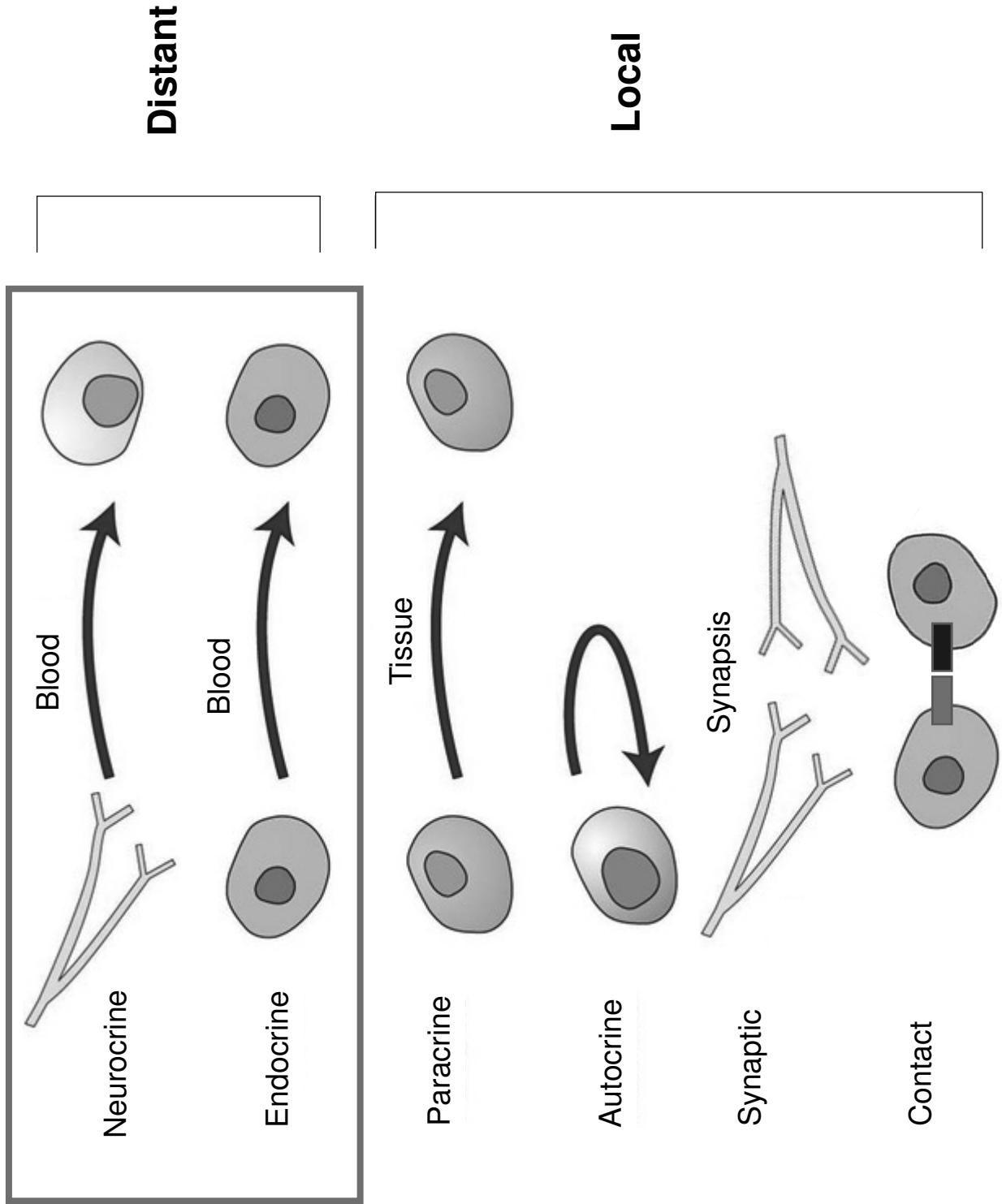
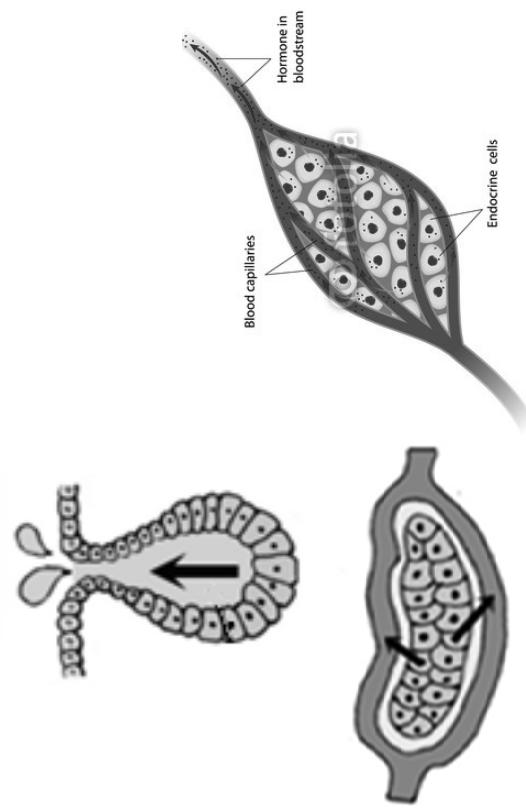
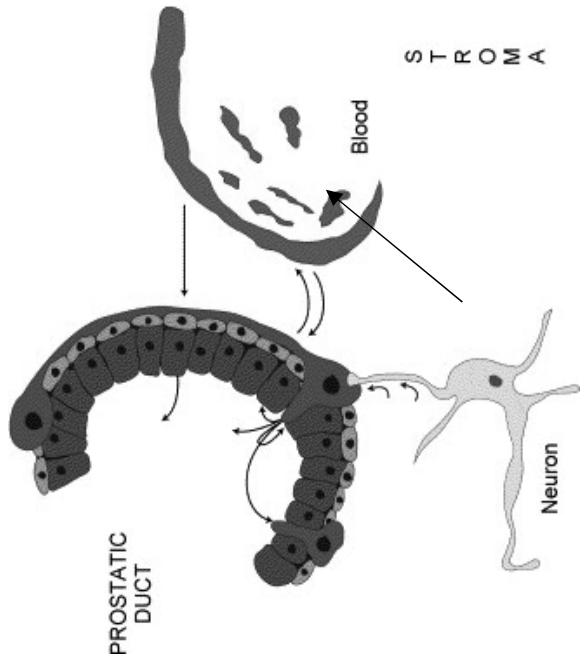


Intercellular communication



General properties of endocrine organs

- Endocrine organs (e.g. pituitary, thyroid, parathyroid, adrenal)
 - Endocrine tissue within other organs (pancreas, gonads, kidneys, placenta)
 - Isolated endocrine cells (DNES, APUD)
 - Neuroendocrine cells
- Common developmental scheme
- invagination of epithelia, losing contact with the original tissue
 - ducts absents

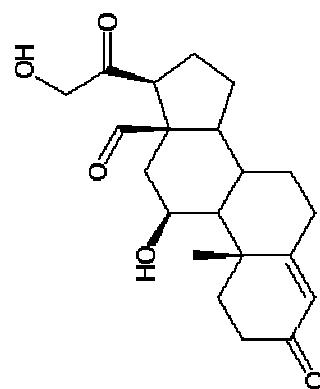
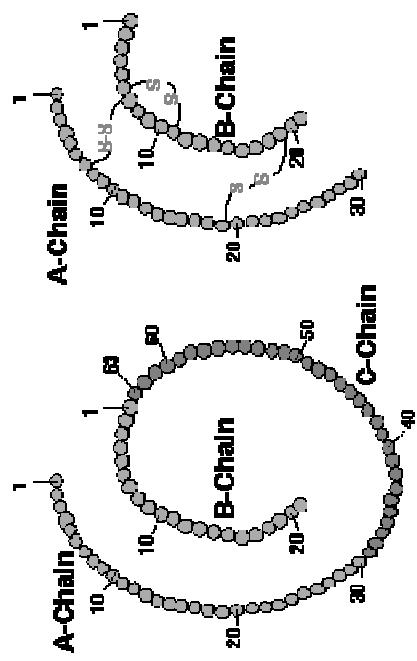
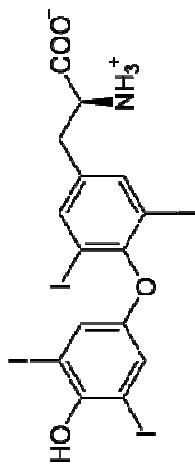


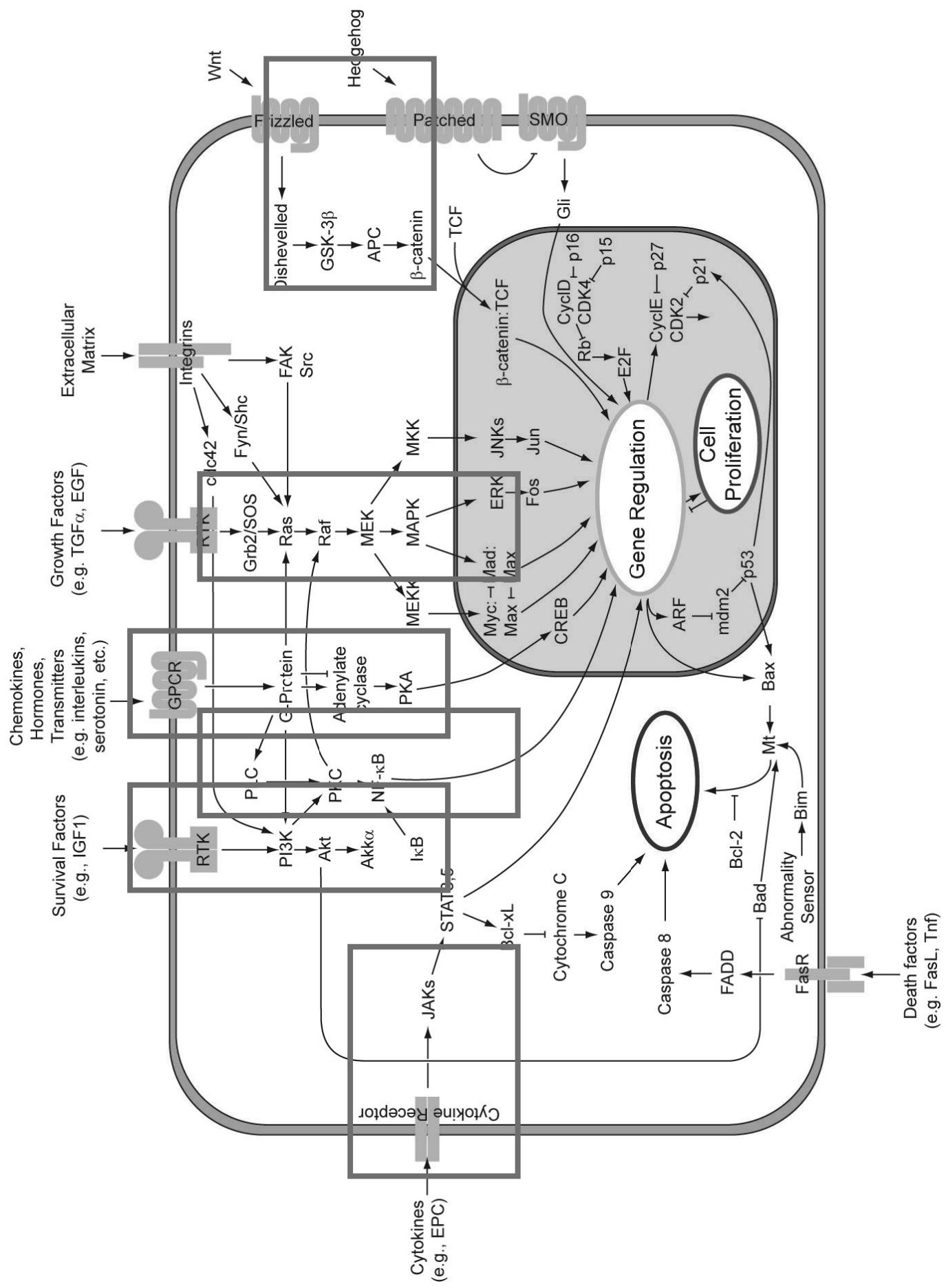
General properties of endocrine organs

- c.t. capsule + septa
- Trabecules of glandular epithelium, follicles or clusters of glandular cells
 - Neurosecretory cells
- Or
- Capillary network
 - Fenestrated capillaries
 - Sinusoids
- Merocrine secretion
 - not only hormones – endocrine gland is *sensu lato* also liver

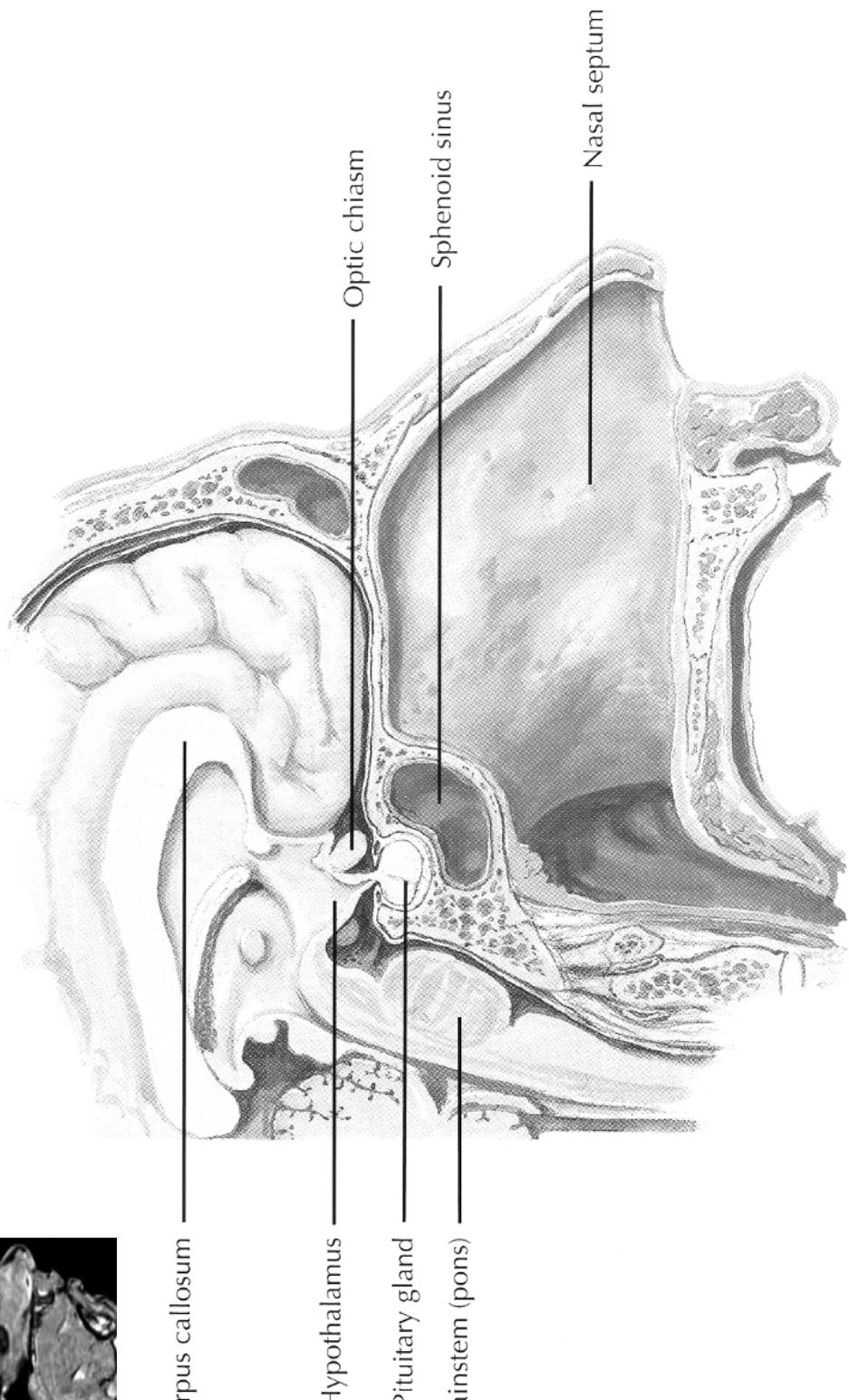
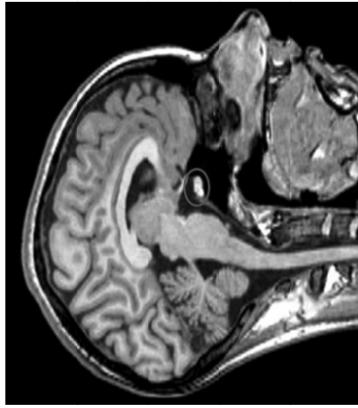
General properties of hormones

- **steroids** – hydrophobic, intracytoplasmic or nuclear receptors (sex hormones, corticoids)
- **proteins and polypeptides** – hydrophilic, plasma membrane receptors (insulin, pituitary hormones, PTH, ...)
- **amino acids** and their derivatives (adrenalin, noradrenalin, thyroxin)



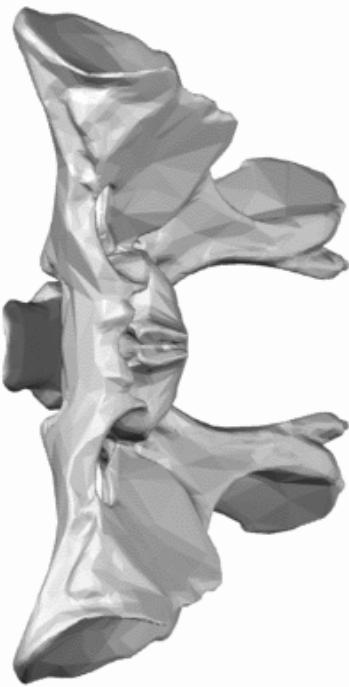
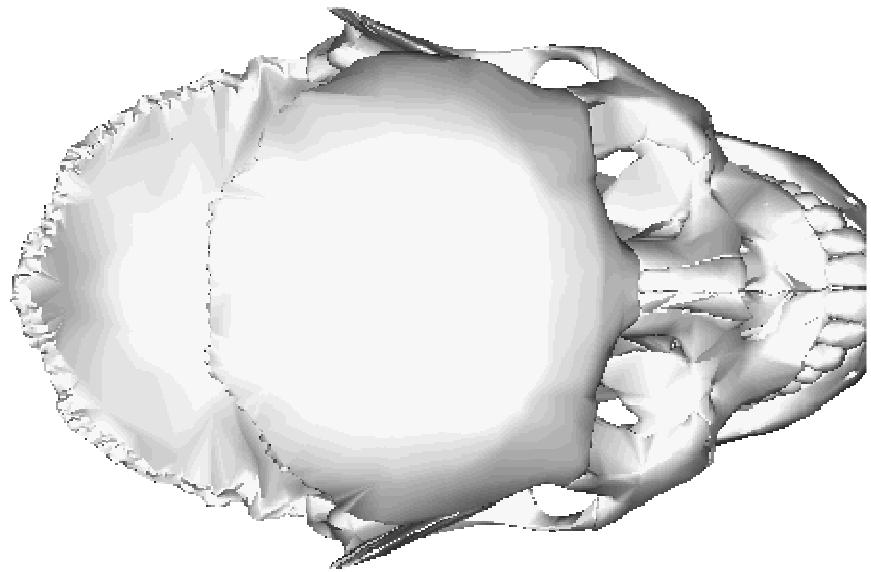


Pituitary gland (*gl. pituitaria*)

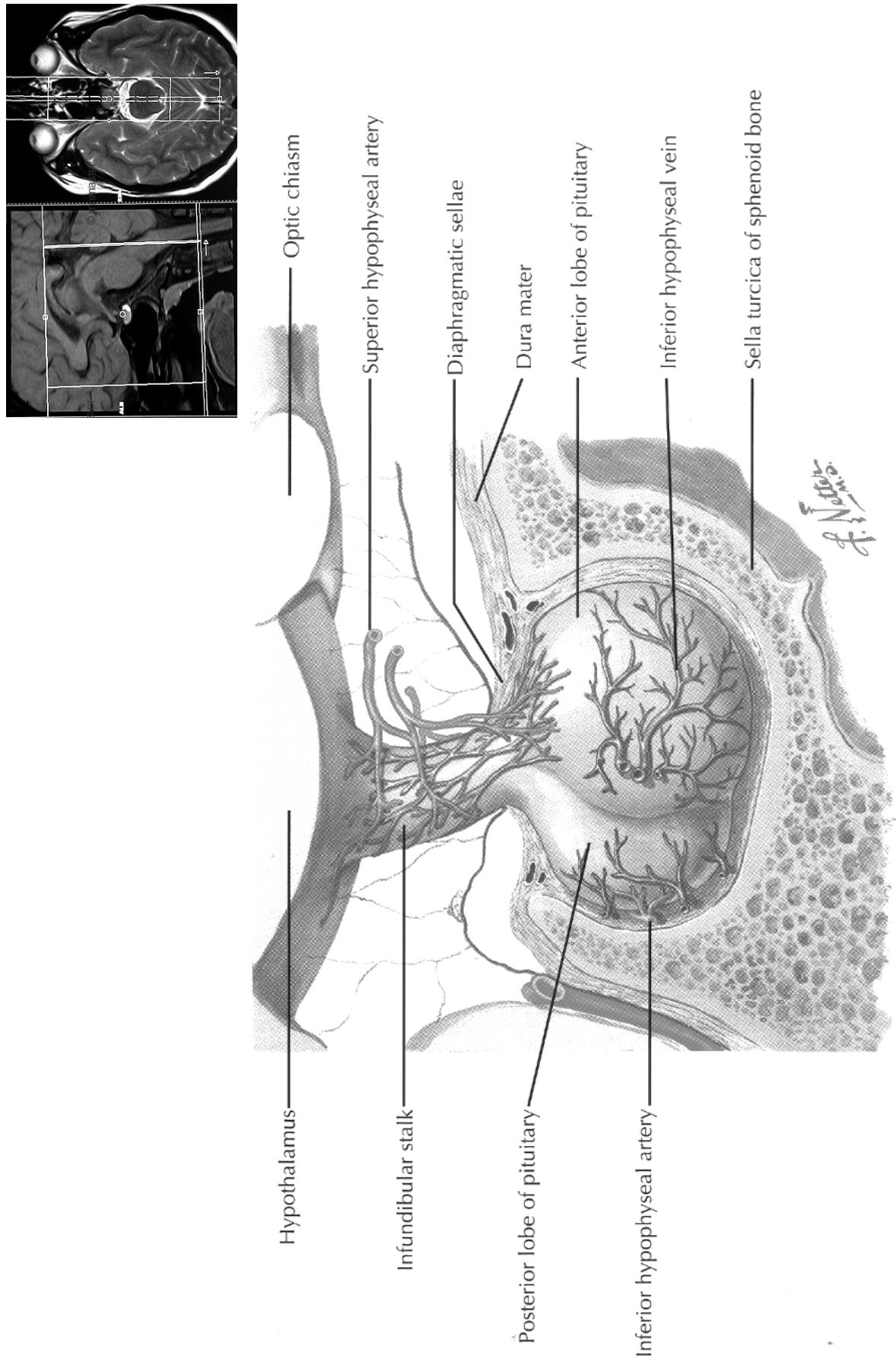


Pituitary gland (*gl. pituitaria*)

- sphenoid bone
- sella turcica
- fossa hypophysialis

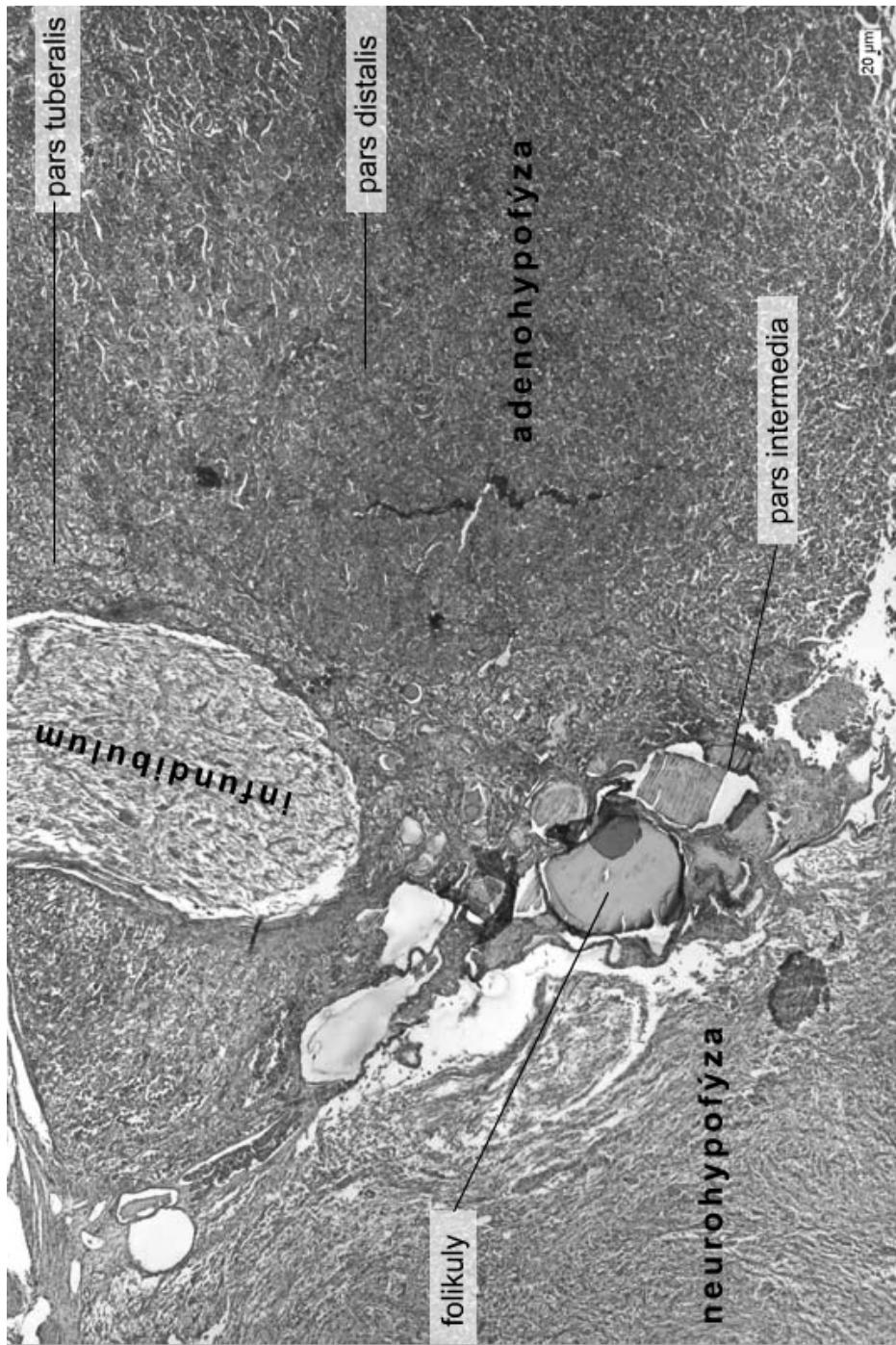


Pituitary gland (*gl. pituitaria*)



