Drug-induced thyroid dysfunction

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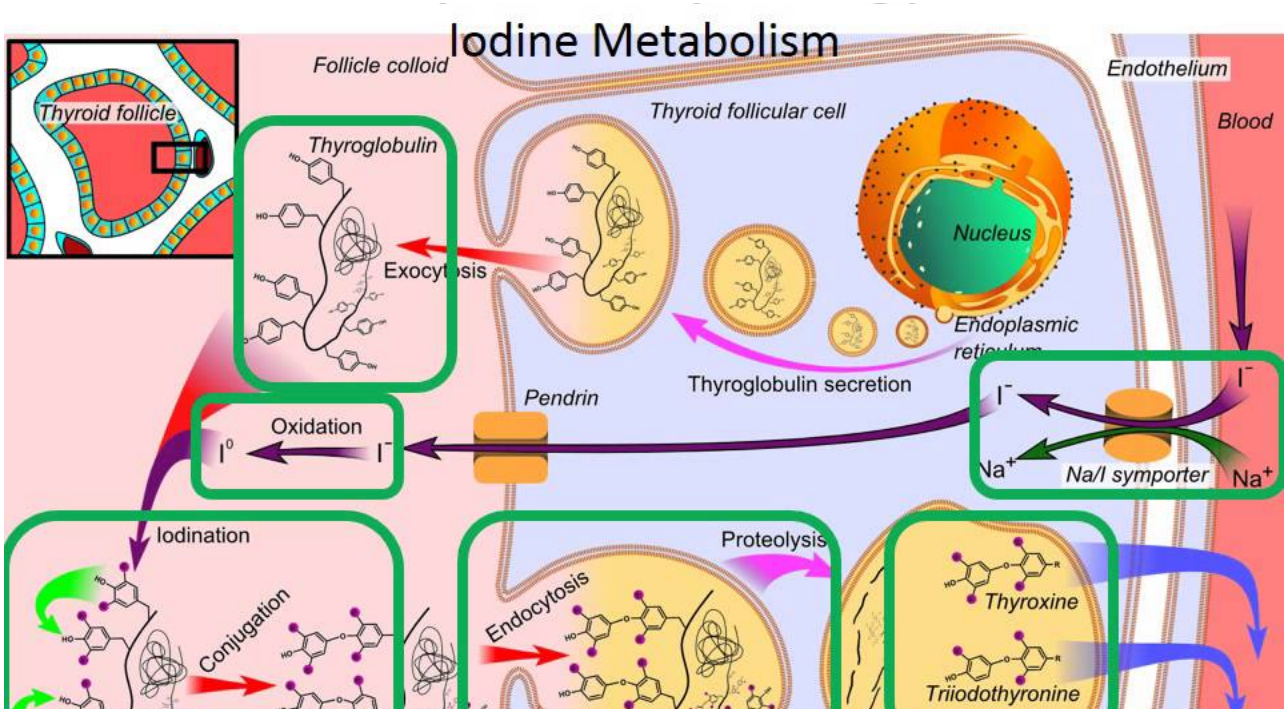
Thyroid iodide (I^-)/iodine (I^0) metabolism



1. *Synthesis of thyroglobulin in the ER and secretion by exocytosis.*
2. *Na/I symporter pumps iodide (I^-) into follicular cell.*
3. *Pendrin-mediated passive transfer of I^- in the follicular lumen.*
4. *In the colloid, I^- is oxidized to iodine (I^0) by thyroid peroxidase.*
5. *I^0 iodinates TG on Tyr residues.*
6. *By conjugation, adjacent Tyr residues are paired together.*
7. *The entire complex re-enters the follicular cell by endocytosis.*
8. *Proteolysis by various proteases liberates T4 and T3, which enter the blood.*

Iodine-containing compounds potentially associated with iodine-induced thyrotoxicosis (IIT)

Dietary reference intake: **150 µg**

Tolerable upper intake level (adult): **1,100 µg/day**

Thyroid needs: **70 µg/day**

- **Radiological contrast agents**
- **Topical iodine preparations**
- **Food components**: algae, erythrosine, hamburger thyroiditis
- **Drugs**: amiodarone, vitamins, expectorants, potassium iodide…

Agents inhibiting thyroid hormone synthesis and/or secretion

- **Blockade of iodide transport into the thyroid (Na/I symporter)**:
  Lithium, KI, perchlorate, bromide

- **Impairment of TG synthesis and iodotyrosine coupling**:
  ATD, sulfonylureas, sulfonamides, ketoconazole

