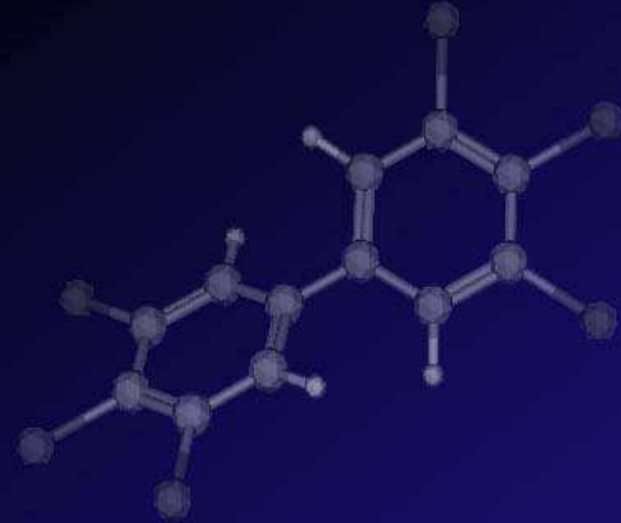
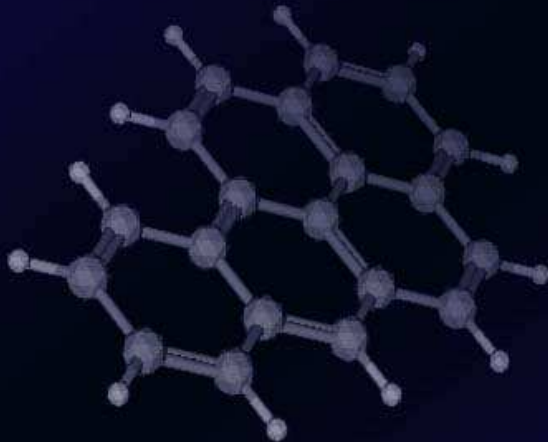


Thyroid hormones



Thyroid hormones

Regulation of metabolism

- increasing oxygen consumption
- modulating levels of other hormones
(insulin, glucagon, somatotropin, adrenalin)
- important in cell differentiation
- crucial role in development of CNS, gonads
and bones

Effects of thyroid disruption



Hypothyroidism



Hyperthyroidism

Effects of thyroid disruption

- In prenatal development - severe damage of CNS (cretinism, delayed eye opening, cognition)
- Megalotestis
- Histological changes in thyroid gland (goitre)

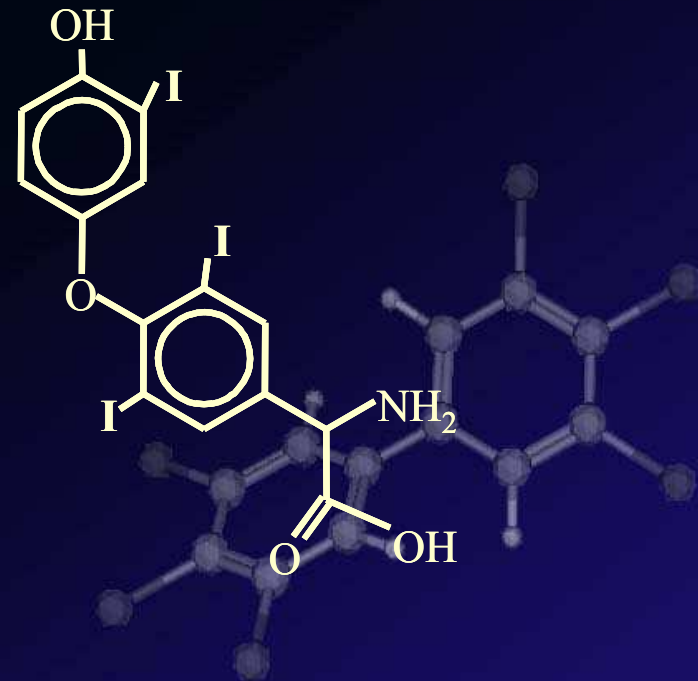


Thyroid hormones

- T4 – prohormone
- 5'-deiodination leads to active form, T3



Thyroxine (T₄)



3,5,3'-Triiodothyronine (T₃)

