The Immune System & Endocrine Disorders

•Important •Explanation

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Hypersensitivity Reactions

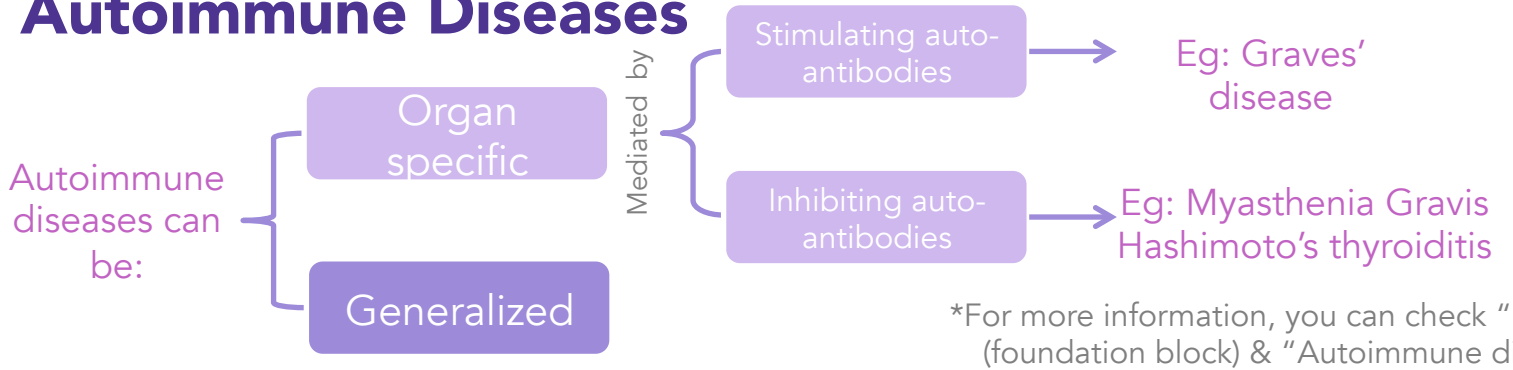
Type I	Type II	Type III	Type IV
• Mediates allergic inflammation • IgE mediated Ex: anaphylaxis	•Immune responses against antigens that are integral part of cell membrane and are usually associated with autoimmune disorders •Antibody mediated (igg or igm) Ex: Blood transfusion reactions	• Mediated by immune complexes and cause vasculitis Ex: SLE	• Purely cell mediated immune response associated with chronic inflammation Ex: contact dermatitis

Mnemonic

ABCD: I = allergic anaphylactic II = antibody III = immune complex IV = delayed

For further reading, click HERE

Autoimmune Diseases



*For more information, you can check "Hypersensitivity" lecture (foundation block) & "Autoimmune diseases" lecture (MSK)

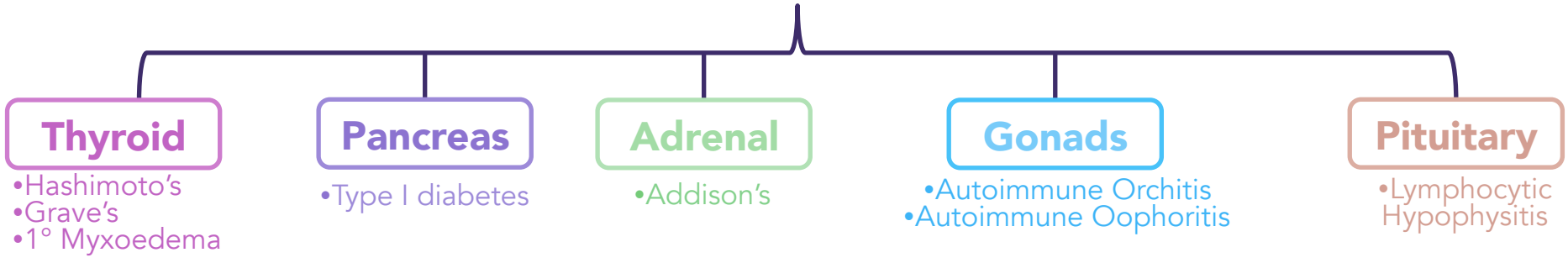
Introduction

- ✧ Many endocrine disorders are organ-specific autoimmune diseases.
- ✧ Organ-specific Autoimmune Diseases:
- ✓ 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:

① Humoral (Antibodies) Immunity:
The antibodies may *over-stimulate* or *block* the normal function of the target organ.

