thyroid disease

Thyroxine: amino acid derived hormone

How it works

- Iodide found in the plasma is actively transported into cells of the thyroid gland through the sodium iodide symporter (NIS)
- Iodide itself is not very reactive
- Thyroid peroxidase activates the iodide and is incorporated into thyroglobulin
    - PTU and methimazole inhibit the action of the peroxidase, treating hyperthyroidism
- Some of the tyrosines become mono- or di-iodo tryosines
- The molecules couple
    - DIT + DIT = T4 (usually)
    - DIT + MIT = T3 (occasionally)
- Main players: NIS, peroxidase, TSH receptor, thyroglobulin
    - A defect in any of these proteins will cause hypothyroidism
    - Can be screened in newborns
    - Most common cause: thyroid doesn't develop
    - TSH levels very high (i.e. thyroid hormone levels low)
- T4 goes out into the body and is converted by peripheral tissue into T3

Measuring TSH levels determines thyroid status

- The most important test
- Tests tissue adequacy and how well the thyroid is functioning, i.e. are they sensing enough thyroid hormone?
- Hyperthyroidism: overactive so it decreases TSH levels
- Hypothyroidism: underactive so it increases TSH levels

TSH receptor

- Senses how much TSH is present
- The more TSH present, the more it binds to the receptor, and the more thyroid hormone is produced

Hyperthyroidism

- **Grave's Disease**
    - Autoimmune disease
    - An antibody/immunoglobulin binds to the receptor and activates it, turning on the signal, which can't be turned off, causing too much thyroid action
    - Symptoms
        - Goiters (thyroid twice as large)
        - Proptosis: eye disease
- **Control** of hyperthyroidism
    - Giving huge amounts of stable iodine blocks the activation step
    - Blocking peroxidase with PTU or MMI (takes several weeks)
    - Block release of thyroid hormone using stable iodine or lithium
    - PTU and MMI blocks the conversion of T4 to T3
    - β blockers reverses symptoms
    - Surgery and radioactive iodine to destroy part of the thyroid

Hypothyroidism

- **Hashimoto's Disease**
    - Most common cause of hypothyroidism
    - Thyroid gland is gradually destroyed by a variety of cell and antibody mediated immune processes
    - Gradual destruction of follicle cells in thyroid gland

    - Autoantibodies against thyroid peroxidase, thryoglobulin, and TSH receptors
- **Control** of hypothyroidism
    - Levo-thyroxine

Thyroid cancer

- Only cause: childhood radiation
- RET is not expressed in thyroid cells because of an inactive promoter
- Radiation energy packets break DNA in 2 places
- That piece of DNA turns upside down and gets reincorporated ("somatic inversion")
- The tyrosine kinase part of the RET gene now lies on the active promoter
- It has lost its transmembrane portion, now it is inside the cell
- Turned on and cannot be turned off
- Treatment: medication that targets the tyrosine kinase

Drug influences

- Affect binding proteins (TBG)
    - ↑TBG: estrogens, tamoxifen (↑T4, same T3, same TSH)
    - ↓TBG: androgens, glucocorticoids
    - Displaced TBG: aspirin, salicylates
- Affect metabolism
    - ↑Hepatic metabolism by activating P450: Phenobarbital, rifampin, phenytoin
    - ↓5'-deiodinase activity: ↓T4→T3 conversion: β-blockers, glucocorticoids, PTU
- Alter secretion
    - ↓Thyroid hormone secretion: lithium, aminoglutethimide
    - Both ↑ & ↓ thyroid hormone secretion: iodine, amiodarone
    - Amiodarone
        - Inhibits T4→T3 conversion (yet normal TSH levels)
        - Causes hypothyroidism
            - Wolff-Chaikoff effect: ↑iodine = ↓T4 synthesis
            - Treat with T4 replacement therapy
        - Causes hyperthyroidism
            - Less common, difficult to treat
            - Jod-Basedow: iodine-induced
            - Destructive thyroiditis (inflammation)
- ↓TSH secretion
    - Induces hypothyroidism
    - Mostly in hospital critical care unit
    - Dopamine, glucocorticoids, octreotide
- ↓T4 absorption
    - Colestipol, cholestyramine, ferrous sulfate, calcium carbonate, sucralfate
- Cytokines

IFN-a

- Interferon from hepatitis C patients that induces thyroid dysfunction because patients develop antithyroid antibodies