Immunology
435

The Immune System & Endocrine Disorders

Objectives:

1. To recognize that many endocrine disorders are organ-specific autoimmune diseases.
2. To understand the mechanisms of damage which take place at endocrine glands and their consequences.
3. To know the important examples of autoimmunity which affect different endocrine glands and the pathogenesis of these disorders.

مصدر مذاكرة

Kindly check our editing file before studying the document.

References: Girls&boys doctors slides&notes , Team 434

Revised by
خولة العماري & هشام الغفيلي

Red= important pink= female doctor notes blue= male doctor notes gray= extra notes

Introduction:

- Many endocrine disorders are organ-specific autoimmune diseases.
- Organ-specific Autoimmune Diseases: (majority)
- The immune response is directed to a target antigen unique to *a single organ*.
- The manifestations are largely limited to *that organ*.

The damage may be directly mediated by: (may be both of them)

① Humoral (Antibodies) Immunity

The antibodies may *over-stimulate* or *block* the normal function of the target organ.

② Cell-mediated Immunity (CMI)

Examples of autoimmune endocrine diseases

Thyroid	1) **Hashimoto's disease:** Autoantibodies against thyroid peroxidase. (1st cause of hypothyroidism if iodide is sufficient) 2) **Primary myxoedema:** Atrophy of the thyroid. 3) **Graves' disease:** Autoantibodies against Thyroid Stimulating Hormone receptor (TSH-R).
pancreas	Type I diabetes.
adrenal	**Addison's Disease:** A chronic endocrine disorder; adrenal glands produce insufficient steroid hormones
gonads	1) **Autoimmune Oophoritis:** Inflammation of the ovaries. 2) **Autoimmune Orchitis:** Testicular pain involving swelling, inflammation and infection.
pituitary	**Lymphocytic Hypophysitis:** Low production of one or more hormones by the pituitary gland due to autoantibodies and autoimmunity

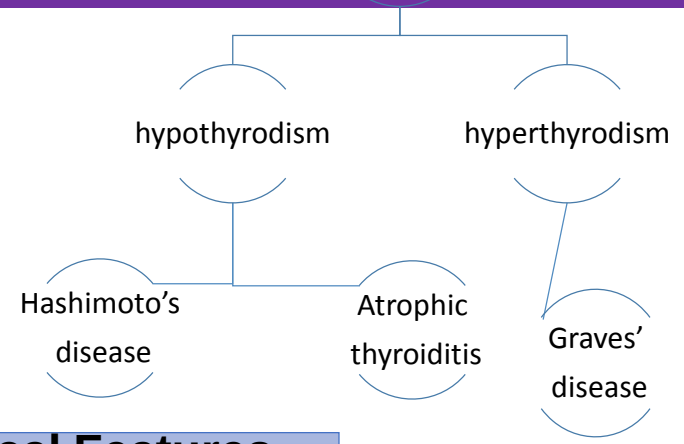
SOME AUTOIMMUNE DISEASES IN HUMANS

Disease	Self-antigen	Immune response
Organ-specific autoimmune diseases		
Addison's disease	Adrenal cells	Auto-antibodies
Autoimmune hemolytic anemia	RBC membrane proteins	Auto-antibodies
Goodpasture's syndrome	Renal and lung basement membranes	Auto-antibodies
Graves' disease	Thyroid-stimulating hormone receptor	Auto-antibody (stimulating)
Hashimoto's thyroiditis	Thyroid proteins and cells	T_{DTH} cells, auto-antibodies
Idiopathic thrombocyopenia purpura	Platelet membrane proteins	Auto-antibodies
Insulin-dependent diabetes mellitus	Pancreatic beta cells	T_{DTH} cells, auto-antibodies
Myasthenia gravis	Acetylcholine receptors	Auto-antibody (blocking)
Myocardial infarction	Heart	Auto-antibodies
Pernicious anemia	Gastric parietal cells; intrinsic factor	Auto-antibody
Poststreptococcal glomerulonephritis	Kidney	Antigen-antibody complexes
Spontaneous infertility	Sperm	Auto-antibodies
Systemic autoimmune disease		
Ankylosing spondylitis	Vertebrae	Immune complexes
Multiple sclerosis	Brain or white matter	T_{DTH} and T_C cells, auto-antibodies
Rheumatoid arthritis	Connective tissue, IgG	Auto-antibodies, immune complexes
Scleroderma	Nuclei, heart, lungs, gastrointestinal tract, kidney	Auto-antibodies
Sjogren's syndrome	Salivary gland, liver, kidney, thryoid	Auto-antibodies
Systemic lupus erythematosus (SLE)	DNA, nuclear protein, RBC and platelet membranes	Auto-antobidies, immune complexes

Thyroid Autoimmunity

1- Hashimoto's Thyroiditis / Chronic Lymphocytic Thyroiditis

- Male: Female ratio is 1:3, Frequently seen in middle-aged women.
- Associated with HLA II, Predisposing effect: DR4.
- Protective role: DR13 (people with DR13 are less likely to get the disease).
- Anti-thyroid peroxidase and anti-thyroglobulin antibodies.
- There will be symptoms of hypothyroidism.