② Cell-mediated Immunity (CMI):
immune response that does not involve antibodies, but rather involves the activation of phagocytes, antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen.

Examples of Autoimmune Endocrine Diseases



Examples of Autoimmune Endocrine Diseases cont.

- **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.*

- **Adrenal:**
  - *Addison's Disease:* A 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 Hashimoto's Thyroiditis / Chronic Lymphocytic Thyroiditis

- ✧ Male: Female ratio is 1:3.
- ✧ Frequently seen in middle-aged women.
- ✧ Associated with HLA-B8, Predisposing effect: DR4[1] and Protective role: DR13[2]

- ✧ **Individuals produce auto-antibodies and sensitized TH1 cells specific for thyroid antigens: (both of which are involved in the uptake of iodine)**
- ✓ Antiperoxidase.
- ✓ Anti-thyroglobulin antibodies.

- ✧ **The DTH (Delayed Type 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[3] inflammatory response causes:**
- ✓ A goiter, or visible enlargement of the thyroid gland, (a physiological response to hypothyroidism) .
- ✓ Formation of antibodies to thyroid proteins (thyroid peroxidase and thyroglobulin which are involved in iodine uptake)
- ✧ **Clinical Features:**
- ✓ Fatigue.
- ✓ Loss of energy
- ✓ Cold intolerance.
- ✓ Weight gain.
- ✓ Mental slowing.
- ✓ Enlarged thyroid.

1: (DRB1*04-DQB1*03-DQA1*03).
2:(DRB1*13-DQB1*06-DQA1*01).
3: Resultant

Binding of the auto-antibodies to specific proteins.

↓

Interferes with iodine uptake and leads to

↓

Decreased production of thyroid hormones.

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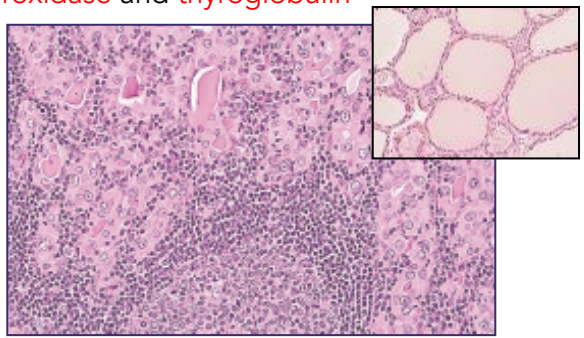
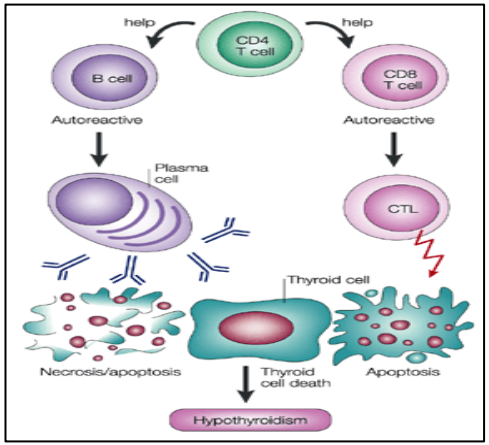
***Hypo*thyroidism**



