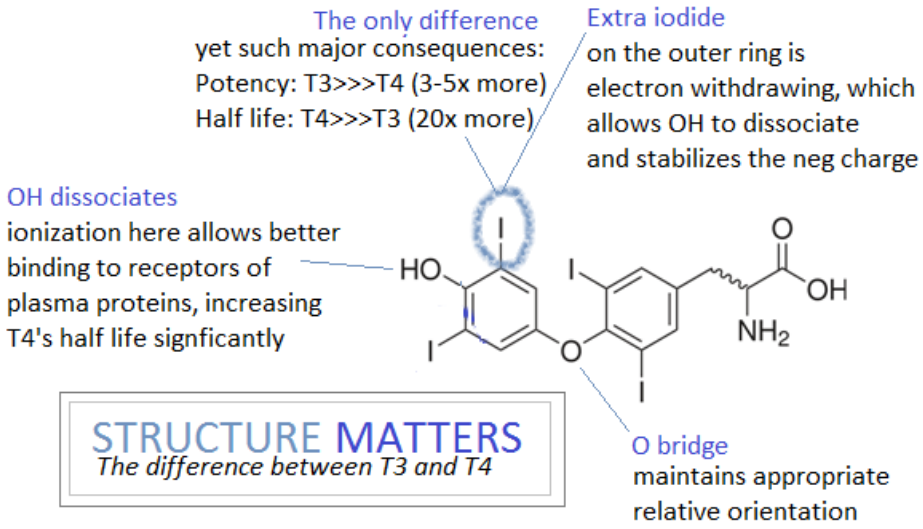
THYROID HORMONES



THE BRIEF// lipophilic hormones synthesized from L-Tyr by follicular cells (single epithelial layer surrounding colloid) in thyroid gland, regulated by TSH from the anterior pituitary

NOTE THE VOCAB//

Iodine=$\mathbf{I_2}$ Iodide=$\mathbf{I^-}$

T4 = thyroxine, prohormone to T3

Thyronine = thyroxine without the iodides

T3 = thyroid hormone

TBG = thyroid binding globulin: carries thyroid hormones in blood

Tg = thyroglobulin: used to make T3 and T4

Potency: T3>>>T4 (3-5x more)
Half life: T4>>>T3 (20x more)
Why the difference?
Due to the ionization of 4'-OH of the phenol, it binds better to receptors on plasma proteins. The only difference between T4 and T3 is the presence of the extra I on the outer ring of T4, which is extremely electron withdrawing, allowing OH to dissociate relatively easily and become ionized (i.e. lower pKa). This simple difference gives them very different biological activities.

HOW TO MAKE THYROID HORMONES//

1. IODIDE TRAPPING

- Follicular cells produce *thyroglobulin* (precursor to thyroid hormones)
- Iodide is actively transported from the bloodstream into the thyroid follicles by the *NIS* (Na+/I- symporter) which is stimulated by TSH
- Uptake of iodide is the *rate limiting step* in synthesis

2. ORGANIFICATION REACTION

- Goal: *oxidation of I-, iodination of Tyr*
- *TPO* (thyroperoxidase) catalyzes the reaction in which I- is bound to Tyr residues of Tg forming either *MIT* or *DIT*
  - *MIT* = monoiodotyrosine (i.e. 1 iodine)
  - *DIT*= diiodotyrosine (i.e. 2 iodines)

3. COUPLING REACTION

- Catalyzed by *TPO*: MIT+DIT=*T3* or DIT+DIT=*T4*

4. PROTEOLYSIS

- The thyroid hormones must be *released from Tg*
- Endosomes merge with lysosomes to digest the protein via *proteases*, which digest the iodinated Tg to release the hormones T4 and T3
- Transport: hormones are either bound to *TBG*, transthyretin, or albumin
- Binding protects it from metabolism and secretion

5. PERIPHERAL CONVERSION

- Conversion from *T4→T3* occurs in peripheral target tissue
- The enzyme responsible for the conversion is *iodothyronine deiodinase*, which takes off one iodide
- Deiodinase can either *activate or inactivate* thyroid hormones:
  - *Activate:* remove I- from outer ring to form T3
  - *Inactivate:* remove I- from inner ring to form rT3

- There are *3 types* of deiodinase enzymes:

Type 1	Liver, kidneys, thyroid	Can deiodinate both rings, makes T3 for *circulation*
Type 2	Heart, skeletal muscles, CNS, fat	Deiodinates *outer* ring only (*activator*), makes T3 for *local use*
Type 3	All tissues	Deiodinates *inner* ring only (*inactivator*)

PTU can inhibit Type 1 deiodinase

METABOLISM// T3 and T4 can be metabolized by deamination of NH_3, conjugation at outer ring, ether bond cleavage of O bridge, or inner ring deiodination

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HYPOTHYROIDISM *the case of the underachiever*

HYPoTHYROIDISM

Solution: supplement with thyroid hormone, natural or synthetic

Natural: thyroid extract, e.g. from a pig

Synthetic: levothyroxine

Contains only T4, so doesn't work for patients who have problem converting T4→T3

Fairly safe and well-tolerated, even in pregnancy

Caution: may aggravate heart conditions, so titrate slowly

HYPERTHYROIDISM *the case of the overachiever*

HYPerTHYROIDISM

Solution: either destroy thyroid tissue or block the synthesis of the hormone

Destroy: either via surgery or radioactive iodine ^{131}I

Block synthesis: high-dose iodine or complex anions to block entry, thionamides (PTU or MMI) to block synthesis

PTU: propylthiouracil *MMI: methimazole*

Destroy thyroid tissue

→*Surgery:* take it out!

→^{131}I *Radioactive iodine:* blast it!

- Stable isotope: 127I
- Radioactive isotope: 131I, which has a heavier nuclei (neutron rich) and is less stable will spontaneously emit a β particle during radioactive decay to form the stable isotope of xenon, 131Xe
- These β particles can kill cells in two ways: directly or indirectly
  - Directly: β particles have enough energy to break C=C bonds in DNA
  - Indirectly: β particles + H_2O → $^{\cdot}OH$ (hydroxyl radical) that wreaks havoc through oxidative damage
  - Indirect is a better killer than direct
- Most widely recommended permanent treatment because it works well! Since the thyroid gland is the only organ that absorbs iodine, it is very selectively targeted with little radiation exposure or side effects to the rest of the body
- The only danger is the possibility of killing too many cells and causing hypothyroidism

Blocking synthesis *block entry or block synthesis*

- ***Block entry*** by competing at the NIS, which uptakes iodide and is the rate limiting step
  Block using high concentrations of iodine (inhibits NIS, TPO, and release) or using complex anions that are of similar size and charge to iodide but are not metabolized
- ***Block synthesis*** using thionamides (drug of choice)
  It works by inhibiting TPO, which blocks the incorporation of iodine into Tyr residues of Tg → no MIT or DIT formed (no coupling reaction)
  Just like how the thyroid gland selectively takes up radioactive iodine, it also traps thionamides so drugs go directly to the tissue! Yay!
  PTU: inhibits Type 1 deiodinase
  MMI: 10x more potent than PTU, doesn't inhibit Type 1 deiodinase
  Carbimazole: converted to MMI *in vivo*, made to improve taste and slow rate of release