ENDOCRINE SYSTEM

= integrated and widely distributed group of organs that orchestrate metabolic equilibrium and homeostasis between different organs of the body

- signaling = extracellular secreted molecules:
  • autocrine
  • paracrine  *distance of action*
  • endocrine
    = hormones

- regulation of secretion - feedback inhibition
HORMONES - ways of action

- Signaling through interaction with cell surface receptors
  1. Peptide hormones (growth h., insulin)
  2. Small oligopeptide molecules (epinephrine, histamine = few amino acids)
   - **Second messengers** - activated after surface receptor binding = cAMP, IP₃, Ca²⁺ influx
     (activation protein synthesis, proliferation, differentiation, gene expression…)
- Steroid hormones - diffuse across the membrane - interact inside of the cell: - DNA

Endocrine diseases: - underproduction
  - overproduction
  - mass lesions under/over-production
PITUITARY GLAND

~ 1 cm, in sella turcica, 0.5 g
- adenohypophysis (80 %)
- neuropypophysis (posterior)

Aterior pituitary - portal system - hypothalamic releasing hormones

Staining - acidophilic / basophilic / chromophobic
PITUITARY hormone-producing cells

Anterior
1. Somatotrophs: GH (acidophilic, ~50%)
2. Lactotrophs: Prolactin (acidophilic)
3. Corticotrophs: ACTH, MSH, edorphins, lipotrophin (basophilic)
4. Thyreotrophs: TSH (pale)
5. Gonadotrophs: FSH, LH

Posterior
- axonal processes from nerve cell bodies of the hypothalamus
stored hormones:
- oxytocin
- vasopressin
Hyperpituitarism

most frequently - **adenoma** (composed of single cell type)
- microadenoma < 1 cm < macroadenoma
- carcinoma less frequent
prolactin cell adenoma (1/3) < quiet < ACTH

**Adenoma morphology:** soft, well circumscribed
- compress optic chiasm, cranial nerves
- erode sella turcica
- some = invasive growth
Hyperpituitarism (cont.)

Adenoma gross morphology
Hyperpituitarism (cont.)

Adenoma microscopy: uniform polygonal cells, stroma is sparse

Clinical:
- endocrine abnormalities
- radiographic abnormalities of sella turcica
- visual defects (temporal q.)
- intracranial pressure (headache, nausea, vomit)
- expanding mass - hypopituitarism
Pituitary adenomas

Prolactinomas (30 %)
- prolactinemia: amenorrhea, galactorrhea, ↓ libido, infertility

Growth hormone adenoma - GH hypersecretion stimulates hepatic secretion of Insulin-like Growth Factor-1 (IGF-1)
→ gigantismus (children)
→ acromegaly (adults)
(gonadal dysfunction, DM, hypertension)

Corticotroph cell adenoma - usually microadenomas
hypercortisolism (Cushing syndrome)
• if pituitary adenoma - ACTH↑, cortisol↑ (Cushing disease)
• removal of adrenals - pituitary tumor - ACTH precursors of ACTH - hyperpigmentation (Nelson sy)
Other anterior pituitary adenomas

**Mixed adenomas** - produce GH, Prolactin

**Gonadotroph adenoma** - LH, FSH inefficient secretion = = clinically silent = neurological manifestations

**Thyreotroph adenomas** - TSH, rare, hyperthyreoidism

**Null cell adenomas** - lead to hypopituitarism

acute hemorrhage = pituitary apoplexy

**Pituitary carcinoma** - rare
Hypopituitarism

- diseases of the pituitary
  - tumors
  - pituitary surgery / radiation
  - Rathke cleft cyst (lined by ciliated cuboidal epithelium)
  - Pituitary apoplexy (sudden headache, diplopia, hypopituitarism)
  - Ischemic necrosis and Sheehan sy. (=post partum necrosis) (pregnancy - 2\times\text{enlargement} - \text{not vessels. DIC, shock})
  - Empty sella syndrome (surgery, radiation, infarction)
  - Genetic defect - congenital deficiencies

- diseases of hypothalamus
  - Hypothalamic tumors - craniopharyngeom, gliomas, metastases (lung, breast)
  - Infiltrative processes, infections, -sarciodosis, Tbc

Manifestations: hypothyreoidism, hypoadrenalism, palor (MSH), genital atrophy, impotence, amenorrhea, libido
Radke´s cleft cyst
Posterior pituitary syndromes

- axonal processes from nerve cells of the supraoptic and paraventricular nuclei of hypothalamus

- **oxytocin** - uterus, breast ducts.

