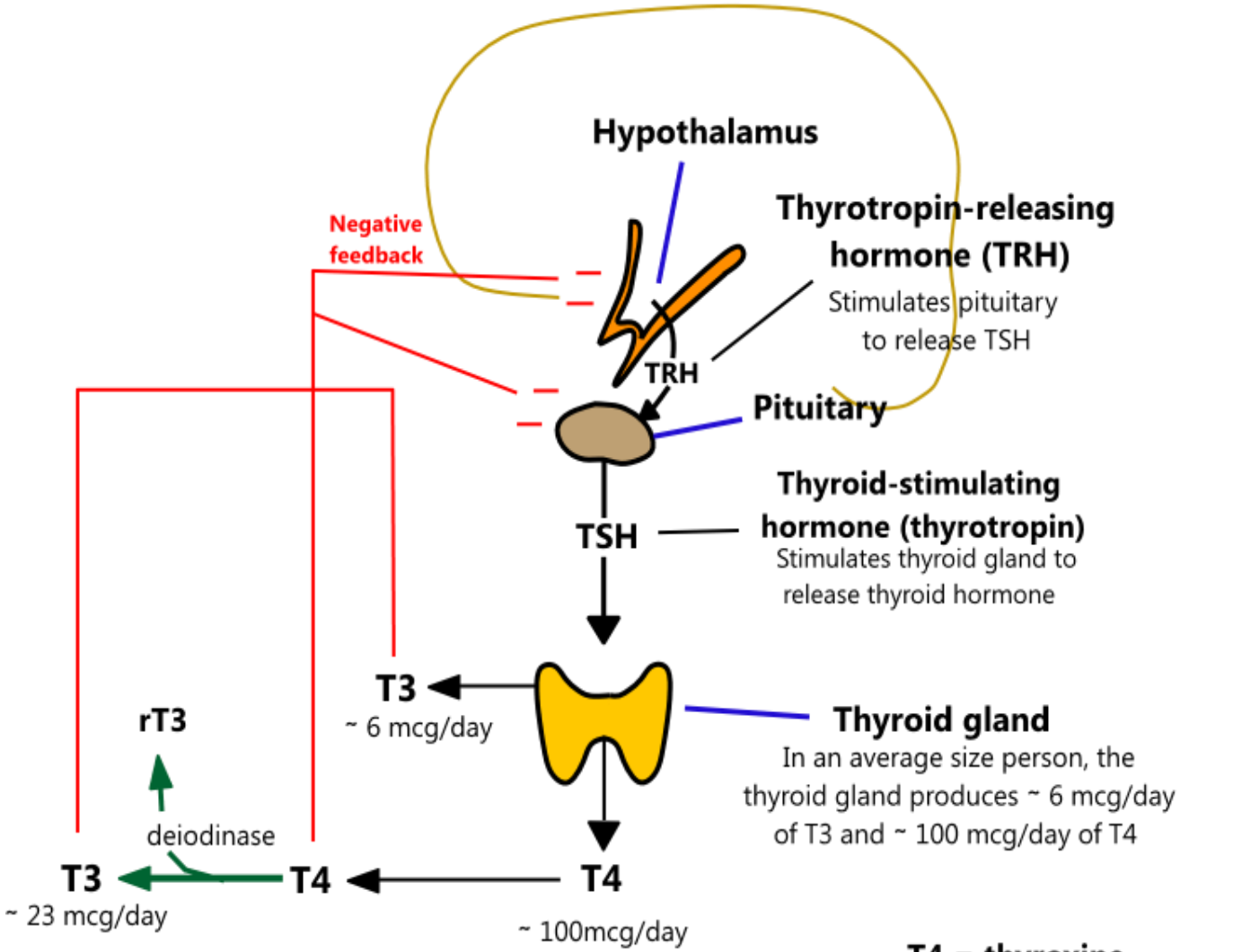
Drugs affecting Thyroid function

Agenda

- HPT axis and factors affecting thyroid function
- Mechanisms causing thyroid dysfunction
- Highlighting iodine, amiodarone and lithium
- Interferons, interleukins, monoclonal antibodies & tyrosine kinase inhibiters
- Endocrine disruptors