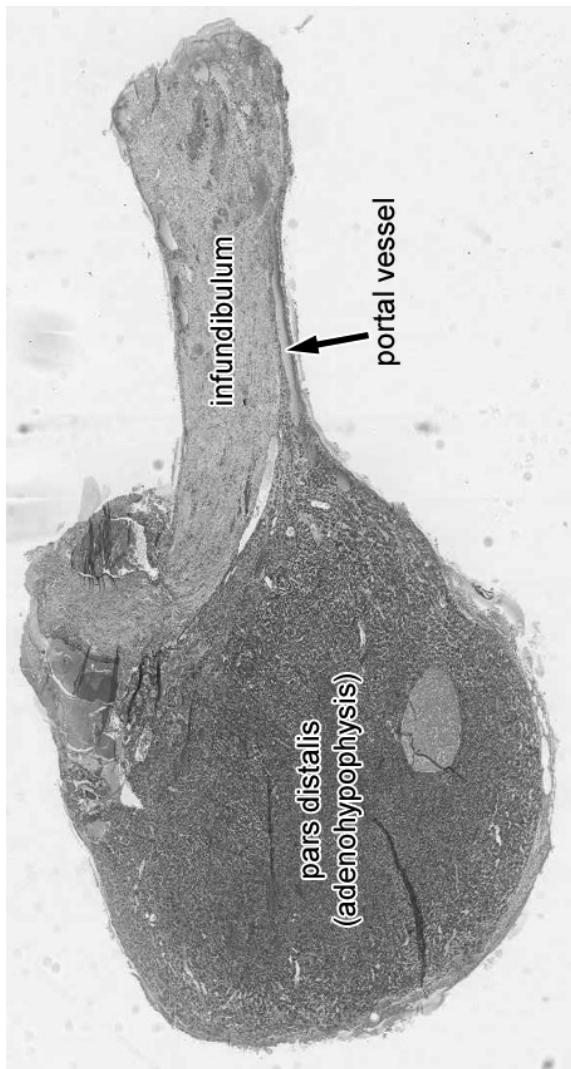
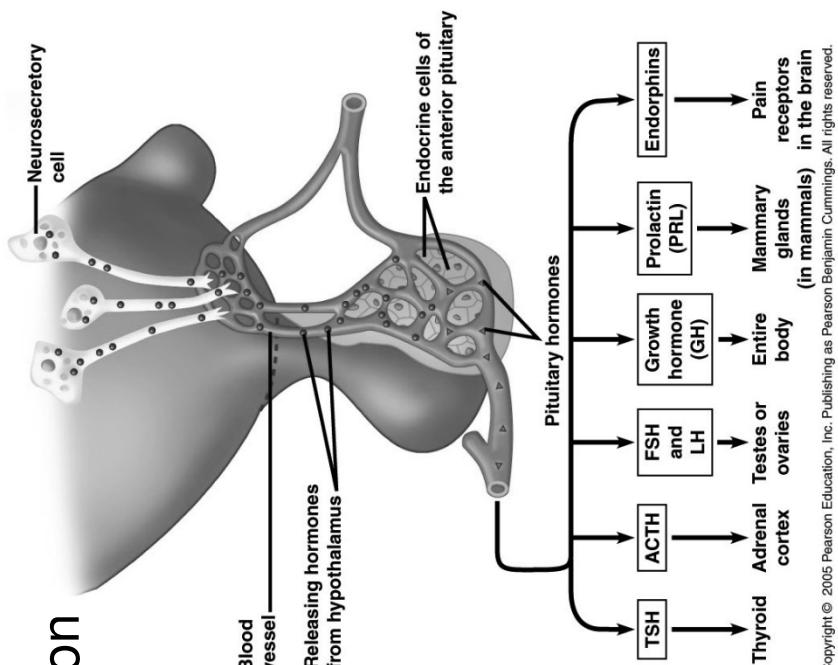
Pituitary gland (gl. pituitaria)

- adenohypophysis (*pars distalis*, *pars tuberalis*, *pars intermedia*)
- neurohypophysis (*pars nervosa*)
- *infundibulum*, *eminentia mediana*



Pituitary gland (*gl. pituitaria*)

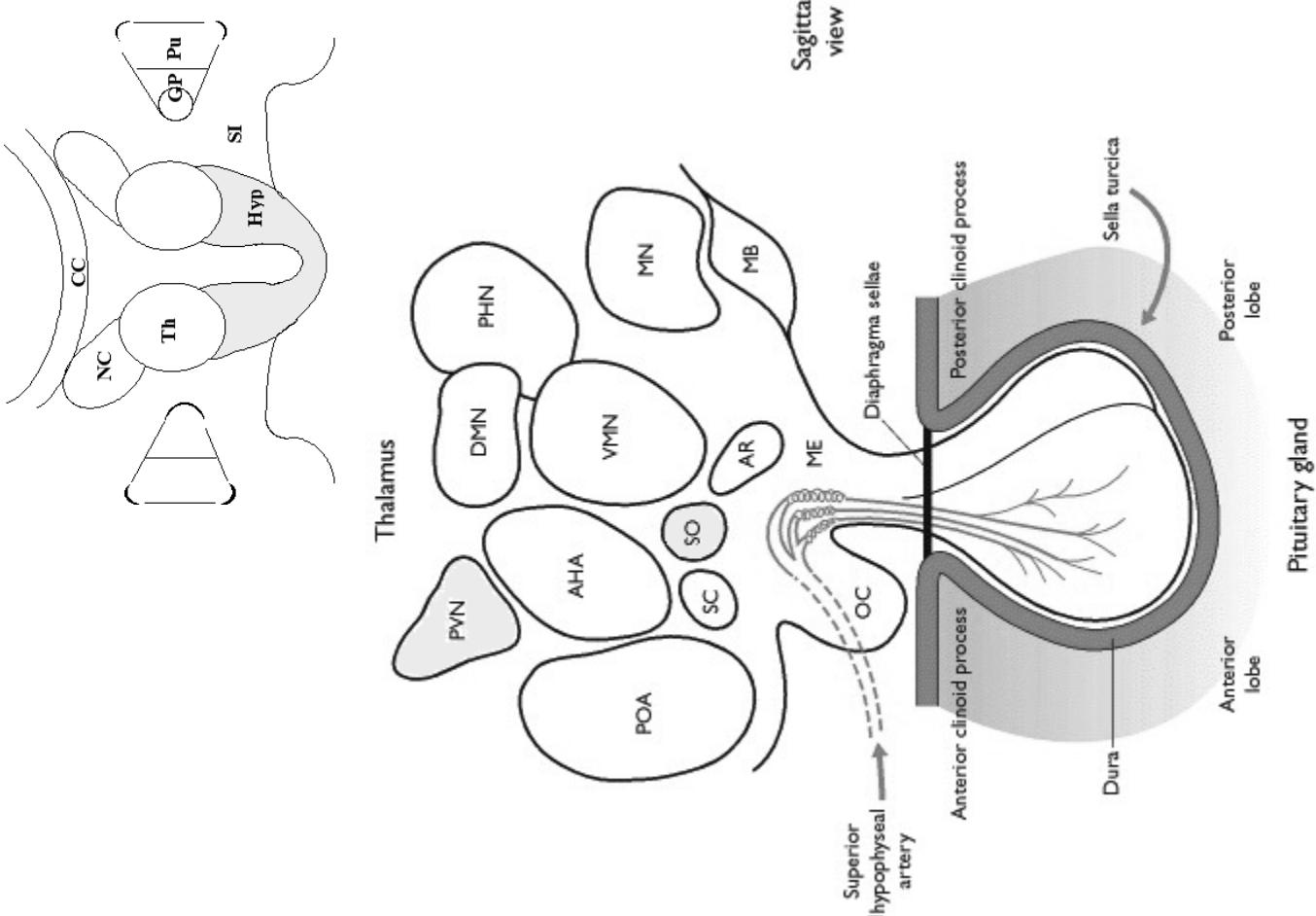
- adenohypophysis - glandotropic hormones, prolactin, GH
- neurohypophysis - hypothalamic hormones - ADH, oxytocin
- anatomical and functional association with hypothalamus
- capillary systems and neuroendocrine secretion



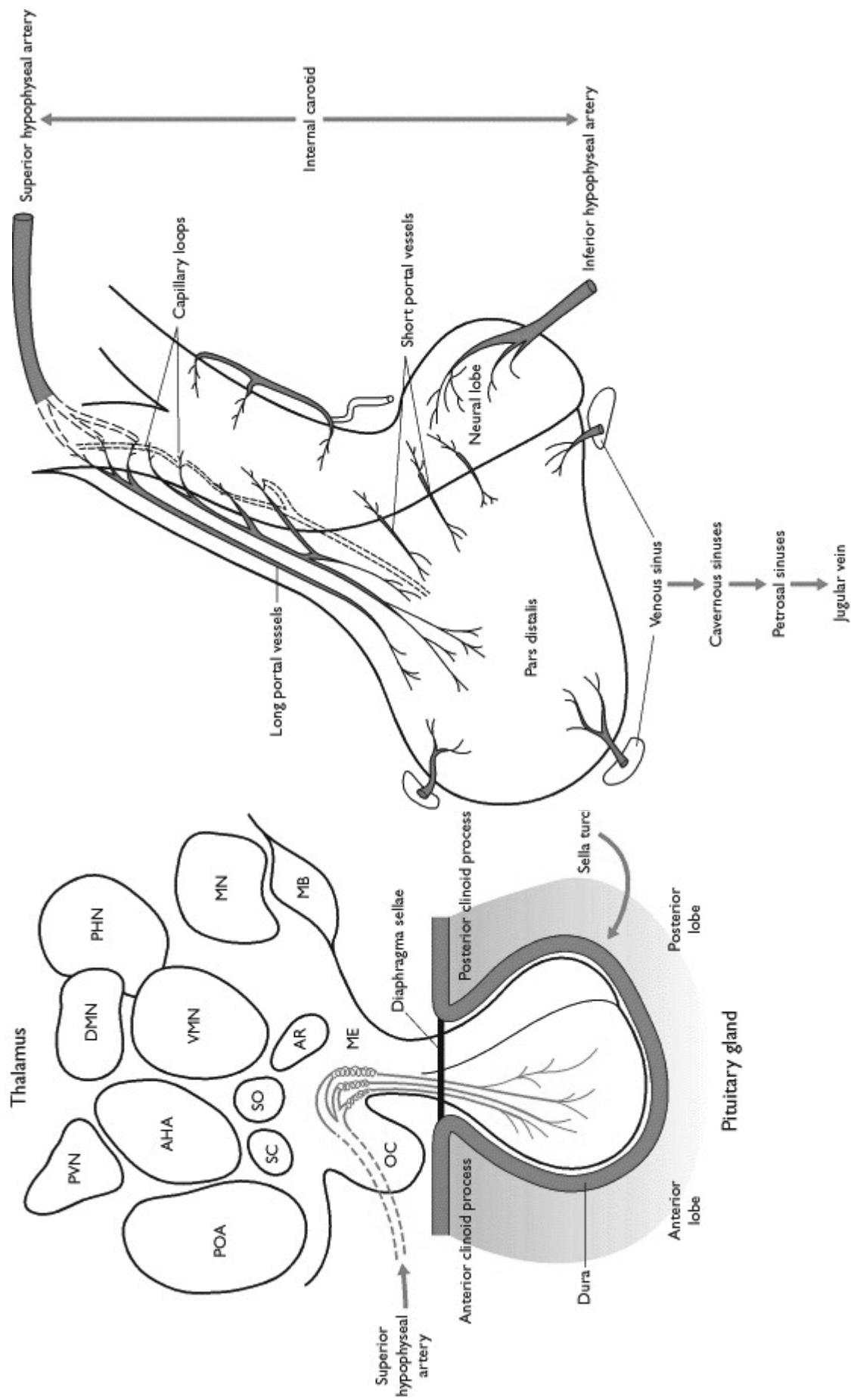
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Hypothalamus

- small region of diencephalon
- complex neuroarchitecture
- core of the limbic system
- complex functions
 - regulation of temperature, emotions, eating behavior, circadian rhythms
 - hormonal regulation controlled by various stimuli (osmoreception, concentration of nutrients, electrolytes, systemic functions - pain)
- hypothalamic nuclei
 - *n. supraopticus, n. paraventricularis*
 - magnocellular neurons - *tractus hypothalamo-hypophysialis*
 - parvocellular neurons - capillaries in *eminentia mediana*



Hypothalamo-hypophyseal system



Mechanism of neurosecretion

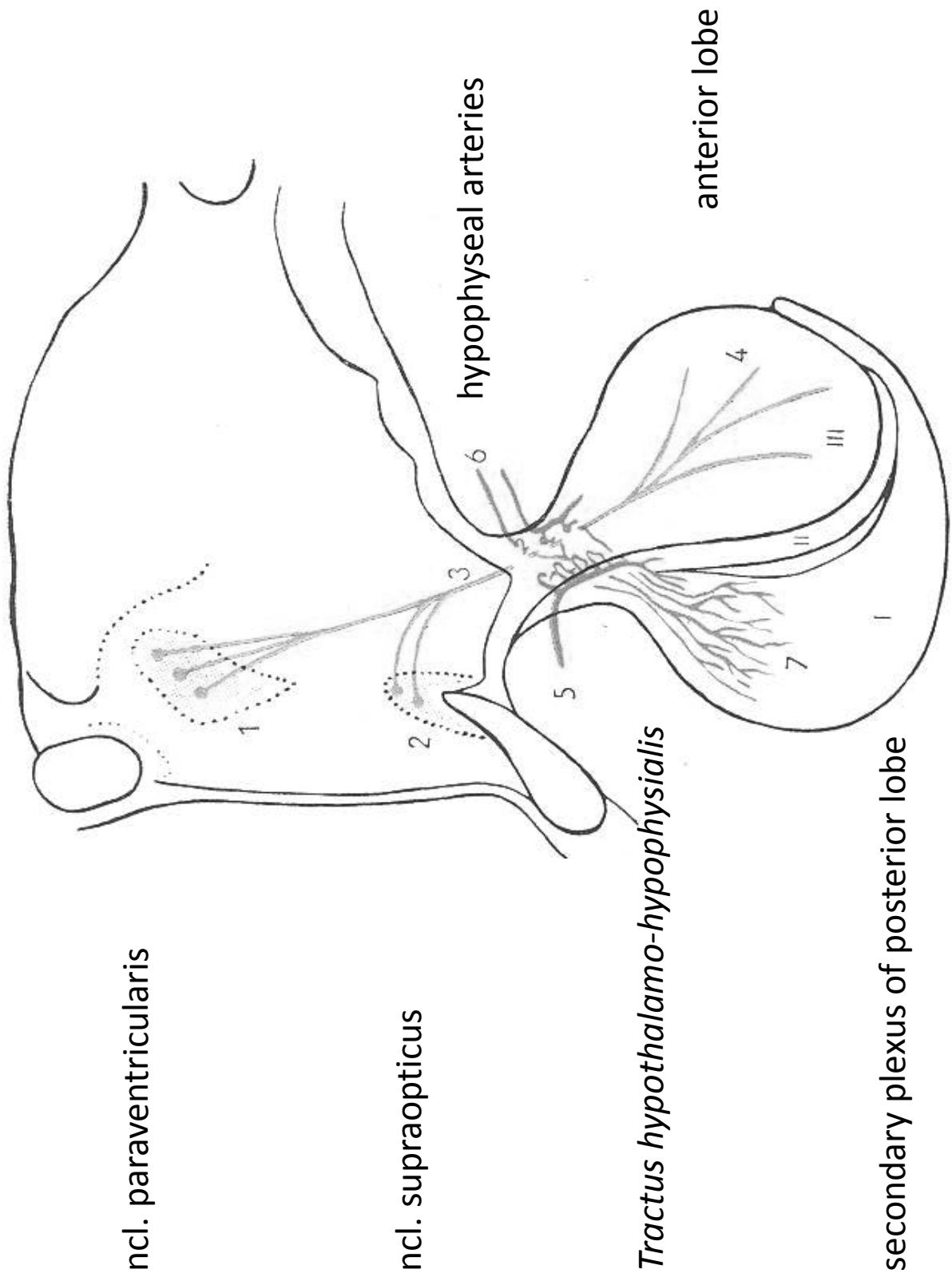
Tractus hypothalamo-hypophysialis

- axons of magnocellular neurons in nucleus supraopticus and paraventricularis
- terminating on fenestrated capillaries in neurohypophysis
- synthesis of prohormones → during axonal transport maturation
- capillary plexus from arteria hypophysialis inferior (branch of arteria carotis interna → sinus cavernosus

Hypophyseal portal system

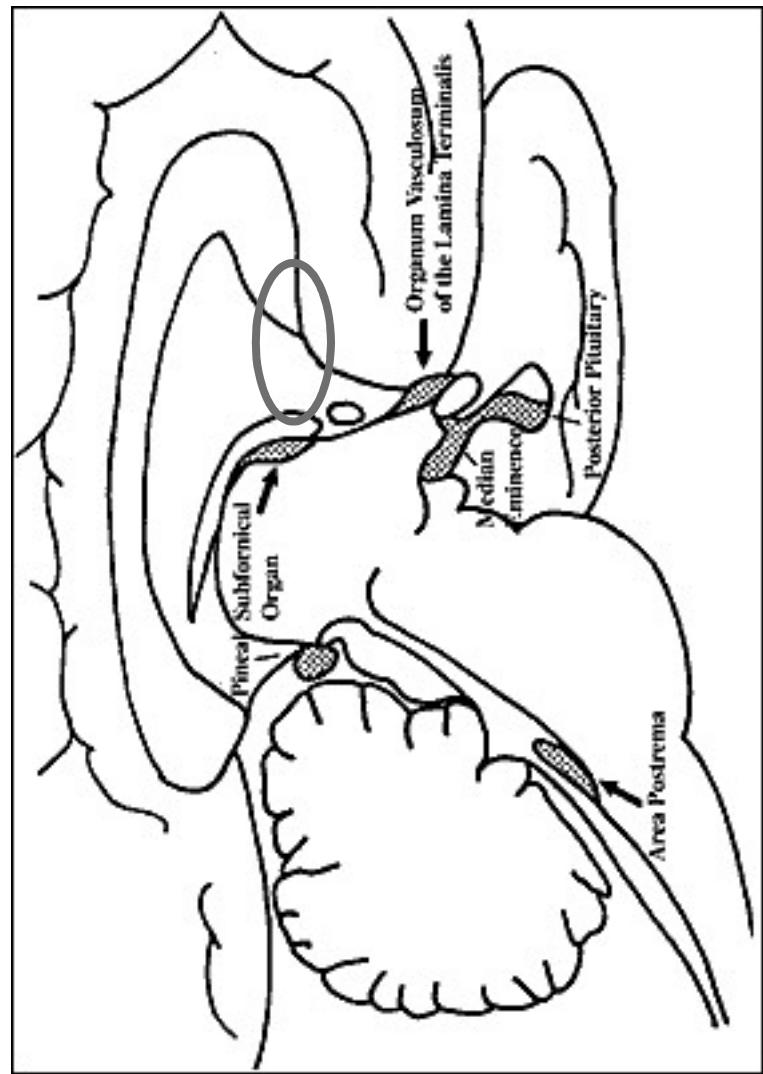
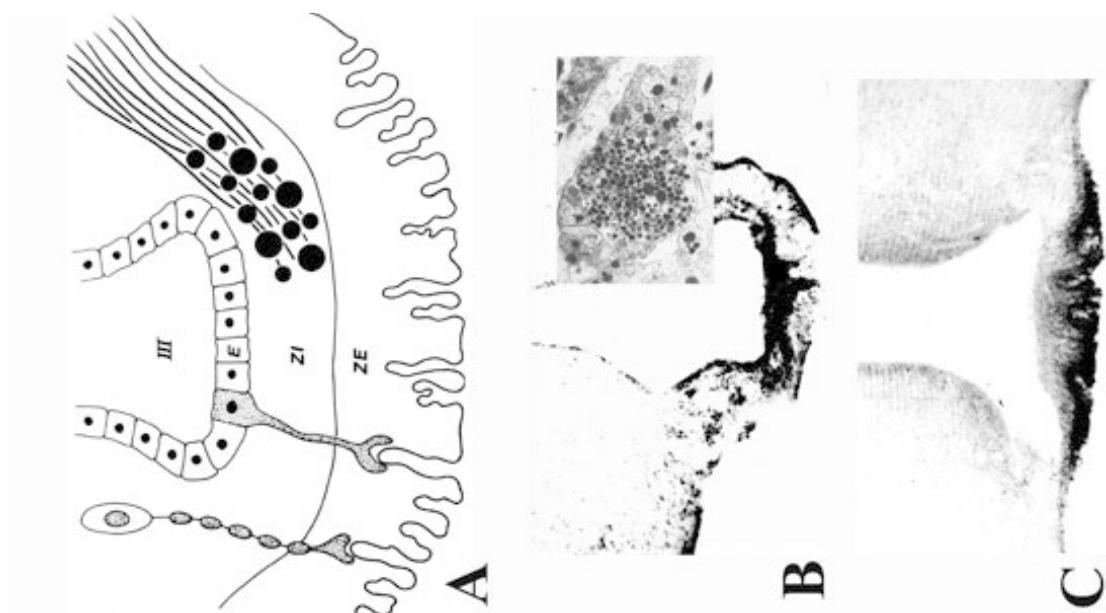
- parvocellular neurons e.g. in nucleus arcuatus, preopticus, paraventricularis and nuclei tuberales
- axonal transport onto primary capillary plexus in eminentia mediana (from anterior and posterior superior hypophyseal arteries) → hypophyseal portal veins → secondary capillary plexus in adenohypophysis → inferior hypophyseal portal veins → v. jugulares internae

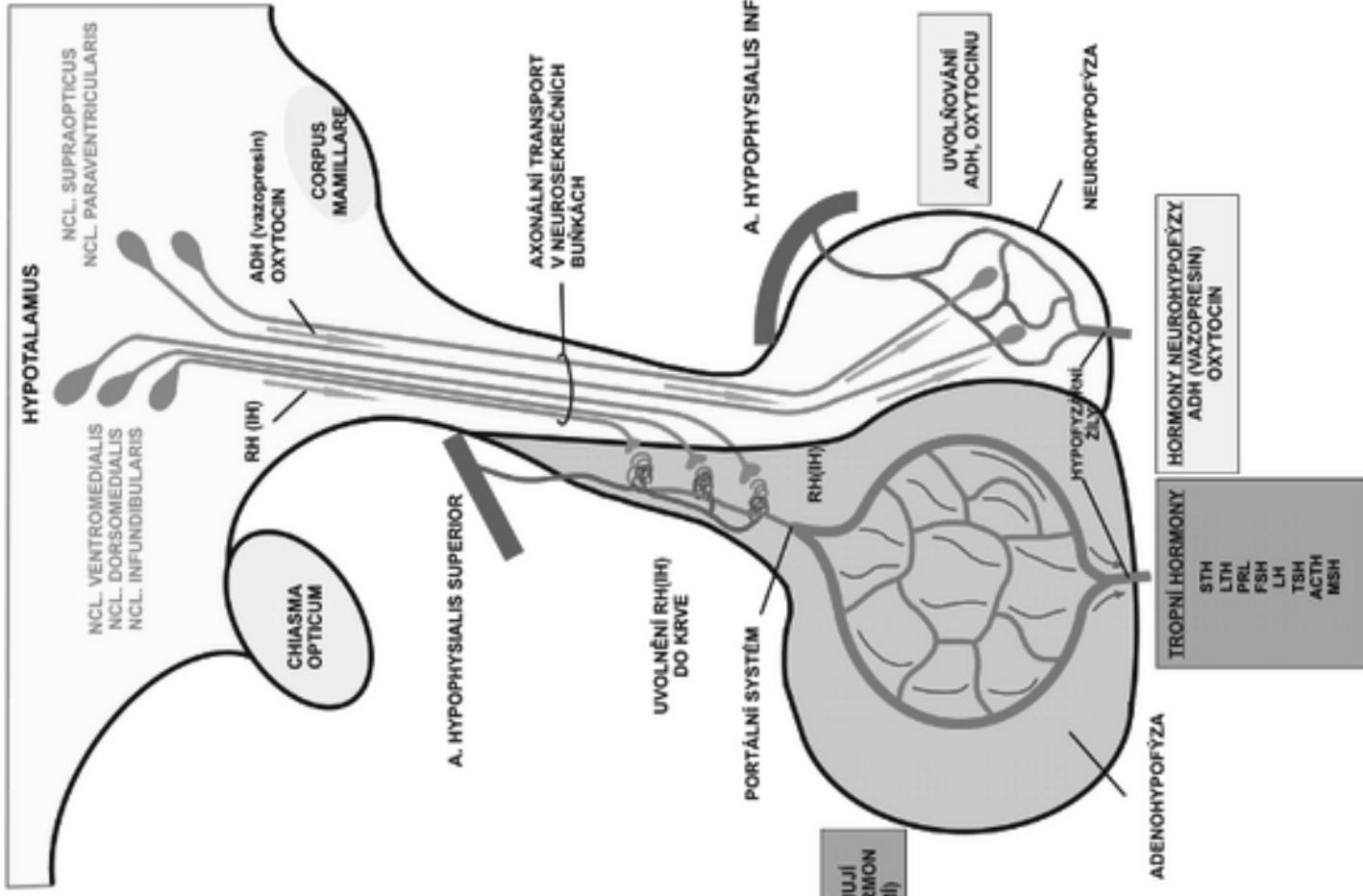
Capillary system of hypophysis



Eminentia mediana

- elevated part of tuber cinereum, (detachment of infundibulum p. nervosa)
- neurohemal area hematoencephalic barrier open
- fenestrated capillaries with large perivascular spaces