Hashimoto's thyroiditis showing intense *lymphocyte infiltration.*

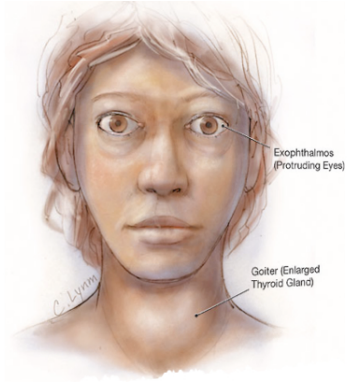


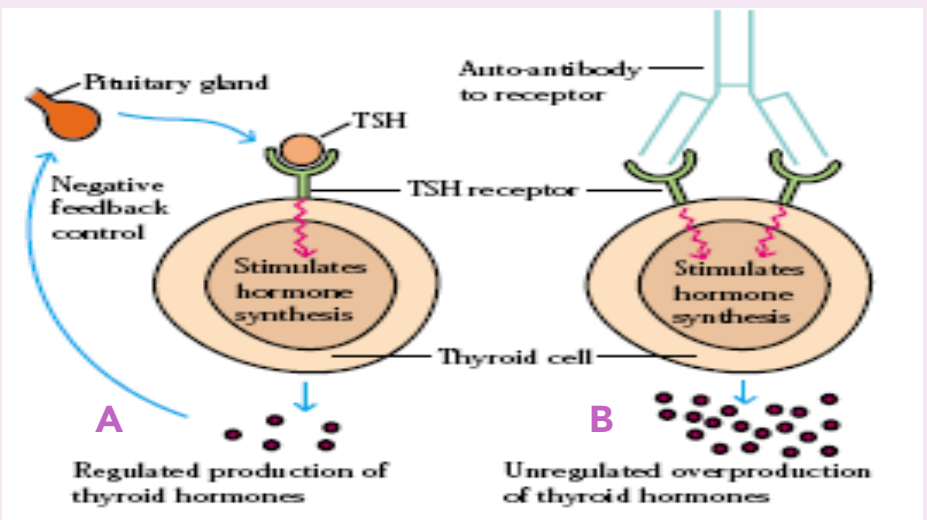
Thyroid Autoimmunity cont.

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

- ✧ Male: Female ratio is 1:7.
- ✧ Associated with HLA-B8, Predisposing effect for DR3[1] and a protective effect for DR7[2].

- ✧ **Clincal Features:**
- ✓ Agitation.
- ✓ Sleep disturbance.
- ✓ Sweating.
- ✓ Palpitations.
- ✓ Muscle weakness.
- ✓ Weight loss despite increased appetite.
- ✓ Goiter.
- ✓ Tremor.
- ✓ Ophthalmopathy.





Pathophysiology

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: In 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.
- o 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.

1: (DRB1*03-DQB1*02-DQA1*05)
2: (DRB1*07-DQB1*02-DQA1*02)

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.

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)

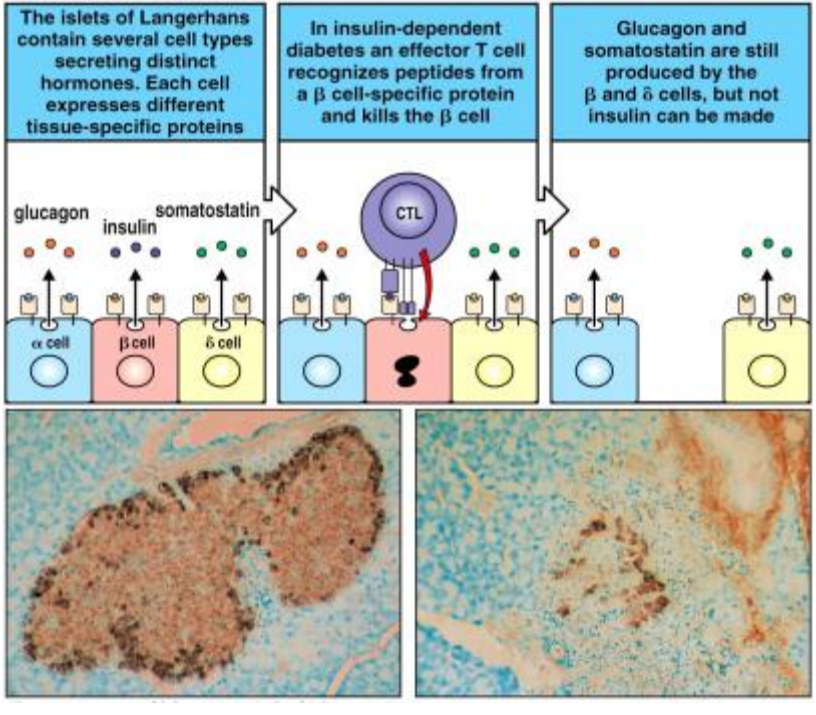
↓

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

Three mechanisms are responsible for the islet cell destruction:

- ✧ Genetic susceptibility:
- ✓ HLA-DQ alleles.
- ✧ Autoimmunity.
- ✧ Environmental factors.
- ✓ Infections: Coxsackie virus or 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.