Hypothalamic-pituitary-thyroid axis



Factors that Affect Thyroid Function

T4

Factors that contribute to proper production of thyroid hormones
- Nutrients: iron, iodine, tyrosine, zinc, selenium vitamin E, B2, B3, B6, C, D

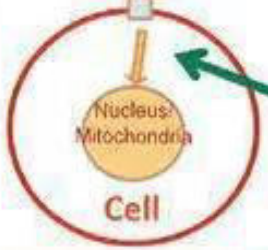
Factors that inhibit proper production of thyroid hormones
- Stress
- Infection, trauma, radiation, medications
- Fluoride (antagonist to iodine)
- Toxins: pesticides, mercury, cadmium, lead
- Autoimmune disease: Celiac

Factors that increase conversion of T4 to RT3
- Stress
- Trauma
- Low-calorie diet
- Inflammation (cytokines, etc.)
- Toxins
- Infections
- Liver/kidney dysfunction
- Certain medications

Factors that increase conversion of T4 to T3
- Selenium
- Zinc

RT3 T3

T3 and RT3 compete for binding sites



Factors that improve cellular sensitivity to thyroid hormones
- Vitamin A
- Exercise
- Zinc

Commonly used medications and its effects on thyroid hormone levels

Decrease TSH secretion:

- Glucocorticoids: inhibit TSH release
- Dopamine: blocks TSH release
- Octreotide: inhibits TSH release
- Bexarotene: suppresses pituitary TSH-β promoter

Alter thyroid hormone secretion:

- Decrease thyroid hormone secretion: iodide, amiodarone, lithium
- Increase thyroid hormone secretion: iodide, amiodarone

Decrease T4 absorption:

- Cholesystramine, colestipol, sucralfate, ferrous sulfate, aluminum hydroxide, omeprazole

Alter T4 and T3 transport in serum:

- Increase serum TBG: estrogens, heroin, methadone, mitotane, fluorouracil
- Decrease serum TBG: androgens, anabolic steroids
- Displacement from protein-binding sites: furosemide, salicylates, meclofenamate, heparin

Alter T4 and T3 metabolism:

- Increase hepatic metabolism: phenobarbital and rifampin
- Increase hepatic metabolism and displace from binding proteins: phenytoin and carbamazepine

Cytokine mediated:

- Interferon (IFN) α

Immune reconstitution:

- Alemtuzumab

Hypothyroidism (tyrosine kinase inhibitors):

- Sunitinib: ? destructive thyroiditis,? blockade of iodine uptake,? inhibition of peroxidase activity
- Imatinib: ? induction of uridine diphosphate-glucuronosylotransferases (UGTs)

Kundra P, Burman KD. Med Clin N Am 96 (2012) 283–295

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TSH Suppression

- Dopamine infusions at greater than 1 mg/kg/min are known to block TSH release
- Glucocorticoids, particularly dexamethasone, at as low a dose as 0.5 mg/d and hydrocortisone at 100 mg/d, inhibit TSH secretion; clinically higher doses of dexamethasone (ie, >4 mg per day) inhibit extrathyroidal T3 production, leading to lower TSH values
- Bexarotene, a retinoid X receptor ligand, suppresses the pituitary TSH-β promoter, leading to central hypothyroidism (values < 0.05 mU/L)
- Thyroid function gradually returns to normal after therapy withdrawal

Brabant K, Prank C, Hoang-Vu RD, et al. JCEM 1991;72(1):145–50
Agner T, Hagen C, Anderson A, et al. JCEM 1986;62(4):778–82
Brabant G, Brabant U, Ranft K, et al. JCEM 1987;65(1):83–8