- **ADH (vasopressin)** →
  - deficiency  Diabetes insipidus, polyuria
    (head trauma, tumors - craniopharyngeoma, inflammation)
  - excess  (usually small cells Ca of the lung)
    readsorption of water → hyponatremia
THYROID GLAND

15-20 g, right/left lobe, isthmus
- hypothalamus - TRH
- pituitary - TSH - follicular epithelium uptake of thyreoglobulin from colloid - T4, T3 ... carbohydrate, lipid catabolism

Basal metabolic rate - constant adaptation (pregnancy, puberty, stress)
- excess - hyperthyreoidism
- deficiency - hypothyreoidism

C cells = parafollicular (interstitium)
- calcitonin... deposition of $\text{Ca}^{2+}$ in bones
Hyperthyroidism

Thyreotoxicosis causes:
• hyperplasia (Graves d.)
• exogenous hormone supply
• hyperfunctional goiter
• hyperfunctional adenoma
• thyroiditis

Hyperthyroidism - primary
(intrinsic thyroid abnormality)
- secondary
(pituitary TSH tumor, struma ovarii, …)

Hypothyroidism

Structural / functional derangement

Primary hypothyroidism
1. Hashimoto thyroiditis
2. Surgery, radiation, drugs, infiltr. neoplasms, inflammation

Secondary hypothyroidism
- TSH deficiency
(hypopituitarism, tumor…)

Tertiary hypothyroidism
= central: TRH delivery block
Manifestations of hypothyroidism

**Cretenism** - in infancy/early childhood
most frequent in areas w/low iodine
  = endemic C.
  sporadic C. = inborn defect
  → impared skeleton, CNS, facial features, protruding tongue

**Myxedema** - slowing physical and mental activity, cold intolerance, edema + matrix subst. deposition
  low voice, large tongue
**THYROIDITIS**

**Infections** - acute / chronic (bacterial, Tbc, fungal)

**Hashimoto thyroiditis** - lymphomatous struma

max. 60 y., female

T-cell defect: diminished Ts => thyroid-specific Th:

1. Stimulate secretion of anti-thyroid Ab
2. Induce CD8+ Ly cytotoxic to thyroid

**autoantibodies against:** - thyroglobulin, thyroid peroxidase
- TSH receptor (**block** TSH action)
- Iodine transporter

**Morphology:** - Thyroid gl. is enlarged
- extensive infiltration by Ly, Pc, +germinal centers
- follicles are small, sometimes lined by eosinophilic Hürtle cells
- fibrosis
Hashimoto thyroiditis
Subacute lymphocytic thyroiditis
= silent thyroiditis
- painless slight enlargement
- Ly infiltration (no germinal centers)
- hyperthyroidism (temporary 2-4 mo, from injured tissue)
- no autoantibodies

Riedel thyroiditis
- rare, cause ? (viral ?)
- extensive fibrosis
THYROIDITIS (cont.)

Subacute (granulomatus) thyroiditis

- also De Quervain thyroiditis
- 40 y., female, painful

Cause:
- viral infection or post v.i. process
  (usually after upper resp. infection)
- adenoviruses, mesles, coxackie, mumps, ...
- the process is self limited

Morphology:
- slightly enlarged
- involved areas are yellowish
- aggregates of Ly, Mf, Pc,
  multinucleated giant cells
GRAVES DISEASE (Basedow struma)

triad of clinical findings:
1. Hyperthyroidism, gland enlargement
2. Exophthalmus
3. Infiltrative dermatopathy - periorbital myxedema

20 - 40 y., mostly female = 1-2 %

Autoimmune disease:
• autoantibodies to TSH receptor (previously known as LATS) specific for Graves disease ...hormone↑, growth ↑

mechanisms:
• molecular mimicry (some exogenous Ag are similar to tissue components)
• T-cell autoimmunity (T cells direct against MHC proteins on cells) with B cells → autoantibodies
Morphology:
- symmetrical enlargement
- diffuse hypertrophy + hyperplasia
  = follicular cells - tall, crowded
    → papillae
  = B-lymphocyte aggregates

Exophtalmus:
= Infiltrative ophthalmopathy
- increased volume of:
  retroorbital connective tissue
  extraocular muscles
  (inflammation ~ TSH receptor on
  muscles, matrix deposition, fibrosis)
GOITER
= enlargement of the thyroid