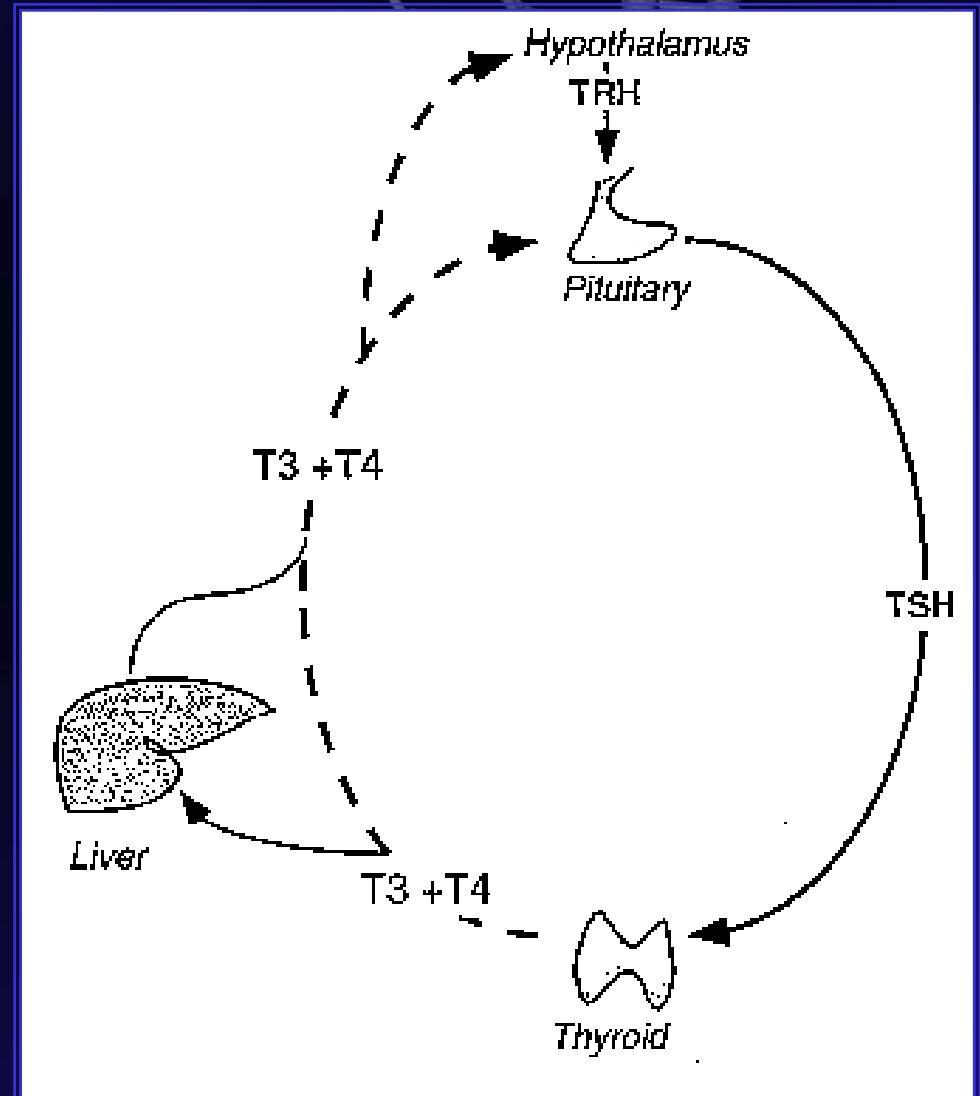
Thyroid hormones

- T4 and small amount of T3 produced in thyroid gland
- Most T3 produced by deiodination in target tissues (deiodinases)
- T4 synthesis - iodination of tyrosin residues on thyroglobulin
- coupling of two iodotyrosines conducted by thyroid peroxidase



Pituitary-thyroid axis

- Regulation of thyroid synthesis
- Negative feedback
- TSH stimulates both I⁻ uptake and iodination of tyrosine residues on Tg