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Effects of iodine

- Varied effects, depending on the dose and duration of exposure and on the underlying thyroid condition
- Short-term iodine exposure (usually up to 7–10 days) can inhibit thyroid hormone secretion (Wolff-Chaikoff effect)
- Continued iodine exposure leads to escape from this inhibition and hyperthyroidism can result (Jod-Basedow phenomenon)

Braverman L. Iodine induced thyroid disease. 3rd thyroid symposium, AMA

Effects of iodine

- Iodide-induced hyperthyroidism generally develops in individuals with MNG or hyperfunctioning thyroid adenoma secondary to the Jod-Basedow phenomenon
- Iodide-induced hypothyroidism generally develops secondary to a failure to escape from the Wolff-Chaikoff effect in chronic autoimmune thyroid disease, or Graves hyperthyroidism
- Iodide inhibits thyroidal organification (Wolff-Chaikoff) but usually in up to 48 hours there is a decrease in sodium iodide symporter activity to allow restoration of organification (hence escape from Wolff-Chaikoff)

Braverman L. Iodine induced thyroid disease. 3rd thyroid symposium, AMA

Effects of Amiodarone
Hypothyroidism

- Overt hypothyroidism (TSH >10 mU/L) 5% , SCH (TSH 4.5–10 mU/L) developed in an additional 25%
- Hashimoto thyroiditis is the most common risk factor
- Typically occurs between 6 and 12 months of treatment initiation
- Decrease in serum T3 levels and an increase in serum T4, free T4, reverse T4, and TSH levels
- Decrease in intracellular T4 transport, inhibition of type 1 5’ -deiodinase and pituitary type 2 5’ -deiodinase, as well as antagonizing T3 binding to its nuclear receptor in the pituitary
- The dose of L-T4 needed to normalize TSH may be higher as a result of the decreased intrapituitary T3 production caused by inhibition of pituitary type 2 5’ -deiodinase

Norman MF, Lavin TN. J Clin Invest 1989;83:306–13

Effects of Amiodarone
Hyperthyroidism

- 2 mechanisms:
  - iodine-induced hyperthyroidism
  - induction of thyroiditis
- 3% to 5% of patients treated with amiodarone become hyperthyroid, usually between 4 months and 3 years after the initiation of the drug
- 2 types
  - Type 1 typically occurs with nontoxic MNG or Graves disease *(pre-existing thyroid disease): Abs sometimes +, uptake low/absent, Tt with thionamides*
  - Type 2 - drug-induced destructive thyroiditis: *Abs-, uptake low/absent, Tt with glucocorticoids*
  - *Many patients have an overlap syndrome between type 1 and type 2 disease*

Batcher EL, Tang XC, Singh BN, et al, SAFE-T Investigators. Am J Med 2007;120(10):880–5

Effects of Lithium on thyroid

- Can cause goiter, hypothyroidism, chronic autoimmune thyroiditis, and possibly hyperthyroidism
- Mechanism - *not well understood*
  - In vitro, decreases colloid droplet formation within thyroid follicular cells, a reflection of decreased pinocytosis of colloid from the follicular lumen
  - Efficiency of proteolytic digestion of thyroglobulin within phagolysosomes may be impaired
  - Inhibition of thyroid hormone results in an increase in pituitary TSH and an enlarged thyroid gland (prevalence of goiter may be as high as 50% and usually occurs within the first 2 years of treatment)
- Hypothyroidism has been reported in 5% to 20% of patients treated with lithium, usually occurs within the first 2 years of therapy, and tends to be subclinical in nature
- Lithium treatment usually need not be discontinued if LT4 is initiated

Shine B et al. Lancet. 2015 Aug 1;386(9992):461-8.
Kibirige et al. Thyroid Research 2013, 6:3

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Common medications and effects on thyroid - mechanisms