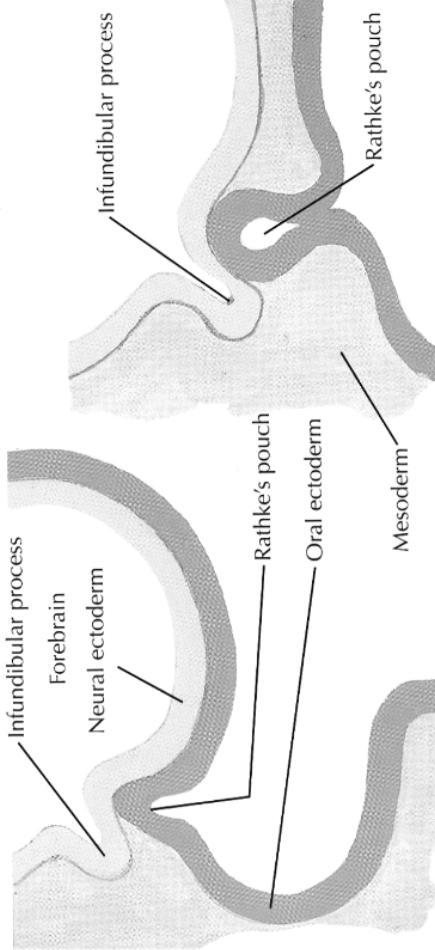


RH - stimulující hormony (z hypothalamu)
IH - inhibující hormony (z hypothalamu)

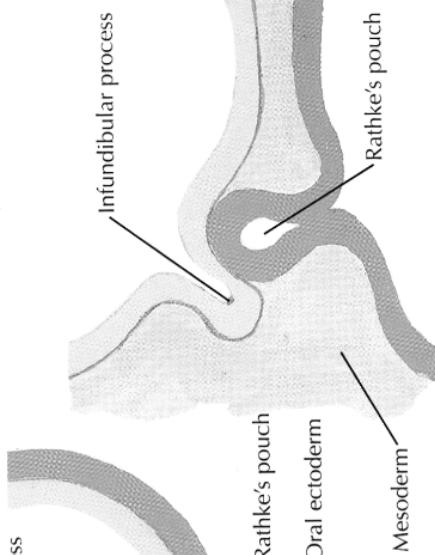
ADH - antidiuretický hormon
STH - somatotropní hormon
LTH - luteotropní hormon
PRL - prolaktin
FSH - folikuly stimulující hormon
LH - luteinizující hormon
TSH - thyreotropní hormon
ACTH - adrenokortikotropní hormon
MSH - melanocyty stimulující hormon

Embryonal development of pituitary gl.

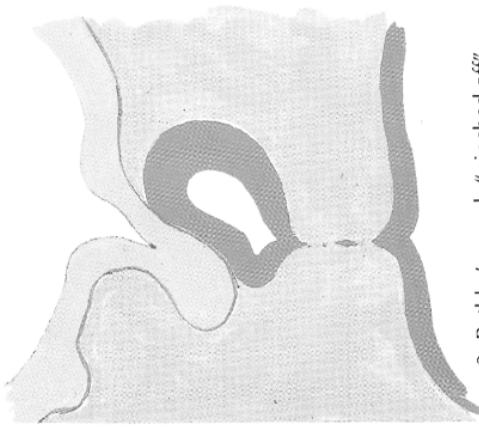
- Ectoderm (Rathke's pouch)
- Neuroectoderm of ventral wall of diencephalon



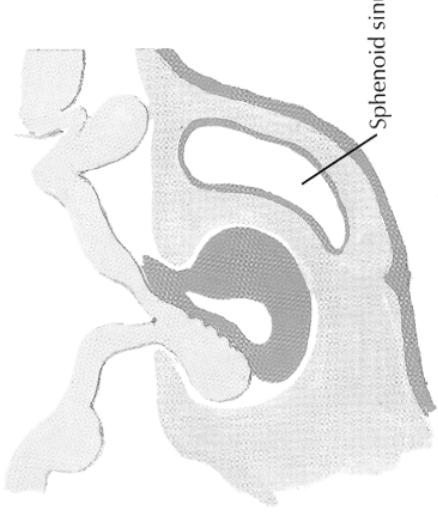
1. Beginning formation of Rathke's pouch and infundibular process



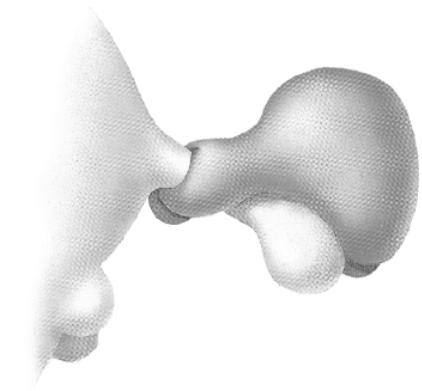
2. Neck of Rathke's pouch constricted by growth of mesoderm



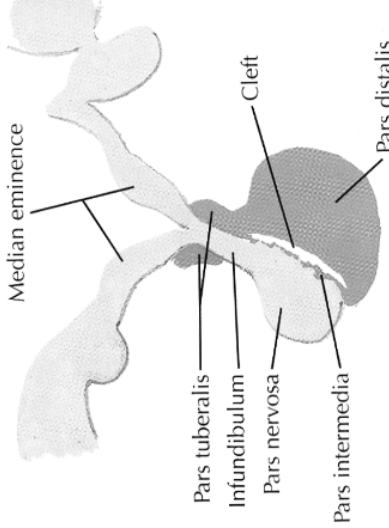
3. Rathke's pouch "pinched off"



4. "Pinched off" segment conforms to neural process, forming pars distalis, pars intermedia and pars tuberalis

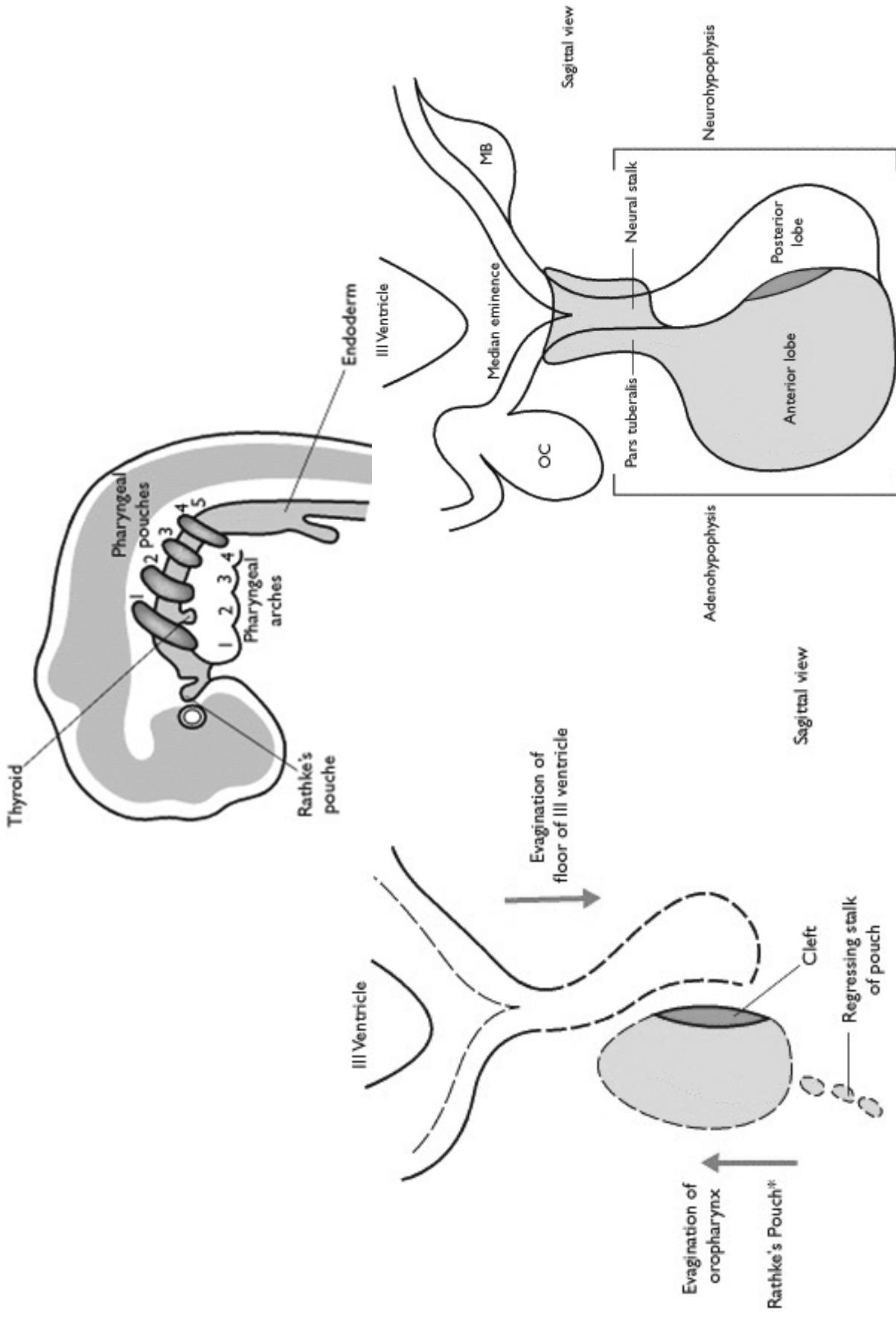


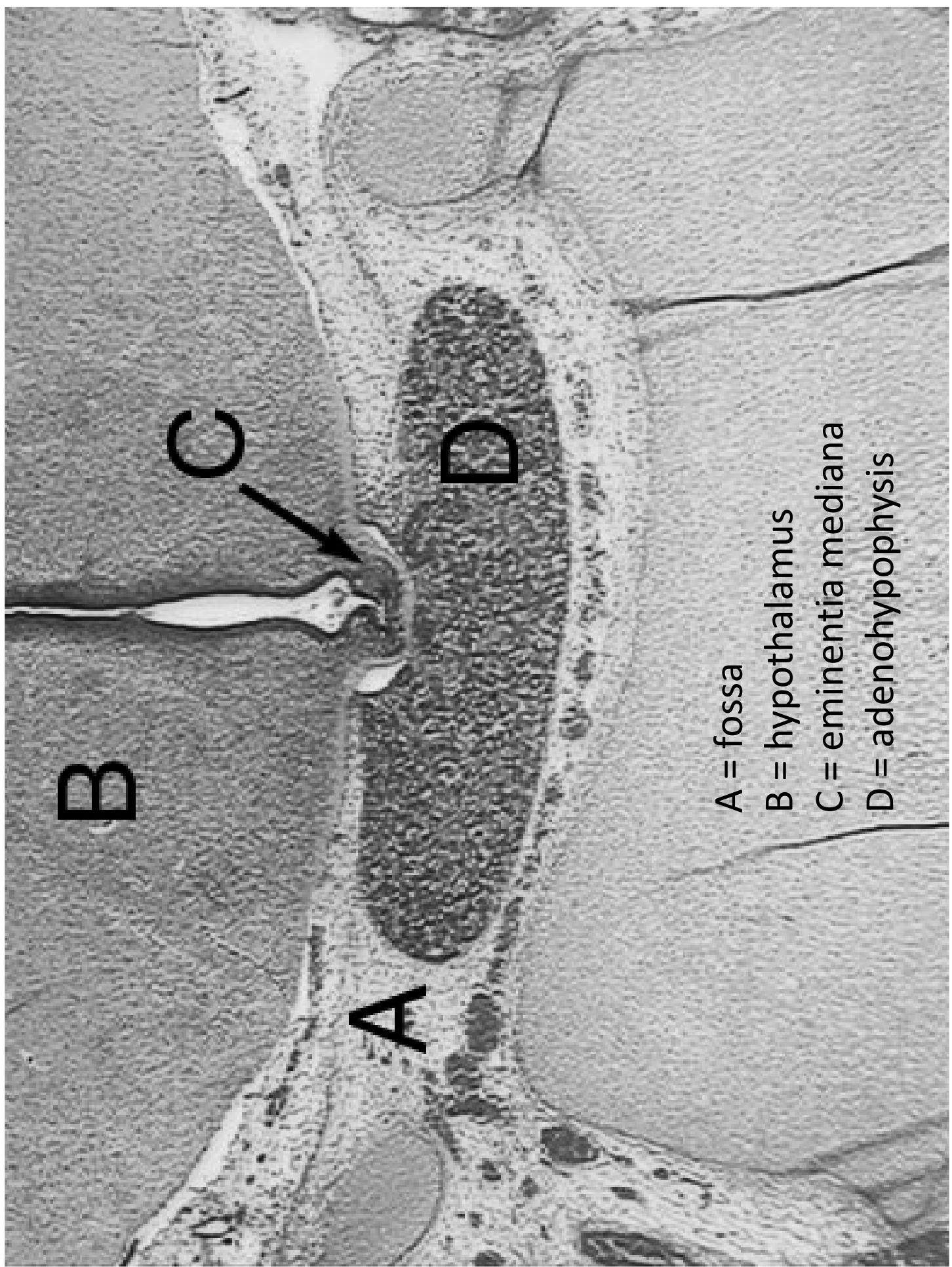
5. Pars tuberalis encircles infundibular stalk (lateral surface view)



6. Mature form

Embryonal development of pituitary gl.





A = fossa
B = hypothalamus
C = eminentia mediana
D = adenohypophysis

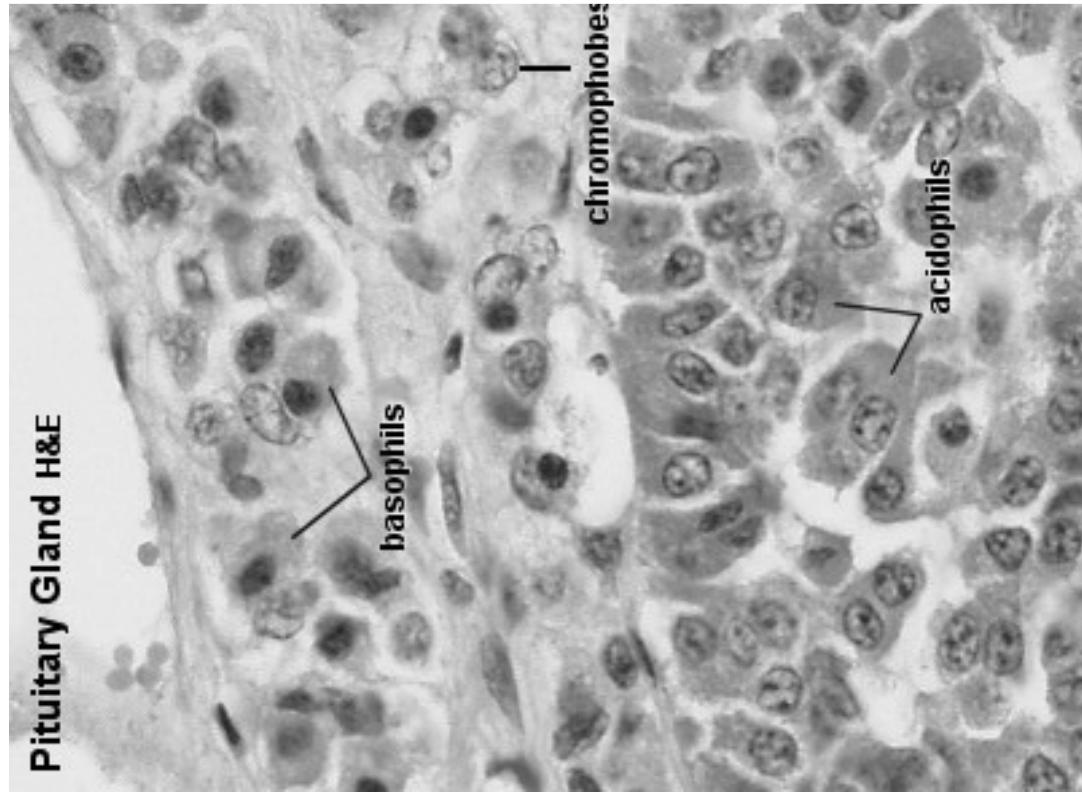
Adenohypophysis (anterior lobe)

Chromophilic cells

Acidophils

Nonglandotropic

- direct effect on target tissues



Bazophils

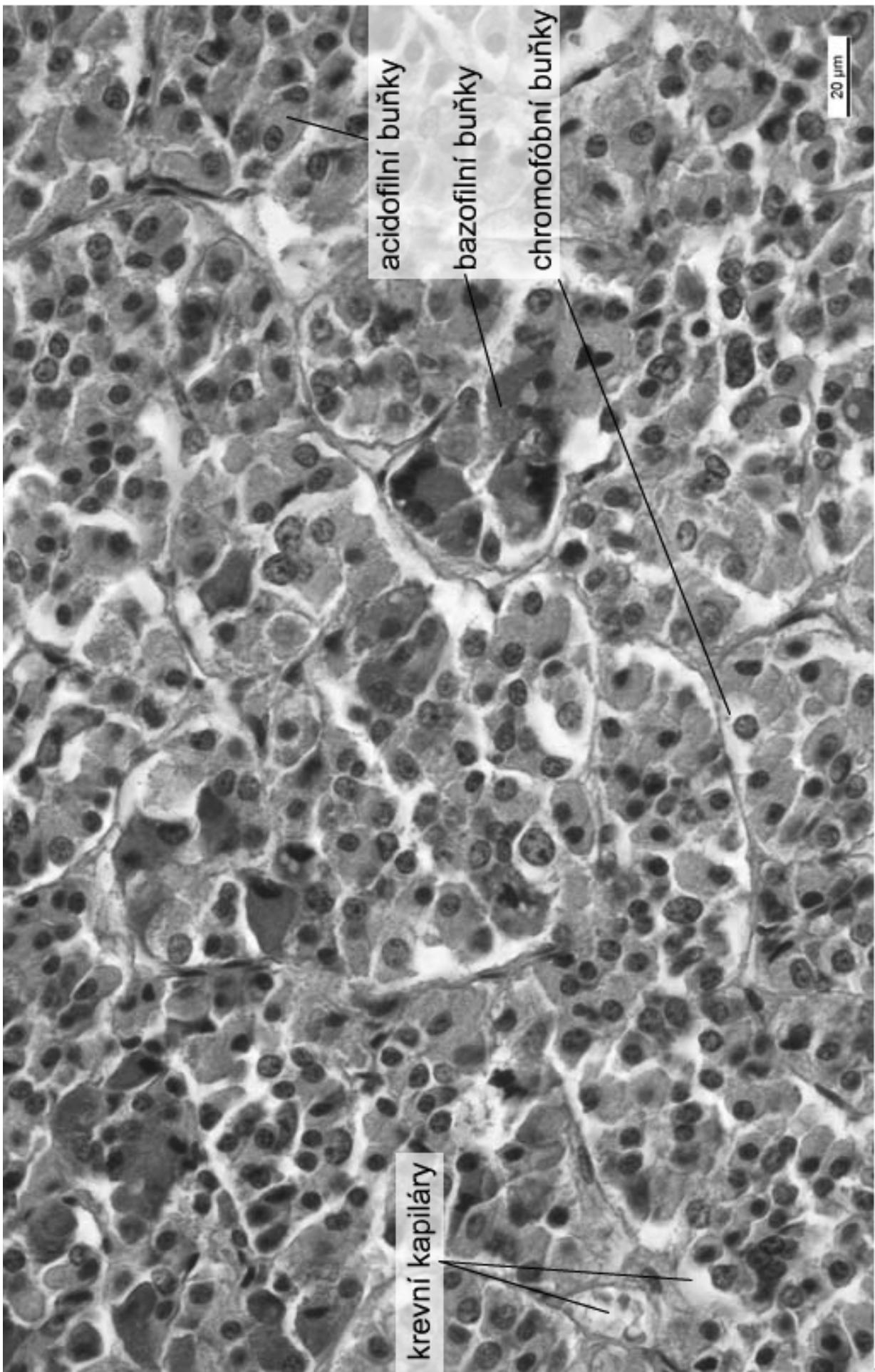
Glandotropic

- regulation of other endocrine glands

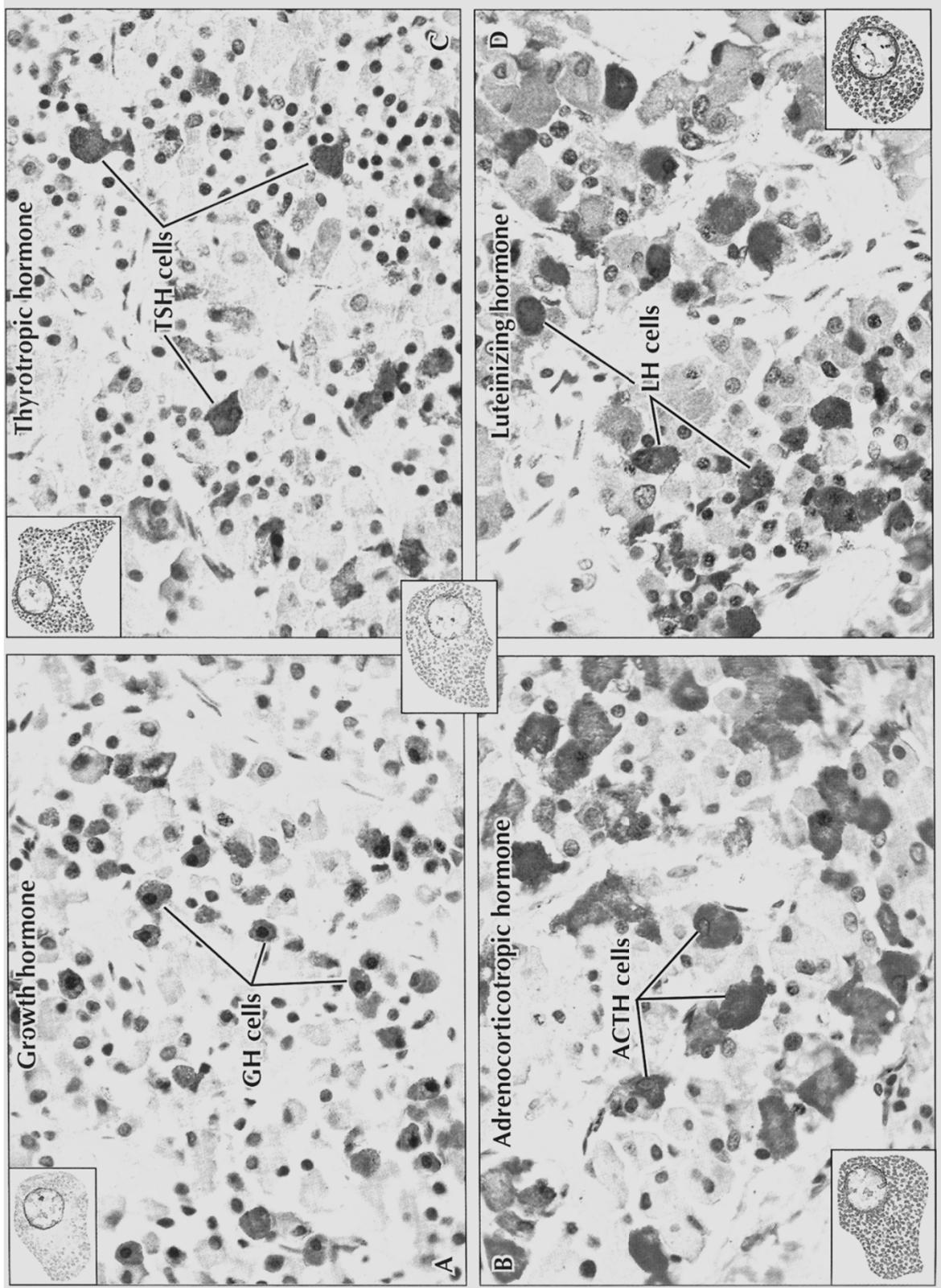
Chromophobic cells

- undifferentiated cells
- degranulated ("empty") chromophils
- stromal cells

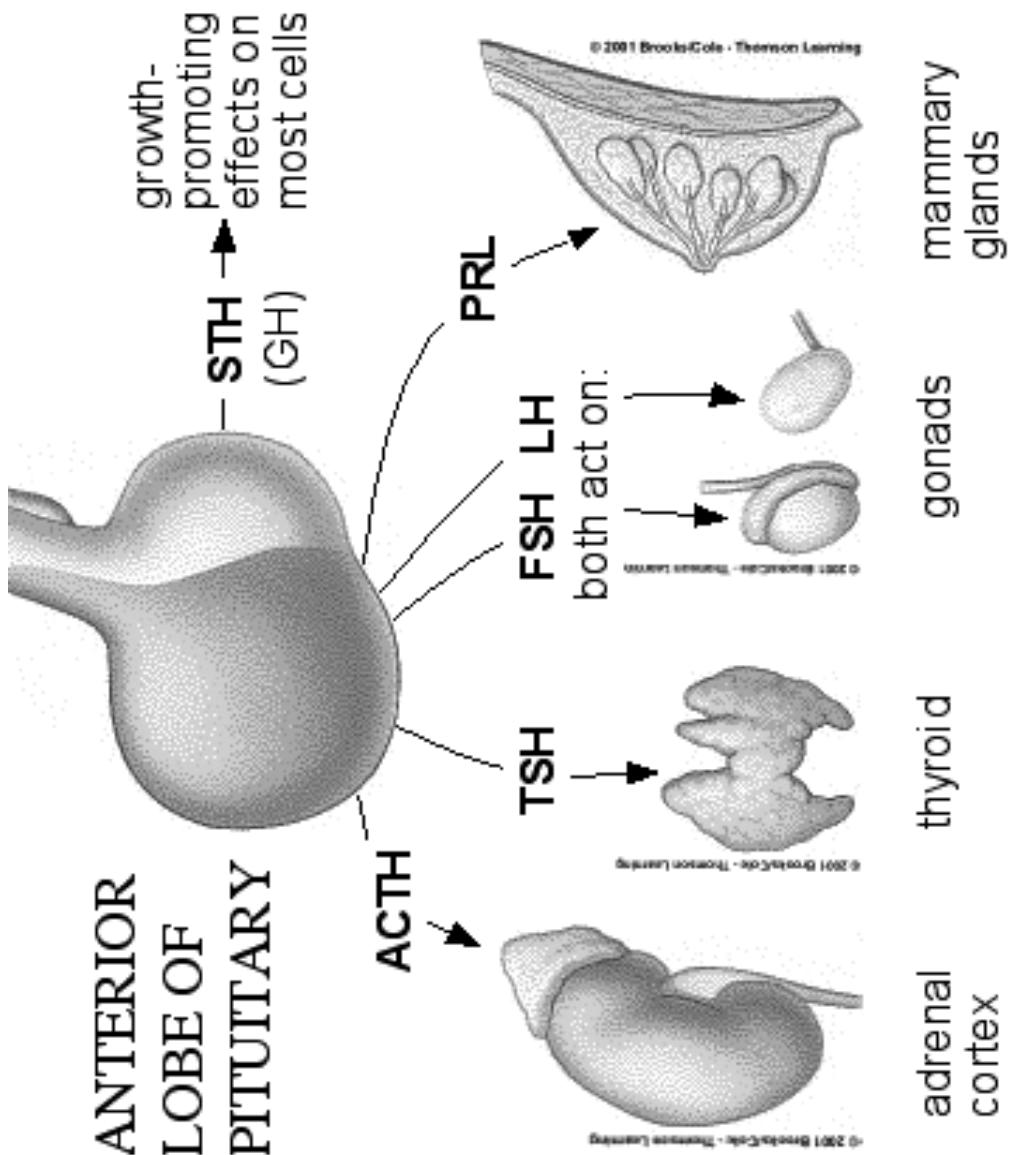
Adenohypophysis (anterior lobe)



