Pathology of the Endocrine System

Jantima Tanboon, MD

1. Endocrine
2. Paracrine
3. Autocrine
4. Neuroendocrine

HYPOTHALAMUS

PITUITARY GLAND
**Bitemporal Hemianopsia**

**Craniopharyngioma**

*Pituitary Development*

- **Anterior**
- **Posterior**

*Normal Anterior and Posterior Pituitary Gland*
### Pituitary Adenoma
- Macroadenoma > 1 cm
- Microadenoma
- Hormone produced +/-
- Mass effect/Stalk effect

### Hyperprolactinemia

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<tr>
<th>Major cause</th>
<th>Major consequences</th>
<th>Therapeutic strategies</th>
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### Growth Hormone from Somatotroph
- Growth hormone adenoma: 2nd MC
- Macroadenoma
- Pituitary dwarfism: GH deficiency in Children

### Hypothalamus and Anterior Pituitary

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### Prolactin from Lactotroph
Prolactinoma: 1st MC pituitary adenoma

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Coarsening of facial features
Macroglossia
Malocclusion and tooth gaps
Acral enlargement
Thick and coarse skin

ACTH from Corticotroph

Cushing disease
- Hypercortisolism by pituitary adenoma
- Hyperpigmentation

Proopiomelanocortin: POMC
- α-terminal fragment
- ACTH
- β-LPH
- γ-LPH
- α-MSH
- CLIP
- β-endorphin

Cushing syndrome
- Adrenal gland
- Ectopic ACTH

Nelson syndrome
- Corticotroph adenoma
- After adrenalectomy
- Loss of inhibitory effect
- Mass effects
- Hyperpigmentation
**LH, FSH from Gonadotroph**

**Hypopituitarism**
- 70-90% (≥75%) parenchymal loss
- Congenital (rare)
- Acquired
  - Non-functioning adenoma
  - Ischemic necrosis
  - Ablation by surgery or radiation
  - Inflammatory lesion
  - Mutation Pit-1

**Sheehan syndrome**
- Postpartum necrosis of anterior pituitary
- Pregnancy
  - Hypertrophy/Hyperplasia of Lactotroph
  - Not increase blood supply
  - Blood loss during delivery
- Agalactia, amenorrhea, hypothyroidism, adrenocortical insufficiency

**Pituitary apoplexy**
- **Sudden** neurologic impairment
- Headache, visual symptoms, altered mental status, and hormonal dysfunction
- Hemorrhage and/or infarction
- Tumor (adenoma)/normal pituitary

**Oxytocin**

**Vasopressin: Antidiuretic hormone**
Diabetes Insipidus: DI
- ADH deficiency
- Clinical: Polyuria, thirst, polydipsia
- Central DI
- Nephrogenic DI
- ¼ associated with craniopharyngioma

Syndrome of inappropriate ADH secretion: SIADH
- Water retention, hyponatremia, hypotonicity
- Excess ADH:
  - Paraneoplastic secretion: Small cell lung CA
  - Tumor trauma inflammation
    - Pulmonary lesion
    - Brain lesion
- Drugs

PINEAL GLAND
- Melatonin: sleep inducer
- Serotonin: neurotransmitter
- Germ cell tumors
- Pineocytoma

THYROID GLAND
- Thyroglossal Duct Cyst
Thyroid gland

- Follicular cell
  - Colloid
  - Thyroglobulin
  - T4
  - T3
- Parafollicular cell (C-cell)
  - Calcitonin

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<th>Site of action</th>
<th>Intracellular effects</th>
<th>Physiological results</th>
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<td>Cell membrane</td>
<td>Stimulates the Na+/K+ ATPase pump</td>
<td>Increased demand for metabolites, e.g. glucose</td>
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<td>Mitochondria</td>
<td>Stimulates growth, replication and activity; basal metabolic rate is raised</td>
<td>Increased heat production, oxygen demand, heat rate, and stroke volume</td>
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<td>Nucleus</td>
<td>Increases expression of enzymes necessary for energy production</td>
<td>Lipolysis, glycolysis, and gluconeogenesis increased to raise blood metabolite levels and cellular metabolite use</td>
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<td>Neonatal cells</td>
<td>Essential for cell division and maturation</td>
<td>Essential for normal development of CNS and skeleton</td>
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Hypothyroidism