Mechanism	Effect
Increased hepatic metabolism of T4	Rifampin, phenytoin, carbmazepine, barbiturates
Decreased thyroidal synthesis	Carbimazole, PTU, lithium
Displacement of T4/T3 from plasma proteins	Furosemide (high doses), NSAIDs, mefenamic acid, carbamazepine, β-blockers
Increased TBG, TT4, TT3	Estrogens, tamoxifen, heroin, methadone
Decrease TBG, TT4, TT3	Androgens, anabolic steroids, glucocorticoids
Impair absorption of LT4	Cholestyramine, aluminium hydroxide, ferrous sulfate, sucralfate, calcium carbonate, PPI

Normally, about 80% of a usual dose of LT4 is absorbed, mostly in the jejunum and the upper part of the ileum

Normal gastric acid secretion seems to be necessary for normal thyroid hormone absorption

Hays MT. Endocr Res 1988;14(2-3):203–24

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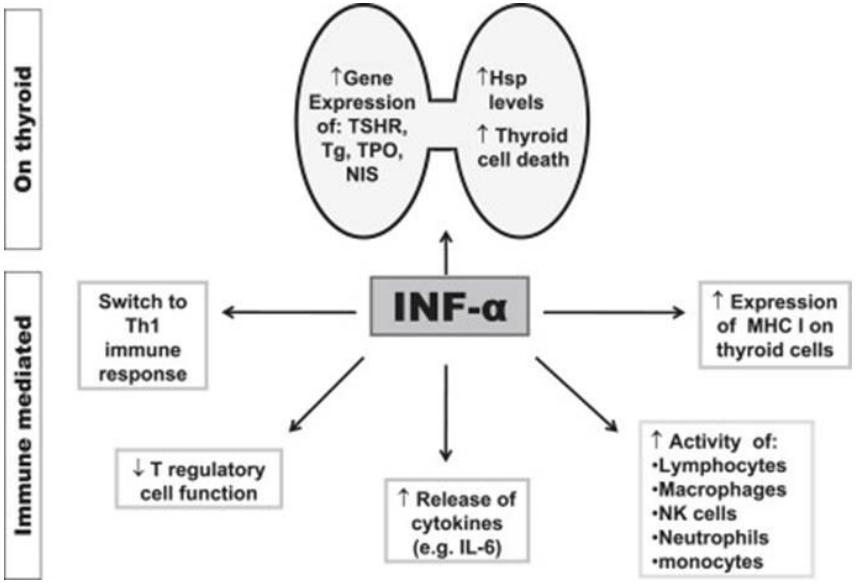
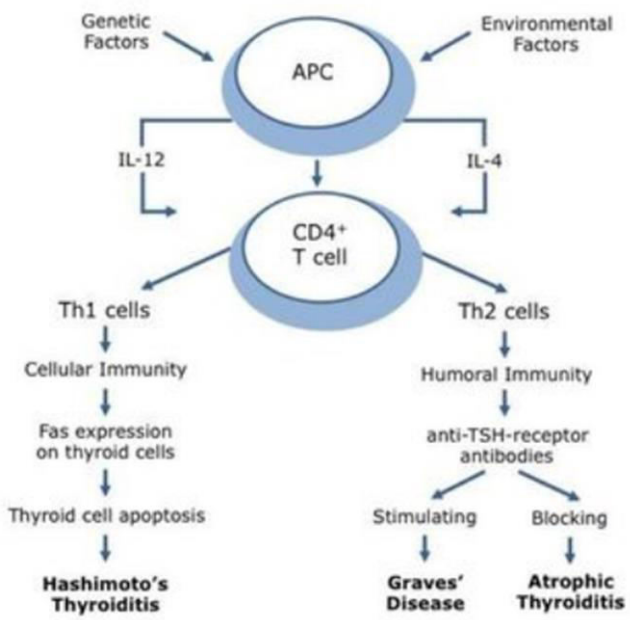
Interferons and thyroid dysfunction