Adenohypophysis (anterior lobe)



ANTERIOR LOBE OF PITUITARY



"FLAT PEG"

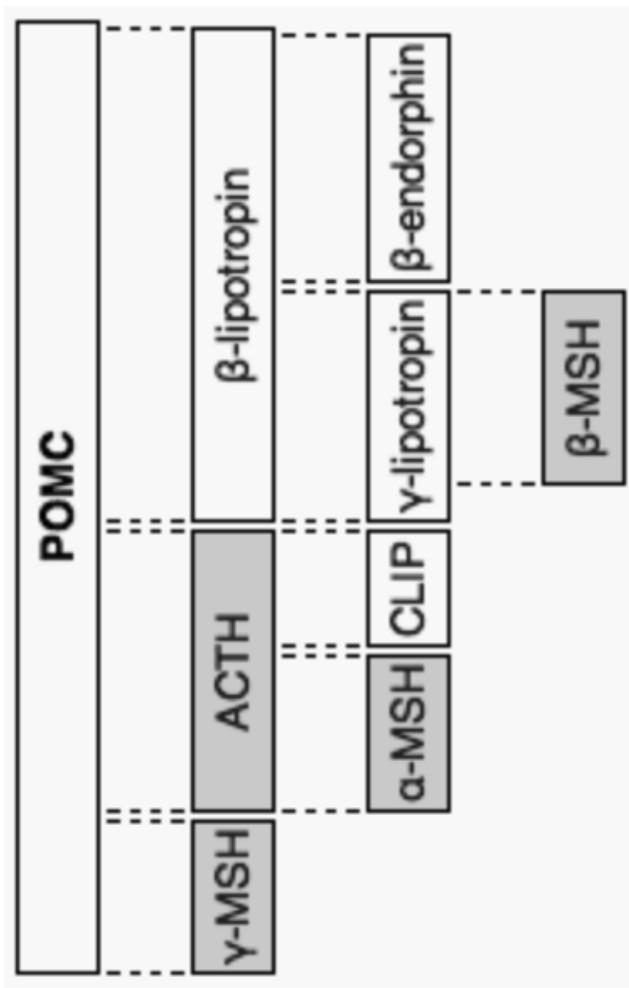
- FSH
- LH
- ACTH
- TSH
- Prolactin
- Endorphins
- Growth hormone

Pro-opio-melanocortin (POMC)

rough ER → pre-prohormon
produced by various tissues

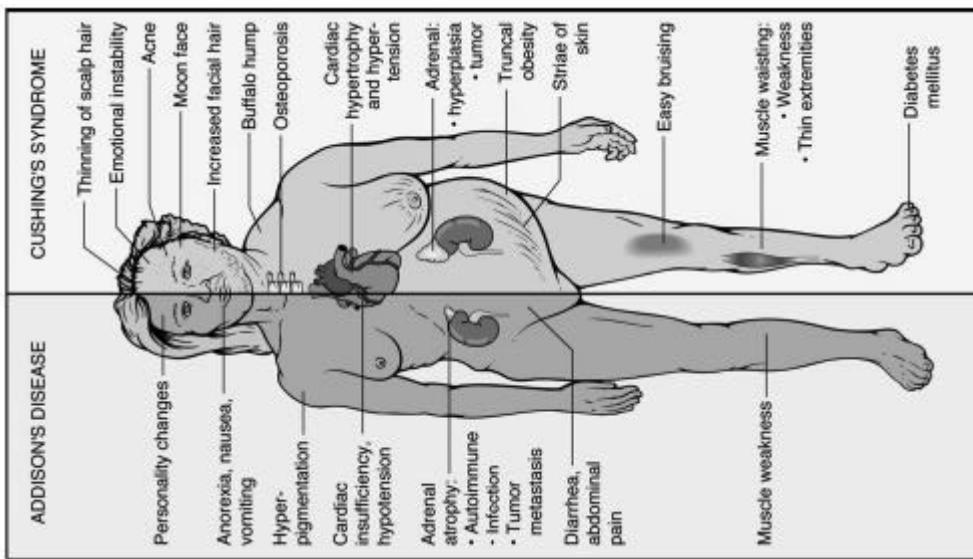
cleavage to

- ACTH (target: adrenal cortex → cortisol)
- MSH (target: melanocytes - mostly in paracrine way)
- lipotropin (lipolysis, steroidogenesis)
- endorphins

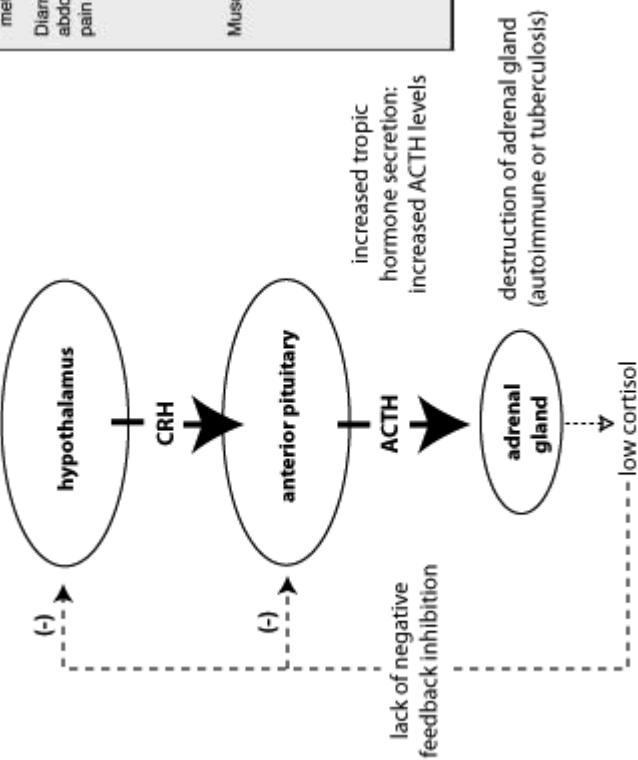


Corticotrophs hypofunction

Corticotrophs hyperfunction



Addison's Disease

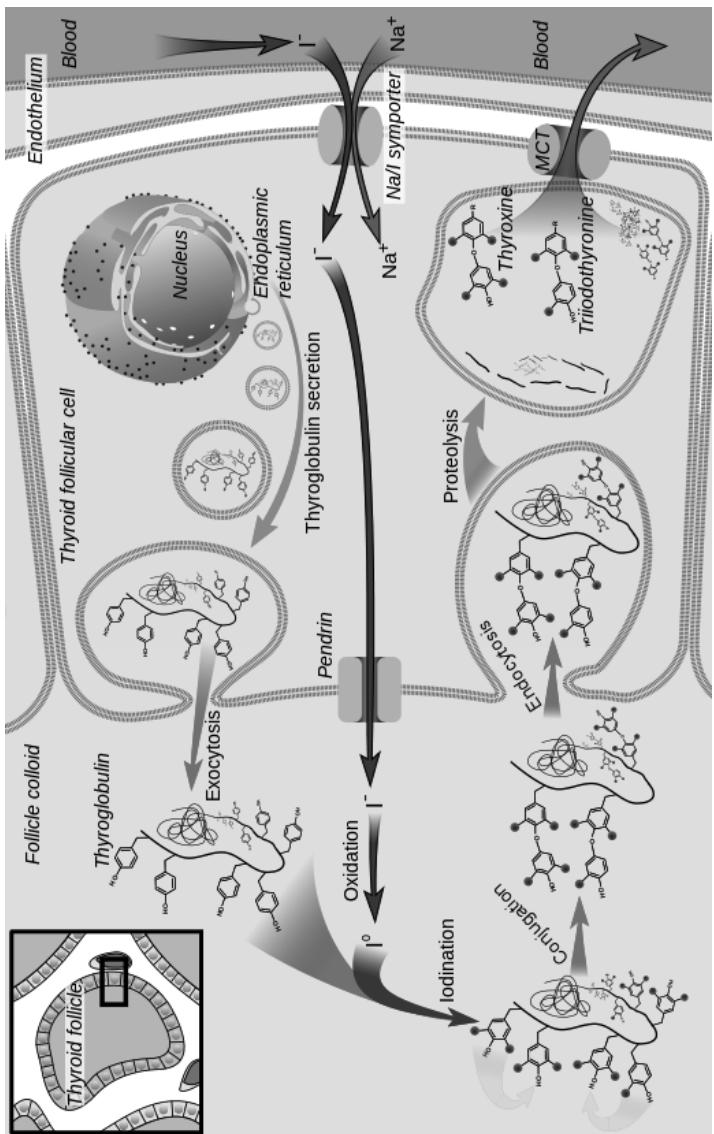


FSH (folitropin), LH (lutropin)

• gonadotropic cells of adenohypophysis stimulated by GnRH			
• glycoproteins, 30kDa			
• heterodimer, two noncovalent bound subunits (a/α - common for - LH, FSH, TSH, hCG, b/β - specific)			
• FSH receptor (testes, ovary, uterus) G-protein coupled receptor			
- glycosylated extracellular domain of 11 leucine rich repeats specific to FSH			
- after ligand binding, activation of G-protein and cAMP signaling			
- alternative activation of MAPK cascade (ERK)			
- complex signaling response (prostaglandins, PLPC, NO)			
	LH		
ovary	follicle development (FSHR in m. <i>granulosa</i> cell/s)	ovulation, development of corpus luteum, production of androgens in thecal cells	
testes	spermatogenesis, FSHR in Sertoli cells	production of testosterone in Leydig cells (expression of LHR)	
extragonadal	FSHR in secretory endometrium of luteal phase uterus (endometrial functions, embryo-endometrial interactions)	uterus, seminal vesicles, prostate, skin... unknown function	

TSH, thyrotropin

- thyrotropic cells of adenohypophysis stimulated by TRH
- production of T4 (thyroxin) a T3 (triiodothyronine) by thyroid gland
- glycoprotein, 28,5 kDa, heterodimer, two noncovalent bound subunits (a, b)
- TSH receptor on thyroid follicular cells
 - G-protein signaling → adenylylcyklase → cAMP
 - cAMP → iodide channels (pendrin), transcription of thyreoglobulin, endo- and exocytic pathway
- cross-reactivity with hCG → in pregnancy - alterations in synthesis of thyroid hormones (gestational hyperthyroidism)



GH, somatotropin, growth hormone

- somatotropic cells of adenohypophysis stimulated by GHRH (somatocrinin)
 - several molecular isoforms (alternative splicing), ~20-24 kDa
 - broad spectrum of target cell types and physiological circuits
 - transcription of DNA, translation of RNA, proteosynthesis
 - lipid use (fatty acid mobilization, conversion to acetyl-CoA)
 - inhibition of direct use of glucose, stimulation of gluconeogenesis
 - transmembrane transport of aminoacids
 - proteosynthesis in chondrocytes and osteoblasts, proliferation, osteogenesis
 - GHR in various tissues
 - RTK, JAK-STAT
- somatomedins
 - small proteins (MW 7,5 kDa), IGF-like
 - produced by liver
- various pathologies associated with GH
 - produced by liver

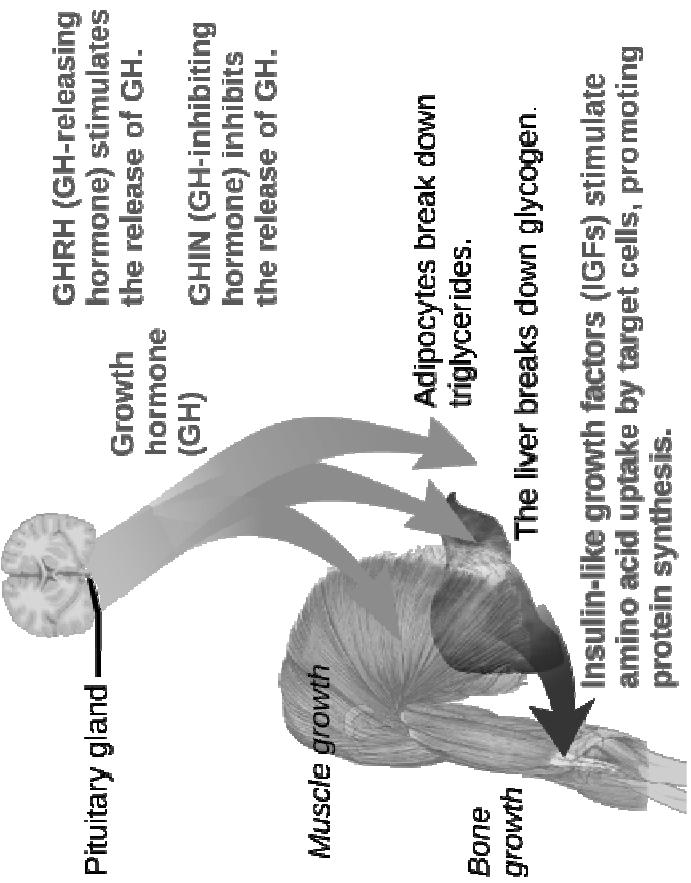


Table 2. Nonclassical Anterior Pituitary Substances and Cell(s) of Origin

Substances	Cell Types
PEPTIDES	
ACTIVIN B, INHIBIN, FOLLISTATIN	F, G
ALDOSTERONE STIMULATING FACTOR	UN
ANGIOTENSIN II (ANGIOTENSINOGEN, ANGIOTENSIN I)	C, G, L, S
CONVERTING ENZYME, CATHEPSIN B, RENIN	G
ATRIAL NATURETIC PEPTIDE	C
CORTICOTROPIN-RELEASING HORMONE-BINDING PROTEIN	G
DYNORPHIN	L, S, T
GALANIN	G
GAWK (CHROMOGRANIN B)	UN
GROWTH HORMONE RELEASING HORMONE	UN
HISTIDYL PROLINE DIKETOPIPERAZINE	UN
MOTILIN	S
NEUROMEDIN B	T
NEUROMEDIN U	C
NEUROPEPTIDE Y	T
NEUROTENSIN	UN
PROTEIN 7B2	G, T
SOMATOSTATIN 2 ⁸	UN
SUBSTANCE P (SUBSTANCE K)	G, L, T
THYROTROPIN RELEASING HORMONE	G, L, S, T
VASOACTIVE INTESTINAL POLYPEPTIDE	G, L, T
GROWTH FACTORS	
BASIC FIBROBLAST GROWTH FACTOR	C, F
CHONDROCYTE GROWTH FACTOR	UN
EPIDERMAL GROWTH FACTOR	G, T
INSULIN-LIKE GROWTH FACTOR I	S, F
NERVE GROWTH FACTOR	UN
PITUITARY CYTOTROPIC FACTOR	UN
TRANSFORMING GROWTH FACTOR ALPHA	L, S, G
VASCULAR ENDOTHELIAL GROWTH FACTOR	F
CYTOKINES	
INTERLEUKIN-1 BETA	T
INTERLEUKIN-6	F
LEUKEMIA INHIBITORY FACTOR	C, F
NEUROTRANSMITTERS	
ACETYLCHOLINE	C, L
NITRIC OXIDE	F

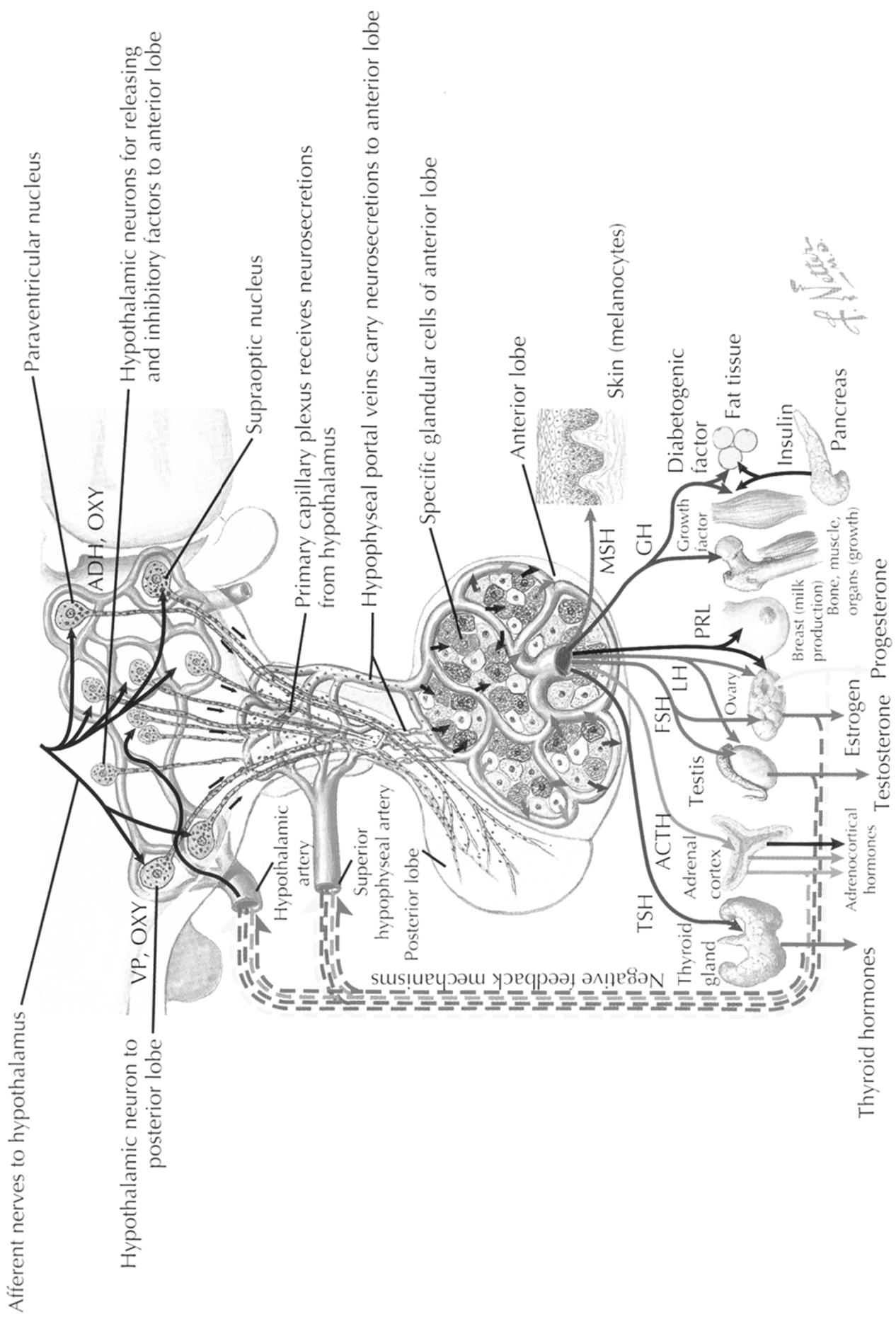
C = corticotroph, F = folliculostellate cell, G = gonadotroph, L = lactotroph,
 S = somatotroph, T = thyrotroph, UN = unknown

Clinical links

Hypophyseal tumors



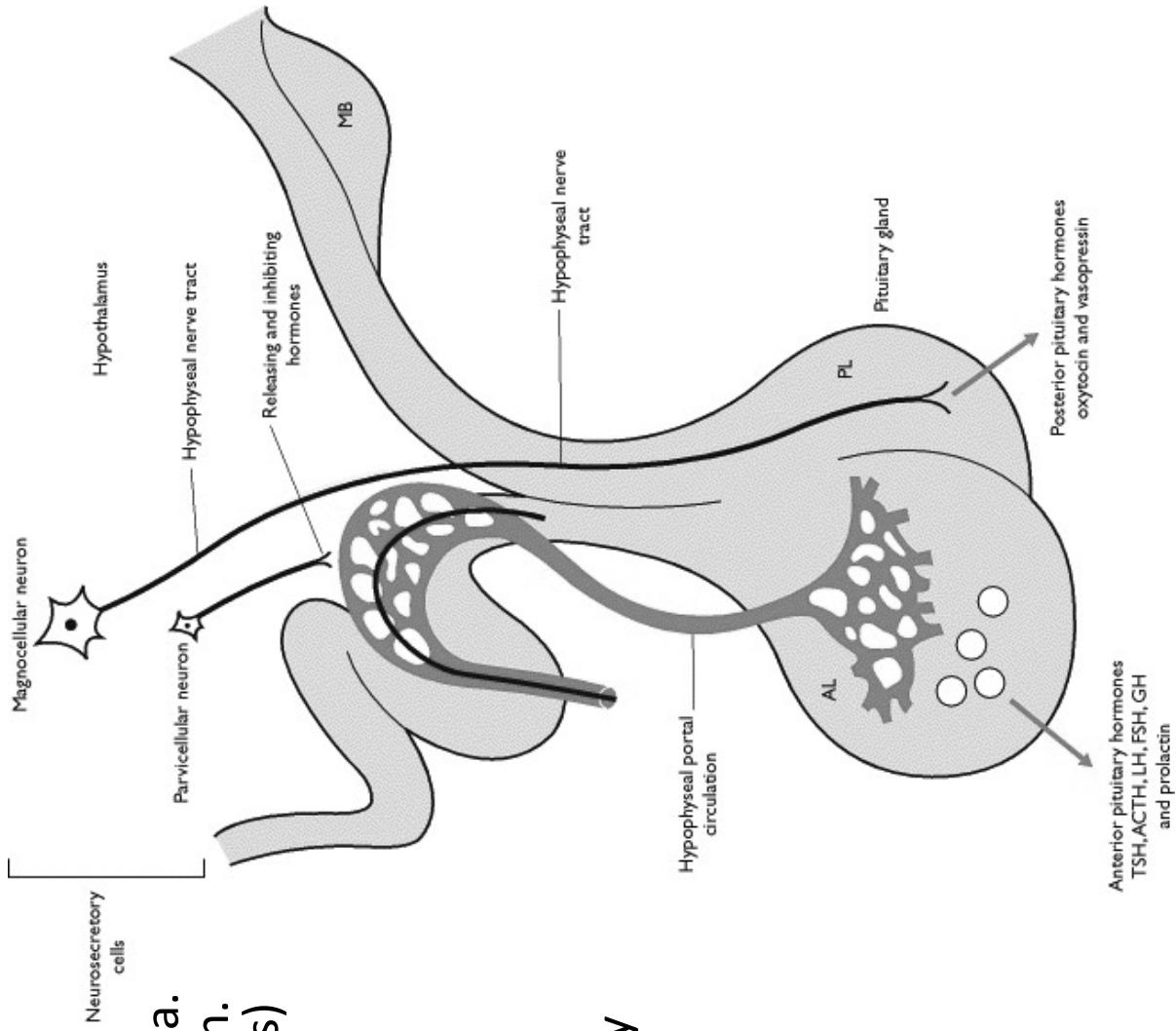
- compression of surrounding structures
(optic chiasma)
- hyperfunction of endocrine component
 - prolactinoma - galactorrhea
 - hypogonadism (alterations of GnRH)
 - gigantism - acromegaly
 - nanism



