Endocrine Pathology

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Essentials of Endocrinology

- **Main function**: releases **hormones** to control cellular activities of target cells
- **Autocrine cells**: secrete substances that control their own function
- **Paracrine cells**: secrete hormones that diffuse to adjacent cells and regulate their action
- **Neuroendocrine**: nervous system exerts regulatory and control functions on endocrine glands
- **Tropic hormones:** secretions that influence the secretions of another endocrine gland (ex. releasing hormones from hypothalamus to anterior pituitary)

Endocrine Specificity

- Most hormones are delivered to their target tissues via the bloodstream, where they bind to a receptor.
- **Intracellular receptors:** steroid and thyroid hormones pass through cell membrane and bind to receptors in the cytoplasm
    - Cause increase in the production of enzymes that enhance a metabolic pathway's activity, altering the target tissue's function
- **Membrane receptors:** binding site for protein, peptide, and amino acid hormones, which cannot enter the cell
    - Hormones active receptor systems - G proteins or protein kinases
    - Alter cytoplasmic concentrations of molecules or ions on which cell processes depend
- Hormone binding to either type of receptors causes alteration of the target cell's level of activity.

Plasma Hormone Level

- Plasma hormone level determined by rate of entering and leaving the blood
    - Rate of entering blood stream determined primarily by secretion rate.
- 2 components:
    - Hormone synthesis from dietary or endogenous precursors
    - Rate of release from the endocrine cell
- Cleared from blood stream either by inactivation or excretion
    - Inactivation at target tissue into nonfunctional forms or in liver into chemically converted inactive forms
    - Excretion by kidneys
- Increased binding rates at target cell induce an increased response.

Endocrine Dysfunction

- **2 types of dysfunction:**
    - **Hypofunction**
    - **Hyperfunction**
- **These two concepts are the basis for much of endocrine pathophysiology and should be the first factors considered in clinical situations.**

Elevated or Depressed Hormone Levels

- Failure of feedback systems
- Dysfunction of an endocrine gland
- Secretory cells are unable to produce, obtain, or convert hormone precursors
- The endocrine gland synthesizes or releases excessive amounts of hormone
- Increased hormone degradation or inactivation

Endocrine Hypofunction

- Defined as inadequate target tissue response
- Causes: hyposecretion or hormone resistance
- **Hyposecretion** may be due to:
- **Agenesis:** lack of gland development
- **Genetic defect** that prevents hormone synthesis
- **Dietary deficiency**

Endocrine Hypofunction

- **Atrophy** of the endocrine gland.
- **Replacement** of normal endocrine tissue with tumor tissue.
- **Surgery** to remove part of a over-secreting gland.
- **Damage** to a functioning gland that is then unable to maintain secretions.
- Often accompanied by high levels of control hormones

Endocrine Hypofunction

- Decreased or insufficient function of gland
- **Hormone resistance:** insensitivity of a target tissue to its hormone
- May be due to:
    - **Hereditary defect** that affects the tissue's ability to synthesize hormone receptors
    - **Autoimmune mechanism** in which an antibody binds to the hormone receptors
    - If faced with a chronically elevated hormone level, the target tissue might reduce the number of hormone receptors

Endocrine Hyperfunction

- Exaggerated target tissue responses
- Usual cause: **hypersecretion** - circulating hormone is present in inappropriately high levels
    - Causes of hypersecretion:
        - Exposure to high levels of tropic hormones
        - Defective feedback control
        - Tumors in the gland- occurs if neoplastic cells retain the ability to secrete functional hormone
- Signs and symptoms of endocrine diseases are often puzzling because of altered functions in many body systems at once.

Alterations of Thyroid Function

- **Hyperthyroidism**
  - Thyrotoxicosis
  - Graves disease
  - Hyperthyroidism resulting from nodular thyroid disease
  - Manifestations related to hypermetabolic state
  - Thyrotoxic crisis
- **Hyperthyroidism**
  - Thyroid gland produces thyroxine hormone
  - An **autoimmune disorder**
  - Significantly accelerates metabolism
    - Sudden weight loss, a rapid or irregular heartbeat, sweating, nervousness or irritability
    - Fatigue, muscle weakness, difficulty sleeping
    - Tremor, sweating
    - Changes in menstrual patterns
    - Increased sensitivity to heat
    - 8 times more common in women