- **Inhibitors of thyroid hormone secretion**:
  Lithium, iodide (in large doses)

- **Undefined or discussed mechanisms**:
  phenylbutazone, thalidomide, interleukin-2, interferon, sunitinib, sorafenib

Agents interfering with extra-thyroidal metabolism of thyroid hormones

Inhibition of T4/T3 conversion
PTU
Glucocorticoids
Propranolol
Amiodarone
Clomipramine

Stimulators of hormone degradation (cytP450) or faecal excretion
Ferrous sulfate
Diphenylhydantoin
Carbamazepine
Phenobarbital
Rifampicin
Imatinib
Coffee

Chemotherapy with tyrosine kinase inhibitors

Induction of primary hypothyroidism or ↗ LT4 requirement

- **Sunitinib** (renal cell carcinoma, imatinib-resistant GI stromal tumors, papillary thyroid cancer)

  ± 40% of cases

- **Sorafenib** (several solid tumors)

  ± 25% of cases

Suggested mechanisms:

- Destructive thyroiditis through inhibition on VEGF receptor ➔Low iodine uptake and thyroid volume shrinkage?
- Antiperoxydase effect?
- Interaction with retinoic acid receptor subtypes (Shu M et al. ***PLoS One*** 2016)?
- Triggering/exacerbation of thyroid autoimmunity (TPO) (Pani et al. ***Thyroid*** 2015)

Lithium

Highly effective in the long-term management of bipolar disorder.

Induction of goiter (up to 60%) and hypothyroidism (up to 40%)

Mechanisms still elusive:

- Net positive intrathyroidal iodine balance (down-regulation of thyroid hormone secretion?)
- Wolff-Chaikoff effect?
- Autoimmunity not increased.
- Direct toxic effect on thyroid (cases of self-limited thyrotoxicosis).

Important message:

The presence of previous thyroid disorders is almost never a reason for lithium abstinence!

Amiodarone

Important class III antiarythmic drug (2 atoms iodine/molecule)

Dailly dose of amiodarone (300 mg) – Half-life 40-60 days!

= 111 mg iodine (10% available as inorganic)

= 30-100x daily dose of inorganic iodine.

Clinical thyroid disorders:

1. *Thyrotoxicosis* (AIT, 2-12%)

   Type I AIT: consequence of iodine load on pre-existing thyroid autonomy.

   Type II AIT: destructive thyrotoxicosis by amiodarone or iodine in excess.

   Differential diagnosis: I^{123} uptake and 99m Tc Sestamibi, nodules and low vascular flow, and Ab to TSHR, TPO, Tg (Type I AIT)

   Treatment of type I AIT: thionamides (but effect blunted by large iodine burden) + potassium perchlorate (inhibitor of NA/I symporter) + amiodarone disruption.

   Treatment of type II AIT: glucocorticoids, amiodarone disruption not obligatory.

2. *Hypothyroidism* (AIH, 5-15%): preexistent or acquired inability to escape from Wolff-Chaikoff effect.

Drugs affecting thyroid hormone replacement therapy

Drugs affecting thyroid hormone absorption

LT4 absorption occurs in duodenum and jejunum and requires stomach acidity.

➔ Antacids (proton-pump inhibitors), H2 receptor antagonists, $CaCO_3$, aluminium hydroxyde, ferrous sulfate (direct binding of LT4),
bile acid sequestrants

Drugs altering thyroid hormone metabolism

Activators of the cytP450 system: rifampicin, phenytoin, carbamazepine, barbiturates, imatinib (TK inhibitor)