Posterior hypophysis (neurohypophysis)

nonmyelinated nerve fibers

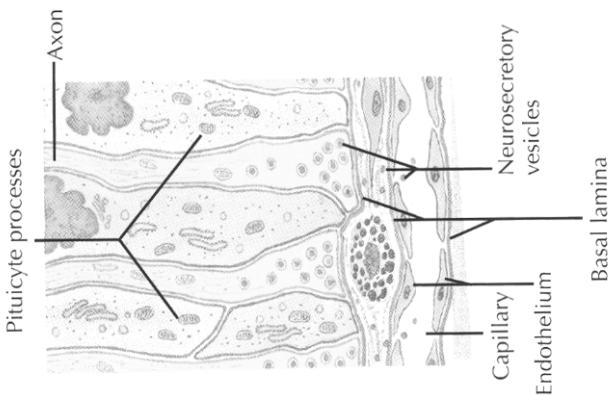
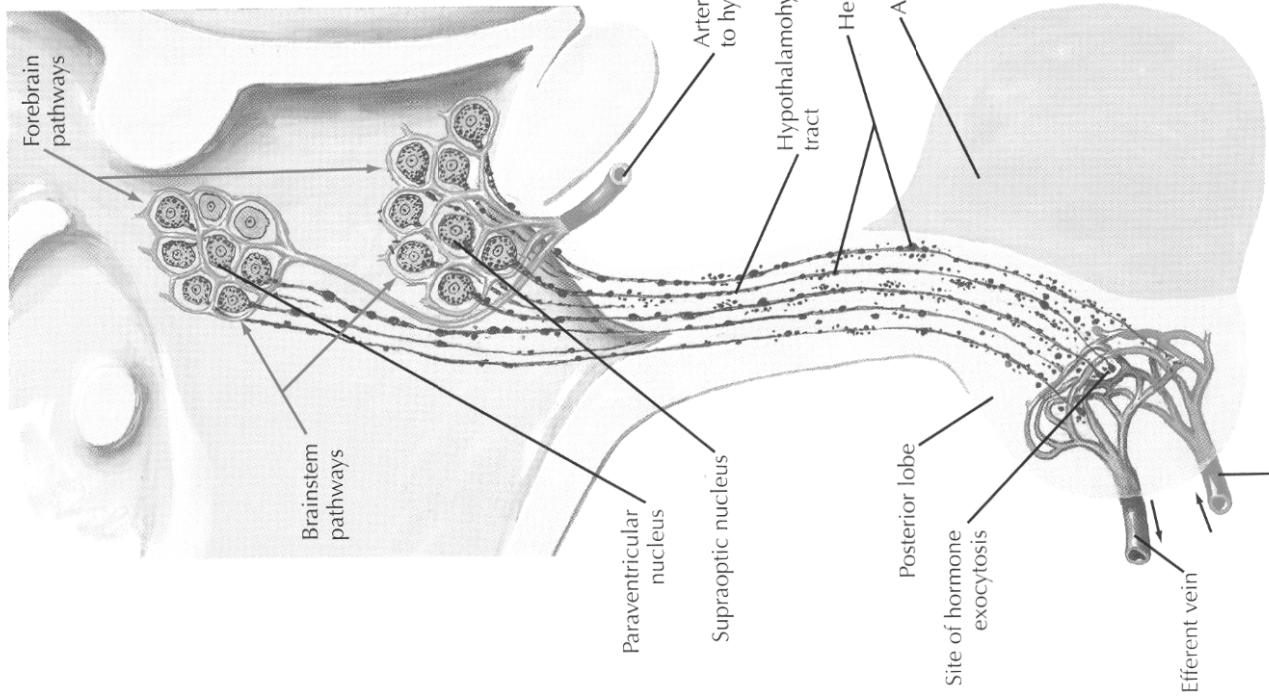
- axons of neurosecretory cells (c.a. 100 000) of hypothalamic nuclei (n. supraopticus and paraventricularis) **pituicytes** (neuroglia)
- astrocyte-like (intermediate filaments, GFAP)
- local control of secretion from neurosecretory termini
- Herring bodies – neurosecretory endings – dilatation close to capillaries



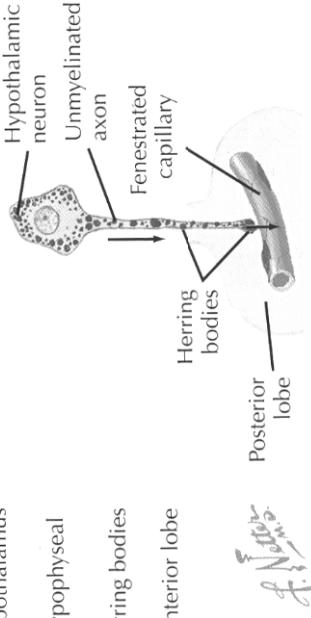
Hormones

- oxytocin (OT)
- antidiuretic hormone (ADH, vasopressin)

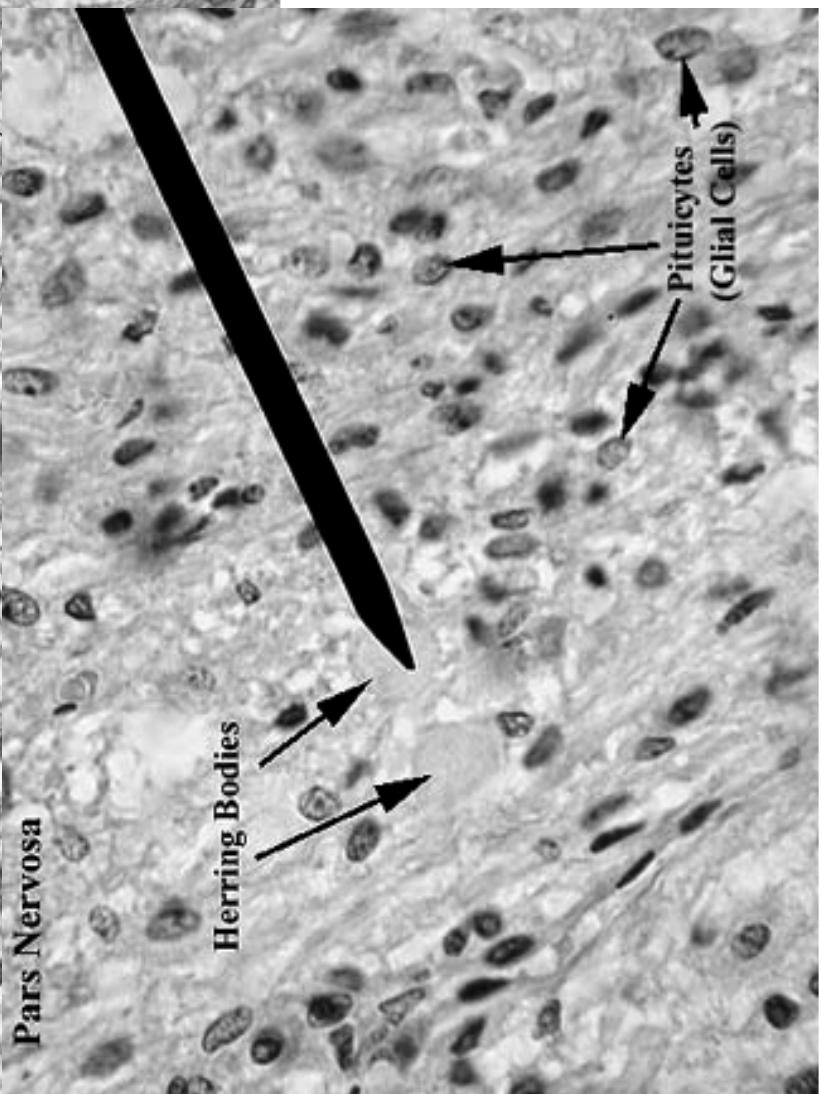
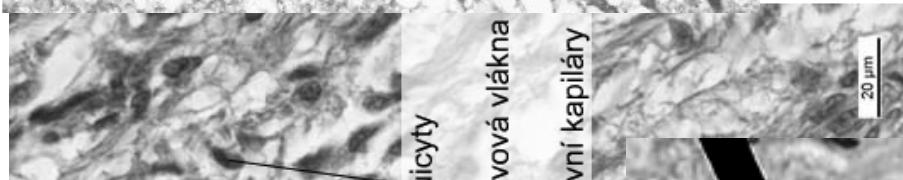
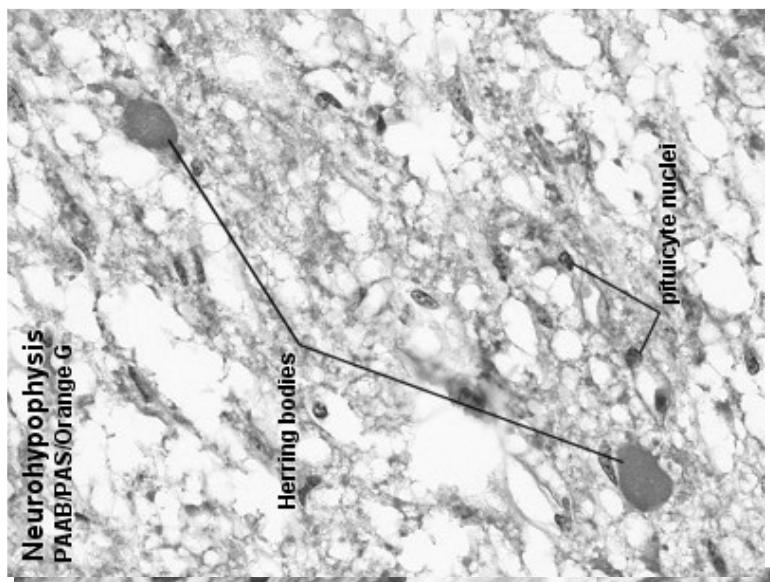
▼ Neurosecretory Ending (posterior pituitary).



▼ Origin of ADH.

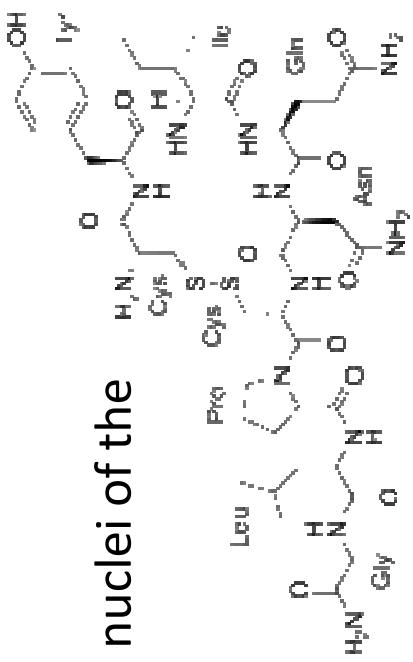


Hormone	Principal Action	Principal Nucleus of Origin
Oxytocin (OXY)	Uterine contraction, milk ejection	Paraventricular
Anti-diuretic hormone (ADH)	Water excretion in kidney, arteriolar constriction	Supraoptic



Oxytocin

- nonapeptide
- magnno-cellular supraoptic and paraventricular nuclei of the hypothalamus
- OR - G-coupled receptor
- lactation reflex
- uterine contraction
- social behavior



Vasopressin

- nonapeptide
- retention of water
- effective in collecting duct and distal convoluted tubule (aquaporine translocations)
- blood pressure regulation by affecting t. media
- diabetes insipidus, hypernatremia, polyuremia



Anatomy	Microscopic anatomy	Hormones and target tissues
	trabecular epithelium in cords and clusters, reticular fibers	
	superior hypophyseal arteries → primary capillary plexus → hypophyseal portal veins + inferior hypophyseal arteries → secondary capillary plexus → hypophyseal portal veins → w. jugulares internae	<p>chromophobes</p> <p>undifferentiated cells degranulated chromophilic cells stromal cells</p> <p>acidophilic non glandotrophic</p> <p>chromophils</p> <p>basophilic glandotrophic</p> <p>thyrotropic cells</p> <p>corticotrophic cells</p> <p>glycoproteins</p> <p>small polypeptides</p> <p>dopamin (PIH) PRF → prolactin</p> <p>somatostatin (GHIH) GHRH → somatotropin (STH)</p> <p>CRH → ACTH, MSH</p> <p>TRH → TSH</p> <p>gonads → cortisol melanocytes</p> <p>thyroid → thyroxin, T3</p> <p>GnRH → FSH (ICSH), LH</p> <p>ADH</p> <p>oxytocin</p> <p>nonmyelinated axons of hypothalamic neurons n. supraopticus, n. paraventricularis (tractus hypothalamohypophysialis), piticytes</p> <p>tubulus reunions, ductus colligens t.media of vessels</p> <p>myometrium of uterus during gravity myoepithelium of lactating mammary gland</p>
	pars distalis	
	pars tuberalis	
	pars intermedia	
	pars nervosa	
		<p>Posterior lobe (neurohypophysis)</p> <p>Anterior lobe (adenohypophysis)</p>

BREAK

To study the effects of the hypothalamo-pituitary-adrenal axis, groups of mice were injected with different hormones. Group A mice were injected with cortisol to mimic effects of Cushing's syndrome. Group B mice were injected with a saline solution. Group C mice were injected with a saline solution. Blood samples were later taken from the various groups and average hormone levels were measured and recorded in Table 1.

Table 1. Levels of hormones (in nmol/L) found in blood sample taken from experimental mice groups.

	CRH	ACTH	Cortisol
Group A	20	150	900
Group B	45	430	760
Group C	30	230	400

According to the results of the experiment, which is the most likely identity of hormone X?

Please choose from one of the following options.

- CRH, because Group C's concentration of ACTH and cortisol is lower than that of the control group.
- ACTH, because Group B's concentration of ACTH and cortisol is higher than that of the control group.
- ACTH, because Group C's concentration of ACTH and cortisol is lower than that of the control group.
- CRH, because Group B's concentration of ACTH and cortisol is higher than that of the control group.

Why does a pituitary adenoma cause a patient to have an excess level of cortisol?

Please choose from one of the following options.

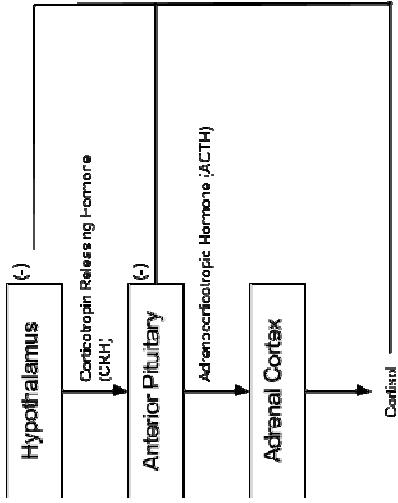
- It increased the size of the hypothalamus.
- Its cells did not respond to CRH.
- Its cells did not respond normally to cortisol.
- It decreased the level of ACTH circulating in the body.

Which of the following can result in a chronic increase in a patient's ACTH and CRH levels?

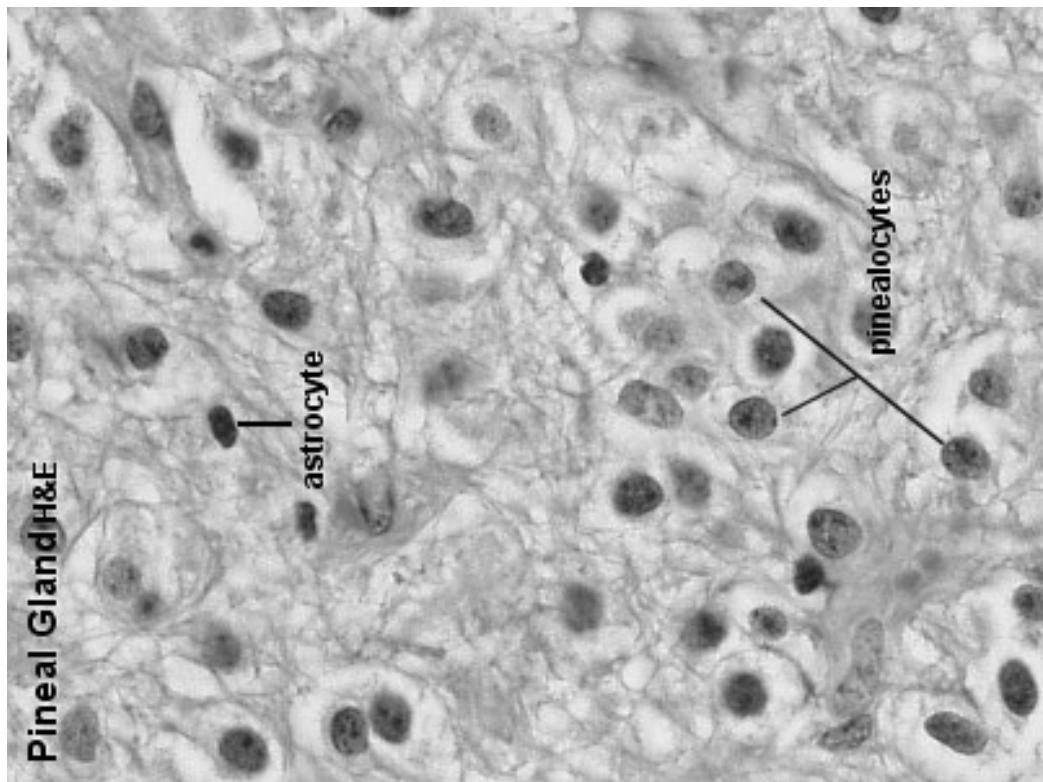
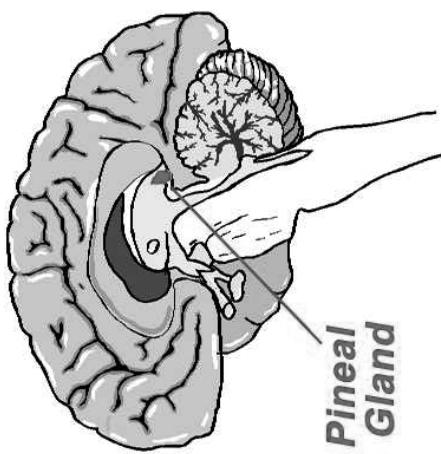
Which of the following would exacerbate the symptoms of Cushing's disease?

Please choose from one of the following options.

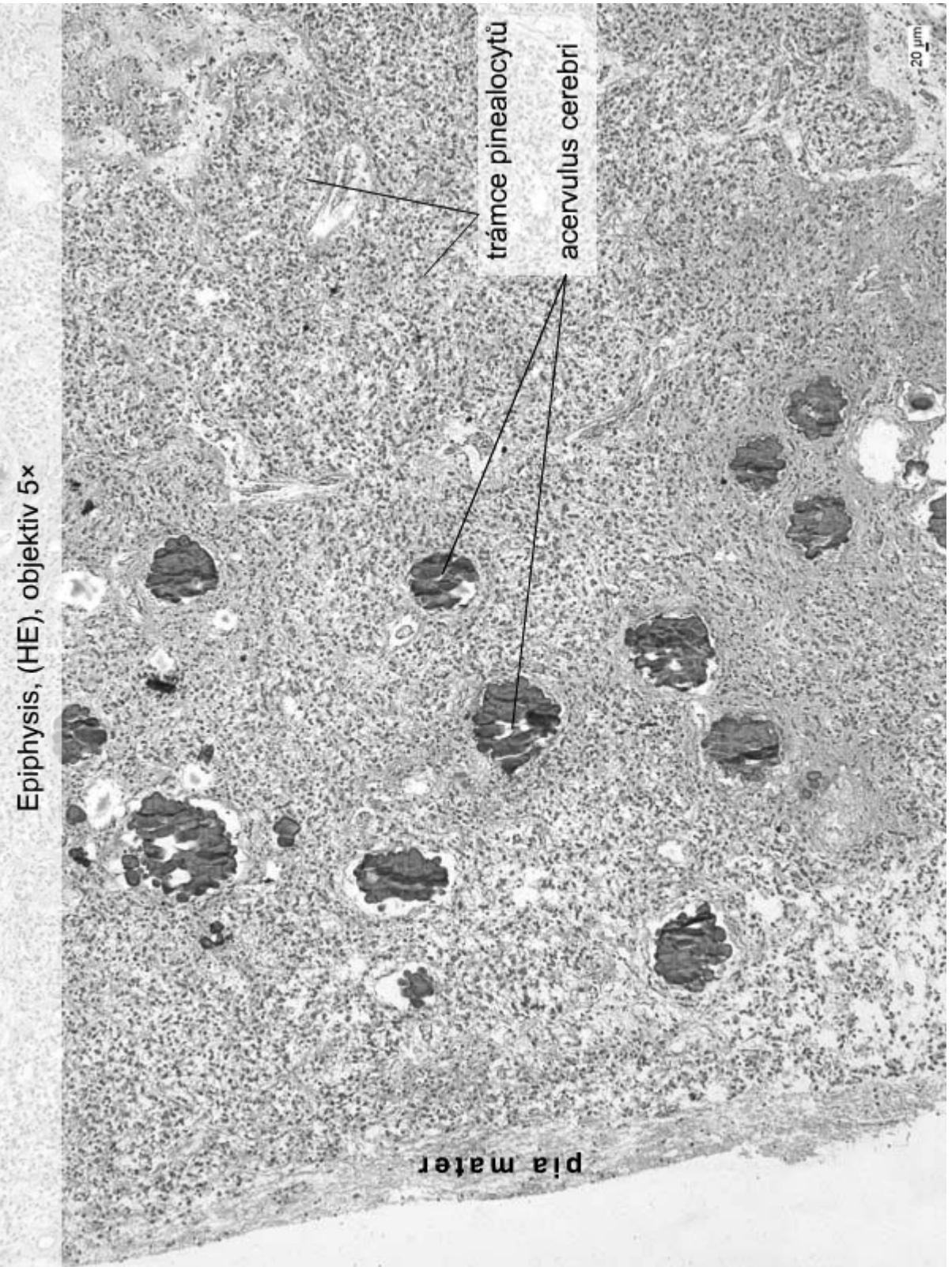
- Somatic cells not responding to cortisol.
- Taking a glucocorticoid receptor antagonist.
- Radiation therapy to treat a pituitary adenoma.
- Taking glucocorticoids to treat asthma.



