Thyroid Hormones
FIGURE 76-1
Microscopic appearance of the thyroid gland, showing secretion of thyroglobulin into the follicles.
Figure 4-4  Thyroid hormones (iodothyronines) and precursors (iodotyrosines) showing their structural formulae. Note that monodeiodination of the outer, or β, benzene ring of thyroxine (T₄) containing the hydroxyl group, produces triiodothyronine (T₃), whereas monodeiodination of the inner, or α ring containing the alanine side chain, produces reverse T₃ (rT₃).
Figure 4-3  Production of T₄, T₃, and rT₃. The principal thyroid gland secretion is T₄, 85% of which is monodeiodinated by peripheral tissues to T₃ and rT₃. Under normal conditions only small amounts of T₃ and rT₃ are derived from thyroidal secretion, a discovery that has led to the concept of T₄ as a prohormone. In nonthyroidal illness peripheral conversion of T₄ to rT₃ is enhanced leading to a reduction in serum T₃ concentration ("sick euthyroid"). The physiological significance of this shift in T₄ metabolism is not well understood.
Exophthalmos
Endemic Goiter, a Hypertrophy of the Thyroid Gland Resulting from Iodine Deficiency
ENDEMIC GOITRES:

• were common in Central Europe, the area around the Great Lakes in the USA,
• China, the Peruvian Andes,
Iodine:
• Sources: Iodized salt, dairy products, fish
• Adult RDA: 150 µg
• The average dietary intake - 500 µg /day
• Dietary intake below 50 µg /day - synthesis of thyroid hormones inadequate

Iodide:
• a circulating (extrathyroidal) pool - 250 - 750 µg
• the total iodide content of the thyroid - 7 500 µg
FIGURE 7-8 Steps in the synthesis of thyroid hormones. Each step is stimulated by thyroid-stimulating hormone. DIT = diiodotyrosine; I⁻ = iodide; MIT = moniodotyrosine; T₃ = triiodothyronine; T₄ = thyroxine; TG = thyroglobulin.
Synthesis

• Iodide (I⁻) pump (“trap”) (inhibited by high blood I⁻ level)

• Conversion of I⁻ to I₂ /THYROID PEROXIDASE/

• Binding of iodine with thyroglobulin /THYROID PEROXIDASE/

→ monoiiodotyrosine (MIT), diiodotyrosine (DIT)

• Coupling of DIT (MIT) and DIT - oxidative condensation /THYROID PEROXIDASE ?/

• Storage of the thyroid hormones in the follicular colloid

Secretion

• Formation of pinocytic vesicles

• Fusion with lysosomes → digestive vesicles

• Digestion of thyroglobulin, liberation of the thyroid hormones

• Deiodination of iodinated tyrosine residues (MIT, DIT) which had not been coupled (deiodinase)
Figure 76–3

Chemistry of thyroxine and triiodothyronine formation.
### Transport of Thyroid Hormones in the Blood

<table>
<thead>
<tr>
<th>Bound</th>
<th>$T_4$</th>
<th>$T_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroxine-binding globulin (TBG):</td>
<td>99.98%</td>
<td>99.8%</td>
</tr>
<tr>
<td>Thyroxine-binding prealbumin (TBPA):</td>
<td>67%</td>
<td>46%</td>
</tr>
<tr>
<td>(Transthyretin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin:</td>
<td>13%</td>
<td>53%</td>
</tr>
<tr>
<td>Free</td>
<td>0.02%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

#### Plasma levels

<table>
<thead>
<tr>
<th></th>
<th>$T_4$ (µg/dl)</th>
<th>$T_3$ (µg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>8</td>
<td>0.15</td>
</tr>
<tr>
<td>Free</td>
<td>2 ng/dl</td>
<td>0.3 ng/dl</td>
</tr>
</tbody>
</table>
Thyroxine                         Triiodothyronine