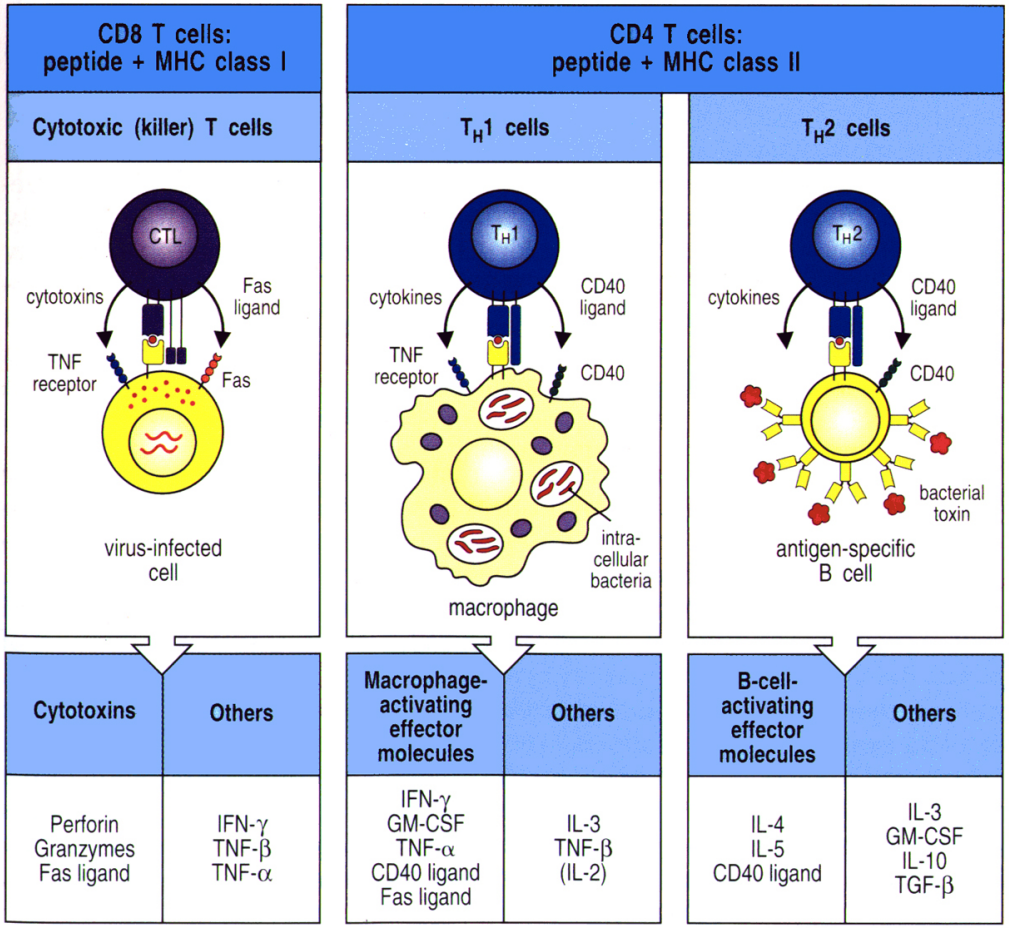
Estradiol *per os*

Dose adjustment because of ↗ TBG

Immunomodulation of thyroid function/physiology

- **Interferon α**
- **Interleukin-2 (IL-2)**
- **Alemtuzumab**
- **Anti-retroviral therapy (HAART)**

Types of T-cell responses



Interferon α (IFNα)

Treatment of hepatitis C, and other infectious and malignant conditions (mainly carcinoids, breast cancer).

Induction of autoimmunity up to 15-20%

Transient, destructive thyrotoxicosis (50%) without secondary development of autoimmunity (≠ post-partum thyroiditis)