➢ Individuals produce auto-antibodies and sensitized TH1 cells specific for thyroid antigens: (confirm the autoimmune cause)

- Anti-thyroid peroxidase. (more frequent & specific)
- Anti-thyroglobulin antibodies.

➢ **The DTH (Delayed Type (IV) Hypersensitivity) response is characterized by:**

An intense infiltration of the thyroid gland by lymphocytes, macrophages, and plasma cells, which form lymphocytic follicles and germinal centers.

➢ **The ensuing inflammatory response causes:**

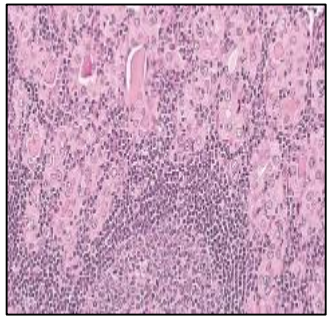
- A goiter(not specific for hashimoto) or visible enlargement of the thyroid gland, (physiological response to hypothyroidism)
- Formation of antibodies to thyroid proteins (thyroid peroxidase and thyroglobulin) (both of which are involved in the uptake of iodine) (patient will have problem in iodine uptake)

pathogenesis

Bindining of the auto-antibodies to specific protiens. → Interferes with iodine uptake and leads to → Decreased production of thyroid hormonenes → (hypothyrodism)

Clinical Features:

1. Fatigue.
2. Loss of energy
3. Cold intolerance.
4. Weight gain.
5. Mental slowing.
6. Enlarged thyroid.



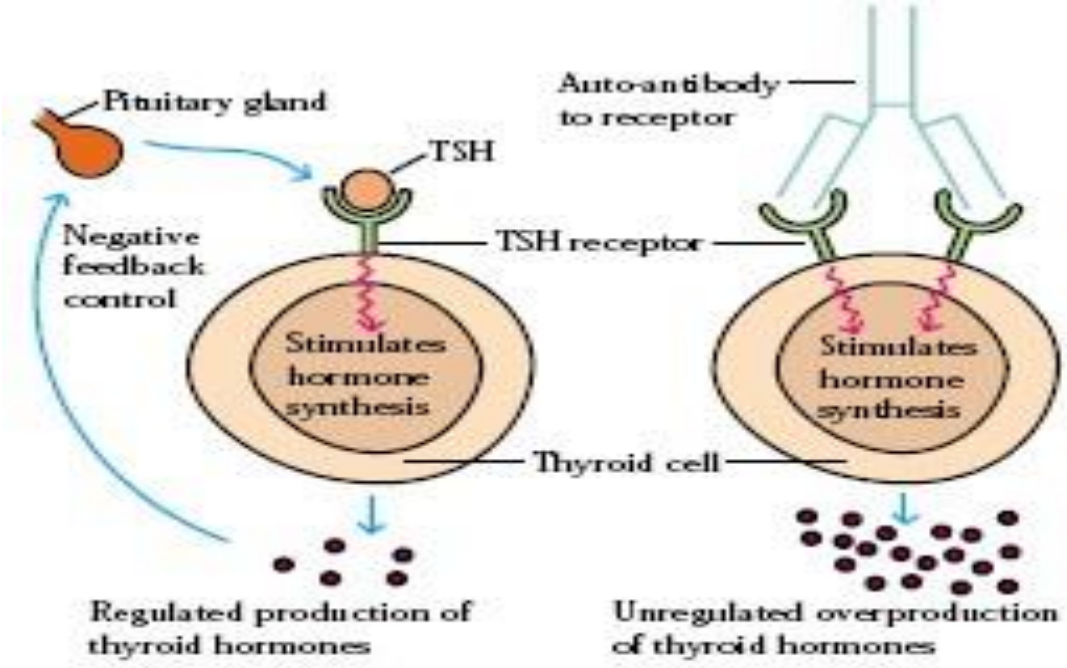
Hashimoto's thyroiditis showing intense lymphocyte infiltration.