- Binding affinity of TBG and other plasma proteins
  6 times greater

- Release to the tissues
  Slower

- Biologic half-life
  Longer (6-7 days)                               1 day

- Binding with intracellular proteins
  Stronger
Figure 4-3  Production of T₄, T₃, and rT₃. The principal thyroid gland secretion is T₄, 85% of which is monodeiodinated by peripheral tissues to T₃ and rT₃. Under normal conditions only small amounts of T₃ and rT₃ are derived from thyroidal secretion, a discovery that has led to the concept of T₄ as a prohormone. In nonthyroidal illness peripheral conversion of T₄ to rT₃ is enhanced leading to a reduction in serum T₃ concentration ("sick euthyroid"). The physiological significance of this shift in T₄ metabolism is not well understood.
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Case 1

My old good friend Shirley called me last Monday to invite me to dinner. Shirley is a 43-year-old university teacher. I have known her for over 20 years, since we studied at the University. However we have not met within the last year. I was very surprised that I did not recognize her voice on the phone. It was hoarse and deep as that of a man, especially smoking. Besides Shirley spoke slower than usual and mainly about her complains. She told me that in spite of eating less her weight had increased by 16 lb in the last year, but she has attributed her weight gain to “getting older”. Later Shirley complained that she has very little energy, always feels weak, tired, and cold (when everyone is hot). She also suffers from muscle cramps and stiffness.

When I saw her in the evening, I noticed that Shirley’s neck was very full. Her face was slightly edematous and her skin was dry and cold. She added that she was constipated and had too frequent menses.

I suspected that Shirley had ————.
FIGURE 76-8
Patient with myxedema. (Courtesy Dr. Herbert Langford.)
Hypothyroidism

Figure 4-16  Chronic myxedema in the adult. Notice the classical "swollen" appearance of her skin, which is especially prominent in the face. (Courtesy of Dr. Mark Molitch.)
Natasha is a 23-year old woman who has always dieted to keep her weight on an “acceptable” level. However, within the last three months she has lost 20 lb in spite of a big appetite. She also notes that she always wants the thermostat set lower than her apartment mates. She complains of heart palpitations, increased frequency and softening of bowel movements, difficulty sleeping, irritability, and irregular menstrual periods. Besides she easily gets tired. During interview she was restless and she spoke very quickly.

On physical examination Natasha weighted only 110 lb. Her skin was smooth and warm. Her heart rate was 110 beats/min and her arterial pressure was 160/70. She had a tremor in her fingers and hands. Natasha had a wide-eye stare, and her lower neck appeared full; these characteristics were not present in photographs taken 1 year earlier.

Based on her symptoms, I suspected that Natasha had _ _ _ _ _ _ .
Figure 76-1. Orbitopathy tarczyczna: A - łagodna (retrakcja powieki, niewielkie wysunięcie prawej gałki ocznej bez innych objawów ze strony tkanek miękkich), B - jawna (ryc. B. udostępnili prof. dr hab. med. Ewa Bar-Andziak)
THYROID HORMONES

- nuclear transcription of large numbers of genes
- ↑ formation of RNA, proteins (enzymatic, structural, others)
- ↑ functional activity throughout the body

↑ BMR;

↑ oxygen consumption, ↑ energy production (ATP and heat)

<table>
<thead>
<tr>
<th>HYPERTHYROIDISM</th>
<th>HYPOTHYROIDISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Signs</td>
</tr>
<tr>
<td>↑ appetite</td>
<td>Sweating</td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
</tr>
<tr>
<td>Heat sensitivity</td>
<td></td>
</tr>
<tr>
<td>Relative vitamin deficiency</td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>Signs</td>
</tr>
<tr>
<td>↓ appetite</td>
<td>Obesity</td>
</tr>
<tr>
<td>Weight gain</td>
<td></td>
</tr>
<tr>
<td>Cold sensitivity</td>
<td></td>
</tr>
</tbody>
</table>
**Carbohydrate Metabolism**
- ↑ rate of absorption from GI tract
- ↑ all aspects of metabolism

