LEARNING OUTCOMES

By the end of the lecture, students will be able to:

I. Explain the mechanism of action of antithyroid drugs in relation to thyroid hormone synthesis and secretion
II. Describe adverse drug reactions of antithyroid drugs
III. Explain the rationale of using thyroxine in replacement and suppressive therapy
IV. Describe pharmacokinetics of thyroxine
OUTLINE....

A. Physiology
B. Mode of action and clinical effects of thyroid hormones
C. Antithyroid drugs – mode of action, pharmacokinetics and ADRs
D. Thyroxine – mode of action, kinetics and therapeutic use
SYNTHESIS AND SECRETION OF THYROID HORMONES

Thyroglobulin

\[ T_4 \]

\[ T_3 \]

\[
\begin{align*}
&\text{HO} - \text{O} - \text{CH}_2 - \text{CHCOOH} \\
&\text{NH}_2
\end{align*}
\]

\[
\begin{align*}
&\text{HO} - \text{O} - \text{CH}_2 - \text{CHCOOH} \\
&R
\end{align*}
\]
SYNTHESIS AND SECRETION OF THYROID HORMONES
SYNTHESIS AND SECRETION OF THYROID HORMONES

1. Uptake of iodide
2. Iodination and coupling
3. Endocytosis and secretion

- Thyroperoxidase + H₂O₂
- Na⁺/I⁻ symporter
- Pendrin
- Protein synthesis
- MIT, DIT
- T₄, T₃
- Colloid
- FOLLICLE LUMEN
- FOLLICLE CELL
- PLASMA
CONVERSION OF $T_4$ TO $T_3$ IN PERIPHERAL TISSUES

- Source of $\sim$80% of circulating triiodothyronine ($T_3$)

![Chemical structures of thyronines]
REGULATION OF THYROID FUNCTION
MECHANISM OF ACTION OF THYROID HORMONES

- Act mainly by the binding of $T_3$ to a specific nuclear receptor
- $T_4$ is not biologically active in normal physiology
- When $T_3$ is bound, the gene transcription is activated, resulting in generation of mRNA and protein synthesis
CLINICAL EFFECTS OF THYROID HORMONES

- Regulation of growth and brain development
- Necessary for thermogenesis
- Increase in the metabolism of carbohydrates, fats and proteins
- Increased heart rate and cardiac output
ANTITHYROID DRUGS

THIOUREYLENES:

1. Carbimazole
2. Methimazole
3. Propylthiouracil
MODE OF ACTION - THIOUREYLENES

Inhibit thyroperoxidase

Inhibit,
1. the iodination of tyrosyl residues in thyroglobulin
2. the coupling of these iodotyrosyl residues to form iodothyronines

Depletion of stores of iodinated thyroglobulin

Gradual reduction in the signs and symptoms of thyrotoxicosis
MODE OF ACTION - THIOUREYLENES

- Methimazole
- Carbimazole
- Propylthiouracil
MODE OF ACTION - PROPYLTHIOURACIL

- Partially inhibits the deiodination of T4 to T₃ in peripheral tissues
Carbimazole is rapidly converted to its active metabolite methimazole.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbimazole</td>
<td>6-15 h</td>
</tr>
<tr>
<td>Propylthiouracil</td>
<td>75 minutes</td>
</tr>
</tbody>
</table>

Cross the placenta and appear in the milk.
Concentrated in the thyroid.
ADVERSE DRUG REACTIONS

- Agranulocytosis:
  - Agranulocytosis develops rapidly. Periodic white cell counts not helpful
  - Reversible on discontinuation of the drug
  - Patients should be instructed to immediately report symptoms of leucopenia i.e. sore throat or fever
  - If these signs or symptoms occur, patients should discontinue their anti-thyroid drug and obtain a white cell count
Propylthiouracil induced hepatotoxicity:
- More common among children and adolescents
- Third drug after paracetamol and isoniazid that requires liver transplantation due to hepatotoxicity
- Mildly altered liver function tests Death

The most common reaction - purpuric, urticarial papular rash
Teratogenicity:
- With carbimazole/methimazole, "aplasia cutis congenita"
- Reserve propylthiouracil use for patients who are in their first trimester of pregnancy, or who are allergic to or intolerant of methimazole.

- Propylthiouracil should not be used in pediatric patients unless the patient is allergic to or intolerant of methimazole, and there are no other treatment options available.
RADIOIODINE

- When taken orally incorporated into thyroglobulin in a similar way to iodide
- The isotope used is $^{131}$I
- Emits both $\beta$ and $\gamma$ radiation. $\beta$ rays are destructive to tissues
- $^{131}$I has a half-life of 8 days. $\therefore$ its radioactivity lasts $\sim$2 months
- Cytotoxic effect on the gland is delayed for 1-2 months and maximum effect reached in 4 months
Two types:
1. Thyroxine (levothyroxine)
2. Tri-iodothyronine (liothyronine)

Synthetic compounds identical to the natural hormones

Liothyronine has a faster onset but a shorter duration of action ($t_{1/2} = 0.75$ days) . Therefore used only in acute emergencies e.g. myxoedema coma
LEVOThYRoxine

- Drug absorption:
  - ~ 80% absorbed
  - Reduced by food, aluminum-containing antacids, cholestyramine, calcium carbonate, proton pump inhibitors and raloxifene
  - Should be taken on an empty stomach
Drug metabolism:
- Metabolized mainly in the liver
- Hepatic CYP3A4 induction reduces the plasma concentration of the medicine
  e.g. phenytoin, carbamazepine, Rifampicin
• Drug excretion:
  - Excreted partly in the bile and partly in the urine
  - Binding strongly to plasma proteins protect the drug from metabolism an excretion there by increasing $t_{1/2}$
  - Due to the long $t_{1/2}$ (7 days) takes long for clinical effects to be noticed and minimal effect on missing a dose
1. Thyroid hormone replacement therapy in hypothyroidism – to replenish thyroid hormone lost due to illness (e.g. autoimmune thyroiditis) or iatrogenic causes (e.g. Radioiodine or surgery)

2. Suppression of TSH after thyroidectomy and radioiodine in thyroid carcinoma, as TSH is a growth factor for thyroid carcinomas
SUMMARY

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