**Diffuse nontoxic (colloid) goiter**
= endemic (low I, goitrogens)
  hyperplastic stage ~ colloid involution
= sporadic (hereditary defect)

**Nodular goiter**
= recurrent episodes of hyperplasia / involution
  - extreme enlargement, assymetrical
  - clonal proliferation (different proliferative potential of cells)
GOITER
= enlargement of the thyroid gland

decomposed center of a nodule

Nodous goiter
calcification + ossification

bone marrow
NEOPLASMS of the thyroid

**Adenoma**
- 2-3 cm, capsule
- derived from follicular epithelium
- TSH receptor → proliferation
<table>
<thead>
<tr>
<th>Thyroid Adenomas</th>
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<tbody>
<tr>
<td>Embryonal adenoma</td>
</tr>
<tr>
<td>(trabecular)</td>
</tr>
<tr>
<td>- formation of cords of cells</td>
</tr>
<tr>
<td>Colloid adenoma</td>
</tr>
<tr>
<td>(follicular)</td>
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<tr>
<td>- large colloid-filled follicles</td>
</tr>
<tr>
<td>Hürtle cell adenoma</td>
</tr>
<tr>
<td>- large eosinophilic cells</td>
</tr>
<tr>
<td>with granular cytoplasm</td>
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<tr>
<td>Fetal adenoma</td>
</tr>
<tr>
<td>- small follicles,</td>
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<tr>
<td>loose myxoid stroma</td>
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</tbody>
</table>

**Adenomas clinically:**

- **hot** or **cold** nodules
NEOPLASMS of the thyroid

Follicular lesion of uncertain biology
NEOPLASMS of the thyroid

Carcinoma - risk factor N° 1 = radiation
- predisposing factors = nodular goiter, Hashimoto
  Papillary carcinoma ~ 80 %
  (also with Gardner sy.)
  - papillary structure, ligth nuclei
  - psammoma bodies
NEOPLASMS of the thyroid

Follicular carcinoma ~ 15%
- predisposition = nodular goiter
NEOPLASMS of the thyroid

Medullary carcinoma

= neuroendocrine neoplasm (parafollicular C cells, - secrete calcitonin = diagnostic)
80 % sporadical  20 % MEN

adults 40/50  children

- bilateral, multicentric, firm, + necroses, hemorrhages

Histology: polygonal/spindle cells in nests or trabecules.

Amyloid deposits = derived from secreted calcitonin molecules
PARATHYROID GLAND

4 x small glands at pole of the thyroid
- function controlled by $\downarrow$ Ca$^{2+}$ in blood … PTH $\uparrow$ (feedback)

**PTH**: (osteoclast activation, tubular Ca$^{2+}$ readsorption, conversion of provitamin D)

!!! Malignant neoplasms may release PTH related protein (**PTHrP**)

**Hyperparathyroidism**

**Primary:**
- adenoma (usually solitary)
- primary hyperplasia (component of MEN)
- carcinoma (infiltrative growth)

+ bone resorption replaced with fibrous tissue, cysts
+ urinary tract stones
+ metastatic calcification
**Hyperparathyroidism**

**Secondary:** any depression of serum Ca\(^{2+}\)
- renal failure = ↓phosphate excretion → hyperphosphatemia - hypocalcemia
- vitamin D deficiency (decreased Ca\(^{2+}\) reabsorption in GIT)

Clinically: + Parathyroid gland hyperplasia
  + Bone resorption
  + Metastatic calcification

**Hypoparathyroidism**
- less common
  1. Surgically induced
  2. Congenital absence (by thymic aplasia = Di George sy.)
  3. Primary (idiopathic) atrophy = autoimmune disease
  4. Familial hypoparathyroidism

Clinically: + neuromuscular irritability, tetany
  + depression, anxiety
  + heart conduction defect
ADRENAL CORTEX

1. Glucocorticoids (cortisol)
2. Mineralcorticoids (aldosterone)
3. Sex steroids (estrogens, androgens)

HYPERADRENALISM
1. Cushing sy.
2. Hyperaldosteronism
3. Adrenogenital sy. (virilizing)

1. Hypercortisolism
   (Cushing sy.)
Morphological changes at Cushing sy.

- pituitary = Crooke hyaline change (keratin filaments in basophilic cells)
- adrenal glands = cortical - atrophy
  - hyperplasia - diffuse
  - nodular
  - adenoma (Ca is rare)