- Etiology
  - Autoimmune (often subclinical) hypothyroidism
  - Destructive thyroiditis,
  - Graves-like hyperthyroidism
- Incidence: 2.4 – 31 %
- Hypo > Hyper
- Abn TFTs can occur as early as 4 weeks and as late as 23 months after initiation
- Tpo+
- TSH measurements: every 8 to 12 weeks during IFN α treatment



Carella C, Mazziotti G, Amato G, et al. JCEM2004; 89(8):3656–61

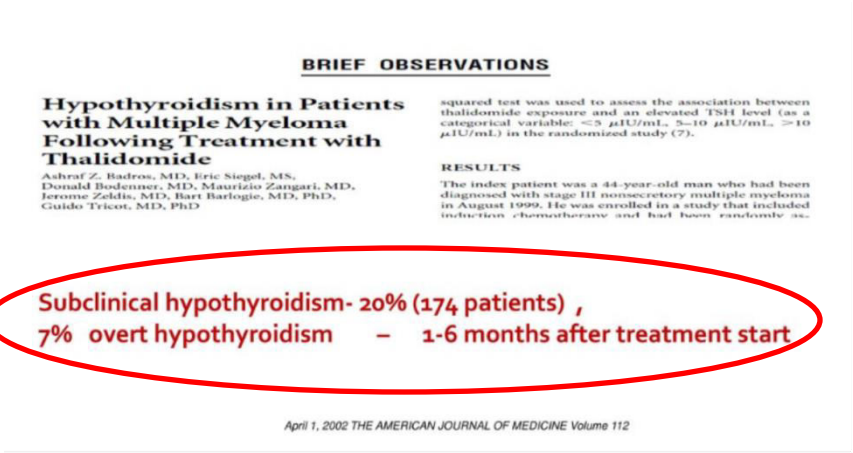
Interleukins and Thyroid



- Induction of thyroid antibodies
- Early phase – destructive thyrotoxicosis with variable degrees of hyperthyroidism
- Hypothyroidism with Tpo+
  - 4 – 17 week after starting therapy, reversible
  - Occurs in 10 – 60% of pts

THYROID Volume 23, Number 11, 2013; Torino et al

Lenalidomide induced thyroid dysfunction



BRIEF OBSERVATIONS

Hypothyroidism in Patients with Multiple Myeloma Following Treatment with Thalidomide

Ashraf Z. Badros, MD, Eric Siegel, MS, Donald Bodenner, MD, Maurizio Zangari, MD, Jerome Zeldis, MD, Bart Barlogie, MD, PhD, Guido Tricot, MD, PhD

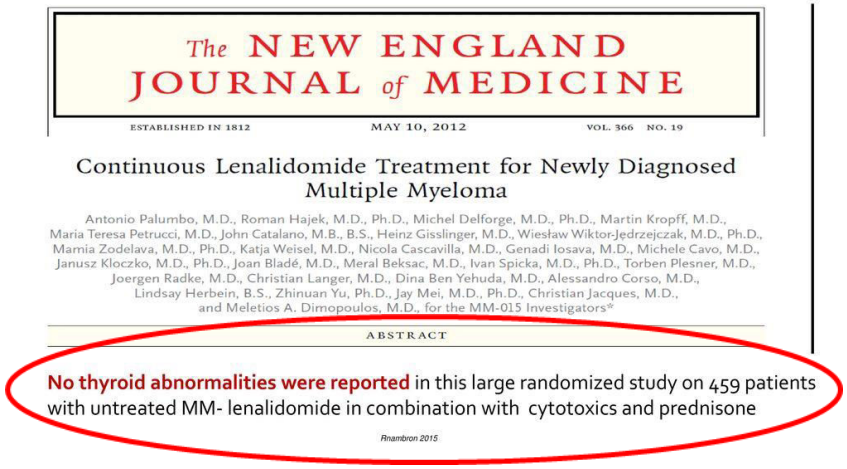
squared test was used to assess the association between thalidomide exposure and an elevated TSH level (as a categorical variable: <5 μIU/mL, 5–10 μIU/mL, >10 μIU/mL) in the randomized study (7).

