Thyroid hormones

Thyroid hormones

Regulation of metabolism

- increasing oxygen consumption
- modulating levels of other hormones (insulin, glucagon, somatotropin, adrenalin)
- important in cell differenciation
- 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 (cretenism, delayed eye opening, cognition)
- Megalotestis
- Histological changes in thyroid gland (goitre)

Thyroid hormones

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

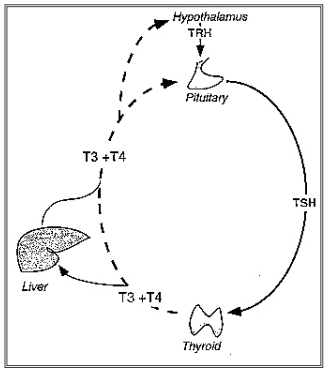
Thyroid hormones

- T4 and small amount of T3 produced in thyroid gland
- **<u>Most T3 produced by deiodination in target tissues (deiodinases)</u>**

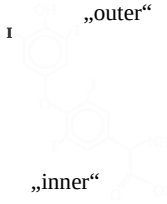
- T4 synthesis - iodination of tyrosin residues on tyreoglobulin
- coupling of two iodotyrosines conducted by thyroid peroxidase

Pituitary-thyroid axis

- Regulation of thyroid synthesis
- Negative feedback
- TSH stimulates both I^- uptake and iodination of tyrosine resides 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 prealbunin (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 witin time of day, age, sensitive to other than biochemical stresses
- Thyroid gland weight and folicular 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)