Epiphysis (*c. pineale*)

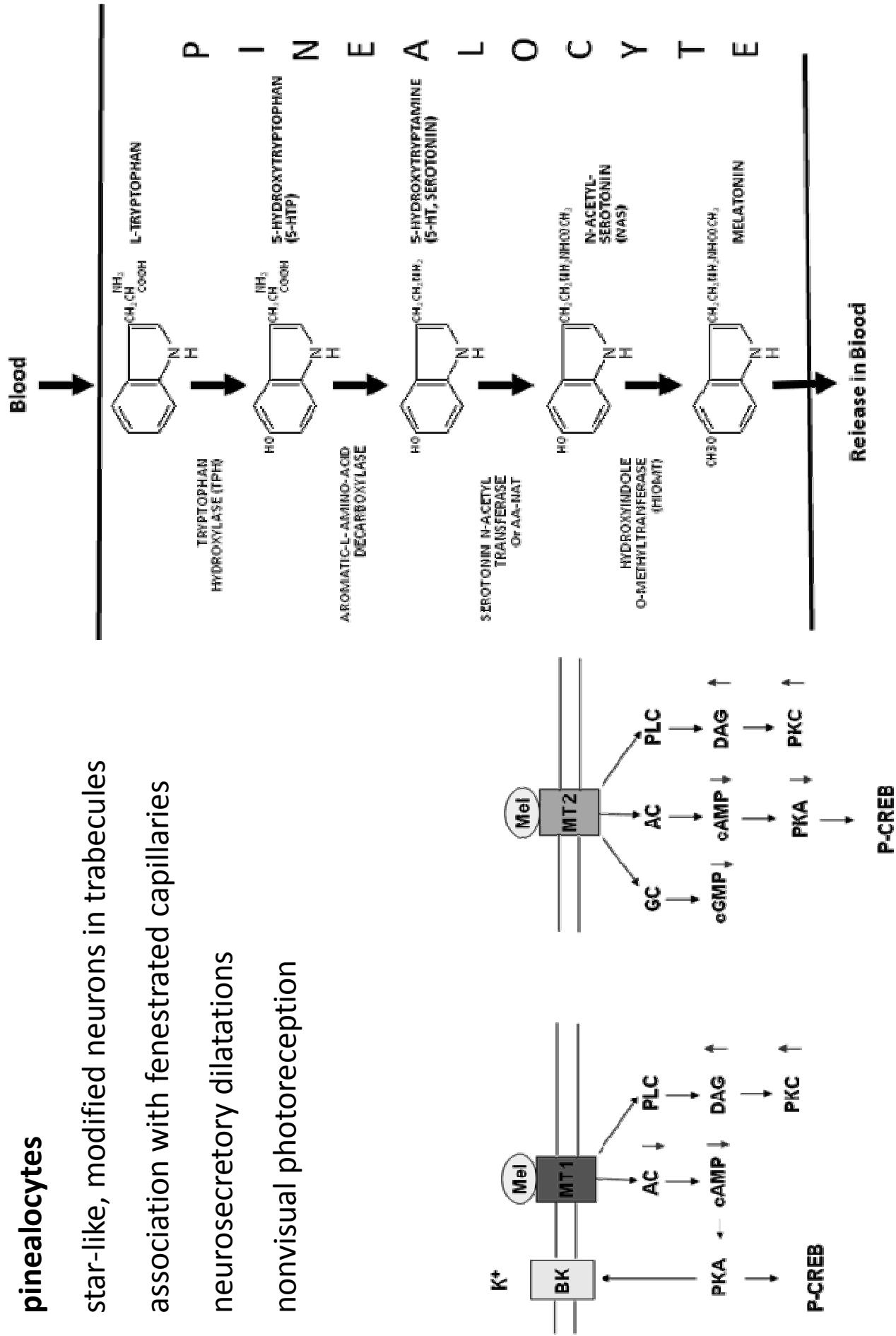


- epithalamus
- c.t. capsule continuous to pia mater
- thin c.t. septa
- nonmyelinated nerve fibers
- **pinealocytes** (95%, large, pale, round nuclei)
- interstitial neuroglia (astrocytes, dark, elongated nuclei)
 - *acervulus cerebri*
- melatonin



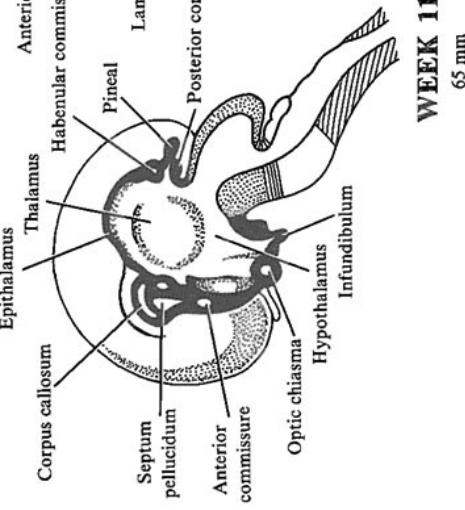
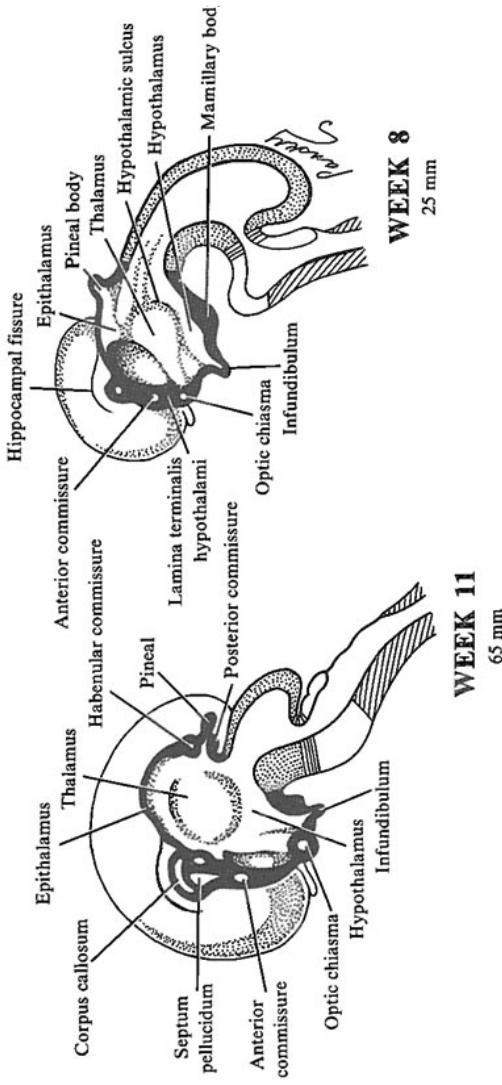
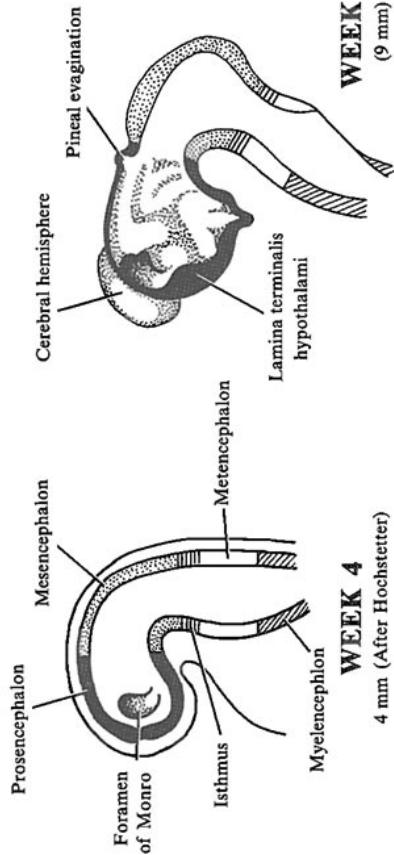
Epiphysis (*C. pineale*)

- pinealocytes
- star-like, modified neurons in trabecules
- association with fenestrated capillaries
- neurosecretory dilatations
- nonvisual photoreception



Embryonic development of epiphysis (*c. pineale*)

- thickening of caudal part of ependyma that does not contribute to development of choroid plexus at the roof of diencephalon
- neuroectoderm



Thyroid gland (*gl. thyroidea*)

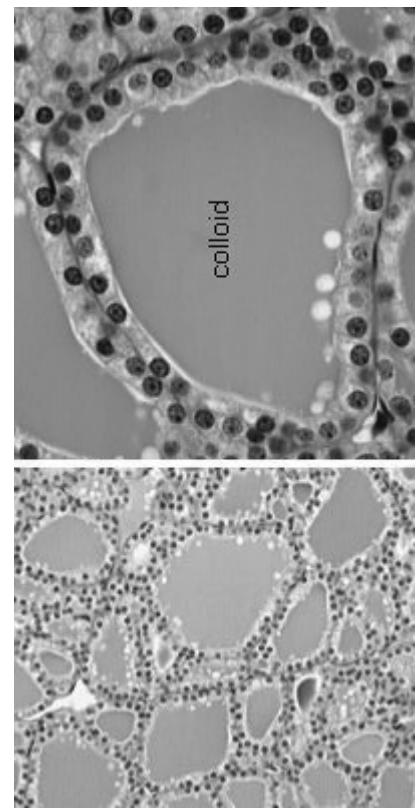
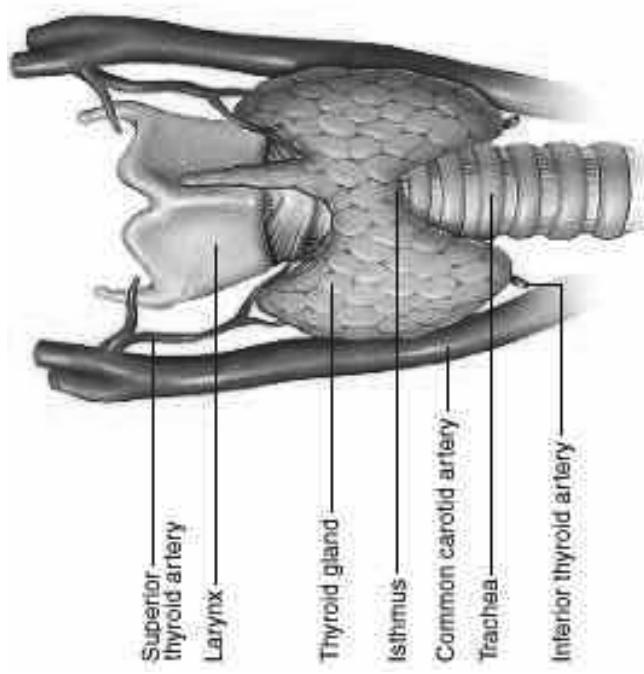
- Follicular cells → thyroid hormones (T₃, T₄)
- C cells → calcitonin

C.t. capsule, septa

Lobes → lobuli - follicles

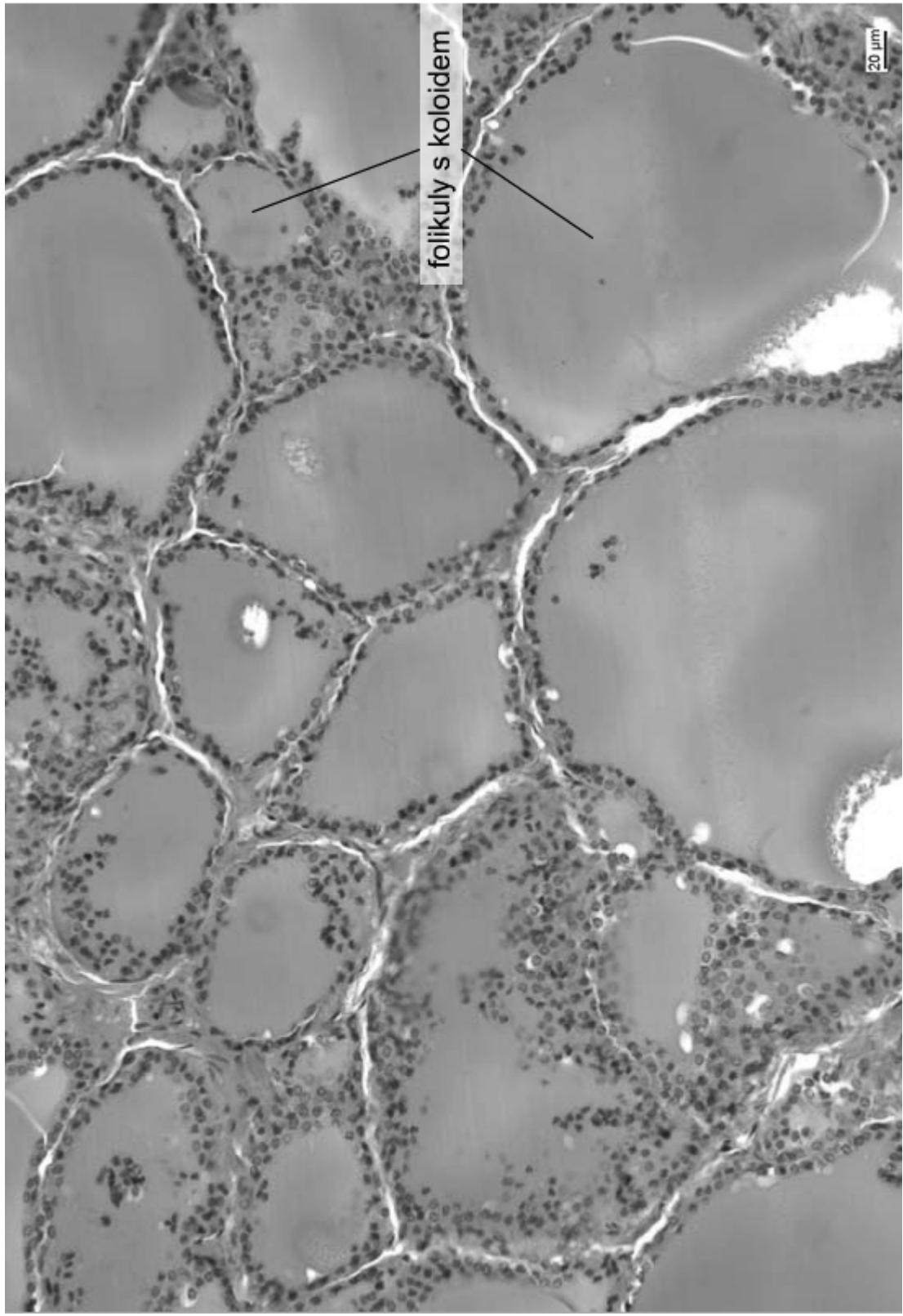
Follicles (50 µm -1 mm)

- separated by interstitial loose collagen c.t.
- simple epithelium (flat to cubic, according to secretory activity)
- colloid

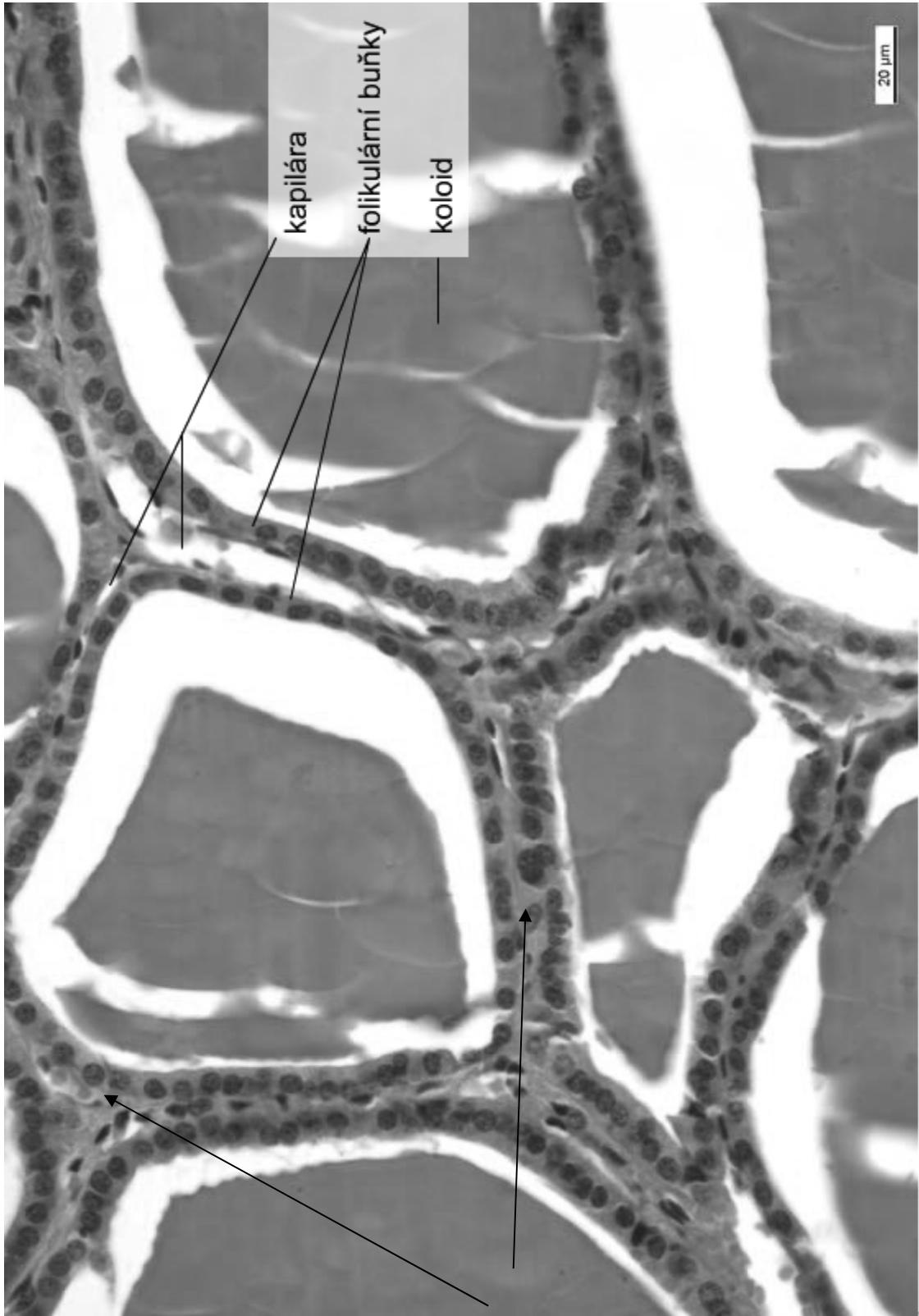


Capillary network from thyroid arteries

Thyroid gland - follicles



Thyroid gland - follicles



C-cells

Follicular cells and C-cells (parafollicular)

Synthesis of T3 and T4

T4 synthesis in thyroid

- sodium-iodide symporter transports two Na⁺ and one I⁻ across the basement membrane across the apical membrane into the colloid of the follicle.
- thyroperoxidase oxidises 2 I⁻ → I₂.
- thyroperoxidase iodinates the tyrosyl residues of thyroglobulin
- (TSH) stimulates the endocytosis of the colloidal content
- endocytic vesicles + lysosomes, lysosomal enzymes cleave T₄ from the iodinated thyroglobulin
- exocytosis

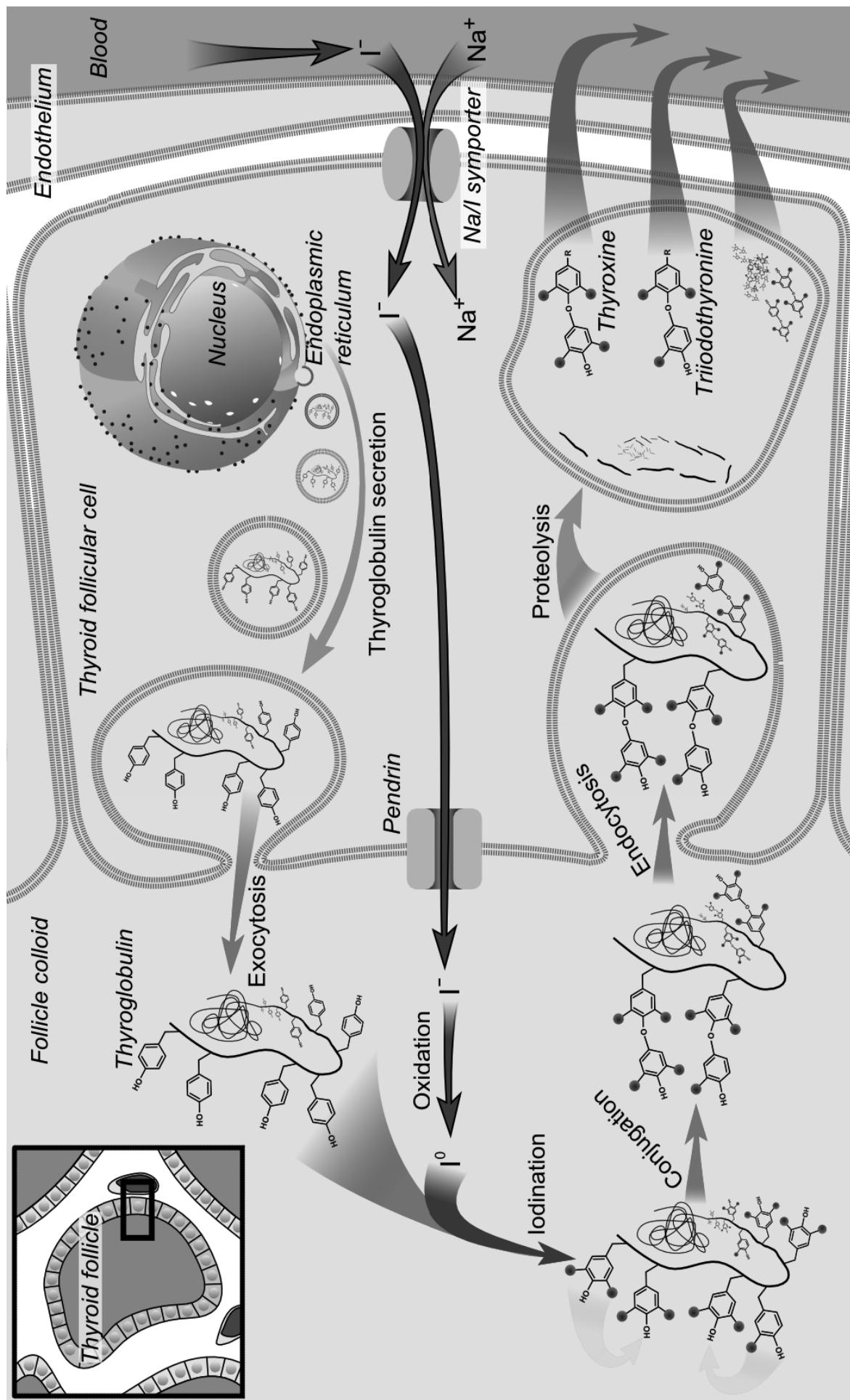
T3 synthesis from T4

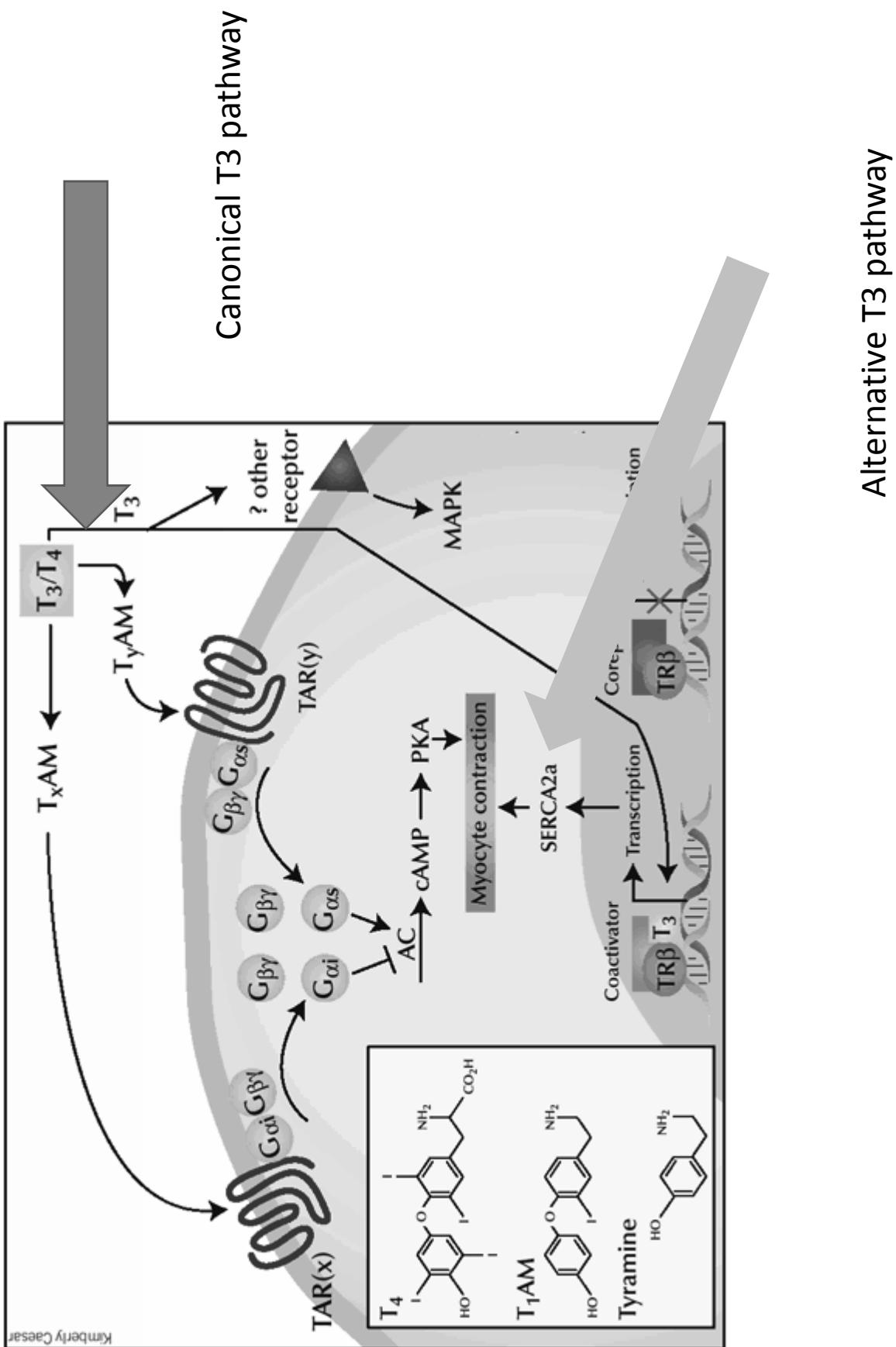
- T4 half-life in blood 6.5 days, T3 2.5 (T4 is a reservoir for T3)
- deiodination by tissue specific deiodinase enzymes generates T3