RESULTS

The index patient was a 44-year-old man who had been diagnosed with stage III nonsecretory multiple myeloma in August 1999. He was enrolled in a study that included induction chemotherapy and had been randomly as-

Subclinical hypothyroidism- 20% (174 patients) ,
7% overt hypothyroidism – 1-6 months after treatment start

April 1, 2002 THE AMERICAN JOURNAL OF MEDICINE Volume 112



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 10, 2012 VOL. 366 NO. 19

Continuous Lenalidomide Treatment for Newly Diagnosed Multiple Myeloma

Antonio Palumbo, M.D., Roman Hajek, M.D., Ph.D., Michel Delforge, M.D., Ph.D., Martin Kropff, M.D., Maria Teresa Petrucci, M.D., John Catalano, M.B., B.S., Heinz Gisslinger, M.D., Wiesław Wiktor-Jędrzejczak, M.D., Ph.D., Mamia Zodelava, M.D., Ph.D., Katja Weisel, M.D., Nicola Cascavilla, M.D., Genadi Iosava, M.D., Michele Cavo, M.D., Janusz Kloczko, M.D., Ph.D., Joan Bladé, M.D., Meral Beksac, M.D., Ivan Spicka, M.D., Ph.D., Torben Plesner, M.D., Joergen Radke, M.D., Christian Langer, M.D., Dina Ben Yehuda, M.D., Alessandro Corso, M.D., Lindsay Herbein, B.S., Zhinuan Yu, Ph.D., Jay Mei, M.D., Ph.D., Christian Jacques, M.D., and Meletios A. Dimopoulos, M.D., for the MM-015 Investigators*

ABSTRACT

No thyroid abnormalities were reported in this large randomized study on 459 patients with untreated MM- lenalidomide in combination with cytotoxics and prednisone

Rnambron 2015

Monoclonal antibodies:

CTLA-4, Programmed Cell death 1 and Programmed Cell Death Ligand 1

- Anti CTL4 Mab- Ipilimumab and tremilimumab
- Breaking the negative immune modulatory effect removes CTLA4-mediated protection from autoimmunity lead to immune-related adverse events (IRAEs)
- **Secondary hypothyroidism and hypophysitis** has incidence 0-17% (variable)
- **Primary thyroid dysfunction 0-2%**
- **Primary adrenal insufficiency 0.3-1.5%**

- Dose dependent -- 1-3mg/kg – 1.8 to 3.3%
  >3mg/kg with or without vaccine – 4.7 to 17%
- Other – hypothyroidism and primary adrenal insufficiency
- Combined with chemo – no endocrine toxicity noted

- Tremelimumab– hypothyroidism- 4%, hypophysitis-0.4%
- Nivolumab- anti PD-1 – hypophysitis -<1%
- Anti PD-L1– hypothyroidism 3%, primary adrenal insuff 1.5%,no hypophysitis

J Clin Endocrinol Metab, April 2013, 98(4):1361–1375

Other monoclonal antibodies

- Alemetuzumab – humanized Mab binding CD52 antigen on lymphocytes and monocytes
- High risk pre treated B cell chronic lymphocytic leukemia
- Thyroid dysfunction – hypothyroidism, thyroiditis and Graves'- only seen when used in autoimmune disease like MS not in cancer (reason unknown)

- Iodine based anticancer radioimmunotherapy- Tositumomab
- Anti CD20 Mab with iodine- Non Hodgkin's lymphoma
- I 131 metaiodobenzylguanidine- pheochromocytoma,neuroblastoma,carcinoid tumors
- Hypothyroidism 9-64% pts 6-24 months later
- Prevention- lugol iodine or potassium perchlorate

Hypothesis: drug-induced lymphopenia in patients with previously existing occult autoimmune thyroiditis predisposes to a reactivation of autoimmune mechanisms when T-lymphocytes are repopulated and thus to an aberrant immune reconstitution

Occurs in Tpo+ individuals

CAMMS223 Trial Investigators, Coles AJ, Compston DA, et al. NEJM. 2008;359:1786–801
Gillard P, Huurman V, Van der Auwera B, et al. Diabetes Care 2009;32:1–8.