Etiology of Grave's Disease

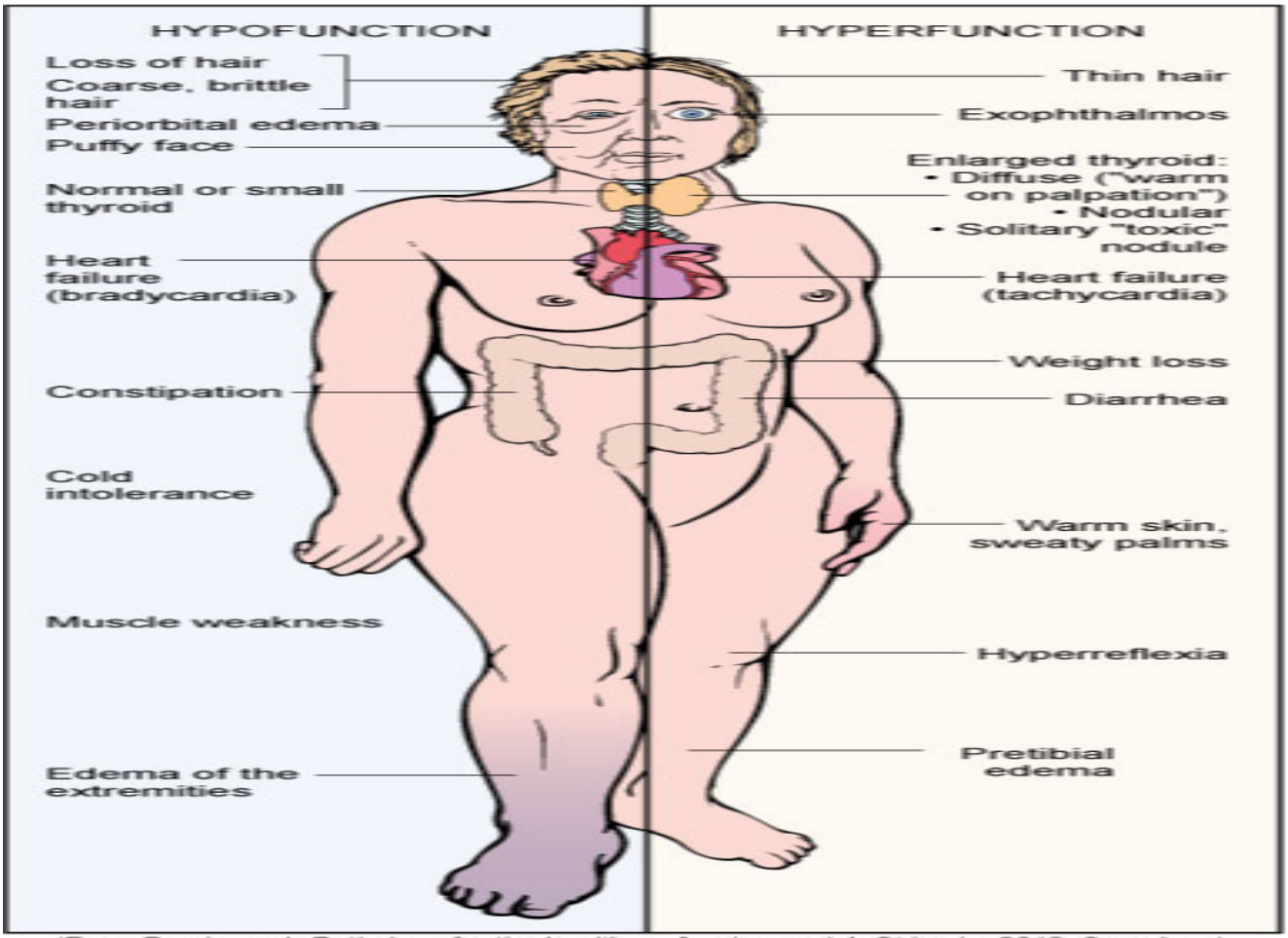
- For autoimmune reasons, a group of B lymphocytes secrete IgG which fits into and stimulates the TSH receptors present on cell membranes which increases the production of thyroid hormone.
- The characteristic exopthalmus is caused by inflammation of the tissue lining the orbit and extraocular muscles. This causes edema and swelling and fibrosis.
- The increased metabolic rate increases appetite and weight gain. The increased rate increases O2 consumption and patient is short of breath.
- Increased sympathetic stimulation is present.
- Causes
  - Graves' disease, an autoimmune disorder, is the most common cause of hyperthyroidism
  - Antibodies produced by your immune system stimulate your thyroid to produce too much thyroxine
  - Hyperfunctioning thyroid nodules
  - Thyroiditis
- Diagnosis
  - Radioactive iodine uptake test
  - Thyroid scan
  - Increased T3 & T4
  - Increased ANA titers