**Lipid Metabolism**
- ↑ lipolysis, ↑ blood FFA level
- ↓ blood cholesterol level

**HYPOTHYROIDISM**
- ↑ blood cholesterol level
- ↓ severe atherosclerosis
**Protein Metabolism**

- ↑ synthesis, ↑ breakdown
- Action synergetic with GH and IGFs
  (promotion of protein synthesis, bone formation)

**Hypothyroidism**
- ↑ catabolism
- Muscle weakness
  (thyrotoxic myopathy)
- Muscle stiffness
  - ↑ muscle mass
  - ↑ mucopolisaccharides
FIGURE 76-8
Patient with myxedema. (Courtesy Dr. Herbert Langford.)
Skin, Connective tissue

- integrity of collagen
- ↓ synthesis, ↑ degradation of mucopolisaccharides

HYPOTHYROIDISM

Cool, dry skin

Myxedema (nonpitting edema)

Accumulation of mucopolisaccharides ("-" charge)

↓

Retention of osmotically active cations (Na⁺)

↓

Retention of water

↓

Puffiness of skin
Nervous System
(fetal life, childhood)

- Essential for normal growth and development of brain; Proliferation of axons, branching of dendrites, synaptogenesis
  - Cell migration, growth of cerebral cortex
  - Myelin formation

Congenital Hypothyroidism
Cretinism (mental retardation)
Failure of growth, thickened facial features
Nervous System

(Adults)

- ↑ rapidity of cerebration

<table>
<thead>
<tr>
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<th>HYPOTHYROIDISM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Signs</td>
</tr>
<tr>
<td>Rapid mentation</td>
<td>Emotional liability</td>
</tr>
<tr>
<td>Irritability</td>
<td></td>
</tr>
<tr>
<td>Difficulty sleeping</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>Tremor</td>
</tr>
<tr>
<td></td>
<td>Slow mentation</td>
</tr>
<tr>
<td></td>
<td>Dementia</td>
</tr>
<tr>
<td></td>
<td>Somnolence</td>
</tr>
</tbody>
</table>
**Bone, Growth**

- Essential for normal growth and skeletal maturation;
  - Growth of bone
  - Maturation of epiphyseal growth centres
  - Ossification of cartilage
  - Closure of epiphyses

**HYPERTHYROIDISM**
- Excessive skeletal growth
- Earlier closure of epiphyses
- Bone resorption

**HYPOTHYROIDISM**
- Retarded growth rate
- Delayed closure of epiphyses
Cardiovascular System

↑ blood flow, ↑ cardiac output
(↑ stroke volume, ↑ heart rate)

• ↑ myocardial calcium uptake, ↑ Na⁺,K⁺-ATPase activity, ↑ α-MHC (myosin heavy chain)
• ↑ number, ↑ affinity of β-adrenergic receptors (heart)
  ↓ sensitivity to catecholamines
  Adrenergic stimulation of the heart
  ↓ Vasodilatation
  ↑ heat, CO₂ production

HYPERTHYROIDISM

Symptoms
- Tachycardia
- Arrhythmia
- Systolic hypertension

HYPOTHYROIDISM

Symptoms
- Angina pectoris
- Bradycardia

Signs
- Signs
Respiratory System

• ↑ rate of breathing, ↑ depth of breathing,

Gastrointestinal System

↑ motility of GI tract

↑ secretion

HYPERTHYROIDISM

↑ frequency and softening of bowel movements

Diarrhea

HYPOTHYROIDISM

Constipation
Figure 76–8

Patient with exophthalmic hyperthyroidism. Note protrusion of the eyes and retraction of the superior eyelids. The basal metabolic rate was +40. (Courtesy Dr. Leonard Posey.)
Infiltrative ophthalmopathy - Exophthalmos
Figure 10-6 Interaction of hypothalamus, anterior pituitary, and thyroid.
**Figure 4-8** Schematic representation of the pathogenesis of Graves' disease. TSI, synthesized by B lymphocytes, stimulates thyroid gland activity in a manner similar to TSH. Negative feedback by thyroid hormones results in TSH suppression. Unlike TSH, TSI is not under negative feedback control and hyperthyroidism may ensue.
Thank you