THYROID AND ANTITHYROID DRUGS

Pinpilai Jutasompakorn, MD

Department of Pharmacology

Faculty of Medicine Siriraj Hospital

วัตถุประสงค์

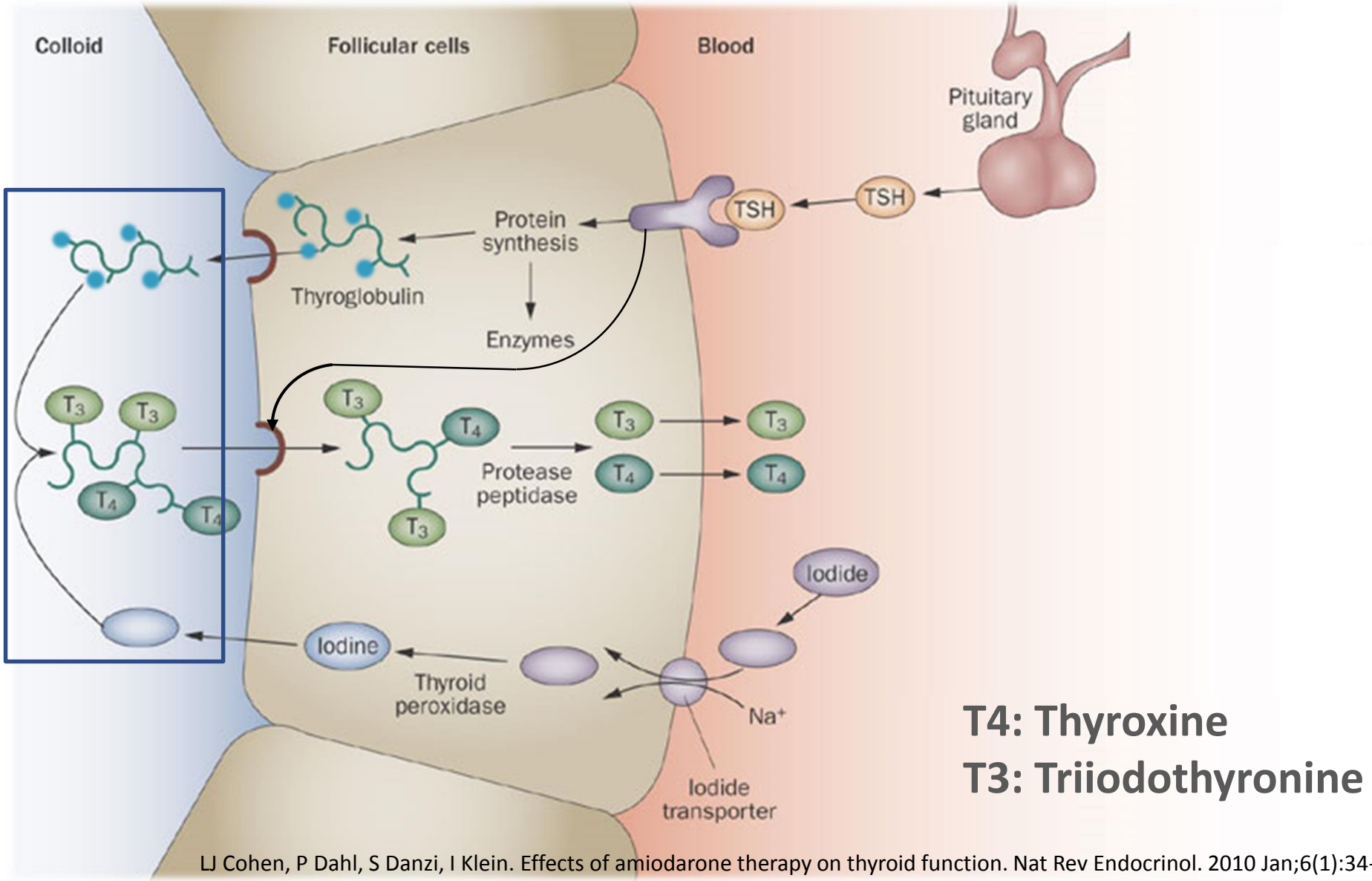
เมื่อสิ้นสุดการเรียนการสอนแล้วนักศึกษาสามารถ

1. อธิบายกลไกการออกฤทธิ์ของ thyroid และ antithyroid drugs
2. อธิบายคุณสมบัติทางเภสัชจลนศาสตร์ ฤทธิ์แทรกแซงและปฏิกิริยาระหว่างยาของ thyroid และ antithyroid drugs ที่สำคัญ
3. บอกหลักการทั่วไปของการใช้ thyroid และ antithyroid drugs ในทางคลินิก
4. บอกชื่อยาที่สำคัญและกลไกของยาดังกล่าวที่มีผลต่อไทรอยด์ฮอร์โมน

SCOPE

- **Thyroid hormone & drugs affecting thyroid function**
- **Hypothyroidism & hormone replacement therapy**
  - **Levothyroxine**
- **Hyperthyroidism & antithyroid agents**
  - β-blocker
  - **Thioamides (PTU and MMI)**
  - Corticosteroids
  - Iodine and Iodine-Containing Agents

Thyroid Hormone synthesis

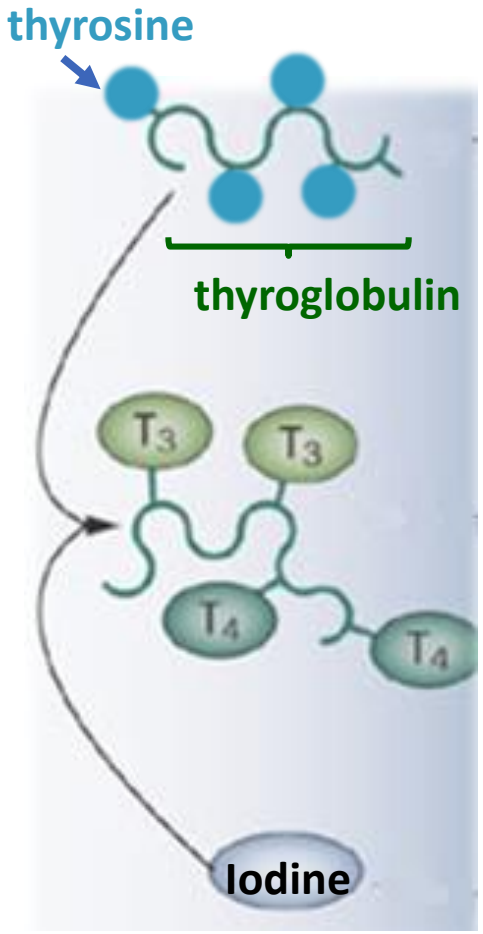


T4: Thyroxine

T3: Triiodothyronine

LJ Cohen, P Dahl, S Danzi, I Klein. Effects of amiodarone therapy on thyroid function. Nat Rev Endocrinol. 2010 Jan;6(1):34-41.