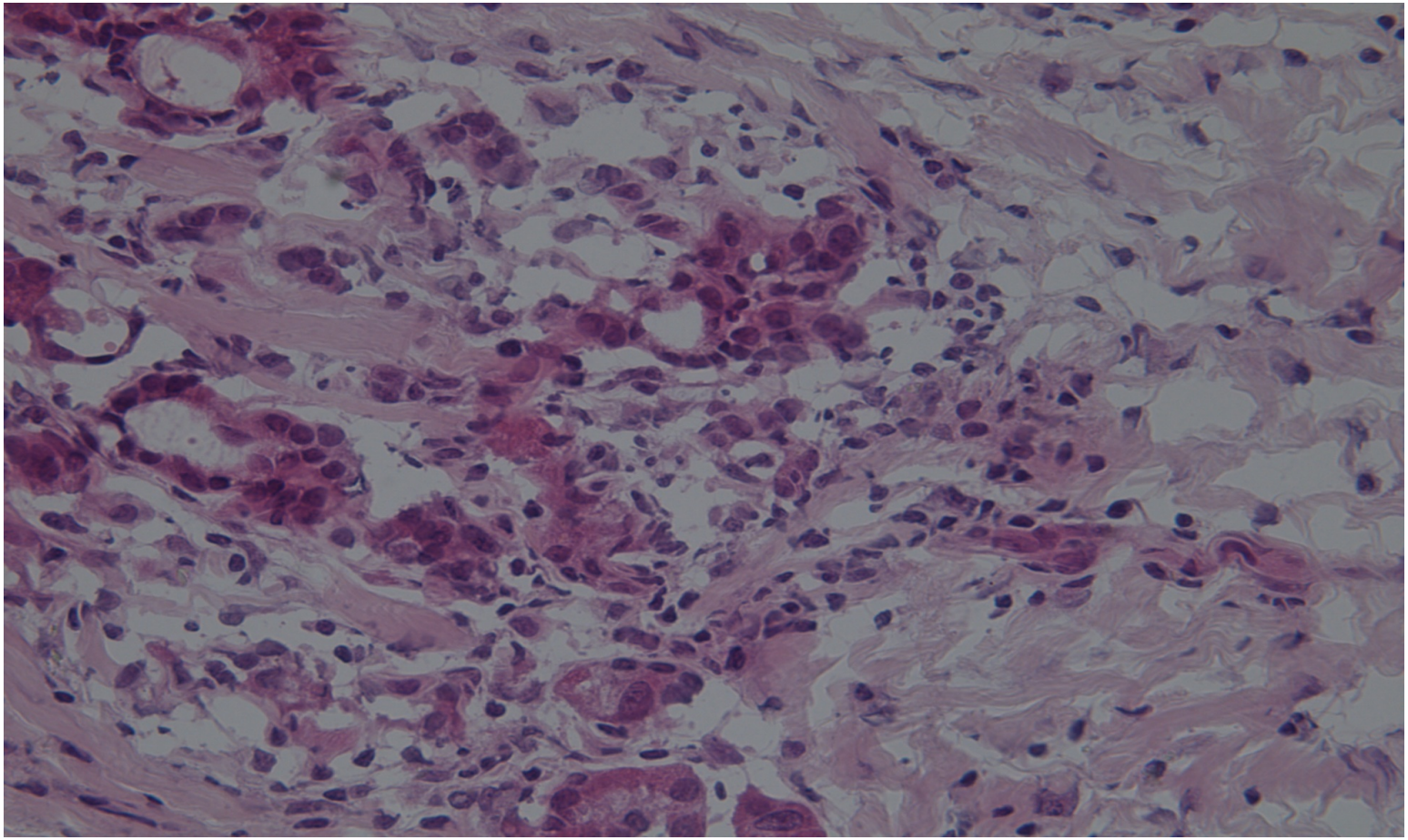
Induction of thyroid dysfunction: 2-8% of cases.

- Most frequent: hypothyroidism (Hashimoto or type 2 autoimmune thyroiditis)
- Transient thyrotoxicosis (from inflammatory destructive thyroiditis)
- More rarely, induction of Graves' disease or Type 3 autoimmune thyroiditis

Treatment

- Hypothyroidism: LT4
- Thyrotoxicosis: β-blockers
- Hyperthyroidism: recommendation for ^{131}I or surgery (hepatic effects of ATD).

Thyroiditis, inflammation and destruction of thyroid parenchyme in a patient treated with IFNα



Maiga et al., ***Rev Méd Liège*** 2015, **70**: 390-394

Interleukin-2 (IL-2)

Treatment of melanoma and metastatic renal cell carcinoma.

Induction of hypothyroidism (20-50% of cases) with anti-TPO, TG Abs.

Sometimes, transient destructive thyrotoxicosis with T-cell infiltrate in thyroid but negative thyroid Ab (pure cell-mediated autoimmunity)

Treatment:

LT4

Beta-blockers for transient thyrotoxicosis.

Alemtuzumab

= humanized mAb to CD52, a glycosylphosphatidylinositol (GPI) low MW glycoprotein anchored and expressed at very high density in membrane of normal and malignant lymphoid B and T cells.

Treatment of B and T cell malignancies and autoimmune diseases (rheumatoid arthritis but mainly relapsing-remitting multiple sclerosis/MS).

Induction of cell destruction via activation of CDC and ADCC.

Main adverse events:

- Wide immunosuppression and secondary infections.
- Immunogenicity of the drug!
- Autoimmune thrombocytopenia.
- Autoimmune glomerulonephritis.
- Autoimmune hypothyroidism.
- Induction of autoimmune hyperthyroidism (up to 30% of cases) with *de novo* Abs to TSHR. MS patients are peculiarly susceptible (common locus in MS and Graves': *CD40*).

Mechanism: reconstitution of the immune system (after profound immune suppression and lymphopenia like during alemtuzumab treatment) with unbalanced expansion of self-reactive T cells.

Anti-retroviral therapy (HAART)

Treatment of HIV-positive patients.

Some studies suggest that HAART may precipitate Type 3 autoimmune thyroiditis (Graves' disease) in predisposed subjects.

Proposed mechanism:

Reconstitution of the immune system (after profound immune suppression and lymphopenia like during alemtuzumab treatment) with unbalanced expansion of self-reactive T cells (see Alemtuzumab).

References

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Thank you for your attention!