Clinically: - hypertension, weight↑
- adipose tissue deposition - buffalo neck
  - moon facies
- glucocorticoids - induce gluconeogenesis
  (hyperglycemia, glycosuria, polydipsia)
  - osteoporosis, skin atrophy, hirsutism, menstrual abnorm.
**Adrenals**: enlarged, cortex over 5 mm thick, in the left adrenal a compact node 14 mm

*Dg*: Hyperplasia and adenoma of adrenal glands
2. Primary hyperaldosteronism

Na\(^+\) retention, K\(^+\) excretion = hypertension, hypokalemia
- usually adenoma or hyperplasia of the cortex

*Primary*: = overproduction of aldosterone (adenoma) → suppression of renin-angiotensin system

*Secondary*: activation of renin-angiotensin system (congest. heart failure, low renal perfusion = nephrosclerosis) → aldosterone release
HYPERADRENALISM

3. Adrenogenital syndromes

*Causes:* - adrenocortical neoplasms
  - congenital adrenal hyperplasias (lack of cortisol → synthesis of other steroids

21-hydroxylase deficiency → no mineralocorticoids
  1. Salt-wasting sy. (hyperkalemia, acidosis, hypotension)
  2. Simple virilizing (= incomplete defect → genital ambiguity)
  3. Late onset adrenal virilism (minimal defect → hirsutism)

Treatment = administration of glucocorticoids → suppress ACTH
Adrenal insufficiency

Waterhouse-Friderichsen sy.
- bacterial infection with septicemia → hypotension, shock, DIC
  = bilateral massive adrenal hemorrhage
- more common in children

Secondary adrenocortical insuff.
- primary disorders of hypotalamus or pituitary (cancer, radiation, infarction…)
  => ACTH ↓ … no hyperpigmentation

Primary adrenocortical insufficiency (Addison disease)
- autoimmune adrenalitis (antiadrenal antibodies)
  - infections (Tbc, fungi)
  - metastatic neoplasms (lung, breast)
  => ACTH ↑ … hyperpigmentation
Adrenocortical neoplasms

- adrenocortical adenomas (mostly inactive)
- adrenocortical carcinomas (rare, active → virilism, hyperadrenalism)
ADRENAL MEDULLA

- neuroendocrine cells
  (chromaffin) + supporting cells
  → catecholamines

Similar cells dispersed =
= extra-adrenal system (paraganglia)

Most important diseases =
neoplasms
- pheochromocytoma (chromaf.)
- neuroblastoma (neuronal cells)
Pheochromocytoma

- uncommon neoplasm → catecholamines +/- peptide hormones
  - hypertension, tachycardia, sweating
- only rare metastasizing
- Extraadrenal tumors, chromaffin negative = paragangliomas
10% of pheochromocytomas = part of familial syndromes
  (MEN, von Recklinhausen, Von Hippel-Lindau + renal cell Ca)
Neuroblastoma

- most common extracranial tumor in children
  - adrenal medulla
  - sympathetic nerve system

Clinical: metastases to liver, bones. Urine: NE, vanillylmandelic ac.
MULTIPLE ENDOCRINE NEOPLASIA

MEN = familial disease with multiple endocrine hyperplasias / tumors
    = autosomal dominant

MEN I. (Werner sy.)
Parathyroid, Pancreas, Pituitary = 3Ps

Clinical: Zollinger-Ellison sy., hypoglycemia
MEN II.
- II A (Sipple syndroma)
  Pheochromocytoma,
  Medullary Ca,
  Parathyroid hyperplasia

- II B (= III.)
  Pheochromocytoma
  Medullary Ca
  Neuroma
Glandula pinealis

100-200 mg,
neuroglial stroma + nests of pinealocytes
- neurosecretory granules (melatonin)

Rarely - tumors:  
  * germinal* (seminoma, ovarian dysgerminoma)
  * teratoma* 
  * pinealoma* (rare)  
  - pinealoblastoma
  - pinealocytoma

  (compression of hypothalamus, 
  of channel of Sylvius)
β-cells of pancreas release: insulin (30-60% caught by liver)

c-peptide (only 12% caught by liver)

⇒ C-peptide is more reliable marker of functional status of β-cells

Diabetes: I. type - insufficiency of β-cells (disappearance)

  level of C-peptide < 0.2 nmol/l = I. type DM

II. type – deranged utilisation of insulin, level of C-peptide must not be deranged