Thyroid Hormone synthesis



Adapted from LJ Cohen, P Dahl, S Danzi, I Klein.
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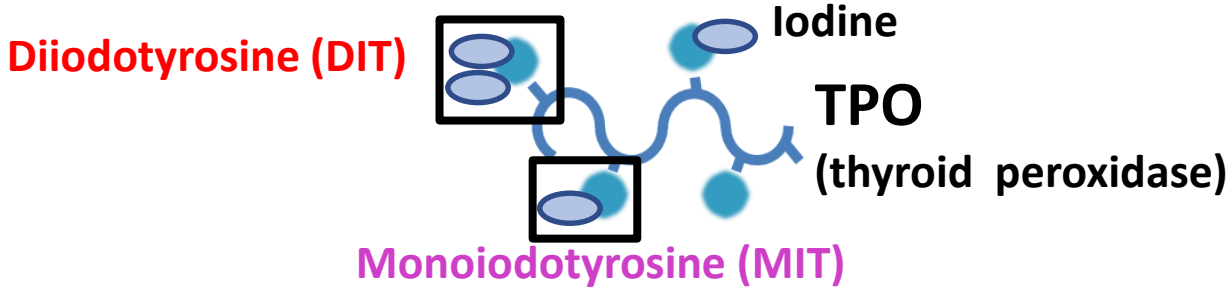
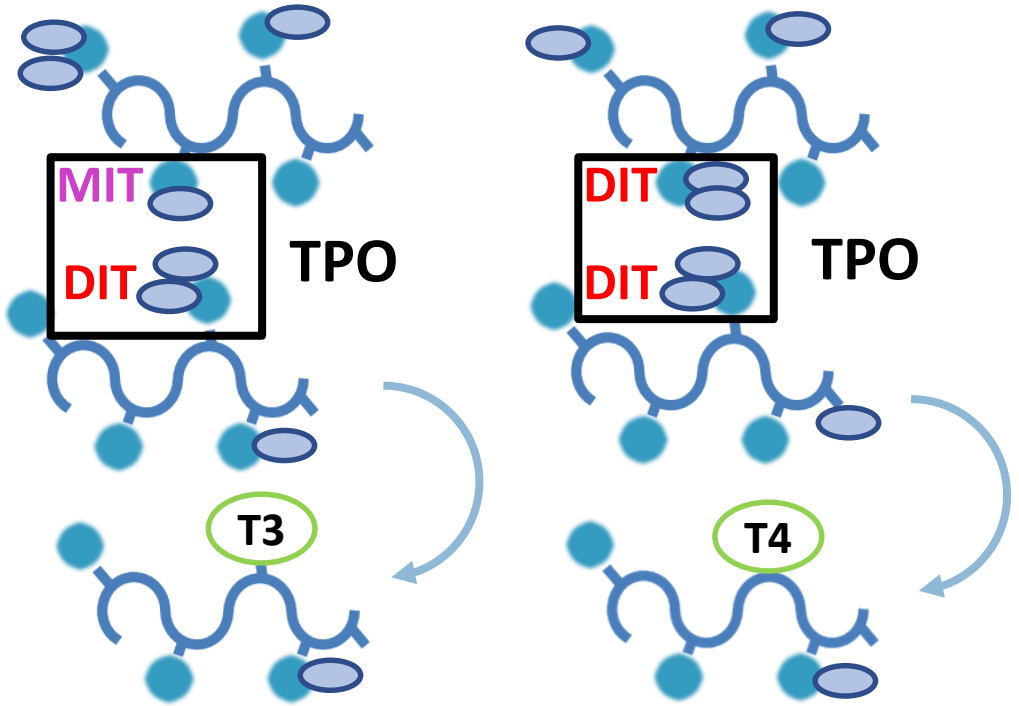
Nat Rev Endocrinol. 2010 Jan;6(1):34-41.

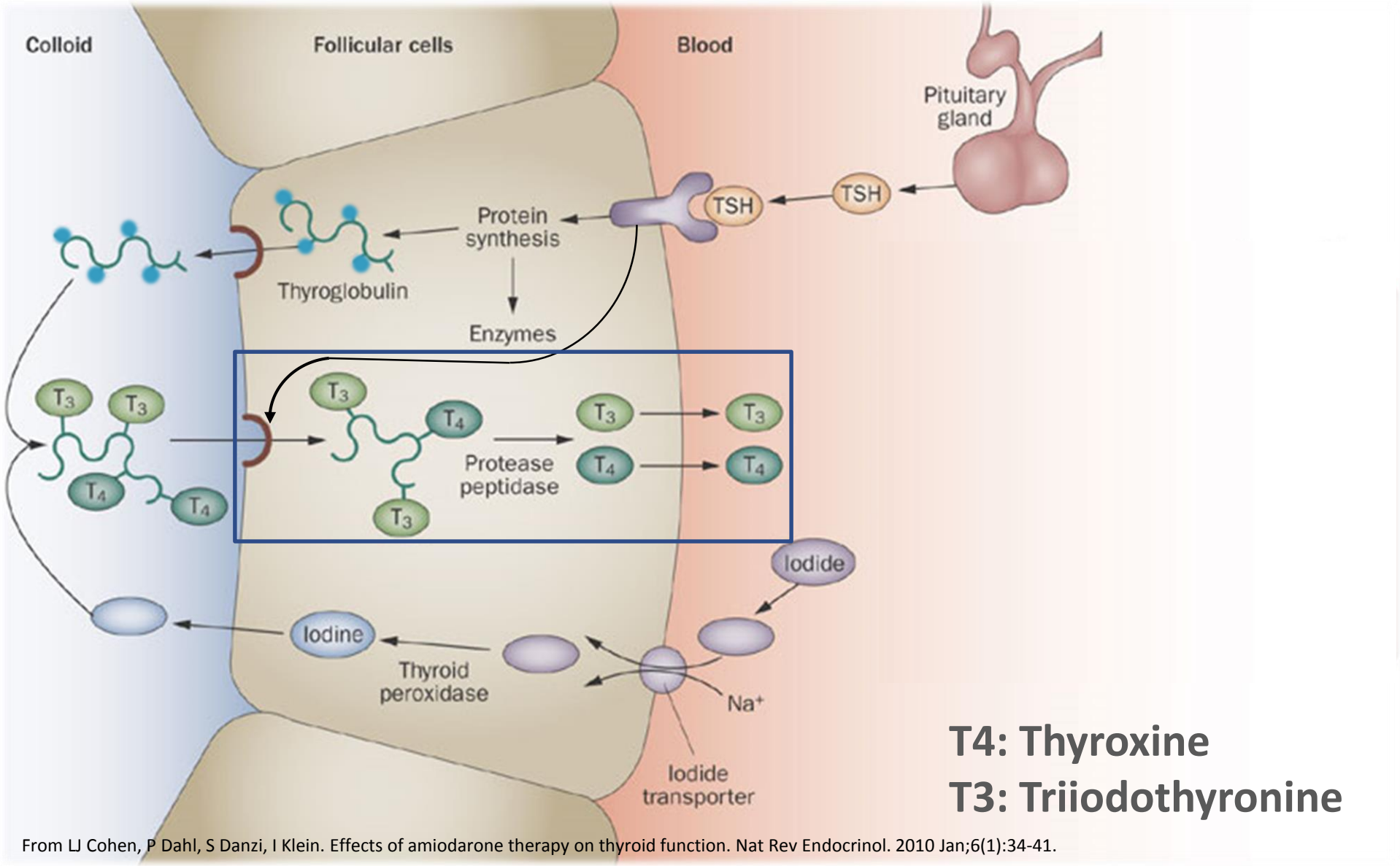
Organification (thyroglobulin iodination)