- Hypothyroid cretinism
- Neurologic cretinism
- Thyroid dysgenesis
- Others

Goitrous hypothyroidism

- Impaired synthesis of thyroid hormone
- Dietary iodine deficiency
- TSH compensates → euthyroid
Diffuse Non-Toxic Goiter

Nodular/Multinodular Goiter
Further develop toxic nodular goiter

Hashimoto thyroiditis
- MC for non-endemic hypothyroidism
- Chronic lymphocytic thyroiditis, struma lymphomatosa
- Autoimmune disease: antithyroid antibody
- Early stage: Hashitoxicosis

Graves disease
- Autoimmune disease
- Thyroid-stimulating immunoglobulin (TSI)

Other Thyroiditis
- Acute thyroiditis
- Subacute (granulomatous) thyroiditis
- Silent thyroiditis
- Riedel thyroiditis
Acute thyroiditis

- Infectious: Bacteria, fungus
- Fever, chill, malaise, swollen neck
- MC: *Streptococcus, Staphylococcus, Pneumococcus*

Subacute (granulomatous) thyroiditis

- Granulomatous thyroiditis
- De Quervain thyroiditis
- Non suppurative thyroiditis
- Viral infection:
  - Coxackie, Mumps, Influenza, Echoviruses, Adenoviruses
- Transient:
  - Pain, fever, malaise, fatigue, enlarged thyroid, tender

Silent thyroiditis

- Painless thyroiditis
- Lymphocytic thyroiditis
- Painless thyroid enlargement
- Self-limited hypothyroidism
- Post partum period

Reidel thyroiditis

- Exothyroidal soft tissue
- Fibrosis of other organs
- Hard/ fixed → suspicious CA
- Unknown etiology
- Autoimmune?

Neoplasms of the thyroid

- Solitary nodules
- Young patients
- Nodules in males
- Hx of radiation
- Hot nodules (benign)
- Adenoma
- Papillary CA (75-85%)
- Follicular (10-20%)
- Medullary CA (5%)
- Anaplastic CA (<5%)
Follicular Adenoma

- MC thyroid carcinoma
- Lymphatic spread
- MC in children and young adolescent
- Iodine excess
- Radiation
- Genetic factors
- Familial adenomatous polyposis
- Mutation of RET (10q11.2)

Papillary Thyroid Carcinoma

- MC thyroid carcinoma
- Lymphatic spread
- MC in children and young adolescent
- Iodine excess
- Radiation
- Genetic factors
- Familial adenomatous polyposis
- Mutation of RET (10q11.2)

Fine Needle Aspiration Cytology (FNA)
Thyroid Gland

- Anaplastic carcinoma
  - Undifferentiated thyroid carcinoma
  - Elderly
  - Develop from
    - Long-standing goiter
    - Low-grade thyroid cancer
    - Radiation
  - Rapid enlarged mass, Aggressive tumor:
Medullary thyroid carcinoma

- C-cell
- Calcitonin, serotonin, ACTH, somatostatin
- Precursor lesion: C-cell hyperplasia
- Mutation of RET

PARATHYROID GLANDS

Hypercalcemia

- Solid tumor: lung, breast, head and neck, renal cancer
- Hematologic malignancy: multiple myeloma
- Clinically apparent hypercalcemia
- Asymptomatic hypercalcemia
**ENDOCRINE PANCREAS**

- Endodermal derivatives
- Four major cell types:
  - $\beta$: 68% insulin
  - $\alpha$: 20% glucagon
  - $\delta$: 10% somatostatin
  - PP: 2% pancreatic polypeptide
- Two minor cell types:
  - D1: vasoactive polypeptide
  - Enterochromaffin cell serotonin

**Obesity**

- BMI 25-29.9 = overweight
- BMI >40 = obese
- **Male**
  - Waist > 102 cm (40 inch)
  - Waist: hip ratio > 0.9
- **Female**
  - Waist > 88 cm (35 inch)
  - Waist: hip ratio > 0.85
Hyperglycemia

