The Investigations of the Thyroid gland

Essential for understanding this presentation:

1) **Anatomy:** The Thyroid Gland and its surroundings

2) **Biochemistry:** Hormones produced by the Thyroid Gland

3) **Physiology:** Function of the hormones produced by the Thyroid Gland

First then can one start on a journey to investigate abnormal functions of the Thyroid gland
The Investigations of the Thyroid Gland

Objectives:

1) Describe the mechanisms of endocrine hypofunction and hyperfunction.

2) Differentiate among primary, secondary and tertiary endocrine disorders.
The Investigations of the Thyroid Gland

Discuss - based on the normal physiology - the *rationale* behind

3) **Symptoms** of a dysfunctional Thyroid Gland.

4) The **investigations** the Thyroid Gland.
The Investigations of the Thyroid Gland

Essential for understanding the investigations

1) **Anatomy:**

2) **Biochemistry:**

3) **Physiology:**

4) **Diseases**
Essential anatomy

Connections to/from hypothalamus (nerve and vessels) to the Thyroid gland

The hypophyseal portal system

From Porth and Matfin Pathophysiology – Concepts of Altered Health states 2009
Essential anatomy

Relations

Trachea

Muscles

Main Arteries

http://fitsweb.uchc.edu/student/selectives/Luzietti/Thyroid_anatomy.htm

Anterior
Essential anatomy

Relations

Main Arteries

http://fitsweb.uchc.edu/student/selectives/Luzietti/Thyroid_anatomy.htm

Anterior
Essential anatomy

Relations

Main veins

http://fitsweb.uchc.edu/student/selectives/Luzietti/Thyroid_anatomy.htm

Anterior
Essential anatomy

Relations

Lymph drainage

http://fitsweb.uchc.edu/student/selectives/Luzietti/Thyroid_anatomy.htm

Anterior
Essential anatomy

Relations

Nerves

http://fitsweb.uchc.edu/student/selectives/Luzietti/Thyroid_anatomy.htm

Anterior
Which nerves are missing?

Vagus Nerves

Recurrent Laryngeal Nerves

Always double check that you have it all
Any other glands close by?

Parathyroid gland

Why is it important?

Aberrant tissue

The thyroid gland begins to develop as a median thickening of endoderm on the floor of the pharynx between the first and second pharyngeal pouches. This area later invaginates to form the median diverticulum, which appears in the later half of the fourth week. This thyroid diverticulum grows further, becoming a solid cellular cord called the thyroglossal duct. The duct grows caudally and bifurcates to give rise to the thyroid lobes and the isthmus.
The Investigations of the Thyroid Gland

Essential for understanding the investigations

1) Anatomy:

2) Biochemistry:

3) Physiology:

4) Diseases
Essential biochemistry

Follicle lumen

Thyrocyte

Capillary

Bizhanova A, Kopp P Endocrinology 2009;150:1084-1090
TSH signaling via the TSH receptor controls thyroid hormone synthesis.

Uptake of iodide into the thyrocytes is mediated by an intrinsic membrane glycoprotein, the \textit{sodium-iodide symporter} (NIS), which actively cotransports two \(\text{Na}^+\) per each iodide anion.

NIS is dependent on the \(\text{Na}\) gradient created by the \text{Na/K-ATPase}
TSH can increase expression of NIS in the basolateral membrane of thyrocytes.

Transcription

m-RNA

Protein synthesis

Bizhanova A, Kopp P Endocrinology 2009;150:1084-1090
H$_2$O$_2$ is produced by the calcium- and reduced nicotinamide adenine dinucleotide phosphate-dependent (NADPH) enzyme DUOX2.

DUOX2 requires a specific maturation factor, DUOXA2.

At the apical membrane, iodide efflux is, in part, mediated by pendrin (PDS/SLC26A4).
At the cell-colloid interface, iodide is oxidized by **TPO** (thyroid peroxidase or thyroperoxidase) in the presence of $\text{H}_2\text{O}_2$.

**Thyroglobulin** (TG), which is secreted into the follicular lumen, serves as matrix for synthesis of T4 and T3.
TG secreted into the follicular lumen, serves as matrix for synthesis of T4 and T3.

