond in the 1C position changes conformation from a chair to a ________
Adding a substituent to the 16C and 6C positions in the α-conformation, decreases mineralocorticoid activity.

Adding a fluoride or chloride at the 9C position in the α-conformation increases mineralocorticoid and glucocorticoid activity.

Adding a double bond to the 1-carbon position increases mineralocorticoid and glucocorticoid activity.

Adding a 16-OH or 16-methyl increases glucocorticoid activity.

Having a double bond in the 1C position changes conformation from a chair to a boat.
Structure Activity Relationships w/ Corticosteroids

- Name the following corticosteroids and state if they have high salt retention, moderate to low salt retention, or low to no salt retention
Fludrocortisone, high

Cortisol, moderate/low

Cortisone, moderate/low

Prednisolone, moderate/low

Prednisone, moderate/low

Betamethasone, low/none

Dexamethasone, low/none

Name the following corticosteroids and state if they have high salt retention, moderate to low salt retention, or low to no salt retention.
How does a halogen at the C9 position impact metabolism of the 11-OH?

What can be done to inhibit CYP oxidation at the C6 position?

How does a substituent (methyl group) at the C6 position impact metabolism of the C3-carbonyl and the 4,5 double bond?

Where could you place a substituent to inhibit reduction of the C20 carbonyl?
How does a halogen at the C9 position impact metabolism of the 11-OH?
- Prevents oxidation, slows metabolism

What can be done to inhibit CYP oxidation at the C6 position?
- Place methyl group at C6

How does a substituent (methyl group) at the C6 position impact metabolism of the C3-carbonyl and the 4,5 double bond?
- Prevents reduction of C3-carbonyl and 4,5 double bond; slows metabolism

Where could you place a substituent to inhibit reduction of the C20 carbonyl?
- At C16
Cushing’s Syndrome

- Match the symptom with the excess hormone that causes it:
  - Weight gain/redistribution; buffalo hump
  - Hyperpigmentation
  - Depression
  - Hirsutism
  - Osteopenia
  - Alopecia
  - Acne

- **Hormones: ACTH, cortisol, CRH, androgens**

- What are the two types of ACTH-dependent and two types of ACTH-independent forms of Cushing’s syndrome?
Cushing’s Syndrome

- **Match the symptom with the excess hormone that causes it:**
  - Weight gain/redistribution; buffalo hump – cortisol
  - Hyperpigmentation – ACTH
  - Depression – cortisol
  - Hirsutism – androgens
  - Osteopenia – cortisol
  - Alopecia – androgens
  - Acne – androgens

- **Hormones: ACTH, cortisol, CRH, androgens**

- What are the two types of ACTH-dependent and two types of ACTH-independent forms of Cushing’s syndrome?
  - **ACTH dependent**
    - Pituitary adenoma – secretes excess ACTH
    - Ectopic ACTH syndrome – a tumor somewhere other than the pituitary gland is releasing ACTH
  - **ACTH independent**
    - Adrenal cortical adenoma – secretes excess cortisol
    - Adrenal cortical carcinoma – malignant
What are the three types of non-pharmacologic treatment options for Cushing’s syndrome?

What are the two types of pharmacologic treatment options available?
What are the three types of non-pharmacologic treatment options for Cushing’s syndrome?

Surgery, radiation, bilateral adrenalectomy

What are the two types of pharmacologic treatment options available?

Adrenal enzyme inhibitors
ACTH secretion inhibitors
Pharmacologic Treatment for Cushing’s Syndrome

- What are indications for using pharmacologic treatment to treat Cushing’s Syndrome?
- Name three types of adrenal enzyme inhibitors and what hormone secretions they suppress
- Why do many patients relapse after treatment? What can help decrease the relapse rate?
- What is pasareotide? Can this be used to treat carcinomas?
- What are two important monitoring parameters with these treatments?
Pharmacologic Treatment for Cushing’s Syndrome

- What are indications for using pharmacologic treatment to treat Cushing’s Syndrome?
  - Patients w/ contraindications to surgery, who have relapsed after treatment, or as an adjunct to radiation

- Name three adrenal enzyme inhibitors and what hormone secretions they suppress
  - Ketoconazole – inhibits aldosterone, cortisol, and testosterone synthesis
  - Metyrapone – inhibits cortisol synthesis
  - Mitotane – inhibits cortisol and androgen synthesis. At high doses can cause adrenal necrosis

- Why do many patients relapse after treatment? What can help decrease the relapse rate?
  - Tumor compensates by increasing ACTH release, so dose has to keep increasing to work. Combination therapy w/ radiation can help

- What is pasireotide? Can this be used to treat carcinomas?
  - ACTH secretion inhibitor. Can only be used for adenomas, not carcinomas

- What are two important monitoring parameters with these treatments?
  - AM plasma cortisol, 24 hour urinary cortisol
Conn’s Syndrome

- Which hormone is in excess in Conn’s syndrome?
- State if each of the following are primary or secondary causes of Conn’s syndrome:
  - Adrenal adenoma
  - Idiopathic
  - Extraadrenal hormone elevations
- What are two major clinical symptoms of Conn’s syndrome?
- Which lab value is used to diagnose Conn’s syndrome. What is the cutoff?
- How do spironolactone and eplerenone work?
- Why would eplerenone be used over spironolactone?
Conn’s Syndrome