Advanced glycation end product (AGE)
- Crosslinking polypeptides
- Resistant to proteolytic enzyme
- AGE residues in plasma proteins

Activation of protein kinase C
- VEGF: Vasoconstrictor; endothelin 1
- Vasodilator: endothelial nitric oxide synthase (eNOS)
- Profibrogenic molecules (TGF-β)
- Procoagulant molecule (PAI-1)
- Pro-inflammatory cytokines

Polyol pathways in nerve, lens, kidneys
Adrenal glands

1. **Glucocorticoids (cortisol):**
   - Z fasciculata/Z reticularis

2. **Mineralocorticoids (aldosterone):**
   - Z glomerulosa

3. **Sex steroids (estrogens and androgens):**

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**Hypercortisolism**

**Endogenous hypercortisolism**
- 70-80% primary ACTH hypersecretion
  - ACTH-producing microadenoma
  - Corticotroph cell hyperplasia
- 20% primary adrenal neoplasms
  - Adrenal adenoma/ adrenal carcinoma
  - Primary cortical hyperplasia
- 10% ectopic ACTH by non-pituitary tumors

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Physiological effects of cortisol and the symptoms of Cushing’s syndrome

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<th>Effect of cortisol</th>
<th>Related pathology in Cushing’s syndrome</th>
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<td>Fat metabolism</td>
<td>Stimulate lipolysis and fatty acid level in the blood</td>
<td>Fat redistributed to the face, trunk, causing a moon face, buffalo hump and abdominal stretch marks</td>
</tr>
<tr>
<td>Immune system</td>
<td>Suppresses the action and production of immune cells; inhibits the production of cytokines and antibodies</td>
<td>Infection, poor healing, peptic ulceration</td>
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Endocrine system
- Suppresses the secretion of anterior pituitary hormones ACTH, LH, FSH, TSH and GH
- Suppression of growth in children

Nervous system
- Influences fetal and neonatal neuron development; influences behavior and cognitive function, augment the actions of the sympathetic system
- Depression insomina psychosis and confusion
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<td>CHO metabolism</td>
<td>Blood glucose Stimulate gluconeogenesis Prevent glucose uptake</td>
<td>Hyperglycemia and diabetes</td>
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<td>Protein metabolism</td>
<td>Protein breakdown in skeletal muscle, skin and bone to release amino acid</td>
<td>Muscle weakness and wasting; thin easily bruising skin</td>
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### Related pathology in Cushing’s syndrome

- **Muscle weakness and wasting:** thin easily bruising skin
- **Protein metabolism:** breakdown in skeletal muscle, skin and bone to release amino acid
- **Calcium metabolism:**
  - **Blood glucose:**
    - Stimulate gluconeogenesis
    - Prevent glucose uptake
  - **Muscle weakness and wasting:** thin easily bruising skin

### Dexamethasone suppression test

**Cushing syndrome Dx**
- urine 24 hrs free cortisol
- Loss of diurnal pattern of cortisol secretion

**Cause of Cushing syndrome**
- Dexamethasone
- Serum ACTH

1. **Cushing disease** (pituitary)
   - ACTH high
   - Low dose cannot suppress
   - High dose can
2. **Ectopic ACTH**
   - ACTH high
   - Both low dose and high dose cannot
3. **Adrenal tumor**
   - ACTH low
   - Both low dose and high dose cannot

### Conn disease

- **Primary aldosteronism**
- **Increased aldosterone secretion**
- **Increased sodium retention**
- **Increased water retention**
- **Increased blood pressure**

**Diagnosis**
- Increased aldosterone secretion
- Increased sodium retention
- Increased water retention
- Increased blood pressure

**Treatment**
- Medical: ACE inhibitors
- Surgical: Adrenalectomy

**Primary aldosteronism**
- Conn syndrome
- Adrenal adenoma
- Bilateral adrenal hyperplasia
Secondary aldosteronism
Diagnosis: ↑aldosterone, ↑serum renin
- ↓renal perfusion
  arteriolar nephrosclerosis, renal artery stenosis
- Arterial hypovolemia and edema (CHF, cirrhosis, NS)
- Pregnancy (estrogen induced increases