TPO catalyzes iodination of selected tyrosyl residues (organification), which results in the formation of MIT and DIT.

Two iodotyrosines are coupled to form either T4 or T3 (catalyzed by TPO). **Iodinated thyroglobulin** is stored as colloid in the follicular lumen.
Iodinated thyroglobulin is stored as colloid in the follicular lumen. Upon a demand for thyroid hormone secretion, thyroglobulin is internalized into the follicular cell by pinocytosis and digested in lysosomes, which generates T4 and T3 that are released into the bloodstream through unknown mechanisms.
The unused MIT and DIT are retained in the cell and deiodinated by the iodotyrosine dehalogenase 1 (DEHAL1).

The released iodide is recycled for thyroid hormone synthesis.
Essential biochemistry

What does this figure show?

Basically the same as the previous 8 slides

Other growth factors simulates TSH:
1 Insulin-like growth factor I (IGF-1)
2 Epidermal growth factor
3 Transforming growth factor β
4 Endothelins
$T_3$ converted to $T_4$

Reverse $T_3$ is inactive
World health implications


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The Investigations of the Thyroid Gland

Essential for understanding the investigations

1) Anatomy:

2) Biochemistry:

3) Physiology:

4) Diseases
The Investigations of the Thyroid Gland

The $T_3$ and $T_4$ feedback

Don’t forget the Pituitary gland feedback
The T₃ and T₄ are protein bound
99.8% of T₄
99.7% of T₃

The binding proteins are:
• **Thyroxine-binding globulin (TBG)**
• **Transthyretin (TTR)** formerly known as thyroxine-binding pre-albumin (TBPA)
• **Albumin**
# The Investigations of the Thyroid Gland

<table>
<thead>
<tr>
<th>Hormone property</th>
<th>$T_4$</th>
<th>$T_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Concentration total hormone</td>
<td>8 $\mu$g/dL</td>
<td>0.14 $\mu$g/dL</td>
</tr>
<tr>
<td>Fraction of total hormone in free form</td>
<td>0.02%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Free (unbound) hormone</td>
<td>$21 \times 10^{-12} \text{M}$</td>
<td>$6 \times 10^{-12} \text{M}$</td>
</tr>
<tr>
<td>Half-life</td>
<td>7 d</td>
<td>0.75 d</td>
</tr>
<tr>
<td>Fraction directly from the thyroid</td>
<td>100%</td>
<td>20%</td>
</tr>
<tr>
<td>Production rate, including peripheral conversion</td>
<td>90 $\mu$g/d</td>
<td>32 $\mu$g/d</td>
</tr>
<tr>
<td>Intracellular hormone fraction</td>
<td>~ 20%</td>
<td>~ 70%</td>
</tr>
<tr>
<td>Relative metabolic potency</td>
<td>0.3</td>
<td>1</td>
</tr>
<tr>
<td>Receptor binding</td>
<td>$10^{-10} \text{M}$</td>
<td>$10^{-11} \text{M}$</td>
</tr>
</tbody>
</table>

From Harrison’s principles of Internal Medicine 18th edition
Mechanism of thyroid hormone receptor action

The thyroid hormone receptor (TR) and retinoid X receptor (RXR) form heterodimers that bind specifically to thyroid hormone response elements (TRE) in the promoter regions of target genes. In the absence of hormone, TR binds co-repressor (CoR) proteins that silence gene expression.

The numbers refer to a series of ordered reactions that occur in response to thyroid hormone:
1. $T_4$ or $T_3$ enters the nucleus;
2. $T_3$ binding dissociates CoR from TR;
3. Coactivators (CoA) are recruited to the $T_3$-bound receptor;
4. Gene expression is altered.
The Investigations of the Thyroid Gland

Essential for understanding the investigations

1) Anatomy:

2) Biochemistry:

3) Physiology:

4) Diseases
Hyper - & Hypo-functions

In principle only two things can go wrong:

Increased production (over production) of hormones: Hyper…..dism

Decreased production (under production) of hormones: Hypo…..dism

Of cause there can be many underlying causes: Tumor, starvation, infections ......
# Hormone prioritizing