- Which hormone is in excess in Conn’s syndrome? **Aldosterone**
- State if each of the following are primary or secondary causes of Conn’s syndrome:
  - Adrenal adenoma – **primary**
  - Idiopathic – **primary**
  - Extraadrenal hormone elevations – **secondary**
    - BP increases, fluid overload, edema from HF
- What are two major clinical symptoms of Conn’s syndrome? **Resistant hypertension and hypokalemia**
- Which lab value is used to diagnose Conn’s syndrome. What is the cutoff?
  - **Aldosterone: Renin Ratio (ARR). >30**
- How do spironolactone and eplerenone work? They are mineralocorticoid receptor blockers
- Why would eplerenone be used over spironolactone? **For male patients developing gynecomastia**
Addison’s Syndrome

- What is a primary cause of Addison’s syndrome? What are some secondary causes?
- What are four major signs and symptoms of Addison’s syndrome?
- To diagnose this, synthetic ACTH (cosyntropin) is given. What two lab values are used to diagnose the condition? What is done to differentiate between primary and secondary Addison’s. Give cut-off lab values
- Is fludrocortisone acetate used in primary or secondary adrenal insufficiency?
Addison’s Syndrome

- What is a primary cause of Addison’s syndrome? What are some secondary causes?
  - **Primary:** Autoimmune destruction of adrenal glands
  - **Secondary:** long-term glucocorticoid use, pituitary tumor/low ACTH

- What are four major signs and symptoms of Addison’s syndrome? **Weight loss, fatigue, nausea/vomiting, pigmentation of skin**

- To diagnose this, synthetic ACTH (cosyntropin) is given. What two lab values are used to diagnose the condition? What is done to differentiate between primary and secondary Addison’s. Give cut-off lab values
  - Baseline cortisol and post-cosyntropin cortisol. If baseline <3 mcg/dL and post <18 mcg/dL, can diagnose. Get morning ACTH level. If ACTH< 11pmol/L, probably secondary. If ACTH >22pmol/L, probably primary

- Is fludrocortisone acetate used in primary or secondary adrenal insufficiency? **Primary**
Glucocorticoid Therapy

- Place the following corticosteroids in order of least to most potent anti-inflammatory activity:
  - Betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisone, prednisone, triamcinolone

- With which corticosteroids would you also need to add a mineralocorticoid replacement?

- What are the three indications for corticosteroid therapy?

- What are the two categories of adverse effects that can occur with corticosteroid therapy?

- Which formulations produce the most adverse effects?
**Glucocorticoid Therapy**

- Place the following corticosteroids in order of least to most potent anti-inflammatory activity:
  - Cortisone > hydrocortisone > prednisone > triamcinolone > methylprednisolone > dexamethasone > betamethasone

- With which corticosteroids would you also need to add a mineralocorticoid replacement? Triamcinolone, methylprednisolone, dexamethasone, betamethasone

- What are the three indications for corticosteroid therapy? Replacement therapy, anti-inflammatory activity, immunosuppressive effects

- What are the two categories of adverse effects that can occur with corticosteroid therapy? **Withdrawal effects, and long-term use of high doses**

- Which formulations produce the most adverse effects? Oral and IV
Adverse Effects of Corticosteroids

- For each category, choose the correct adverse effect that occurs with corticosteroid use:
  - Fluids and Electrolytes – Hyperkalemia OR Hypokalemia
  - Immune System – Increases or Decreases susceptibility to infection
  - Hematologic –
    - Lymphocytopenia OR lymphocytosis
    - Neutropenia OR neutrophilia
  - Glucose – Hyperglycemia OR hypoglycemia
  - Lipids – Hyperlipidemia OR hypolipidemia
- Which GI effect can occur?
- What is the impact on the eyes?
- What muscle condition can occur?
- What is the effect on bones?
- Increase OR decrease in wound healing?
- What are some oral effects that can occur with the inhaled formulations?
- Can corticosteroids be used in pregnant patients?
Adverse Effects of Corticosteroids

- For each category, choose the correct adverse effect that occurs with corticosteroid use:
  - Fluids and Electrolytes – Hypokalemia
  - Immune System – Increases susceptibility to infection
  - Hematologic –
    - Lymphocytopenia
    - Neutrophilia
  - Glucose – Hyperglycemia
  - Lipids – Hyperlipidemia
  - Which GI effect can occur? Peptic ulcer disease
  - What is the impact on the eyes? Cataracts
  - What muscle condition can occur? Myopathy
  - What is the effect on bones? Osteoporosis
  - Increase OR decrease in wound healing? Decrease

- What are some oral effects that can occur with the inhaled formulations?
  - Throat irritation, oropharyngeal candidiasis

- Can corticosteroids be used in pregnant patients? Category C, weigh risks and benefits
What is the purpose of alternative day therapy?

How is the dose tapered?

What is the concern with decreasing the dose too quickly?

When are we concerned that HPA suppression has occurred?

How long does it take for the HPA axis function to recover?

Which two agents can be used towards the end of dose tapering?
Alternative Day Therapy

- What is the purpose of alternative day therapy?
  - If patient is having too many adverse effects on therapy or if corticosteroid therapy is being discontinued

- How is the dose tapered?
  - **Slowly decrease the off day and increase the on day.** When the on day is at the total dose (and off day is at 0), try decreasing dose to smallest dose that controls the disease

- What is the concern with decreasing the dose too quickly? **Disease flare-up.** Nausea, fatigue, hypotension, hypoglycemia, etc

- When are we concerned that HPA suppression has occurred?
  - **When pt. has been on a high steroid dose for >3 weeks**

- How long does it take for the HPA axis function to recover?
  - 2-3 weeks

- Which two agents can be used towards the end of dose tapering?
  - **Hydrocortisone (20 mg) or prednisone (5 mg)**