Hypothyroidism

- Low levels of thyroid hormones
    - Thyroxine (T-4) and Triiodothyronine (T-3)
- Causes of hypothyroidism
    - Autoimmune disease - Hashimoto thyroiditis
    - Treatment for hyperthyroidism
    - Radiation therapy
    - Thyroid surgery
    - Medications (lithium)
    - Less common causes
        - Congenital disease
        - Pituitary disorder
        - Iodine deficiency
        - Pregnancy
- **Etiology of Hypothroidism**
    - Iodine is essential component to synthesize T3 & T4
    - As the thyroid hormone levels fall in the blood, the pituitary produces more TSH, which generates enlargement of thyroid goiter
        - In some areas low in iodine it is called endemic goiter
- **Pathophysiology of Hypothroidism**
    - Develops slowly with an insidious onset
    - The lowered metabolic rate causes weight gain, lethargy, tiredness, difficulty concentrating, and cold.
    - Can affect the adult brain leading to memory loss, slowed mentation, depression and paranoia.
        - Severe cases is called myxedema madness
    - Decreased metabolic rate reduces heart rate and stroke volume and over time can cause cardiomegaly.
    - Decreased metabolic rate causes decreased GI function and decreased sexual function.
- **Risk factors**
    - Mainly in women over 50
    - Close relative, with an autoimmune disease
    - Prior treatment with radioactive iodine or anti-thyroid medications
    - Received radiation to your neck or upper chest
    - Have had thyroid surgery (partial thyroidectomy)
- **S & S**
    - Tiredness, weakness, slow reaction time, hypotension, cold intolerance, weight gain even when dieting
    - Sluggishness, constipation, muscle weakness
    - Joint pain, stiffness and swelling
    - Brittle fingernails and hair
    - Depression

Hypothyroidism

- **Hypothroidism in pregnancy is serious**
  - Thyroid hormones are essential for development and maturation of the infant and child's brain.
  - Called cretinism in children
    - Stunted growth, large head, learning difficulties, dwarfism, pug nose, short neck.
  - **Cretinism:** hypothyroid in newborns
    - Effects if untreated: physical and mental retardation, and stocky, thick body with infantile proportions



(From Damjanov I: *Pathology for the health professions*, ed 4, St Louis, 2012, Saunders.)

Hypothyroidism
- **Myxdema:** chronic hypothyroid in adults causes glycoproteins to be deposited in the dermis
- Facial puffiness is characteristic sign
- May lead to **myxdema coma**- can be fatal

Goiter: thyroid gland enlargement
- **Diffuse colloid goiter:** generalized enlargement of the thyroid due to increased thyroid stimulating hormone secretions.
- **Multinodular goiter:** nodules form from follicular atrophy and fibrosis
- **Nontoxic goiter:** enlarged gland but hyposecretes hormones
- **Hashimoto's Thyroiditis:** inflammatory cells overtake functional tissue

Pancreatic Islet Cells
- Function: regulate blood glucose levels through the production of insulin and glucagon
- **Diabetes Mellitus:** most common endocrine disorder
- Two forms, with differing pathogenesis:
    - **Juvenile onset DM, type I DM, insulin-dependent DM**
    - **Maturity onset DM, type II DM, non-insulin-dependent DM**

Type 1 Diabetes Mellitus
- Genetic susceptibility
    - Failure of beta cells by autoimmune destruction, requires insulin therapy
- Immunologically mediated destruction of beta cells
- Manifestations:
    - Hyperglycemia
    - Polydipsia
    - Polyuria
    - Polyphagia
    - Weight loss
    - Fatigue

Type 2 Diabetes Mellitus
- Beta cells lose their capacity to produce insulin slowly while target tissue also show reduced sensitivity
- Can be controlled with diet and exercise for a while, insulin therapy required less often
- Maturity-onset diabetes of youth (MODY)
- Gestational diabetes mellitus (GDM)
- Common form of diabetes mellitus type 2
- Initial insulin resistance
- Later loss of beta cells