Photomicrographs of (a) normal thyroid gland showing a follicle lined by cuboidal follicular epithelial cells

YouTube
Hashimoto Thyroiditis Simplified (5:45 min)

2- Graves' Disease Less common than Hashimoto's disease.

- Male: Female ratio up to 1:7. (Autoimmune diseases are more common in woman than men)
- Associated with HLA class II, Predisposing effect for DR3 & protective role: DR7



A. Normally:

The production of thyroid hormones is carefully regulated by thyroid-stimulating hormone (TSH), which is produced by the pituitary gland.

Binding of TSH to a receptor on thyroid cells activates adenylate cyclase and stimulates the synthesis of two thyroid hormones, thyroxine and triiodothyronine. (T_4 &T_3)

B. Graves' disease:

Auto-antibodies bind the receptor for TSH and mimic the normal action of TSH, activating adenylate cyclase and resulting in production of the thyroid hormones.(no –ve feedback)

- ❑ Unlike TSH the autoantibodies are not regulated, and consequently they overstimulate the thyroid.
- ❖ For this reason these auto-antibodies are called: long-acting thyroid-stimulating (LATS) antibodies.

Clinical Features:

1. Agitation.
2. sleep disturbance.
3. Sweating
4. palpitations.
5. Muscle weakness.
6. Weight loss despite increased appetite.
7. Goiter.
8. Tremor.
9. Ophthalmopathy. (exophthalmos mostly bilateral but sometimes unilateral)

YouTube
Graves' Disease (7:30 min)

Pancreas Autoimmunity

1-Insulin-Dependent Diabetes Mellitus (IDDM)

- IDDM is an example of type IV hypersensitivity.
- Type 1 IDDM patients (aprox.10%) are prone to other autoimmune disorders.(ex: celiac disease)

Autoreactive T-cells invade the pancreatic islets

↓

Destroy the insulin secreting beta cells.

↓

Macrophages become activated.

↓

This is frequently referred to as insulitis. (Cell-mediated DTH response)

↓

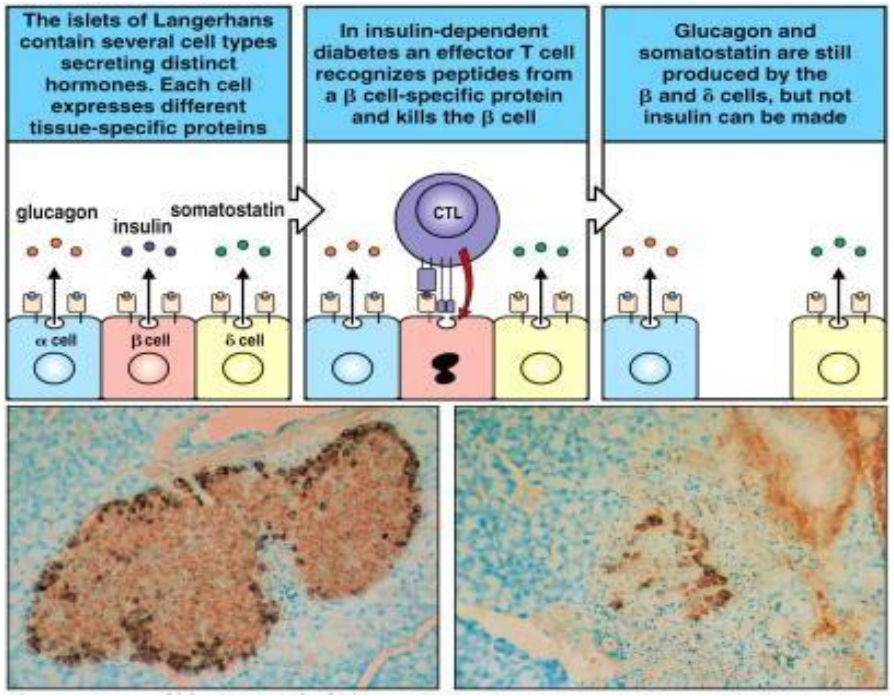
Decreased production of insulin and consequently increased level of blood glucose.

Pathogenesis:

Three mechanisms are responsible for islet cell destruction:

1. Genetic susceptibility (HLA-DQ alleles).(IDDM, DQ D connection)
2. Autoimmunity.
3. Environmental factors.
   Infections:
   Coxsackie virus,
   Echovirus

The most likely scenario is that viruses cause mild beta cell injury, which is followed by an autoimmune reaction against altered beta cells in persons with HLA-linked susceptibility.



pancreatic beta-cell autoreactive T cells (DTH & CTL) and autoantibodies.

