Treatment of hypothyroidism

Lecture 1

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Thyroid hormones

Mechanism

They simulate & stimulate predominant hormonal functions.

1. T4 is converted peripherally into T3 (by deiodinase) which passes into cytoplasm & nuclear membrane, then binds to protein receptors (α & β) in the nucleus to modulate actions of mRNA causing protein synthesis forming e.g. enzymes responsible for various actions.

Biological lag, hours or days.

Receptors are ↑ in hormone - responsive tissue.

Affinity of T3:T4 = 10:1.

2.↑ number & sensitivity of β adrenoceptors → ↑sympathetic activity.

3.↑ activity of growth hormone, cortisol & PTH.

1st mechanism is direct, others are indirect via affecting other hormones.

Actions

1. Metabolic:

Anabolic in young & small dose and catabolic in adults & large dose.

a. Mental, physical & sexual growth. Directly & via growth h.

b.↑ metabolic rate, VD, hotness, sweating & wt. loss.

↑glucose absorption, uptake, peripheral utilization & ↑glycogenolysis.

↑ lipolysis & ↓cholesterol directly and via β receptors & cortisol.

↑O2 consumption (except in brain) & heat production by stimulation of Na+/ K+ ATPase. It produces uncoupling of oxidative phosphorylation, causing decrease ATP (work).

- N.B.

O2 consumption → a. ATP. b. heat.

2. Cardiac : ↑cardiac properties. Directly & via β receptors.

3. Nervous: Tremors, anxiety & insomnia. Directly& via β receptors.

4. ↑bone resorption. Directly & via PTH.

Adverse effects

Dose - dependent.

Metabolic: Hotness, sweating, fever, loss of wt. & weakness.

Cardiac : Palpitation, tachycardia, arrhythmias & angina.

Nervous : Tremors, anxiety & insomnia.

Osteoporosis & fractures.

Goiter is anatomical (enlarged thyroid gland).

Hyperthyroidism is physiological (functional), ↑ T4 &T3 activity.

Thyrotoxicosis is clinical, according to whether TGI (thyroid growth Ig) or TSI (thyroid stimulating Ig) is predominant.

i.e. goiter and hyperthyroidism in different proportions.

Test: TSH - receptor antibodies (TRAbs).

Initial screening of hypo & hyperthyroidism: TSH.

TSH is very sensitive. Twofold change in free T4 → 100- fold change in TSH level.

Free T4 & T3 differentiate between overt & mild or subclinical cases.

In adults hypo & hyperthyroidism in 10% & 2% respectively.

> 95% are subclinical.

Subclinical hyperthyroidism or hypothyroidism: normal free T4 & T3 with ↓ & ↑ TSH respectively.

Subclinical hypothyroidism is a risk factor for cardiovascular mortality (↑LDL, ↑diastolic BP, ↓myocardial contraction & cardiac output) and neuropsychiatric manifestations.

Uses

A) Replacement therapy:

1. Hypothyroidism:

More common in females, older age (age - correlated), whites & pregnancy.

Causes & risk factors:

Autoimmune thyroiditis (Hashimoto disease).
Antithyroperoxidase & antithyroglobulin antibodies.

Family history of thyroid diseases.

May + other endocrine autoimmune diseases.

2. I2 deficiency (occurs in 1/3 people). Goiter is ttt by iodized salt.

3. Iatrogenic:

a. ttt of hyperthyroidism by ↑dose.

b. Amiodarone, lithium, tyrosine kinase inhibitors & interferon α.

4. Irradiation & surgery.

In mild & moderate cases, synthetic T4 (levothyroxine) 25-50ug / day orally for 3 weeks in the morning or at bed time, on empty stomach (interacts with food & drugs) and ↑ dose by 25ug / day every 3-6 weeks till euthyroid state is reached (Css of T4 = 6-8 weeks).

Normal TSH values are attained after months due to delayed re-adaptation of hypothalamic - pituitary axis. Then maintenance dose is used.

Brand - name drug or a constant generic substitution is used due to different bioavailability.

Factors affecting dosage choice:

1. Severity, age, wt., lean mass.

2. In pregnancy, dose is ↑.

No ttt. in pregnancy → diastolic hypertension & severe fetal effects (miscarriage, preterm, death &neonatal cognitive delays).

3. In old & IHD, dose is ↓.

4. T4 has slow onset, long duration, stable plasma concentration and less potency compared to T3.

5. T3 may be used if inadequate response to T4 as in impaired T4 - T3 conversion, genetic polymorphism, fatigue, obesity & mental impairment.

6. In severe myxedema T4 & T3 absorption is ↓, so IV.

2. Myxedema coma:

In ICU. All drugs are IV (↓absorption in other sites).

Severe acute hypothyroidism.T4, 100-500 ug IV, till consciousness.

T3 (liothyronine sodium) IV (l0ug/6 hours) can be given.

Also artificial respiration, glucose, corticosteroids &warming pt.

On recovery change IV to oral therapy.

B) Suppressive therapy:

Large dose of T4 is used to produce -ve feed back suppression of TSH release in:

1. Simple goiter.
2. Papillary carcinoma of thyroid (hormone - dependent tumor).

It ↓tumor growth & ↑survival.

I2 cycle

1. Trapping of iodide into thyroid gland (Iodide pump).
2. Oxidation of I- into I2 by thyroperoxidase in presence of Cu.
3. Iodination of tyrosine forming mono & di-iodo tyrosine (T1 &T2) (organification of iodine within thyroglobulin molecule).
4. Coupling between T1 & T2 → T4 & T3 (5:1).
5. Release by protease enzyme → release of T4 (80%) and T3 (20%) into blood. ↓ by iodides, glucocorticoids & lithium.

In periphery, outer monodeiodination of T4→T3 .

L- carnitine ↓T3 & T4 into cell nucleus.

Functions of TSH:

1. Hypertrophy, hyperplasia &↑vascularity of thyroid gland.
2. Stimulation of the five steps of I2 cycle.