Enzymes involved in thyroid metabolism

- Thyroid peroxidases

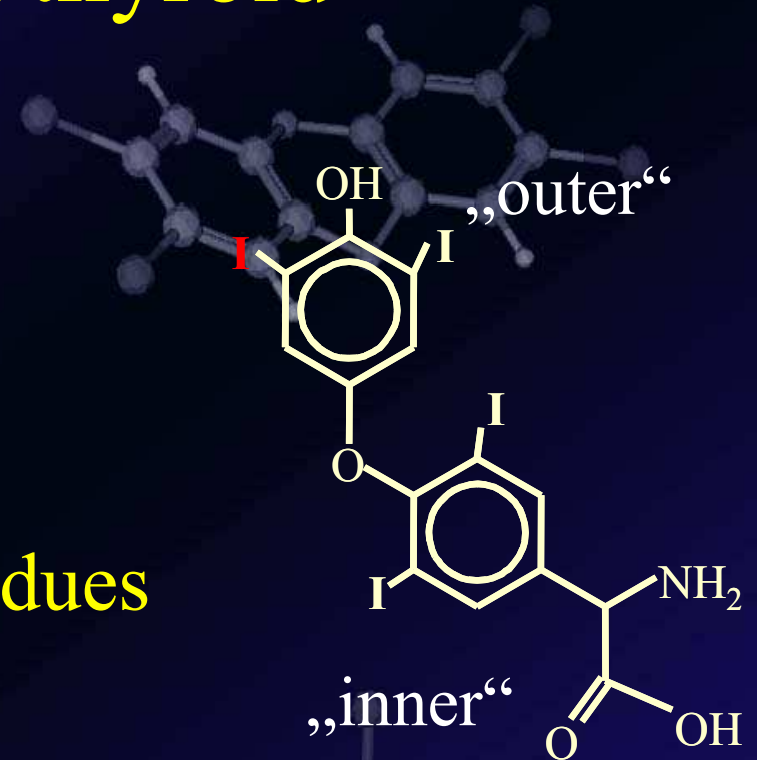
- iodination of tyrosyl residues

- coupling of iodinated tyrosyl residues

- Thyroid deiodinases

- D1, D2 - activation of T4 into T3 via deiodination on „outer“ ring (formation of T3)

- D3 - deactivation into rT3 via deiodination on „inner“ ring



Mechanism of action

- Alike other nuclear receptors

-5 isoforms of TR

-After activation formation of homo- and heterodimers

-Binding to thyroid responsive elements

-Gene expression

Thyroid binding proteins



- Regulating free T4 and T3 levels in blood

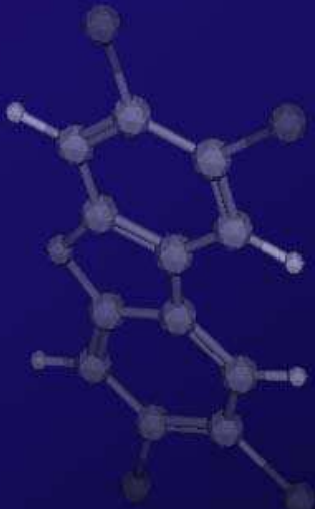
- 3 types :

- Thyroid-binding prealbumin (transthyretin) (20-25%)

- Albumin (5-10%)

- Thyroid binding globulin (75%)





Competitive binding to thyroid binding proteins

- OH-PCBs, brominated and chlorinated flame retardants, DDT, dieldrin

- OH-PCBs – equal affinity to TBP as T4 and T3

- More of free T4 in blood => increased depletion



Competitive binding to TR

- Probably less important than binding to TBP

- Chemicals that affect thyroid signalling in vivo mostly don't bind to TR (DDT, PCBs) or bind with much lesser affinity than T3 (OH-PCBs – 10000x)

Accelerated depletion of TH

- UDP-glucuronosyltransferase – detoxication enzyme (II.biotransformation phase)

- Induced by PCBs, dioxins

- Key enzyme in thyroid catabolism

- Increased by disruption of TBP binding

In vivo assessment

- TH serum levels – simple, nondestructive x variation within time of day, age, sensitive to other than biochemical stresses
- Thyroid gland weight and follicular cells number
- Delayed eye opening, abnormalities in brain development and cognition
- Increased testis weight and sperm counts
- Perchlorate discharge test (TH synthesis)

In vitro assessment

- Enzyme inhibition assays (*thyroid peroxidase, deiodinases*)
- Competitive binding assays with TBP
- TH- dependent proliferation assay (pituitary tumor GH3, thyroid tumors like FRTL-5 cell line) or TSH-dependent proliferation assay (thyroid tumors)
- Receptor-reporter gene assays with luciferase (monkey kidney CV-1, chinese hamster ovary CHO or insect Sf9 cell lines)