Ambiguous genitalia

Hermaphroditism
- True hermaphroditism
- Pseudohermaphroditism: Male (XY), Female (XX)

Salt wasting (classic) adrenogenitalism
- Salt wasting, hyponatremia, hyperkalemia
- Acidosis, hypotension, CVS collapse, death
- Shift production- virilization

Simple virilizing adrenogenitalism without salt wasting
- Less 21-hydroxylase defect
- Genital ambiguity

Nonclassic adrenogenitalism
11β-hydroxylase deficiency
- ↓ cortisol
- ↓ aldosterone and corticosterone
- ↑ sex hormone
- Masculinization, hypertension (11-deoxycorticosterone acts as weak mineralocorticoid)

Adrenal insufficiency

Primary acute adrenocortical insufficiency
1. Chronic adrenocortical insufficiency (crisis):
   - Stress
2. Exogenous corticosteroids
   - Rapid withdrawal
   - Stress
3. Massive adrenal hemorrhage
   - Newborn
   - Anticoagulant therapy
   - Post surgical pt with DIC
   - Bacterial infection: Waterhouse-Friderichsen syndrome

Primary chronic adrenocortical insufficiency: Addison
Secondary adrenocortical insufficiency

Waterhouse-Friderichsen Syndrome
- Bacterial infection
  - Neisseria meningitidis
  - Hemophilus influenzae
  - Pseudomonas
  - Pneumococci
  - Streptococci
- Rapid progressive hypotension, shock
- DIC, skin purpura
- Acute adrenocortical insufficiency

Addison disease
- Primary chronic adrenal insufficiency
- Destruction of adrenal gland
- Detect when ≥ 90% has been destroyed
- Autoimmune disease
- Infection: TB*, Histoplasma, Coccidioides,
- AIDS: MAC, Kaposi sarcoma

Autoimmune polyendocrine syndrome
- Type 1 (APS1)
  = Autoimmune Polyendocrinopathy, Candidiasis, Ectodermal dystrophy (APECED)
- Autoimmune adrenalitis, hypoparathyroidism, idiopathic hypogonadism, pernicious anemia
- AIRE 21q22

Autoimmune polyendocrine syndrome
- Type 2 (APS2)

Addison’s disease
- Gradual onset
- Asthenia: progressive weakness, easy fatigability
- Hyperpigmentation*: ACTH
- Arterial hypotension: Mineralocorticoid activity, hyperkalemia, hyponatermia,
ADRENAL GLANDS:
MEDULLA
- Neural crest
- Cathecolamine

Pheochromocytoma
- Cathecholamine producing
- Hypertension (surgically correctable)
- Urine VMA/metanephrine

Neuroblastoma

MULTIPLE ENDOCRINE NEOPLASIA

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<th>Syndrome</th>
<th>Benign tumors and/or hormonal excess</th>
<th>Malignant tumors and/or hormonal excess</th>
<th>Non-hormonal neoplasia (dermatological)</th>
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           | Thyroid C-cell hyperplasia/C-cell
           | Adenomas
           | Paraneoplastic syndromes |
| MEN II or IIA | Medullary carcinoma
            | Thyroid C-cell hyperplasia/C-cell
            | Adenomas
            | Paraneoplastic syndromes |
| MEN IIB or III | Medullary carcinoma
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Paraneoplastic syndromes: Endocrinopathies

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| Cushing syndrome   | Small cell CA lung
                   | ACTH, ACH-like substance |
| SIADH               | Small cell CA lung
                   | ADH, ANF |

Mutant gene locus
- MEN I: RET
- MEN II or IIA: RET
- MEN IIB or III: RET
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<td>CA breast</td>
<td>TGF-α</td>
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<td>CA kidney</td>
<td>IL-1</td>
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<td>Adult T cell leukemia/lymphoma</td>
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<td>Insulin</td>
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### Causal mechanism

- **Major form of underlying cancer**
  - Squamous cell CA lung
  - CA breast
  - CA kidney
  - CA ovary
  - Adult T cell leukemia/lymphoma

- **Clinical syndromes**
  - Hypoglycemia
  - Hypercalcemia

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**Thank you for your attention**