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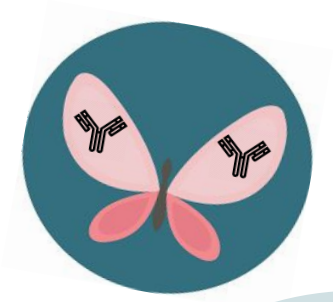

The Immune system and Endocrine disorders

Objectives

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

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Immunology
Team 437

Color index: Important Note

Overview

Why autoimmunity happens?
- Due to failure of tolerance

- Many endocrine disorders are organ-specific autoimmune diseases.
- In **organ-specific autoimmune disease**, the immune response is directed to a **target antigen unique to a single organ.** The manifestations are largely limited to that organ.

One, two or more antigens

  - e.g. If the antigen directed against the thyroid, only the thyroid function will be affected. Same as If It's directed against the adrenal gland only the function of adrenal gland will affected, and so on.
- The damage may be directly mediated by:
  - ***Humoral (Antibodies) Immunity*** the antibodies may **overstimulate** or **block** the normal function of the target organ
  - ***Cell-mediated Immunity (CMI)***

Sometimes both Humoral immunity & CMI at same time causing damage to the organ.

Examples of Autoimmune endocrine diseases:

Thyroid

- Hashimoto's disease
  - Autoantibodies against **thyroid peroxidase.**
- Primary myxoedema
  - Atrophy of the thyroid.
- Graves' disease
  - Autoantibodies against **Thyroid Stimulating Hormone receptor (TSH-R)**

Pancreas

Type I diabetes. Autoantibodies targeting beta cells in the pancreatic islets.

Adrenal

Addison's disease Chronic endocrine disorder; adrenal glands produce **insufficient steroid hormones.**

Gonads

- Autoimmune oophoritis
  - (inflammation of the ovaries)
- 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.

1.Thyroid autoimmunity

- Hypothyroidism
  - Hashimoto's disease.
  - Atrophic thyroiditis.
- Hyperthyroidism
  - Graves' disease.

- Predisposing effect means that people with this subtype or allele of HLA are more vulnerable to have the diseases. In another way: the possibility to have the disease is high.
- Protective effect means the opposite, decrease the possibility to have the disease.

A. Chronic Lymphocytic Thyroiditis (Hashimoto's Thyroiditis)

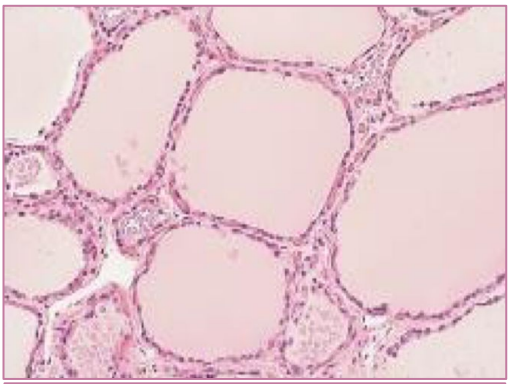
- Male: Female ratio is 1:3
- Associated with HLA **II**
- Predisposing effect: **DR4** (DRB1*04-DQB1*03-DQA1*03).
- Protective role: **DR13** (DRB1*13-DQB1*06-DQA1*01)
- **Anti-thyroid peroxidase and anti-thyroglobulin antibodies.**
- There will be symptoms of hypothyroidism.

Hashimoto's Thyroiditis

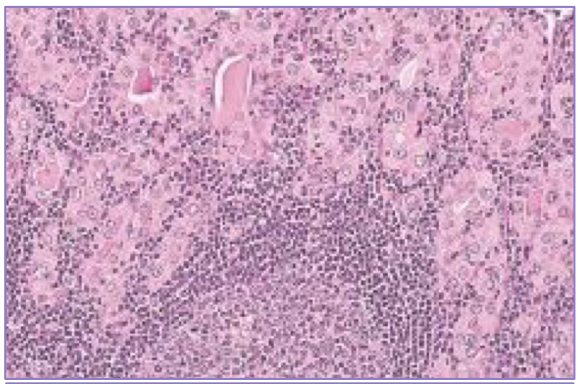
- Frequently seen in middle-aged women
- Individuals produce <u>autoantibodies and sensitized TH1 cells</u> specific for thyroid antigens.
- The DTH response is characterized by an intense infiltration of the thyroid gland by **lymphocytes**, **macrophages**, and **plasma cells**, which form lymphocytic follicles and germinal centers.