Coupling (DIT+MIT or DIT+DIT)



Thyroid Hormone synthesis



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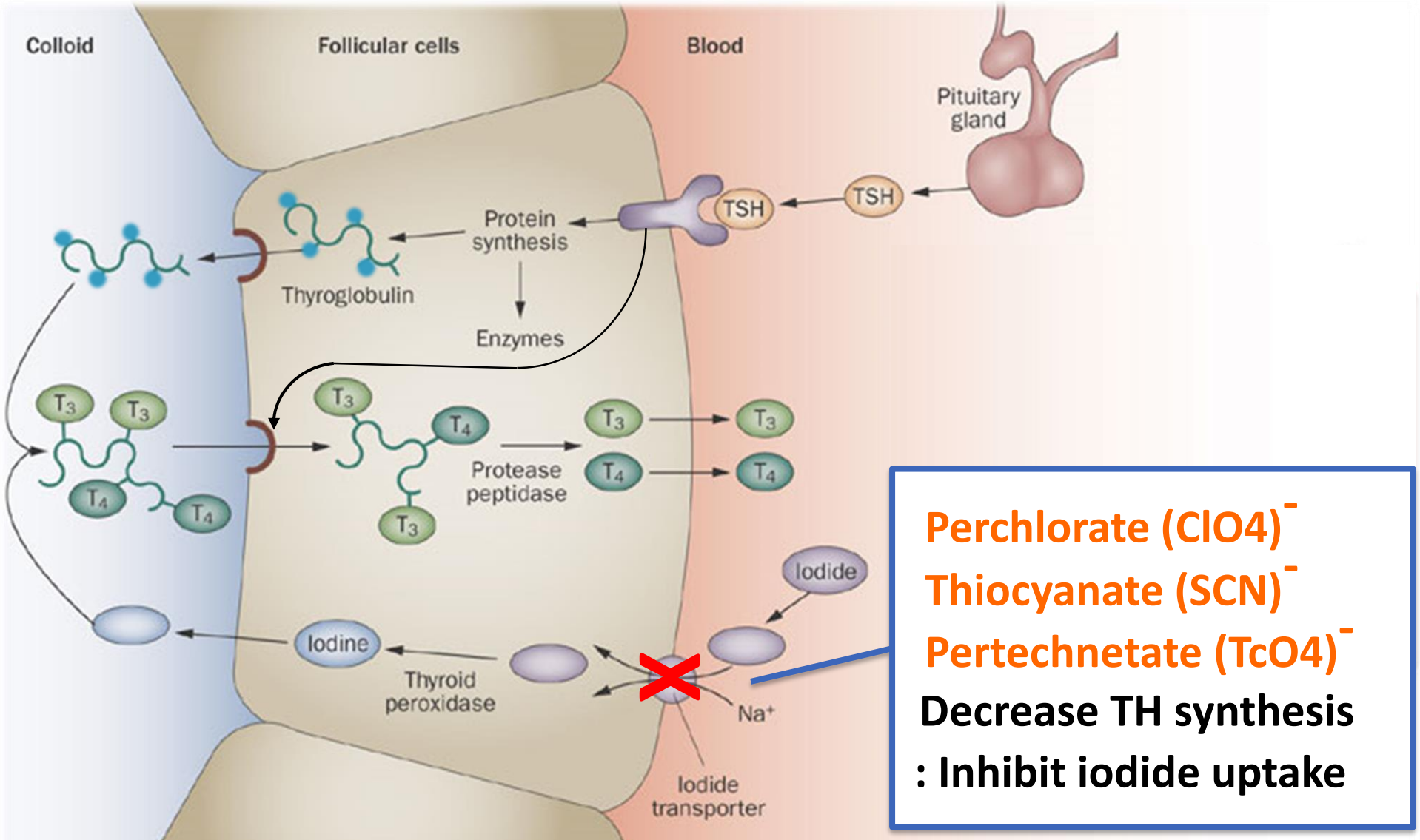
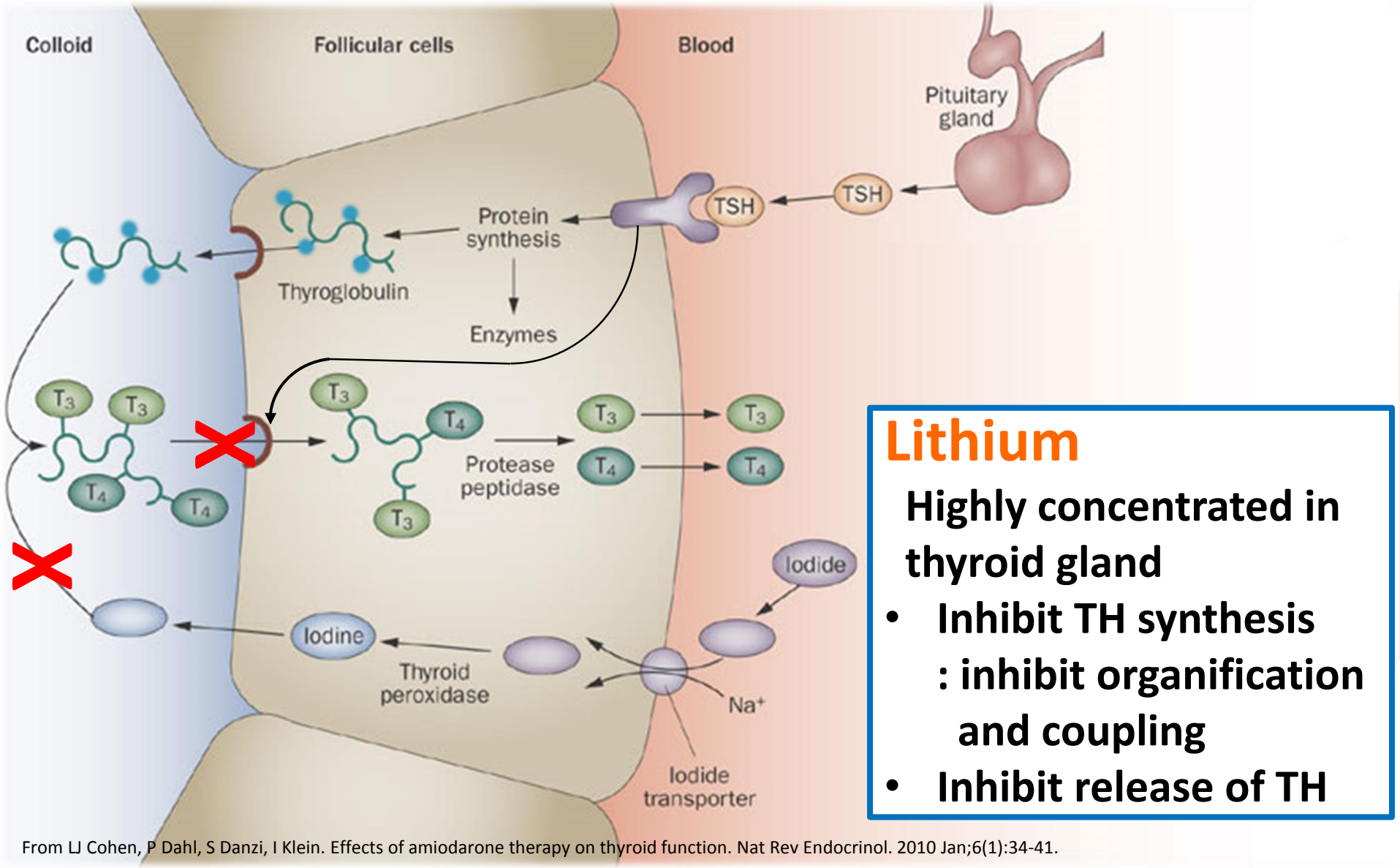
Drugs affecting TH synthesis



