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 iodothyrosine 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
- Imatiniib
- 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)
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\textsuperscript{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, CaCO₃, 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 $\alpha$
- Interleukin-2 (IL-2)
- Alemtuzumab
- Anti-retroviral therapy (HAART)
Types of T-cell responses

CD8 T cells: peptide + MHC class I
- Cytotoxic (killer) T cells
  - CTL
  - Cytotoxins: Perforin, Granzymes, Fas ligand
  - TNF receptor
  - Fas ligand
  - Virus-infected cell

CD4 T cells: peptide + MHC class II
- T_{H1} cells
  - Cytokines: IFN-γ, TNF-α, TNF-β
  - CD40 ligand
  - Intracellular bacteria
- T_{H2} cells
  - Cytokines: IL-4, IL-5, IL-10, GM-CSF
  - CD40 ligand
  - Antigen-specific B cell

Macrophage-activating effector molecules:
- IFN-γ
- GM-CSF
- TNF-α
- CD40 ligand
- Fas ligand
- IL-2

B-cell-activating effector molecules:
- IL-3
- IL-10
- TGF-β
Interferon \( \alpha \) (IFN\( \alpha \))

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: \( \beta \)-blockers
- Hyperthyroidism: recommendation for \(^{131}\text{I} \) 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!