THYROID PATHOPHYSIOLOGY

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TOPICS

I. Hormone synthesis
II. Hormone transport, metabolism
III. Regulation
Thyroxine (T4)
3,5,3',5'-Tetraiodothyronine

Deiodinase 1 or 2
(5'-Deiodination)

Tri-iodothyronine (T3)
3,5,3'-Triiodothyronine

Deiodinase 3≥2
(5'-Deiodination)

Reverse T3 (rT3)
3,3',5'-Triiodothyronine
I. HORMONE SYNTHESIS

1. Trapping
   150-200ug iodine, albumin, 20-40 % geographical, cretinism, supplementation NIS, selective, mutation
   monovalent anion:
   pertechnetate, perchlorate, thiocyanate
HORMONE SYNTHESIS

2. Organification

apical, oxidation

peroxidase  anti-TPO

thyroglobulin 600 kDa, tyrosil residues
diff.cc., thyroiditis
HORMONE SYNTHESIS

3. Coupling
   TPO ether linkage
   from MIT, DIT: T3, T4
   dyshormogenesis
HORMONE SYNTHESIS

4. Liberation

  pinocytosis, hidrolysis: T4, T3

5. Dehalogenase: deiodination

  Type I: thyroid, liver, kidney
  Type II: pituitary, brain, fat, thyroid
  autoregulation, impaired, medicaments
  Type III: inactivates, rT3
I. HORMONE SYNTHESIS

Therapeutic impact

1. Iodine
   oxidation, coupling, liberation
   Wolff-Chaikoff, goiter, hypo, hyper

2. Thiourea, mercaptoimidazole
   oxidation, coupling, (immune)

3. Lithium, steroids
   liberation, (rT3)
II. TRANSPORT 1.

1. Binding proteins
   TBG, albumin, TBPA

2. Free hormones!
T4: 60-150 nmol/l  0.02%  10-20 pmol/l
T3: 1-3 nmol/l      0.3%   3-6 pmol/l

metabolic potency!
TRANSPORT 2.

TBG, transthyretin, albumin
Normal protein cc. Normo-hyper-hypo
Abnormal binding protein conc.
  Elevated: estrogens, hepatitis, genetic
  Decreased: steroids, nephrosis, liver, genetic
Free homone!
(Medicaments: antiinflammatory, carbamazepine,
salicylates, phentoine, sulphonureas, -amid, etc.)
III. METABOLISM

1. Conversion (deiodination)
   - T3: 5’deiodination  
   - rT3: 3’ deiodination
   - 80% of T3!, metabolic potency, peripheral autoregulation
   - T3/T4 low: betablocking, thiouracil, steroids
     - sick euthyroid (severe, postop, trauma)
   - T3/T4 high: hyperfunction, T3 hyperthyreosis
     - nodule, hypofunction, iodine deficiency

2. Deaminase, decarboxylase, glucoronoids
<table>
<thead>
<tr>
<th>Hormone Property</th>
<th>$T_4$</th>
<th>$T_3$</th>
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<tbody>
<tr>
<td>Serum concentrations</td>
<td></td>
<td></td>
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<tr>
<td>Total hormone</td>
<td>8 $\mu g/dL$</td>
<td>0.14 $\mu g/dL$</td>
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<tr>
<td>Fraction of total hormone in the free form</td>
<td>0.02%</td>
<td>0.3%</td>
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<tr>
<td>Free hormone</td>
<td>$21 \times 10^{-12} \text{ M}$</td>
<td>$6 \times 10^{-12} \text{ M}$</td>
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<tr>
<td>Serum half-life</td>
<td>7 d</td>
<td>0.75 d</td>
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<td>Fraction directly from the thyroid</td>
<td>100%</td>
<td>20%</td>
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<tr>
<td>Production rate, including peripheral conversion</td>
<td>90 $\mu g/d$</td>
<td>32 $\mu g/d$</td>
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<tr>
<td>Intracellular hormone fraction</td>
<td>$\sim 20%$</td>
<td>$\sim 70%$</td>
</tr>
<tr>
<td>Relative metabolic potency</td>
<td>0.3</td>
<td>1</td>
</tr>
<tr>
<td>Receptor binding</td>
<td>$10^{-10} \text{ M}$</td>
<td>$10^{-11} \text{ M}$</td>
</tr>
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IV. REGULATION