Perchlorate $(ClO4)^-$
Thiocyanate $(SCN)^-$
Pertechnetate $(TcO4)^-$
Decrease TH synthesis
: Inhibit iodide uptake

From LJ Cohen, P Dahl, S Danzi, I Klein. Effects of amiodarone therapy on thyroid function. Nat Rev Endocrinol. 2010 Jan;6(1):34-41.

Drugs affecting TH synthesis



Lithium

Highly concentrated in thyroid gland

- **Inhibit TH synthesis**
  : inhibit organification and coupling
- **Inhibit release of TH**

From LJ Cohen, P Dahl, S Danzi, I Klein. Effects of amiodarone therapy on thyroid function. Nat Rev Endocrinol. 2010 Jan;6(1):34-41.

Drugs affecting TH synthesis

Thioamides:

Propylthiouracil (PTU) & Methimazole (MMI)

- **Inhibit hormone synthesis**

  : inhibit organification and coupling

Drugs affecting TH synthesis

Iodine (High concentration)

- **Inhibit thyroid hormone synthesis**

  : inhibit Iodide uptake and organification

- **Inhibit the release of thyroid hormone**

Radioactive iodine (I-131)

- **Emit ɣ ray and β particles: toxic to cell**
- **Selective local destruction of thyroid gland**

Metabolism and Excretion

Peripheral conversion of T4 to T3

- Deiodination: T4 ⟶ T3

  Type I deiodinase (D1) in liver & kidney

- Accounts for most of the T3 in the body

Inactivation of T4 and T3

- Phase I or phase II metabolism in the liver
- Deiodination by Type III deiodinase (D3)

Excretion: bile and urine

Half-life: T4 - 7 days

T3 - 1 day

Drugs affecting TH metabolism and excretion

Inhibit D1 (Inhibit peripheral conversion)**

- **PTU**
- **Propranolol**
- **Glucocorticoid**
- **Amiodarone**

- Acute & chronic illness
- Caloric deprivation and malnutrition
- Selenium deficiency

Drugs affecting TH metabolism and excretion

Increased hepatic enzyme activity

(Inactivation of thyroid hormone)