Adrenal Autoimmunity

1- Addison's Disease / Autoimmune Adrenocortical Failure

- Is a prototypical organ–specific autoimmune disorder.
- It develops as a consequence of autoimmune destruction of steroid-producing cells in the adrenal gland.(before TB was the 1st cause)
- A major autoantigen is 21-hydroxylase (21OH). which is involved in the biosynthesis of cortisol and aldosterone in the adrenal cortex.
- Female: Male, ratio : 4:1
- Susceptibility gene: HLA-DR3 and/or DR4
  (The most strongly associated DRB1*04 allele is DRB1*04:04)

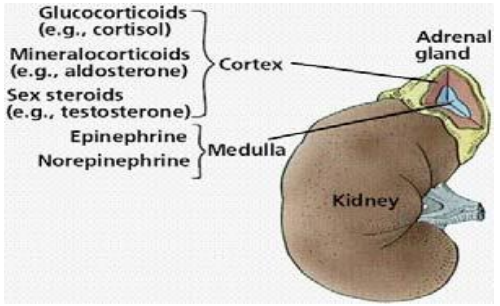
damage to the adrenal cortex may be caused by :

1. **(autoimmune disease):**T cell-mediated injury is likely to be central to pathogenesis, Adrenal Autoantibodies may have a pathogenic role, as yet unclear , or could arise secondary to T cell-mediated tissue damage.
2. Infections
3. Hemorrhage
4. Tumors
5. Use of drugs (anticoagulants).

Clinical Features:

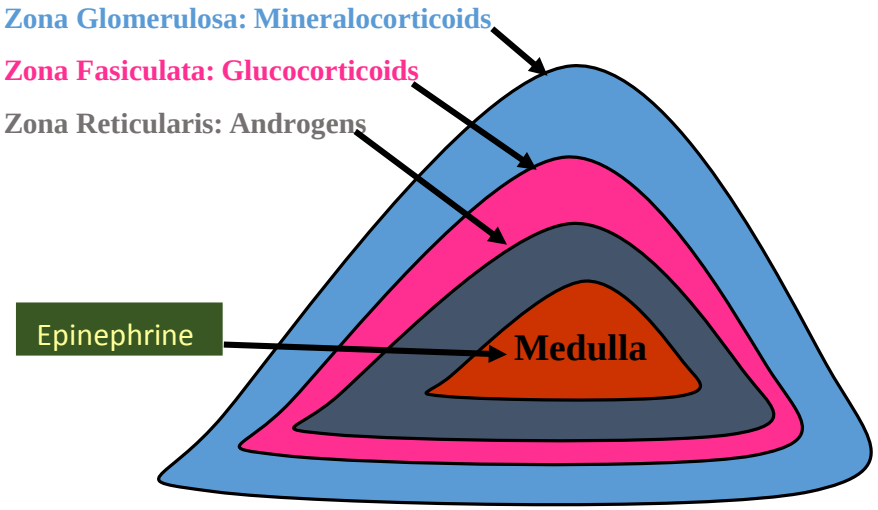
1. Weakness
2. Weight loss
3. Poor appetite
4. Confusion
5. Hyperpigmentation.
6. Hypotension.
7. Weak pulses.
8. Shock.(unconciousness)

Hormones of the adrenal glands



YouTube

Addisons Disease (7:21 min)



MCQs

Q1) Auto antibodies against thyroid stimulating hormone receptors (TSH-R) referred to ?

A- Primary myxoedema .
B- Hashimoto's disease .
C- Graves disease .

Q2) Which of these diseases is associated with HLA class II Predisposing effect for DR3?

A- Chronic Lymphocytic Thyroiditis (Hashimoto's Thyroiditis) .
B- Graves' Disease .
C- Lymphocytic hypophysitis .

Q3) Goiter can be associated with which of the following?

A- Hyperthyroidism .
B- Hypothyroidism .
C- Both .

Q4) A patient developed a goiter after being diagnosed with Hashimoto's thyroiditis. What is the cause ?

A- Inflamed lymph nodes .
B- Hypoactivity of the gland .
C- Compensatory mechanism .

Q5) A major autoantigen in Addison's disease ?

A- 21- hydroxylase (21OH) .
B- 21-Oxidase .
C- 21- Peroxidase .

Q6) Autoimmune inflammation of the ovaries called ?