Note:
- Both CMI & Humoral immunity works here.

Remember::
- TH1 : inflammatory T helper cell, mediates the inflammation by producing cytokines to help in CMI.
- TH2 : gives help to produce the antibody.
- DTH = Delayed type hypersensitivity



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



Hashimoto's thyroiditis showing intense lymphocyte infiltration.

1.Thyroid autoimmunity

Hashimoto's Thyroiditis

The ensuing inflammatory response causes:

- A goiter, or visible enlargement of the thyroid gland, (a physiological response to hypothyroidism)
- Antibodies are formed to a number of thyroid proteins, including:
  - **Thyroglobulin**
  - **Thyroid peroxidase**

    (both of which are involved in the uptake of iodine)

Binding of the auto-antibodies to these proteins

↓

interferes with iodine uptake and leads to

↓

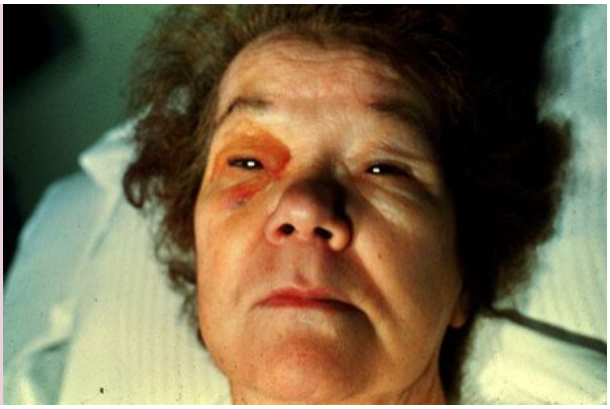
decreased production of thyroid hormones.

↓

(**Hypothyroidism**).

Clinical Features of Hashimoto's

- Fatigue, loss of energy
- Cold intolerance.
- Weight gain.
- Mental slowing.
- Enlarged thyroid.



Very useful video (5:39)

1.Thyroid autoimmunity

B.Graves' Disease

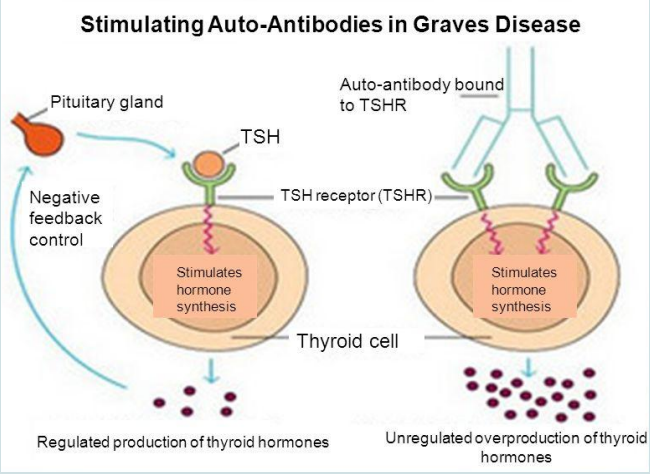
Less common than Hashimoto's disease

- Male: Female ratio up to 1:7
- Associated with HLA class **II**
- Predisposing effect for **DR3** (DRB1*03-DQB1*02-DQA1*05).
- Protective effect for **DR7** (DRB1*07-DQB1*02-DQA1*02).

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.

In Graves' disease autoantibodies bind the receptor for TSH and mimic the normal action of TSH, activating adenylate cyclase and resulting in production of the thyroid hormones.

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.**

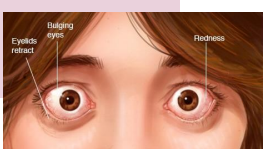


Regulated: has negative feedback, if the concentration of thyroid hormone is high the secretion of TSH will inhibited.