Tyrosine Kinase Inhibitors

- Axitinib
- Sorafenib
- Sunitinib
- Levatinib
- Vandetinib

Affecting TK receptors

- Everolimus
- Temsirolimus

Affecting mToR pathway

- Variable affinity for different kinase receptors
- Thyroid dysfunction with those that inhibit angiogenic pathways : VEGFR & PDGFR
- Incidence 14 – 71%
- Denovo hypo or hperthyroidism, worsen pre existing hypothyroidism

Mechanism of Thyroid Dysfunction with TKI

- Destructive thyroiditis
- Regression of thyroid vascular bed causing ischemic thyroiditis
- Induction of Hashimoto`s thyroiditis
- Impairment in deiodinases

British Journal of Cancer (2008) **99**(3), 448 – 454

Role of endocrine disruptors

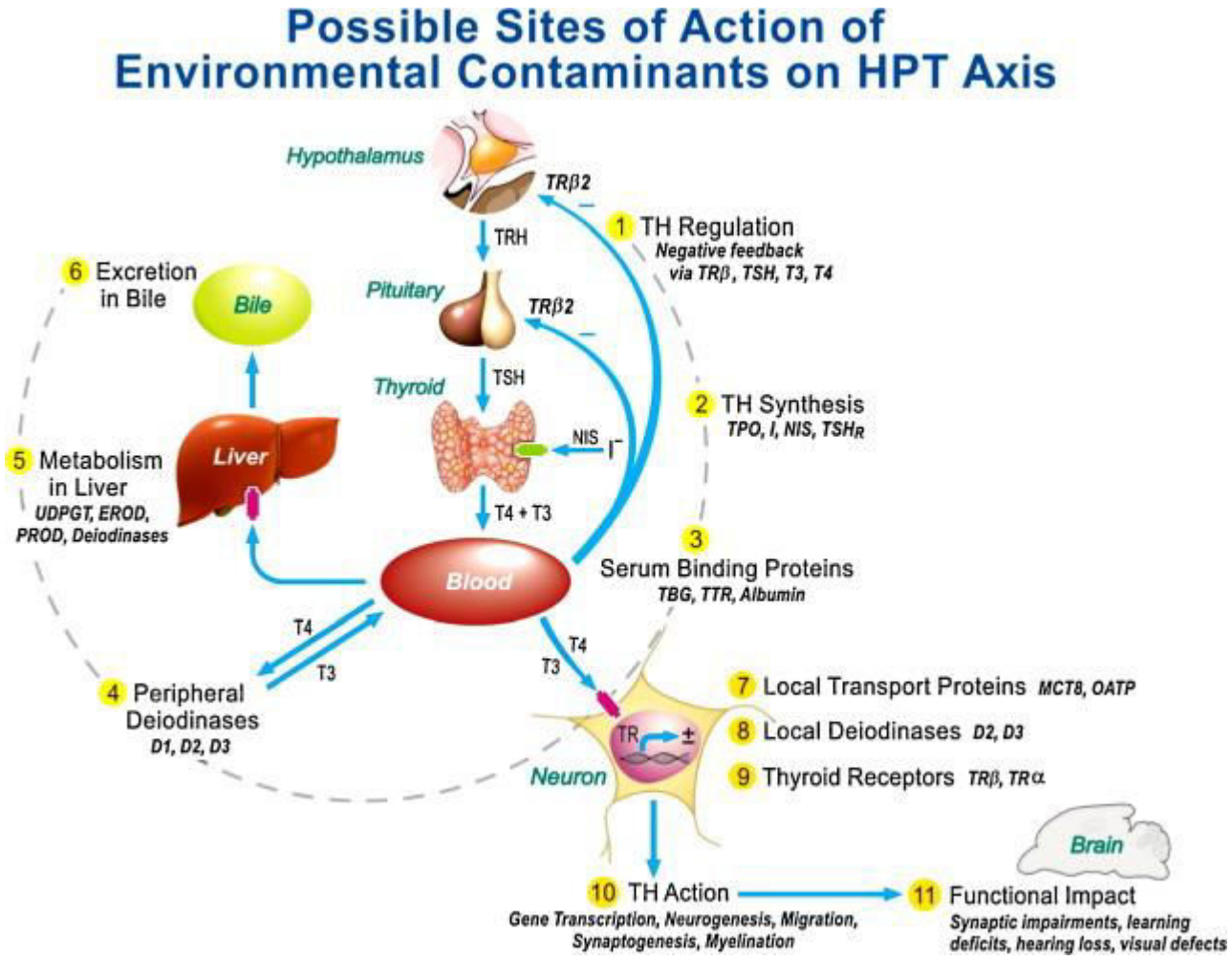


Table 3. Thyroid disruptors: clinical effect and putative mechanism. Notice that some products have several toxic effects

Xenobiotic product	Clinical effect on thyroid metabolism	Putative mechanism
Perchlorates, thiyocyanate, nitrate, phthalates, bromates	Decreases synthesis of T3 and T4	Blocking iodide uptake into thyroid cell
Soy, isoflavones, methimazole, benzophenone 2 (pesticide), amitrole (pesticide)	Decreases synthesis of T3 and T4	Blocking TPO production into thyroid cell
PCBs, pentachlorophenol, flame retardants, phthalates	Possible effect on fetal brain T4 production and brain development	Compete to thyroid transport protein
Dioxin, PBDE, chlordane (pesticide)	Increase billiary elimination of both T4 and T3	Alter transport across cell membrane
Acetochlor (herbicide)	Increase billiary metabolism of both T4 and T3	Enhance hepatic metabolism