- Phenobarbital
- Phenytoin
- Carbamazepine
- Rifampin

Transport of Thyroid Hormone

Most of them are bound form

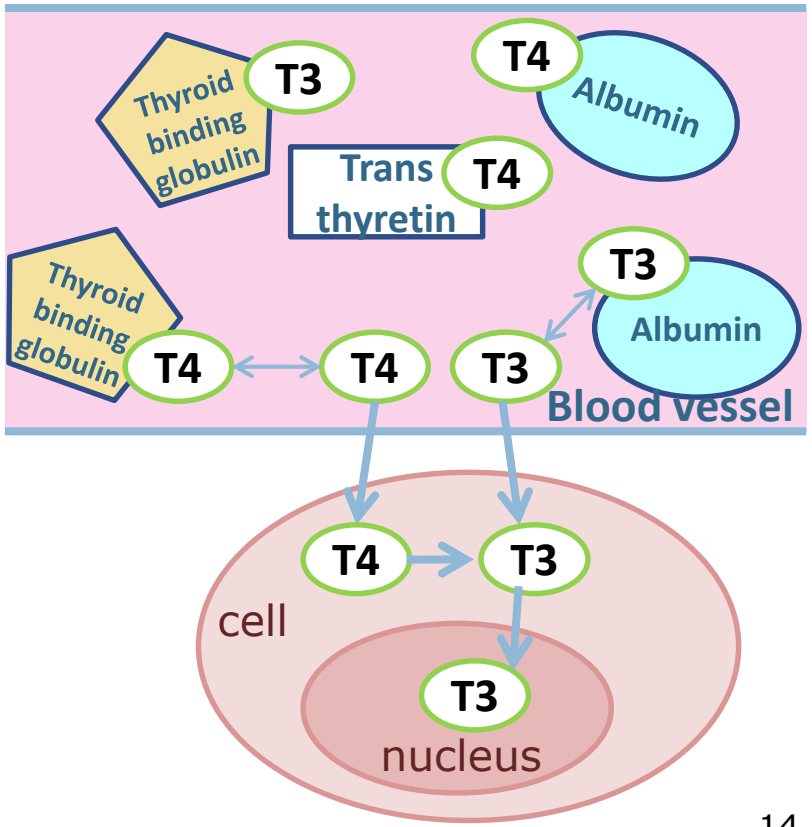
- T4 0.02% unbound
- T3 0.3% unbound

Active form

Thyroid binding proteins

- **Thyroid binding globulin (TBG)**
  : major carrier (high affinity)
- Transthyretin
- Albumin

Protects TH from metabolism & excretion



Drugs affecting TH transport

Change in TBG concentration

↑ TBG: **Estrogens**

↑ Total T3 & total T4

Tamoxifen ,Methadone ,Clofibrate , 5-Fluorouracil

↓ TBG: **Androgens ,Glucocorticoids**

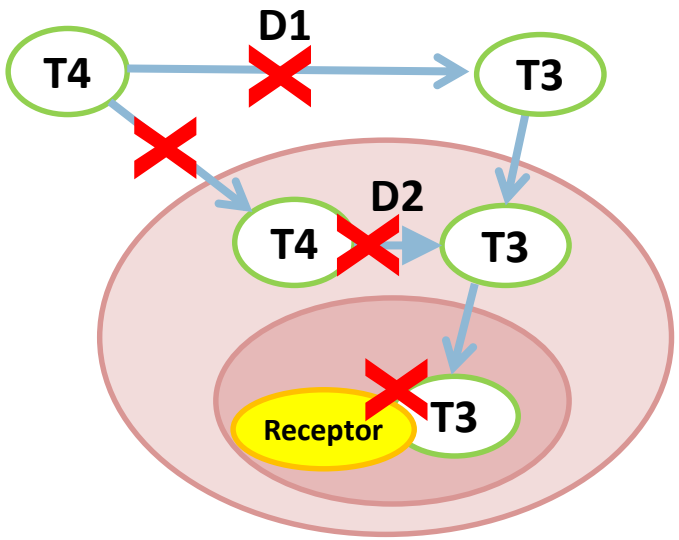
↓ Total T3 & total T4

Thyroid function test : Free form is more accurate

Amiodarone

Intrinsic drug effects

- Inhibit D1 and D2
- Blockade of T4 entry into cell
- Decrease T3 binding to receptor
- Destructive thyroiditis



Amiodarone

Iodine-induced effects

- Failure to escape from Wolff-Chaikoff effect produces **hypothyroidism**
- Unregulated hormone synthesis produces **hyperthyroidism** (Jod-Basedow effect)

Baseline thyroid function test : TSH, FT4, T3

The American Journal of Medicine, Vol 118, No 7, July 2005

Drugs affecting thyroid function

Inhibit iodide uptake	**Iodine,** perchlorate, thiocyanate, pertechnetate
Inhibit organification &coupling	**Iodine, lithium, PTU, MMI**
Inhibition of TH release	**Iodine, lithium**
Inhibit peripheral T3 to T4 conversion	**PTU, Propranolol, Glucocorticoid, Amiodarone**
Increased hepatic enzyme activity	Phenobarbital, Phenytoin, Carbamazepine, Rifampin
Change in TBG concentration **↑ TBG** **↓ TBG**	 **Estrogens** **Androgens ,Glucocorticoid**
↓ binding of T3 and T4 to TBG	Salicylates, mefenamic acid, furosemide
Blocks T3 receptor binding in TH sensitive tissue	**Amiodarone**

Glucocorticoid: decrease TSH, TBG concentration and inhibit peripheral conversion

Hormone replacement therapy in hypothyroidism

Levothyroxine (L-T4) and Liothyronine (L-T3)

- Treatment is almost always with L-T4
- Peripheral deiodination can produce T3 under normal physiologic control

Levothyroxine (L-T4)

Pharmacokinetic

- Absorption from GI tract ranges from 50-80%
  (better on an **empty stomach**)
- **Cholestyramine, iron, calcium, aluminum hydroxide** and soy products may **interfere with absorption**
- Drugs that induce hepatic enzyme: ↑ L-T4 inactivation

(phenytoin, carbamazepine, rifampin)

- Long half-life (7 days)

- A single daily dose improve compliance significantly

- Omission of a single dose has no significant effect

Levothyroxine (L-T4)

Clinical use in hypothyroidism

- 1.6-1.8 µg/kg/d (ideal body weight)
- Initial dose depends on degree of hypothyroidism, age and general health of the patient
- Equilibration of L-T4 require 5-6 weeks
- Goal in primary hypothyroidism

  : **normal TSH** (lower half of reference range)

Levothyroxine (L-T4)

Adverse Effects: Excessive doses causes

- Accelerated bone loss in postmenopausal patients
- Increases cardiac wall thickness and contractility
- Increases risk of atrial fibrillation in elderly

Indication of thyroid hormone

- **Replacement therapy in hypothyroidism**

(Including myxedema coma & subclinical hypothyroidism)

- TSH suppression therapy in thyroid cancer

(Adjuvant therapy of differentiated thyroid cancer)