1. Suprathyroid: a. TSH 31 kDa (alpha, beta), rTSH stimulating, G protein, membrane adenylcyclase
   b. TRH, circadian, stress, neurotransmitters
   negative feedback, FT3 !
   on TSH synthesis - TRH receptors

2. Intrathyroid
   autoregulation: organic iodine content
   goiter, autonomous

3. Peripheral  deiodinase, T3 - rT3
FUNCTION - DIAGNOSIS

1. Hormone serum concentrations in vitro
2. Thyroid hormone synthesis in vivo
3. Regulation (TSH) in vitro
4. Metabolic effects in vivo
FUNCTION - DIAGNOSIS

1. **Hormone serum concentrations**
   immunooassays (RIAs or „alternative”)
   Free! (analogue, solid phase antibody)

**Hyper**: FT3 more sensitive
   T3 hyperhyreosis: early, autonomous

**Hypo**: FT4 more sensitive
Euthyroid hyperthyroxinaemia
   familial or T4-antibodies
FUNCTION - DIAGNOSIS

2. Direct hormone synthesis
- RAIU: I-131, I-123
  iodine pool (CT, amiodaron, vitamins)

**Increased uptake:**
- a. hyperfunction
- b. normofunction: remission, ophtalmopathy
- c. small „pool”: cc, irrad., -ectomy

**Decreased uptake:**
- hypofunction, large „pool”
- Tc-uptake: 4 dosis%

Only before I-131 therapy, for dosis calculation
FUNCTION - DIAGNOSIS

3. Regulation  TSH basal: 0.3-3.5 mIU/l

**hyper:** below 0.1, supersensitive

**hypo:** above 5 mIU/l

**latent hyper**, remission, ophtalmopathy

**latent hypo**

low: depression, steroid, old, sick, pituitary, etc.

high: amiodarone, estrogens, haloperidole, etc.

(TRH response: blunted, exaggerated)

**Single test, outpatient, screening!**
FUNCTION - DIAGNOSIS

4. Metabolic effects
   true effects, but aspecific
   BMR (Krogh-test)
   Achilles tendon reflex, cholesterol, CPK, PEP
FUNCTION - DIAGNOSIS

Diagnostic strategies

1. Outpatients
   TSH and FT3 (5 %) or FT4 (25%)

2. Hospitalized
   Eu - low T4: sick, steroid, betablocking, old
AUTOANTIBODIES

Hyper-normo-hypo function!

Kocher, HLA-B, DRw3, female (10%), associated

1. TSH receptor: stimulating, blocking
   TRAK: Graves’ 95%,
   activity? neonatal, postpartum

2. Anti-TPO (microsomal) and 3. Anti-Tg
   chr. thyroiditis: 90%,
   Graves’ 80%,
   (and subacute, goiter, cc.)

4. Anti-T4, -T3 (very rare, FP results)
Differentiated thyroid carcinomas
Normal serum concentration (factitia!)
Elevated: cc., injury (thyroiditis, postoperative)
Postoperative follow-up of differentiated cc.
    after ablative radioidine (I-131) dose
„AUTONOMY”

Independent from regulation

a. Graves’: stimulating autoantibodies
b. Autonomous nodules
c. Diffuse autonomy

Suppressed TSH
Scintigraphy!
Iodine induced hyperthyroidism (CT, vitamines)
SCINTIGRAPHY

1. I-123 NaI – cyclotron, expensive
2. Tc-99m-pertechnetate routine
   normal: homogenous activity distribution
   Tc-uptake: functional parameter, < 4 % at 20 min
   small field of view camera or pinhole collimator
   Indications: hyperfunction, ectopic, nodule
   Decreased: hypofunction, iodine, factitia, thyroiditis
3. I-131
   whole-body scintigraphy: diff. thyroid cancer
SONOGRAPHY

Spatial resolution, tissue characterization
Nodular
Cysts, degeneration, thyroiditis, autonomous
Cervical lymph nodes
Tracheal compression
Vascularity
1820 normál
586 Diffuz struma magas uptake
1334 nagy hideg göb
jelentős nagyságúi multiplex göbös struma
1408,1551 supr. Előtt, után
283/2000 nagy autonóm adenóma.
1070/2 Hideg göb MIBI felvétellel
30 forró göb
multiplex göbös, nagy hideg göb
THANK YOU