thyroglobulin

triiodothyronin (thyroxin) T₃

tetraiodothyronin (thyroxin) T₄

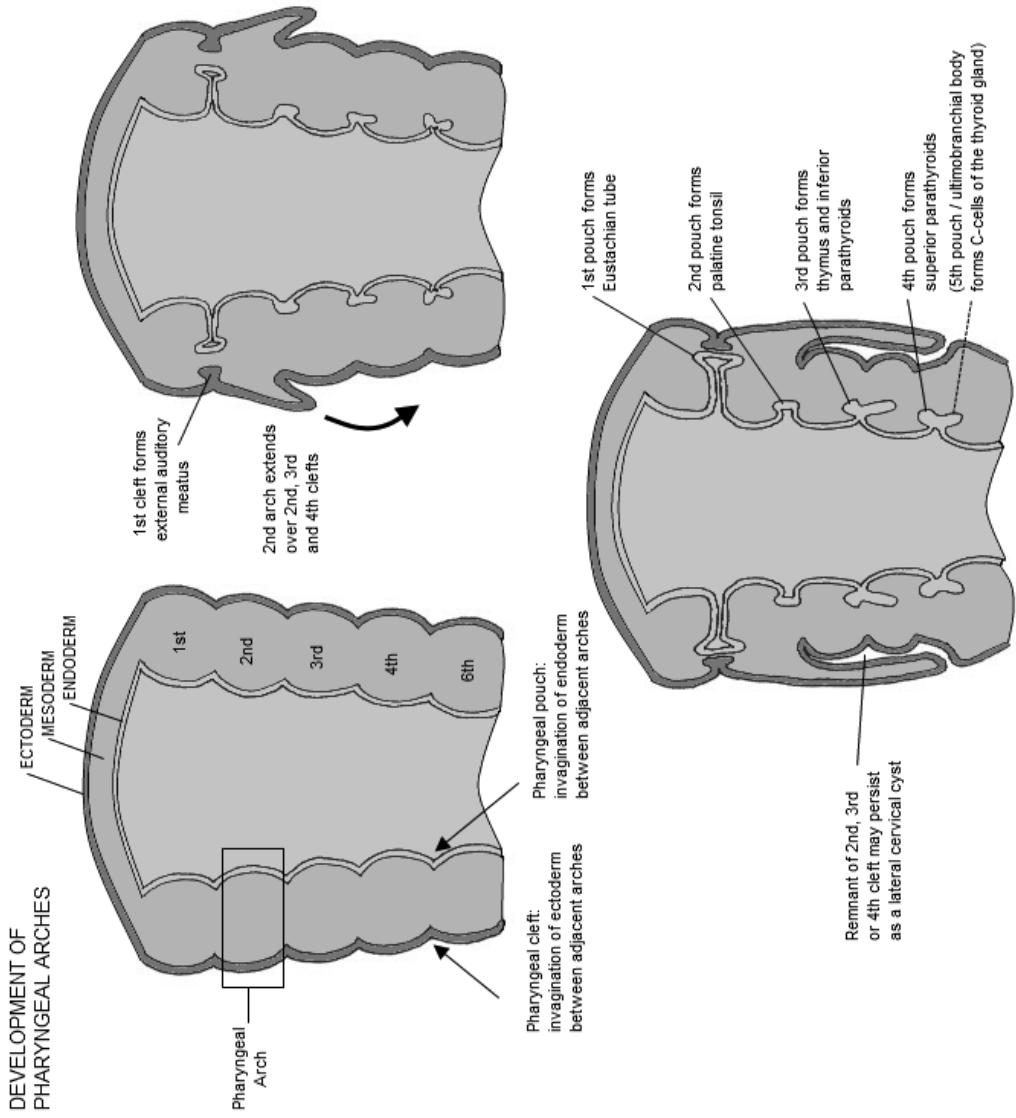




C cells of thyroid

Neuroendocrine cells

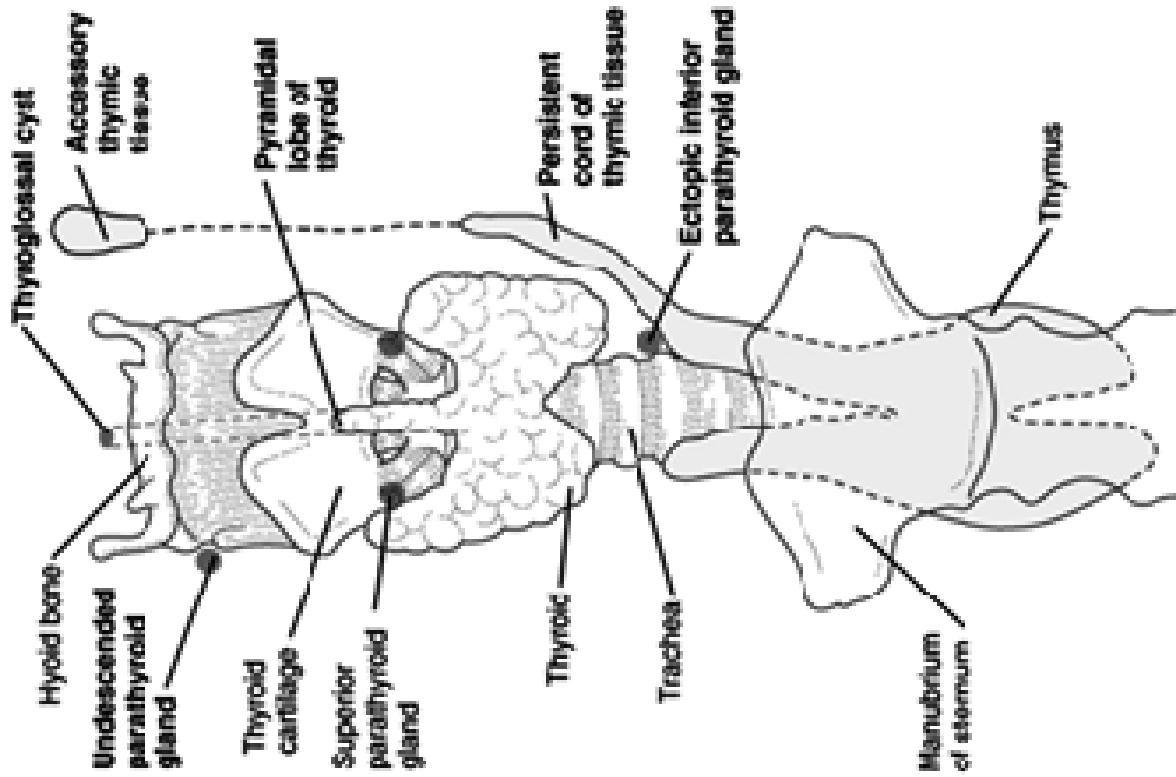
- pale staining
- epithelial basis, under basal lamina no contact with colloid
- derived from neural crest
- associate with ultimobranchial body, (derivative of the 4th pharyngeal pouch)



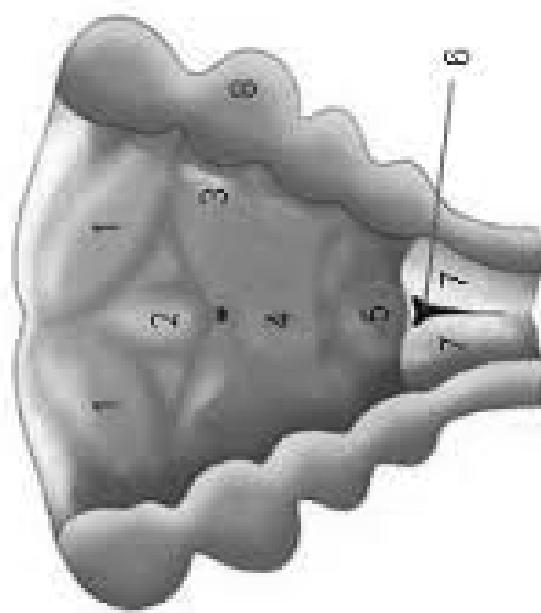
- ## Calcitonin
- inhibition of osteoclasts

Thyroid development

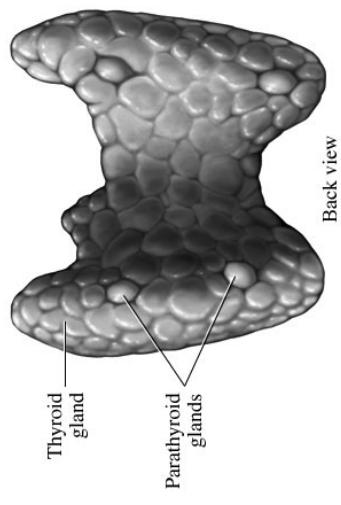
- endodermal proliferation of pharyngeal floor
- hypobranchial eminence and foramen caecum
- bilobed ciberticulum
- ductus thyreoglossus



Cohen: Human Embryology and Developmental Biology, 4th Edition
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Parathyroid gland (gl. parathyreoida)



Back view

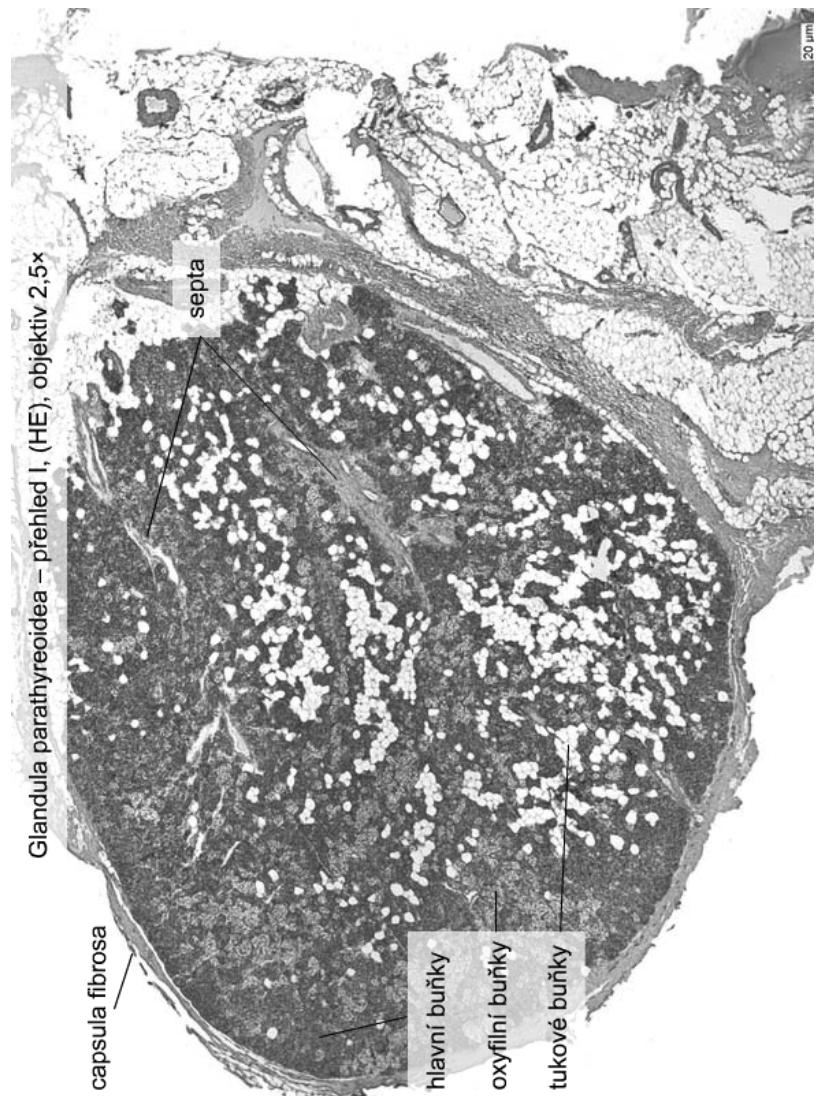
6 mm, 130 mg

c.t. capsule and septa

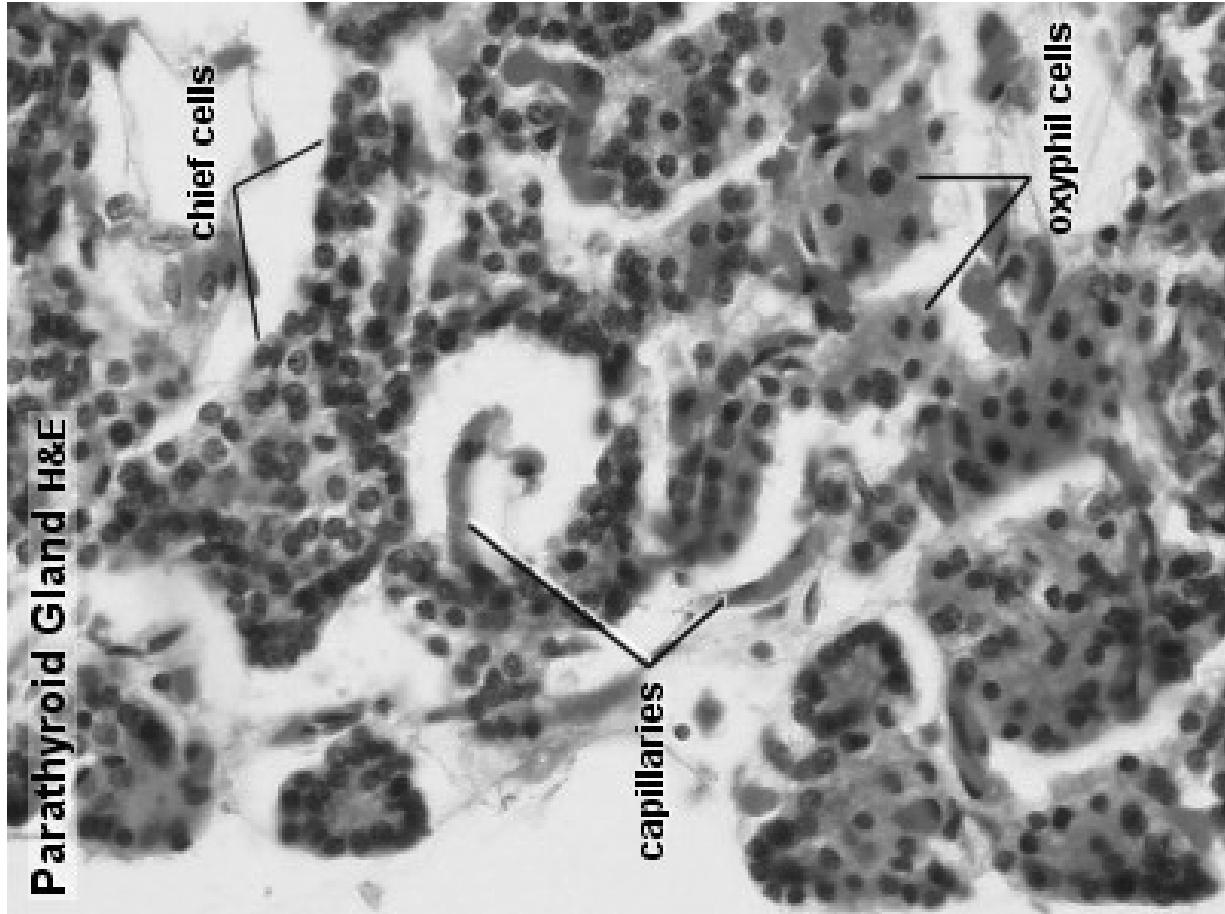
Capillary network

Cords and clusters of glandular cells

- Chief
- Oxyphilic
- Adipose

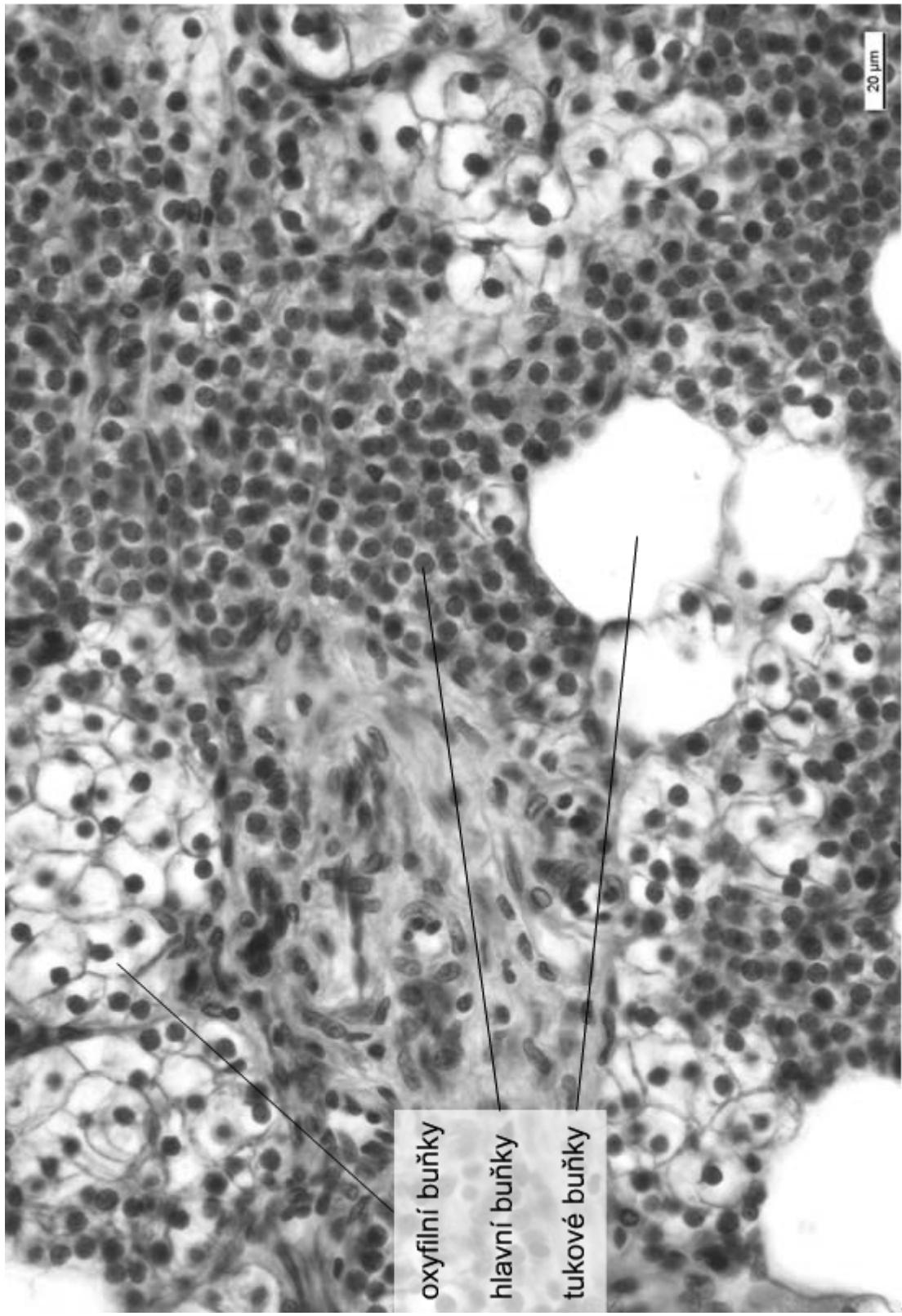


Parathyroid gland (gl. parathyreoida)



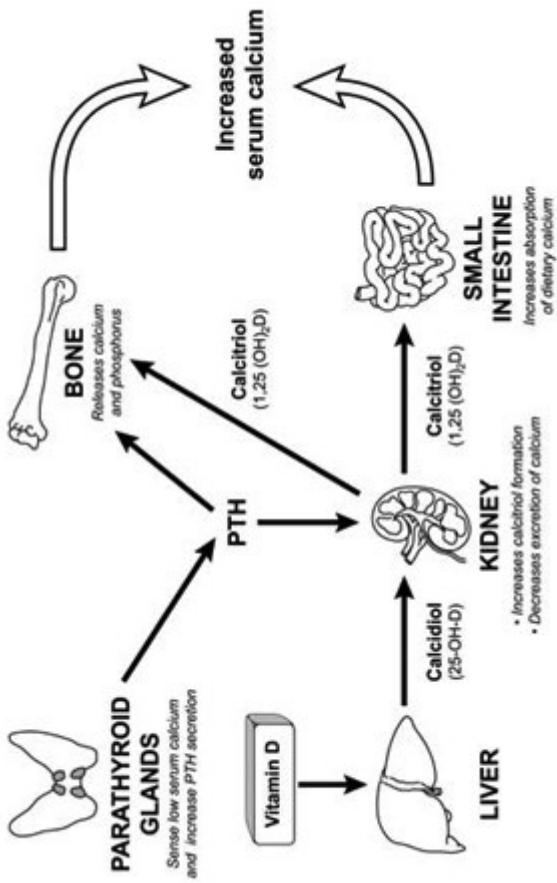
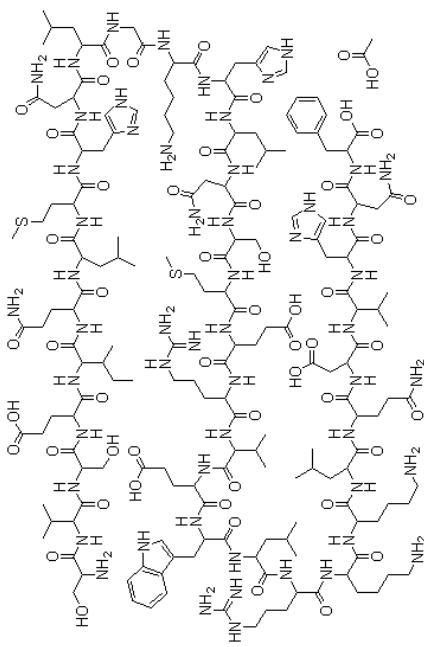
- Chief
 - most abundant
 - small cells (7-10 μ m, big nucleus
 - mildly acidophilic
 - PTH – calcium metabolism
- Oxyphylic
 - large, polyhedral,
 - strongly acidophilic
 - round nucleus
 - glycogen

Parathyroid gland (gl. parathyreoida)

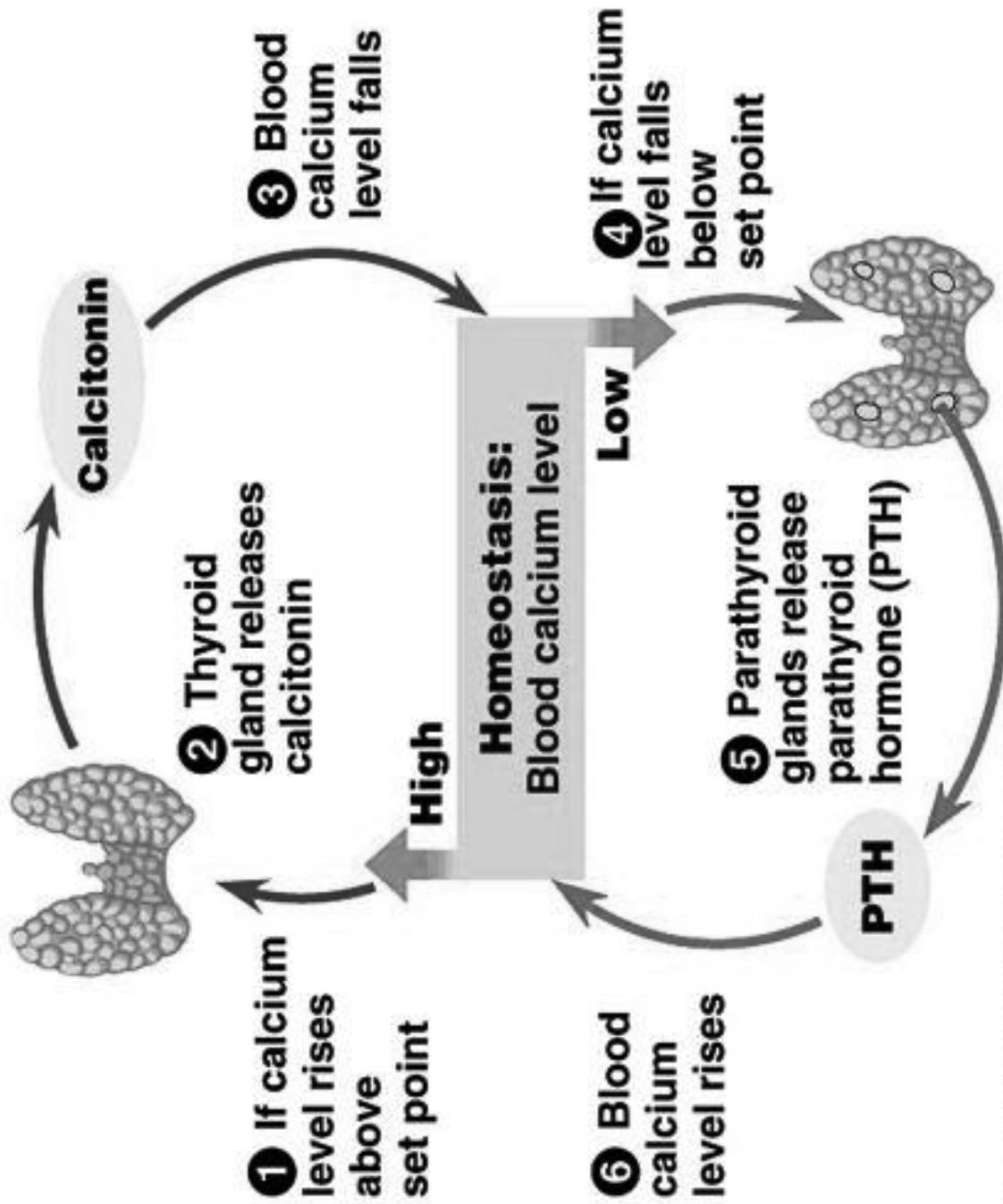


Parathyroid hormone (PTH, parathormone, parathyrin)

- 84 aminoacids
- stimulates resorption by osteoclasts
- enhances resorption of calcium and magnesium in distal tubules and thick ascending limb
- enhances absorption in the intestine (via vD3)