Thyrotoxicosis

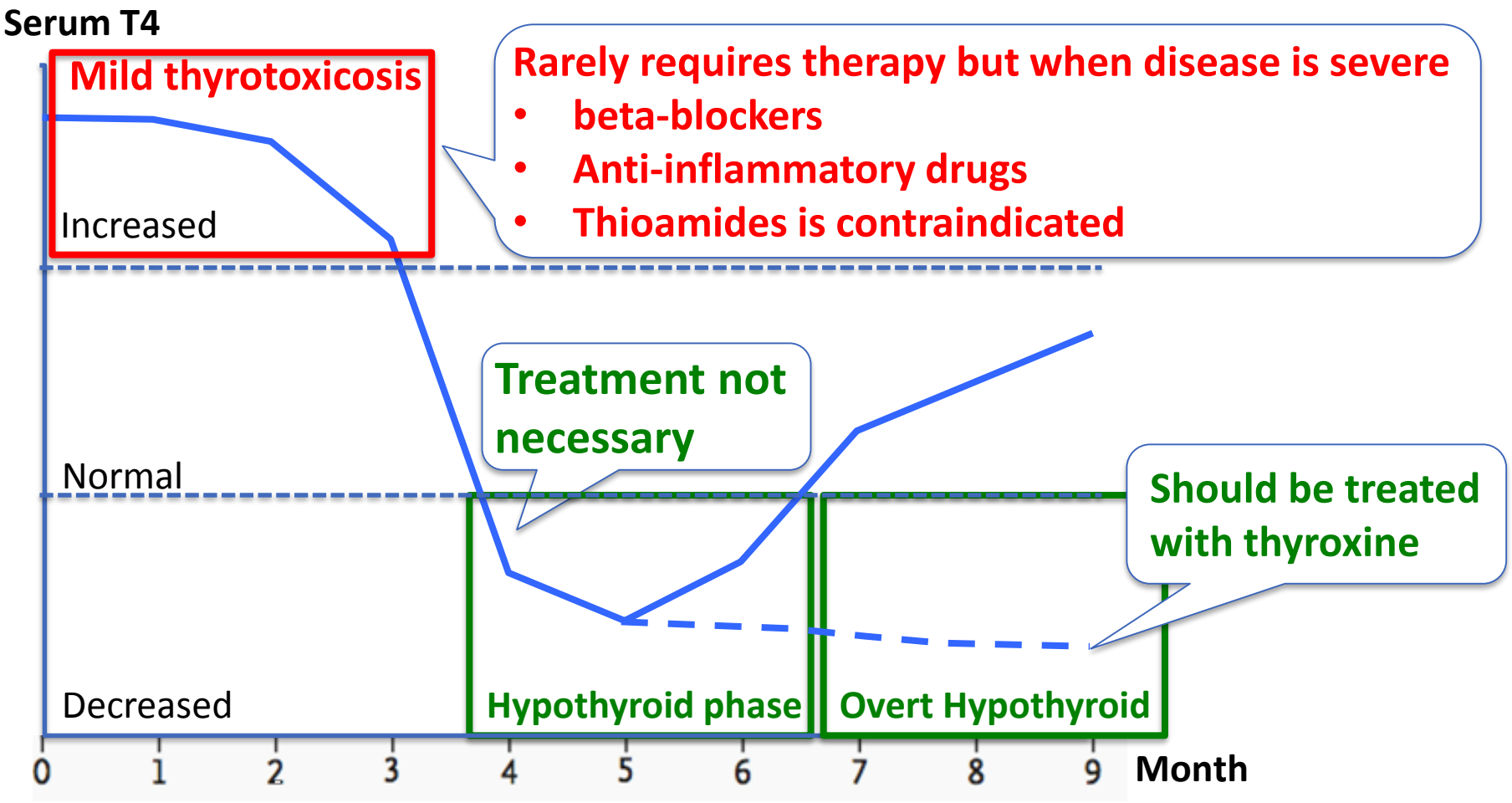
Excessive quantities of thyroid hormones

- Hyperthyroidism : sustained overproduction and release of hormone by thyroid gland
- Inflammation of the thyroid gland (thyroiditis)
- Exogenous thyroid hormone

Different causes of thyrotoxicosis

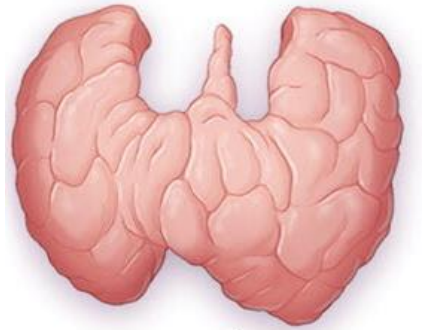
Different in the treatment

Treatment of thyroiditis

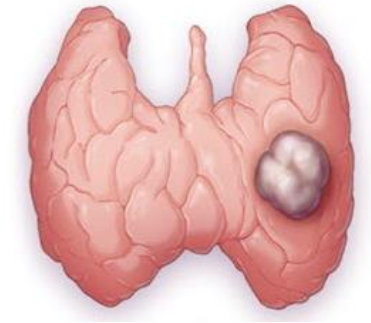


De Quervain thyroiditis, Painless thyroiditis

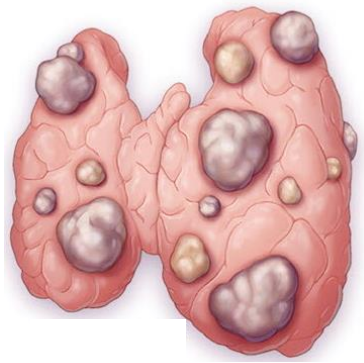
Hyperthyroidism



Graves' disease



Toxic adenoma



Toxic multinodular goiter

From Douglas S. Ross, M.D.Radioiodine Therapy for Hyperthyroidism. N Engl J Med 2011; 364:542-550

Treatment

- **Antithyroid Agents**
- **I-131**
- **Surgery**

Antithyroid Agents

- β-blocker
- Thioamides
- Corticosteroids
- Iodine and Iodine-Containing Agents

β-blocker

- Rapidly decrease some manifestations of thyrotoxicosis
- Most useful before the response to thioamide and radioiodine therapy occurs
- Propranolol: block the conversion of T4 to T3

Thioamides

	Propylthiouracil (PTU)	Methimazole (MMI)
Mechanism of actions	**Inhibit organification & coupling Inhibits peripheral conversion of T4 to T3**	**Inhibit organification & coupling**
Plasma half life	1.5 hours	6 hours
Dosing frequency	**2-3 times daily**	**Once daily**
Serum proteins binding	80-90% bound form	Free form
Onset of activity **(full effect)**	3-4 weeks	3-4 weeks
Initial dosage	150-300 mg/d	15-30 mg/d
Maintenance dosage	100-200 mg/d	5-10 mg/d

Both drugs are accumulated by thyroid gland

N Engl J Med 2005; 352:905-917

Thioamides

Clinical use

- **Treatment for Graves' disease**: remission is possible
- Prefer in severe graves' ophthalmopathy (radioiodine therapy ➔ worsening opthalmopathy)
- Hyperthyroidism in pregnancy, children, adolescents