Type 2 Diabetes Mellitus

- Diagnosis (fasting glucose, postprandial glucose)
- Manifestations (non-specific): fatigue, pruritus, recurrent infections, visual changes, or symptoms of neuropathy; often overweight, dyslipidemic, hyperinsulinemic, and hypertensive

Insulin physiology

- Produced by the beta cells in the islets and lowers blood glucose.
- When glucose levels rise, this is detected by the beta cells and secretory granules of insulin emerge from the cell membrane.
- The insulin then travels in the hepatic portal vein to the liver and then on to all the body tissues in the systemic circulation.
- Insulin is eventually removed from the blood by being broken down by the liver and kidneys
- Insulin lowers blood glucose levels by converting glucose into insoluble glycogen for storage in the liver and muscles.
- Insulin is needed to transfer glucose in tissue fluids through a gate into the cytosol of the cell.
- Without this insulin action, glucose cannot enter the cell and cannot be used by the mitochondria in energy production.
- The irony is that the tissue fluids have to much glucose and the intracellular mitochondria does not have enough.

Insulin and proteins

- Insulin stimulates protein metabolism and increases the movement of amino acid into cells.
- Insulin also prevents the catabolism of proteins.

Insulin and fats

- Insulin promotes the synthesis of fatty acids and glycerol in the blood causing hyperlipidemia.

Insulin receptors

- Insulin can only exert a physiological effect when it is combined with a specific receptor.
- These are transmembrane proteins which means that part of the receptor is inside the cell and part is outside the cell.

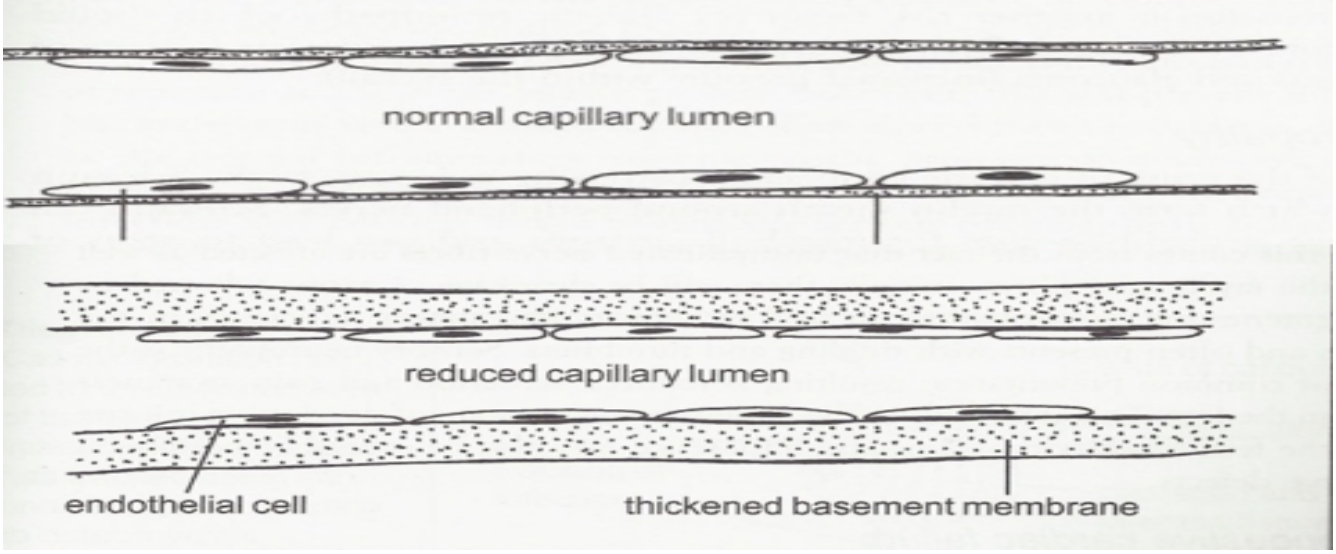
Chronic Complications of Diabetes Mellitus

Macrovascular disease

- Affects large artery walls with fatty deposits that leads to fibrous collagen and plaque formation.
- Coronary artery disease
- Stroke
- Peripheral arterial disease - Leads to ischemia and possible gangrene.
- Diabetic neuropathies
- Infection