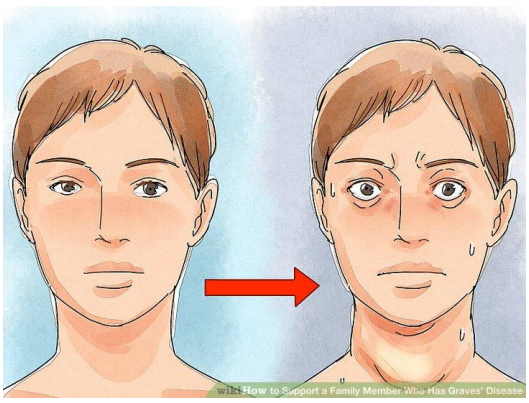
Unregulated: NO negative feedback, this will lead to hyperthyroidism.

Clinical Features of Graves' disease

- Agitation, sleep disturbance.
- Sweating, palpitations.
- Muscle weakness.
- Weight loss despite increased appetite.
- Goiter.
- Tremor.
- Ophthalmopathy.



Explains the picture above. Start at (5:25)



2. Insulin-dependent diabetes mellitus (IDDM)

IDDM is an example of type **IV** hypersensitivity. Type IV is less associated with autoimmunity in comparison with types II & III (stronger)

- Autoreactive T-cells invade the pancreatic islets and destroy the insulin-secreting beta cells.
- Macrophages become activated. →This is frequently referred to as **insulitis**.

(**Cell-mediated DTH response**)

- Macrophages over-activation produce large amount of IFN-gamma, which is an antiviral, upregulate and increase the expression of class II MHC. This will cause over-expression of class II MHC by the B cells and lead to delayed hypersensitivity and ultimately destruction of the pancreatic cells.
- As A result: decreased production of insulin and consequently increased level of blood glucose.

Type 1 Diabetes Mellitus

Pathogenesis

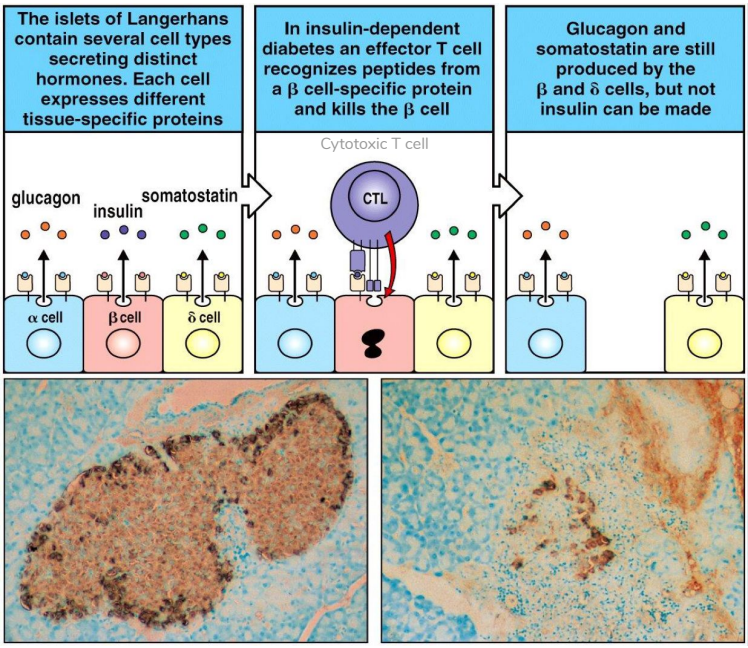
Three mechanisms are responsible for the islet cell destruction:

1. Genetic susceptibility (HLA-DQ alleles).
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 (DQ) susceptibility.

Type 1 IDDM patients (aprox.10%) are prone to other autoimmune disorders

Type I insulin- dependent diabetes



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

DTH response happens through CTL & TH1[TH1=DTH]
In DTH all the three are presenting cells: TH1, Cytotoxic T and B cells.