Toxic multinodular goiters/toxic adenoma

- Radioiodine or surgery
- Thioamides: spontaneous remissions rarely occur

Thioamides

Clinical use

Preparative therapy before radiotherapy or surgery

- Normalize thyroid function
- Decrease a post-treatment increase in thyroid hormone release

Thioamides

Side effects

Minor side effects

- **Cutaneous reactions**

  (urticaria or macular rashes)

- **Arthralgia**

- **GI upset**

Common and equal frequency for both drugs

Major side effects

- **Agranulocytosis**
- **Hepatotoxicity**
- **Vasculitis** (rare)

Excessive amounts of drugs over long periods➔Hypothyroidism

Thioamides

Major side effects: Agranulocytosis

- Absolute granulocyte count < 500/mm3
- **Fever & sore throat**
- **Dose dependent in MMI but idiosyncrasy in PTU**
- Most cases occur within first 3 months of treatment
- **Baseline CBC before initiation of therapy**
- **Immediate cessation of drugs**
- **Use of thioamides is contraindicated**

(Cross-reactivity between PTU & MMI are well documented)

Thioamides

Major side effects: Hepatotoxicity

PTU: hepatocellular injury (↑AST, ALT)

vary in severity (mild transient transaminitis - **liver failure**)

MMI: cholestasis (↑ALP, TB)

complete but slow recovery after drug discontinuation

- Develop approximately 3 months after treatment
- Baseline transaminases, bilirubin, and ALP
- Immediate cessation of drugs
- Alternative thioamides can be used cautiously in drug induced hepatotoxicity

Thioamides

Major side effects: Vasculitis

- Rarely occur
- **PTU > MMI**
- **Use of thioamides is contraindicated**

A 30-year-old male comes to the hospital because of weight loss, increased appetite and tiredness. Physical examination shows diffuse thyroid gland enlargement with bruit. Laboratory studies show markedly decreased serum TSH, elevated T3 and FT4 levels.

A. **Propranolol**
B. **Propylthiouracil (PTU)**
C. **Methimazole (MMI)**

Choice of drugs

Major side effects	PTU	MMI
Agranulocytosis	**Idiosyncrasy**	**Dose dependent**
Hepatotoxicity	**Hepatitis** (liver failure in severe case)	**Cholestasis** (rare)
Vasculitis	**More**	**Less**

Thioamides

Choice of drugs

MMI is usually preferred over PTU because it has **fewer major side effects** and better adherence, **except for**

- **1st trimester pregnancy**: aplasia cutis, choanal and esophageal atresia are associated with MMI
- **Thyrotoxic crisis** (Thyroid storm)

  high dose PTU decrease T4 to T3 conversion

From Karg E, Bere E, Gasper L, Katona M, Turi S. Aplasia cutis congenita after methimazole exposure in utero. Pediatr Dermatol. 2004 Jul-Aug;21(4):491-4.

Thioamides

Response to treatment in Graves's disease

- Metabolic state becomes normal within 6 weeks
- TFT every 4-6 weeks until patient becomes euthyroid then dosage can be reduced substantially to maintenance dose
- Drugs are usually stopped or tapered after 12-18 months

  (normal free T4, T3, TSH)
- Relapse usually occurs within 3-6 months after medication is stopped

Thyrotoxic crisis

An acute life-threatening, hypermetabolic state induced by excessive release of thyroid hormones

- Usually occurring in Graves' disease
- Presentation: fever, tachycardia, hypertension, neurological and GI abnormalities
- Treatment

- **Thioamides (PTU)**
- **Propranolol**
- **Corticosteroid**
- **Iodine**

Iodine

Mechanism of action

- **High concentration of iodine**

  inhibit - Iodide uptake

  - Organification

  - **Release of TH (major action)**

- Rapid slowing of hormone release → effect of iodine is **more quickly** than the effects of thioamides

- Iodine is now rarely used as a sole therapy because iodine may **lose its effect with time**

Iodine

Clinical use

- **Thyrotoxic crisis**
- severe thyrotoxicosis (Impending thyrotoxic crisis)
- Preparation for thyroid surgery

  : decrease in gland vascularity
- Protect the thyroid from radioactive iodine following a nuclear accident

Iodine

Iodine in the treatment of thyrotoxic crisis

- **Lugol's solution** 10 drops twice daily
- **SSKI** (Saturated solution of potassium iodide)
  2-3 drops twice daily

Reactions to Iodine

Not common and usually are not serious

- Rash (which may be acneiform)
- Drug fever
- Sialadenitis, conjunctivitis and rhinitis
- Vasculitis

If any of reactions occur, iodine should be stopped (except sialadenitis)

Radioactive Iodine (I-131)

Clinical use: destruction of thyroid gland

- Hyperthyroidism: Graves' disease without ophthalmopathy
  multinodular goiter, toxic adenoma
- Adjuvant therapy of differentiated thyroid cancer