Triclosan, PCBs, dioxin, difuran, pentachlorophenol (pesticide)	Decrease sulfation of thyroid hormones and possibly decrease peripheral T3 synthesis	Inhibit sulfation
PCBs, octyl methoxycinnamate, FD&C red dye	Decrease peripheral T3 synthesis	Inhibit deiodinase activity
DDT, PCBs	Decrease T3 and T4 production	Inhibit TSH receptor

Polychlorinated biphenyls (PCBs) were commonly used as stabilizing additives in the manufacture of flexible PVC coatings for electrical wiring and electronic components to enhance the heat and fire resistance of the PVC.

Perchlorates are used extensively within the pyrotechnics industry, and ammonium perchlorate is also a component of solid rocket fuel.

Thiyocyanate is used as a precursor for the synthesis of pharmaceuticals and other specialty chemicals.

Dioxins are the by-products of various industrial processes (i.e., bleaching paper pulp, and chemical and pesticide manufacture) and combustion activities (i.e., burning household trash, forest fires, and waste incineration).

Bromates are formed many different ways in municipal drinking water.

Phthalates are mainly used as plasticizers (substances added to plastics to increase their flexibility, transparency, durability, and longevity).

Difuran is used in the elaboration and/or manufacturing of flavor and fragrance agents.

Octyl methoxycinnamate is an compongent used in some sunscreens and lip balms.

Summary

- Drug-induced thyroid disorders are common in clinical practice
- It is important to recognize the various drugs contributing to thyroid dysfunction for a timely intervention to help achieve a euthyroid state
- Generally reversible, but need close watch-up and follow up

Thanks !