A. Orchitis .
B. Addison's .
C. Oophoritis .

Q7) A 22 female lady came to your clinic suffering from weakness, weight loss and she has been noticing that her skin became more tan. What is the tissue that is mostly affected?

A- Adrenal cortex .
B- Thyroid Gland .
C- Ovaries .

Q8) Type 1 diabetes is an autoimmune disease with a prior infection of which kind of the following ?

A- Viral .
B- Bacterial .
C-Fungal .

Answers: 1 -C., 2 -B., 3 -C., 4.-C, 5-A., 6-C., 7-A, 8-A .

Team leaders:
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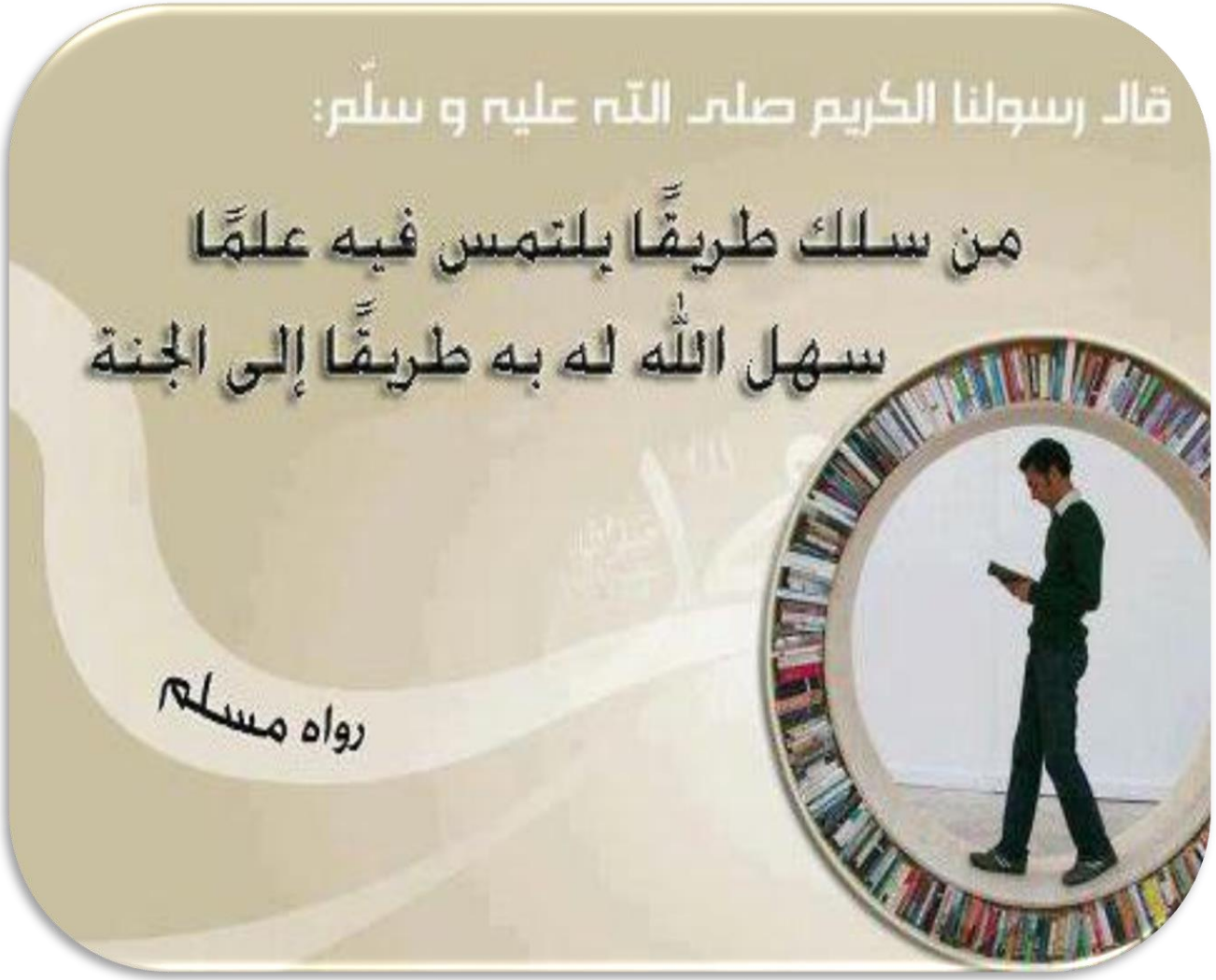

Challenges are what make life interesting and overcoming them is what makes life meaningful

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