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Function (Stimulates)</th>
<th>Releasing factors</th>
<th>Hypo function</th>
<th>Hyper – Function</th>
<th>Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>Adrenal cortical hormone</td>
<td>CRH</td>
<td>Second. Adrenal hypofunction</td>
<td>Cushing disease</td>
<td>1</td>
</tr>
<tr>
<td>MSH</td>
<td>Melanocytes</td>
<td>CRH</td>
<td></td>
<td>Skin pigmentation</td>
<td>1?</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid hormone</td>
<td>TRH</td>
<td>Second. Hypothyroidism</td>
<td>Second. Hyperthyroidism</td>
<td>2</td>
</tr>
<tr>
<td>FSH</td>
<td>F: Ovulation, M: Sperm</td>
<td>GnRH</td>
<td>Infertility</td>
<td>Precocious pupperty</td>
<td>3</td>
</tr>
<tr>
<td>LH</td>
<td>Corpus luteum</td>
<td>GnRH</td>
<td>Sec. hypogonadism</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>GH</td>
<td>Growth</td>
<td>GHRH</td>
<td>Short statute</td>
<td>Acromegaly or gigantism</td>
<td>5</td>
</tr>
<tr>
<td>PRL</td>
<td>Breast feeding</td>
<td></td>
<td>Lactation failure</td>
<td>Amenorrhoea Galactorrhoea</td>
<td>6?</td>
</tr>
</tbody>
</table>

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**Mnemonic:** **Go Look For The Adenoma**

Meaning first goes GH then LH ....... Last ATCH

- Decreased bone density and fat?
- Hyponatremia
- Decreased bone density and fat?
The Investigations of the Thyroid Gland

Essential for understanding the investigations

1) Anatomy:

2) Biochemistry:

3) Physiology:

4) Diseases

Diagnose
Hyperthyroidism

- Fine Hair
- Exophtalmos
- Muscle wasting
- Fine tremor
- Oligomenorrhea
- Pretibial myxedema
- Goiter
- Tachycardia, palpitations, high output failure
- Weight loss
- Nervousness
- Restlessness
- Emotional instability
- Insomnia
- Sweating, Heat intolerance
- Increased appetite

From Porth and Matfin Pathophysiology – Concepts of Altered Health states 2009
## Hyperthyroidism

<table>
<thead>
<tr>
<th>Total T4</th>
<th>Total T3</th>
<th>Free T4</th>
<th>Free T3</th>
<th>TBG</th>
<th>TSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
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Diagnose?
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<tbody>
<tr>
<td>Euthyroid</td>
<td>Normal</td>
<td>Normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
</tr>
</tbody>
</table>

^ = high

˅ = low

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Diagnose?
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<tr>
<td>Hyperthyroid</td>
<td>^</td>
<td>^</td>
<td>^</td>
<td>^</td>
<td>normal</td>
<td>♀ if primary</td>
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^ = high

♀ = low

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</tr>
<tr>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>^ if Secondary</td>
</tr>
<tr>
<td><strong>T3 toxicosis</strong></td>
<td>Normal</td>
<td>^</td>
<td>normal</td>
<td>^</td>
<td>normal</td>
<td>^</td>
</tr>
<tr>
<td><strong>Hypothyroid</strong></td>
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<td>normal</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>^ if secondary</td>
</tr>
<tr>
<td><strong>TBG excess</strong></td>
<td>^</td>
<td>^</td>
<td>normal</td>
<td>normal</td>
<td>^</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>TBG deficiency</strong></td>
<td>^</td>
<td>^</td>
<td>normal</td>
<td>normal</td>
<td>^</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>T4 displacement by drugs</strong></td>
<td>^</td>
<td>normal</td>
<td>Normal or ^</td>
<td>normal</td>
<td>normal</td>
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Hyperthyroidism