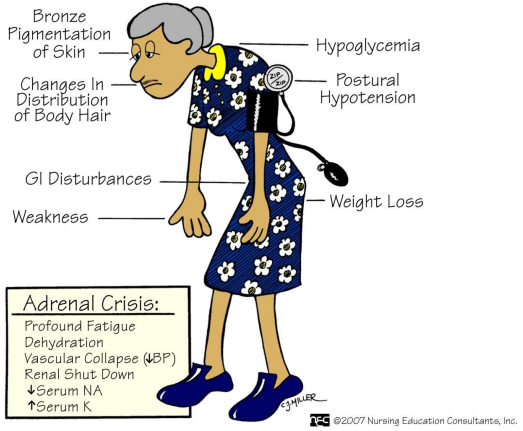


Pancreatic beta-cell autoreactive T cells (DTH & CTL) and autoantibodies

Adrenal Autoimmunity

① Addison's Disease / Autoimmune Adrenocortical Failure

- ✧ Is a prototypical[1] 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.
- ✧ Female to Male ratio 4:1
- ✧ Susceptibility genes:
- ✧ 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 :**

✓ 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.

✓ Infections.

✓ Hemorrhage.

✓ Tumors.

✓ Use of drugs (anticoagulants).

✧ **Clincal Features:**

✓ Weakness

✓ Weight loss

✓ Poor appetite

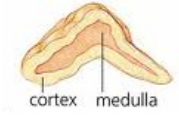
✓ Confusion

✓ Hyperpigmentation.

✓ Hypotension.

✓ Weak pulses.

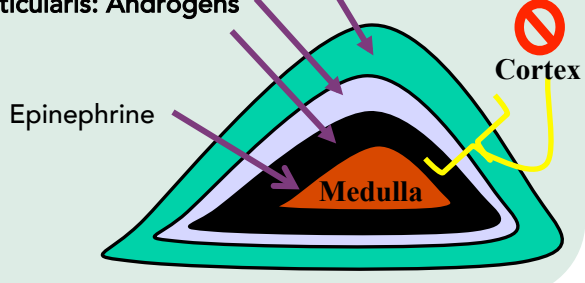
✓ Shock.



Zona Glomerulosa: Mineralocorticoids

Zona Fasiculata: Glucocorticoids

Zona Reticularis: Androgens



Hormones Of The Adrenal Glands

1: Ideal

Answers: 1.B, 2.C, 3.C, 4.A, 5.C, 6.B, 7.C, 8.A, 9.C, 10.A

Multiple Choice Questions

1. Hashimoto's disease autoantibodies are:
A. Stimulatory
B. Blocking Antibodies
C. Both

2. Autoimmune inflammation of the ovaries called:
A. Orchitis
B. Addison's
C. Oophoritis

3. Goiter can be associated with which of the following:
A. Hyperthyroidism
B. Hypothyroidism
C. Both

4. Hashimoto's autoantibodies attack:
A. Thyroglobulin
B. TSH receptor
C. Beta cells of the pancreas

5.Grave's disease associated with which of the following:
A. HLA-DQ
B. HLA-DR
C. HLA-B8

6. Grave's patients will loose their..
A. Ability to release T4
B. Negative feedback that regulates their levels
C. Ability to release T3

7. The mechanisms responsible for developing Insulin dependent diabetes mellitus:
A. HLA-DQ alleles
B. Infection by Coasakie
C. Both

8. Addison's autoantibodies are attacking:
A. 21OH enzyme
B. TSH receptor
C. Peroxidase Enzyme

9. All the following are T cell mediated injury EXCEPT:
A. Addison's
B. IDDM
C. Graves disease

10. 24 female lady came to your clinc 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 Galnd
C. Ovaries