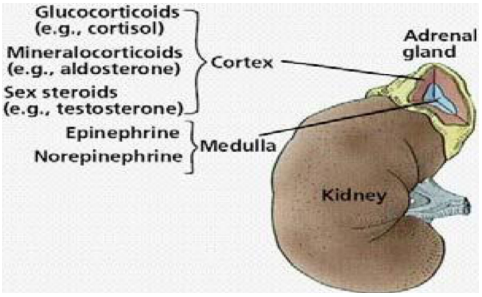
Osmosis 1:36-4:07

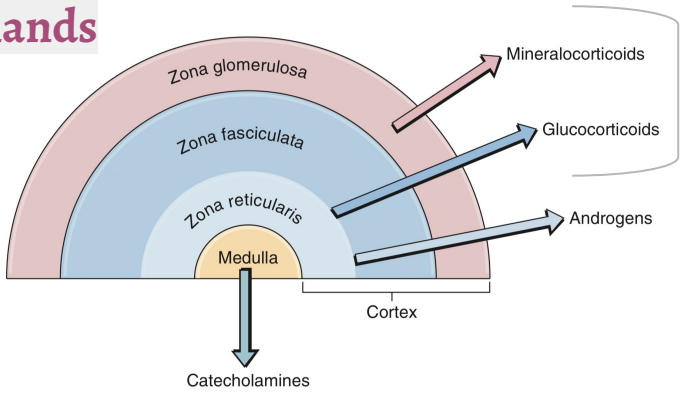
For further understand: 8 min.

3. Autoimmune adrenocortical failure, or Addison's disease.

- Is a prototypical organ–specific autoimmune disorder.
- It develops as a consequence of autoimmune destruction of steroid-producing cells in the adrenal gland.
- A major autoantigen is **21-hydroxylase (21OH)**, which is involved in the biosynthesis of **cortisol** and **aldosterone** in the adrenal cortex.

Hormones of the adrenal glands





Involved in Addison's

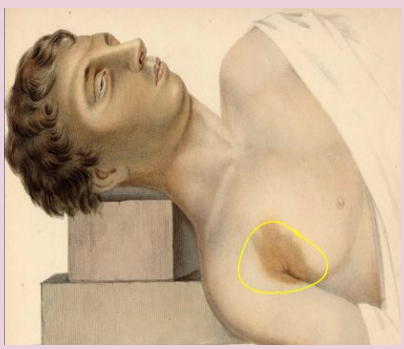
ADDISON'S DISEASE – GENETICS

Unfortunately, females are always more prone to autoimmune disorders.

- Female: Male ratio 4:1
- Susceptibility genes: **HLA-DR3 and/or DR4**
- The most strongly associated DRB1*04 allele is **DRB1*04:04**

Primary adrenal insufficiency: symptoms & Physical findings

- ➔ Weakness
- ➔ Weight loss
- ➔ Poor appetite
- ➔ Confusion
- ➔ **Hyperpigmentation**
- ➔ Hypotension
- ➔ Weak pulses
- ➔ Shock



Damage to the adrenal cortex may be caused by :

1. (Autoimmune disease) Primary
2. Infections
3. Hemorrhage
4. Tumors
5. Use of drugs (anticoagulants).

Secondary

Armando 5:13-12

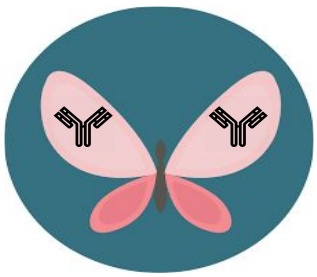
T cell-mediated injury is likely to be central to pathogenesis.
Adrenal Autoantibodies may have a pathogenic role, as yet unclear, or could arise secondary to T cell-mediated tissue damage.

Summary	Hashimoto's	Grave's	IDDM	Addison's
Humoral immunity or CMI ?	Both	Humoral immunity	CMI (DTH) & auto-antibodies	Humoral immunity and CMI
Autoantibodies against?	Thyroglobulin and Thyroid peroxidase	Thyroid stimulating hormone receptors TSH-R	Insulin secreting beta cells	21-hydroxylase enzyme
Predisposing effect	DR4	DR3	HLA-DQ	DR3 , DR4
Protective effect	DR13	DR7	-	-

Quiz

1. Which one of the following is less likely to have Grave's disease?
   a. A person carrying DR13 allele
   b. A person carrying DR3 allele
   c. A person carrying DR7 allele
   d. A person carrying DR4 allele
2. If a person carries DR4 allele that means he is prone to which of the following?
   a. Hashimoto's disease
   b. Grave's disease
   c. Addison's disease
   d. IDDM
3. Autoantibodies against which of the following enzymes is detected in Addison's disease?
   a. 21-hydroxylase
   b. Glutamic acid decarboxylase 65
   c. Hydroxylase
   d. IgG
4. Autoantibodies against Thyroglobulin is found in which of the following?
   a. Hashimoto's disease
   b. Grave's disease
   c. Addison's disease
   d. IDDM

Answers:
1. C
2. A
3. A
4. A



Thanks for checking our team