Surgical removal → Radioactive iodine
L-T4 suppression of serum TSH

Absolute contraindication : pregnancy

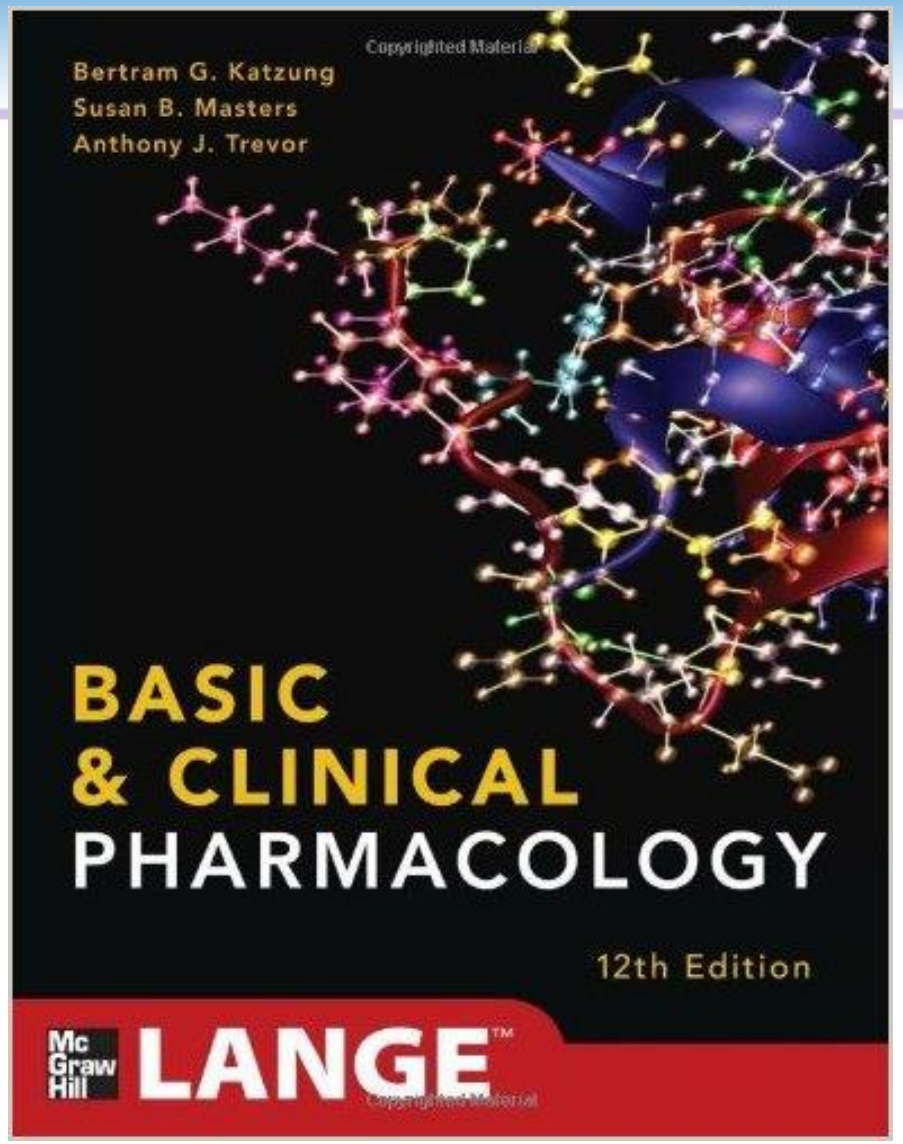
Radioactive Iodine (I-131)

Adverse effects

- Radiation thyroiditis
- Permanent hypothyroidism (80% within 2–6 months)

Lifelong follow-up to ensure that recurrence of disease or hypothyroidism can be treated

Disease	Treatment
Hypothyroidism	**Levothyroxine**
Subclinical hypothyroidism (TSH > 10 mU/L or +thyroid AB or goiter)	**Levothyroxine**
Myxedema coma	**Levothyroxine**
Hyperthyroidism: Graves's disease	**Thionamides (MMI)**± β-blocker Thionamides (MMI)+ β-blocker→Radioiodine/surgery
Hyperthyroidism: Toxic adenoma, Toxic multinodular goiter	Thionamides (MMI)± β-blocker→Radioiodine/surgery
Pregnancy with hyperthyroidism	**Thionamides (PTU in 1st Trimester)**
Thyrotoxic crisis	**Thionamides (PTU)** + Iodine + propronolol + corticosteroid
Preparative therapy for radiotherapy Preparative therapy for surgery	**Thionamides** **Thionamides** + Iodine
Thyroid cancer	Surgery → Radio iodine/**Levothyroxine**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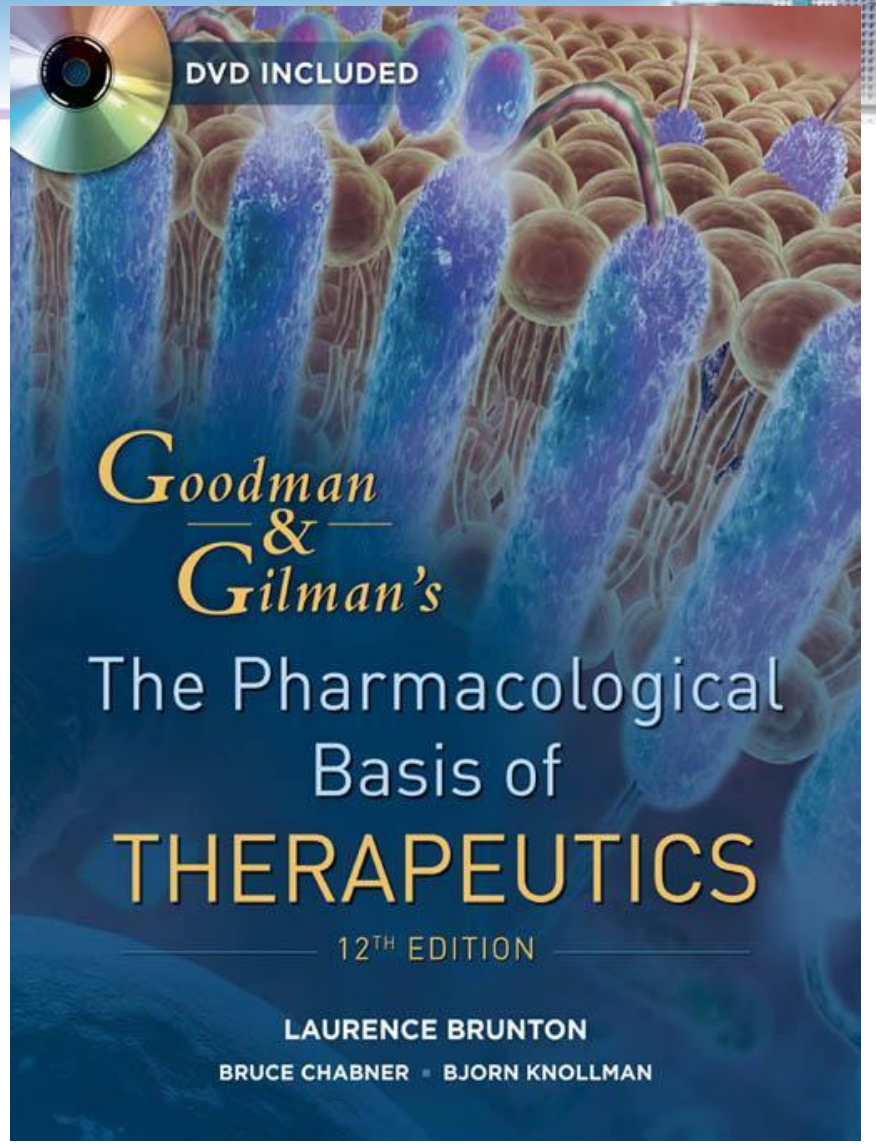
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