Graves Disease

TSH receptor antibodies bind to TSH receptors in retro-orbital connective tissue

T cells produce inflammatory cytokines

? Eye muscle antibodies Swelling in muscle and connective tissues behind eyes

Ophthalmopathy

Clinical presentation of hyperthyroidism

T3 and T4

? TSH receptor antibodies bind to TSH receptors

B cells produce TSH receptor antibodies

? TSH

Pituitary gland

Genetic clonal lack of suppressor T cells

T helper cells multiply

Thyroid gland

Ginsberg J CMAJ 2003;168:575-585


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Hyperthyroidism

EVALUATION OF THYROTOXICOSIS

- Measure TSH, unbound T₄
  - TSH low, unbound T₄ high
    - Primary thyrotoxicosis
      - T₃ toxicosis
        - High
  - TSH low, unbound T₄ normal
  - TSH normal or increased, high unbound T₄
    - TSH-secreting pituitary adenoma or thyroid hormone resistance syndrome
  - TSH and unbound T₄ normal
    - No further tests

Features of Graves’ disease?:
- Yes
  - Graves’ disease
- No
  - Multinodular goiter or toxic adenoma?
    - Yes
      - Toxic nodular hyperthyroidism
    - No
      - Low radionuclide uptake?
        - Yes
          - Destructive thyroiditis, iodine excess or excess thyroid hormone
        - No
          - Rule out other causes including stimulation by chorionic gonadotropin

Harrison’s Principles of Internal Medicine, 19th Edition: www.accessmedicine.com
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Hypothyroidism

Controlling Gland

Gland

TRH

$T_3 + T_4$

TSH

Target Organ

Coarse, dry, brittle hair
Loss of lateral eyebrows
Pallor
Large tongue

Lethargy and impaired memory
Periorbital edema and puffy face
Deep, coarse voice
Diminished perspiration, cold intolerance

Slow pulse, enlarged heart (cardiomegaly)
Gastric atrophy
Constipation

Weight gain

Peripheral edema (hands, feet, etc.)

Menorrhagia (anovulatory cycles)

Muscle weakness

From Porth and Matfin Pathophysiology – Concepts of Altered Health states 2009

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Thyroid Gland 43
Hypothyroidism

From Porth and Matfin Pathophysiology – Concepts of Altered Health states 2009

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# Hypothyroidism

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<th>T3</th>
<th>T4</th>
<th>TRH</th>
<th>Conclusion</th>
</tr>
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<tbody>
<tr>
<td>Slightly elevated</td>
<td>normal</td>
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<td></td>
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**Diagnose?**
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<tr>
<td>elevated</td>
<td></td>
<td></td>
<td></td>
<td>Test for antiTBO and antiTg</td>
</tr>
<tr>
<td>Raised</td>
<td>Low fT4</td>
<td></td>
<td>Normal/elevated</td>
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<tr>
<td>Low</td>
<td>Low fT4</td>
<td>low</td>
<td></td>
<td>Tertiary hypothyroidism</td>
</tr>
<tr>
<td>Low</td>
<td>Low fT4</td>
<td>High</td>
<td></td>
<td>But patient has hypothyroidism symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Consider thyroid hormone resistance</td>
</tr>
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**Diagnose?**
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**Diagnose?**

- Slightly elevated TSH: Compensated hypothyroidism
- Raised TSH: Primary hypothyroidism
- Low TSH: Tertiary hypothyroidism
- Low TSH with high TRH: Secondary hypothyroidism

Test for antiTBO and antiTg.
Hashimoto’s thyroiditis

Antibodies most likely directed against TBO
Hypothyroidism

EVALUATION OF HYPOTHYROIDISM

Measure TSH

- Elevated
  - Measure unbound T₄
    - Normal
      - Mild hypothyroidism
        - TPOAb⁺ or symptomatic
          - T₄ treatment
        - TPOAb⁻, no symptoms
          - Annual follow-up
    - Low
      - Primary hypothyroidism
        - TPOAb⁺
          - Autoimmune hypothyroidism
          - T₄ treatment
        - TPOAb⁻
          - Rule out other causes of hypothyroidism

- Normal
  - Pituitary disease suspected?
    - No
      - No further tests
    - Yes
      - Measure unbound T₄
        - Low
          - No further tests
        - Normal
          - Rule out drug effects, sick euthyroid syndrome, then evaluate anterior pituitary function

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Thyroid Nodule

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