Microvascular disease

- There is a progressive thickening of the basement membranes which narrow the lumen and lowers elasticity.
- This leads to localized ischemia and hypoxia, which causes more vascular compromise.
- Retinopathy
- Diabetic nephropathy



Hypoglycemia

- Low blood sugar
    - Normal levels = 80-110 mg/dL
    - Mild = <80 Significant symptoms <60
- Causes
    - Most are diabetics with to much insulin usage
    - Fasting
    - Alcoholics and liver disease
    - Overeating
    - Pancreatic tumor
    - Addison's disease

Hypoglycemia

- **S & S – occurs when blood sugar < 60 mg**
  - Sweatiness, dizziness, nervousness, shaking
  - Anxiety, faintness, weakness
  - Palpitations, hunger
  - Confusion, inappropriate behavior
- **Diagnosis**
  - Patient's history
  - Glucose tolerance test
  - Fasting glucose and insulin levels
- **Treatment**
  - Glucose now!!

Adrenal Cortex

- Adrenocortical Hypersecretion (Hyperadrenalism)
  - Cushing's Syndrome: cortisol hypersecretion
  - Hyperaldosteronism: hypersecretion by aldosterone-secreting cells.
  - Adrenal virilism: androgen hypersecretion in females, induces various masculine traits
  - Sexual precocity: androgen hypersecretion in young males leads to rapid and premature sexual development
- Adrenocortical Hyposecretion (Hypoadrenalism, Addison's disease)
  - Corticosteroid deficiency- destruction of cortex or suppression of ACTH by therapeutic doses of glucocorticoids
  - Characteristic feature: excess pigmentation and high vulnerability to stress

Hyperparathyroidism

- Usually caused by a parathyroid adenoma
- More common in women
- Often causes bone pain from high calcium
  - Hypercalcemia is also seen in metastatic bone disease (from breast, lung, prostate) and sometimes in pregnancy
- S & S
  - Bones – bone pain from high calcium
  - Stones – kidney stones common
  - Groans – pain and slow muscle contractions
  - Moans – psychiatric and mental changes

Hypoparathyroidism

- Often seen after surgery of thyroid and parathyroid
    - If the parathyroid glands have been removed, then the diagnosis will be permanent
- Results in low serum calcium & high serum phosphate
- S & S
    - Low calcium causes muscle cramps, tetany, & paresthesias
    - Convulsions and arrhythmias
    - Acute onset, especially after thyroid surgery, could lead to respiratory spasm and suffocation – needing tracheostomy

Hypopituitarism

- Pituitary gland fails to produce one or more of its hormones, or doesn't produce enough of them
- Causes
    - Pituitary ademomas
    - Strokes
    - Metastatic carcinomas
    - Primary brain tumors
    - Autoimmune disorders
    - Brain trauma
    - Encephalitis
    - Idiopathic

Signs & Symptoms

- Depending on which hormones are deficient
    - Fatigue , Headaches , Low tolerance for stress
    - Muscle weakness , Nausea
    - Constipation , Weight loss or gain
    - A decline in appetite , Abdominal discomfort
    - Sensitivity to cold or difficulty staying warm
    - Visual disturbances
    - Loss of underarm and pubic hair
    - Joint stiffness
    - Hoarseness
    - Facial puffiness
    - Thirst and excess urination
    - Low blood pressure
    - Lightheadedness when standing
- Men may experience
    - Loss of interest in sexual activity
    - Erectile dysfunction
    - Decrease in facial or body hair

Signs & Symptoms

- Women may experience
  - Irregular or no menstrual periods
  - Infertility
  - Inability to produce milk for breast-feeding
- Children may experience
  - Stunted growth
  - Short stature
  - Slowed sexual development

Hyperpituitarism

- Excessive production of growth hormone, which continues to be produced well into adulthood
  - In adults, since the growth plates are closed, excessive levels cause abnormal growth of hands, feet, and internal organs – called acromegaly
  - In children, excess growth hormone causes increased height known as gigantism
- Diagnosis
  - Elevated GH in blood test
  - Pituitary tumor on CT or MRI

(From Thibodeau GA, Patton KT: *Anatomy & physiology*, ed 6, St Louis, 2007, Mosby.)