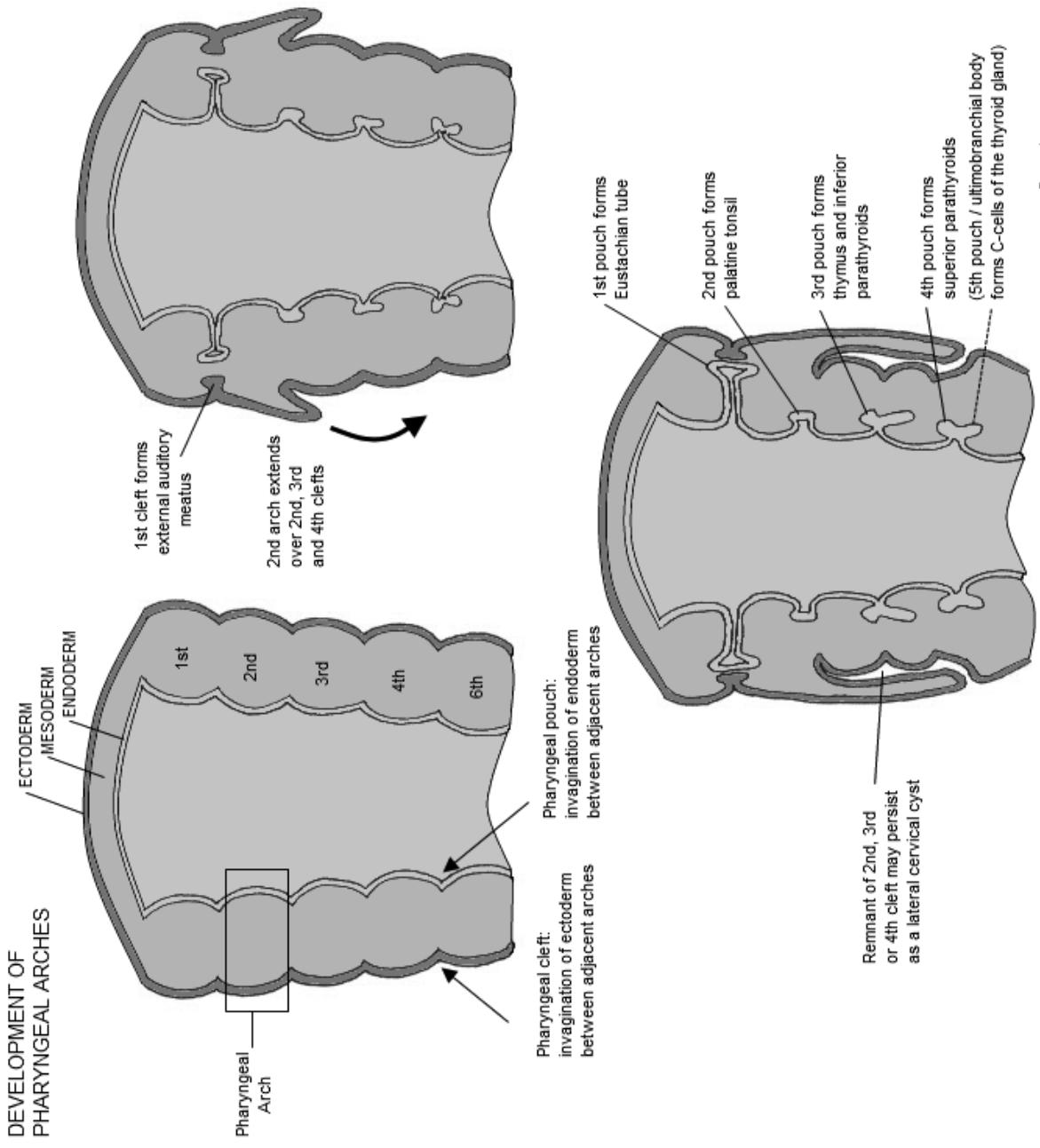
PTH vs. calcitonin



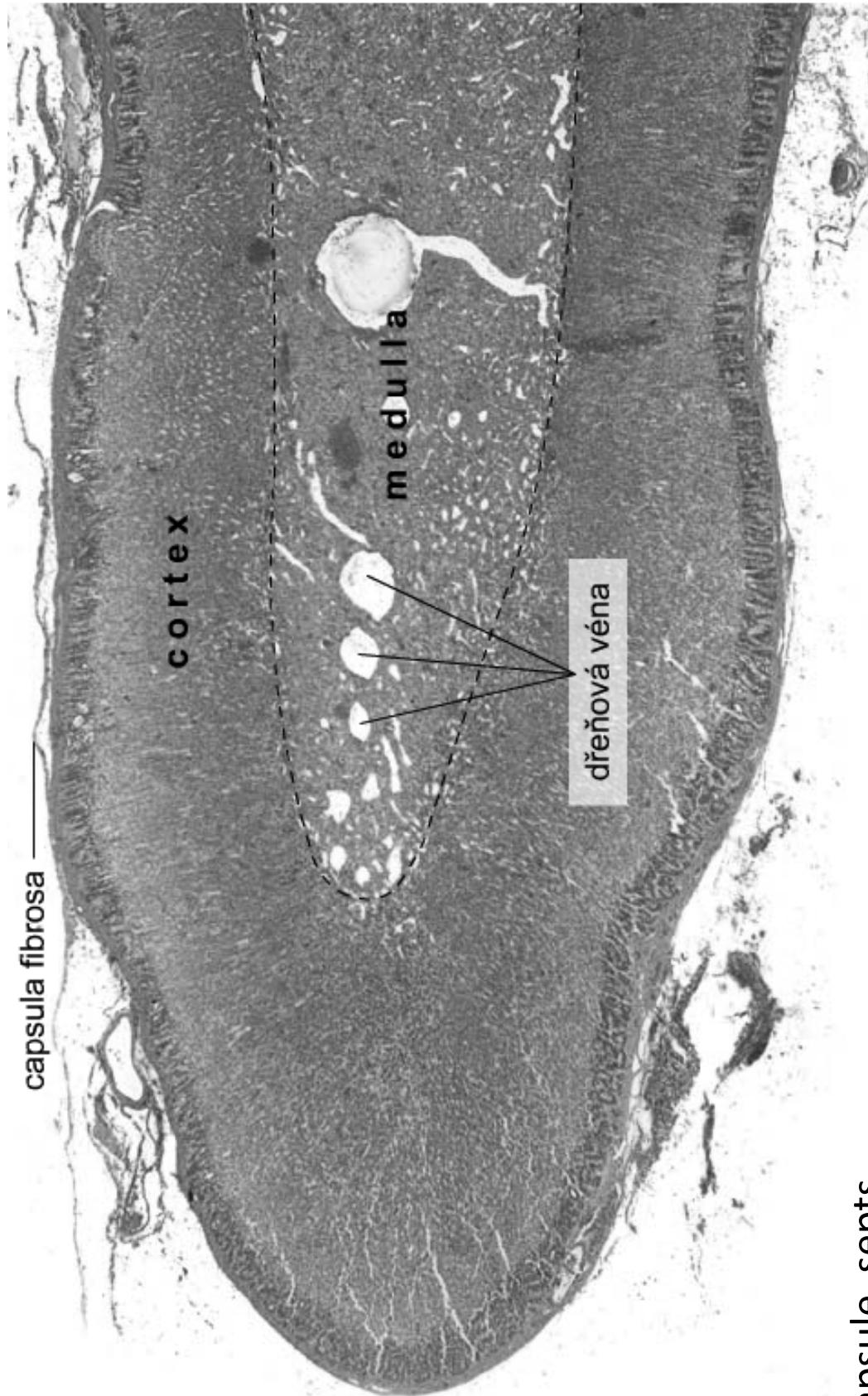
Embryonic development of parathyroid gland

- glandulae parathyroideae superiores from endoderm of 4th pharyngeal pouch
- glandulae parathyroideae inferiores from dorsal process of 3rd pharyngeal pouch
 - together with thymus descend to lower poles of thyroid
- ectopic PTH gland in thymus or mediastinum

Embryonic development of parathyroid gland



Adrenal gland (*corpus suprarenale*)



c.t. capsule, septa

capillary plexus

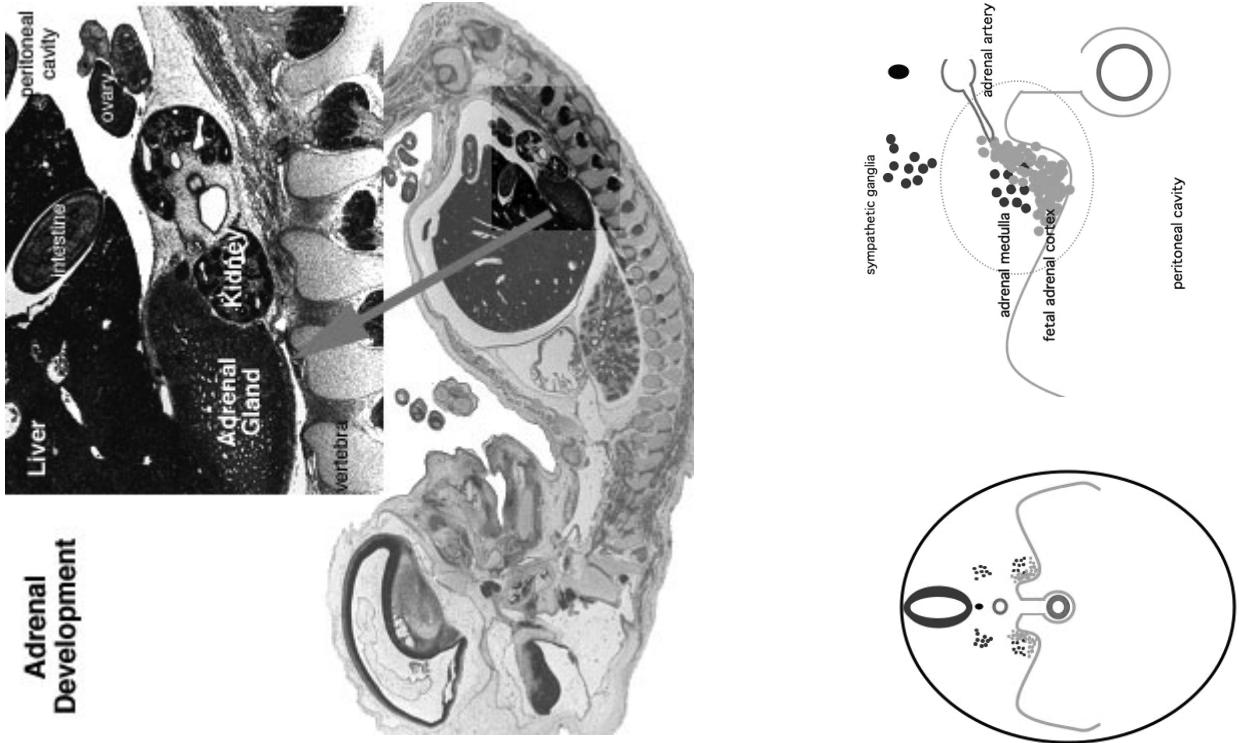
Adrenal development

cortex

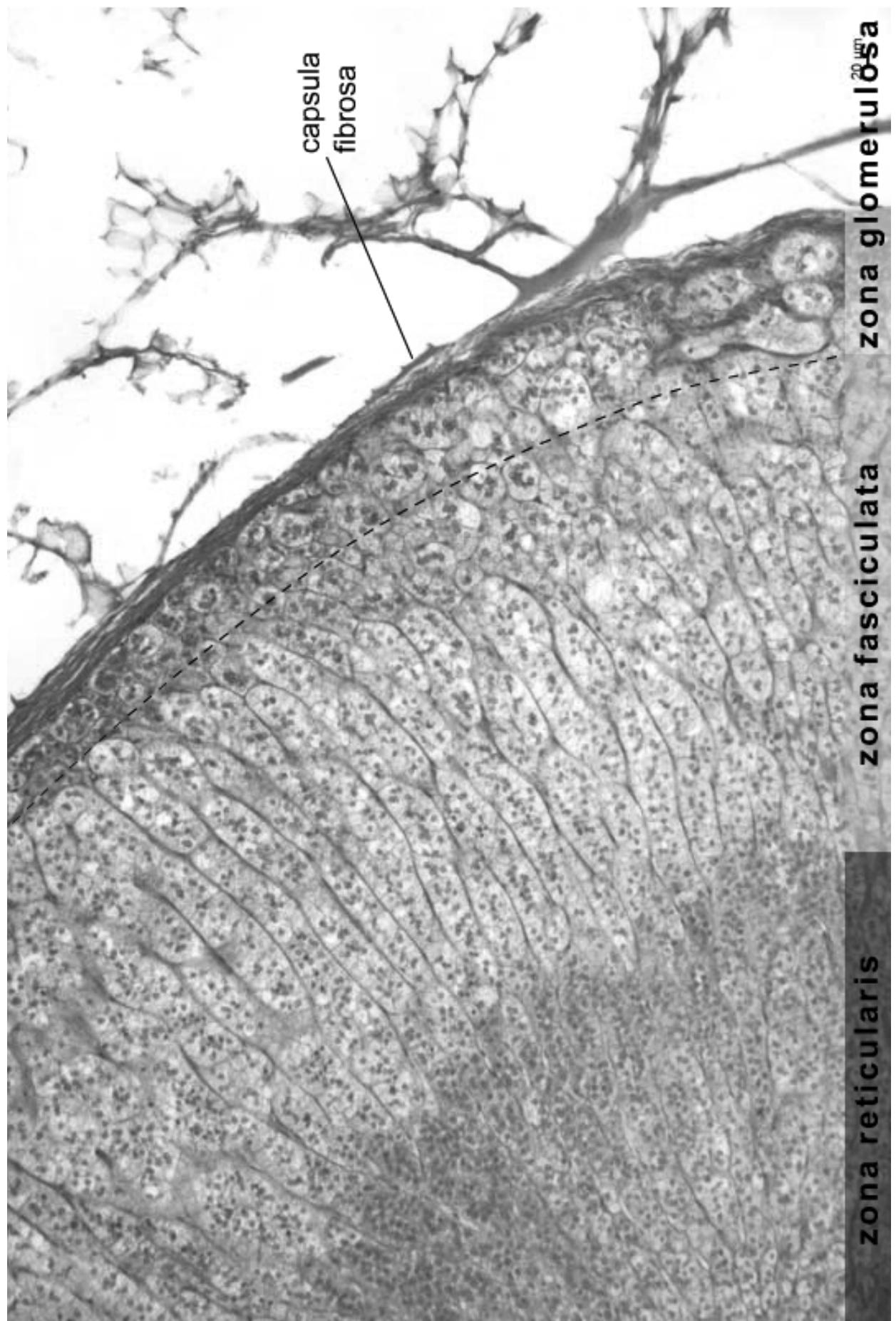
- mesoderm
- mesothelium, coelomic epithelium

medulla

- neural crest



Adrenal cortex

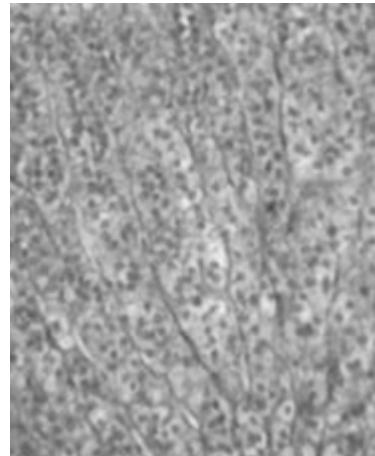
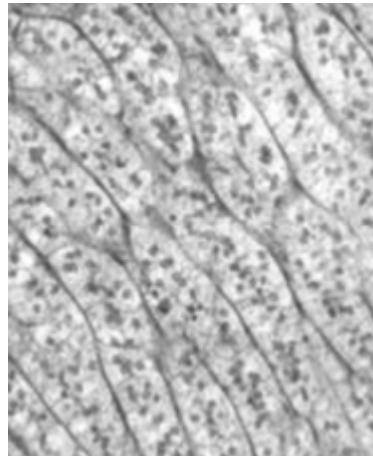
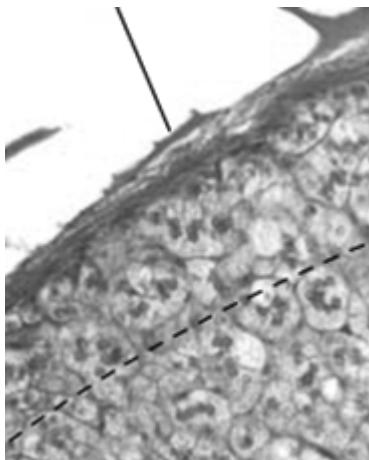


Adrenal cortex

- **Zona glomerulosa (1/10)**
 - thin layer under capsule
 - relatively small cells in coiled glomeruli
 - not abundant lipid droplets
 - **mineralocorticoids**

- **Zona fasciculata (6/10)**
 - radially arranged trabecules
 - lipid droplets in cytoplasm
 - **glucocorticoids**

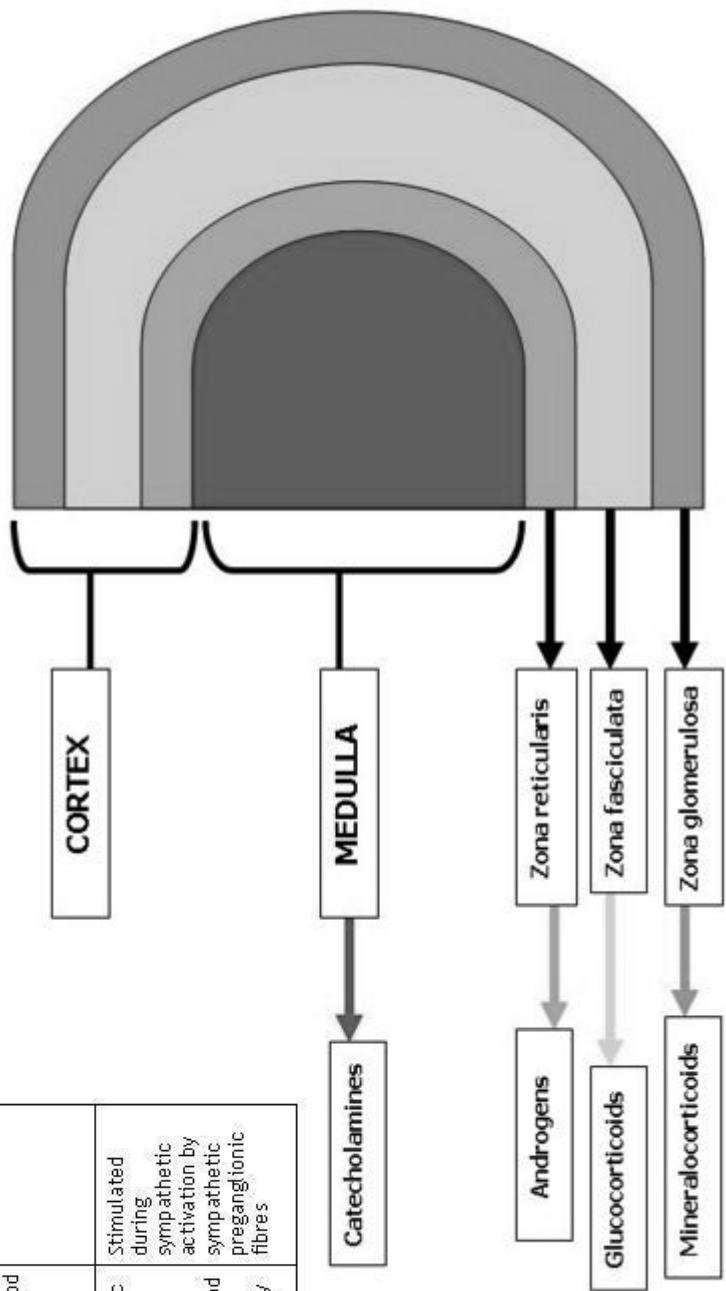
- **Zona reticularis (3/10)**
 - branched trabecules
 - small, acidophilic cells
 - lipofuscin
 - **androgen precursors**



Adrenal cortex hormones

- Steroids produced in cortex = CORTICOSTEROIDS
 - Steroidogenic cells
 - SER, lipid droplets, mitochondria
 - *mineralocorticoids*
 - *glucocorticoids*
 - Aldosteron – *zona glomerulosa*
 - Kortisol – *zona fasciculata*
 - Androgens, estrogens, progesteron – *zona reticularis*

Adrenal cortex hormones



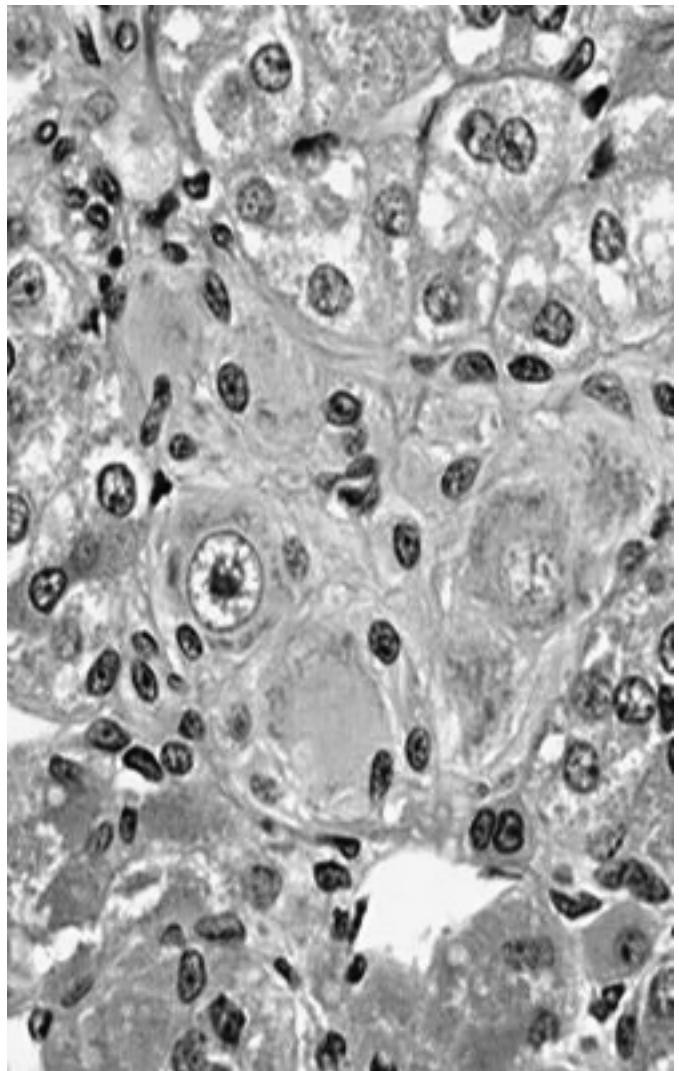
Region/ Zone	Hormone(s)	Primary Targets	Hormonal Effects	Regulatory Control
Cortex Zona glomerulosa	Mineralocorticoids (primarily aldosterone)	Kidneys	Increase renal reabsorption of Na ⁺ and water (especially in the presence of ADH and accelerate urinary loss of K ⁺)	Stimulated by antidiurensin II, elevated plasma K ⁺ , or a fall in plasma Na ⁺ ; inhibited by ANP and BNP
Zona fasciculata	Glucocorticoids [cortisol (hydrocortisone), corticosterone]	Most cells	Release amino acids from skeletal muscles and lipids from adipose tissues; promote peripheral utilization of lipids; anti-inflammatory effects	Stimulated by ACTH from anterior lobe of pituitary gland
Zona reticularis	Androgens	Most cells	Not important in adult men; encourages bone growth, muscle growth, and blood formation in children and women	Stimulated by ACTH
Medulla	Epinephrine, norepinephrine	Most cells	Increase cardiac activity, blood pressure, glycogen breakdown, blood glucose levels; releases lipids by adipose tissue	Stimulated during sympathetic activation by sympathetic preganglionic fibres

Adrenal medulla

Clusters of glandular cells in reticular c.t.

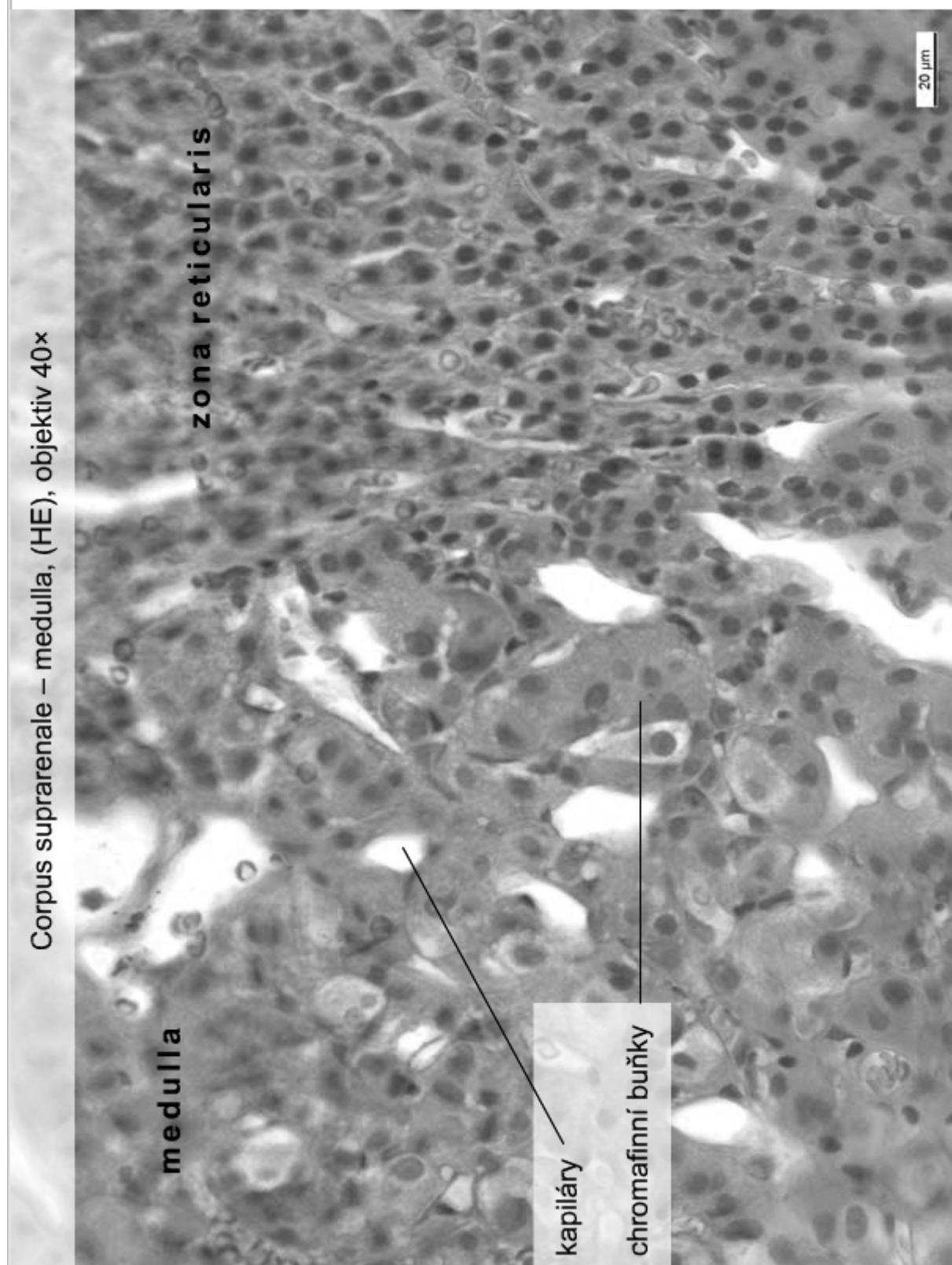
- chromaffin cells – modified postganglionic neurons
- ganglionic cells
- capillaries, venules, nerve fibers

- **adrenaline and noradrenaline**

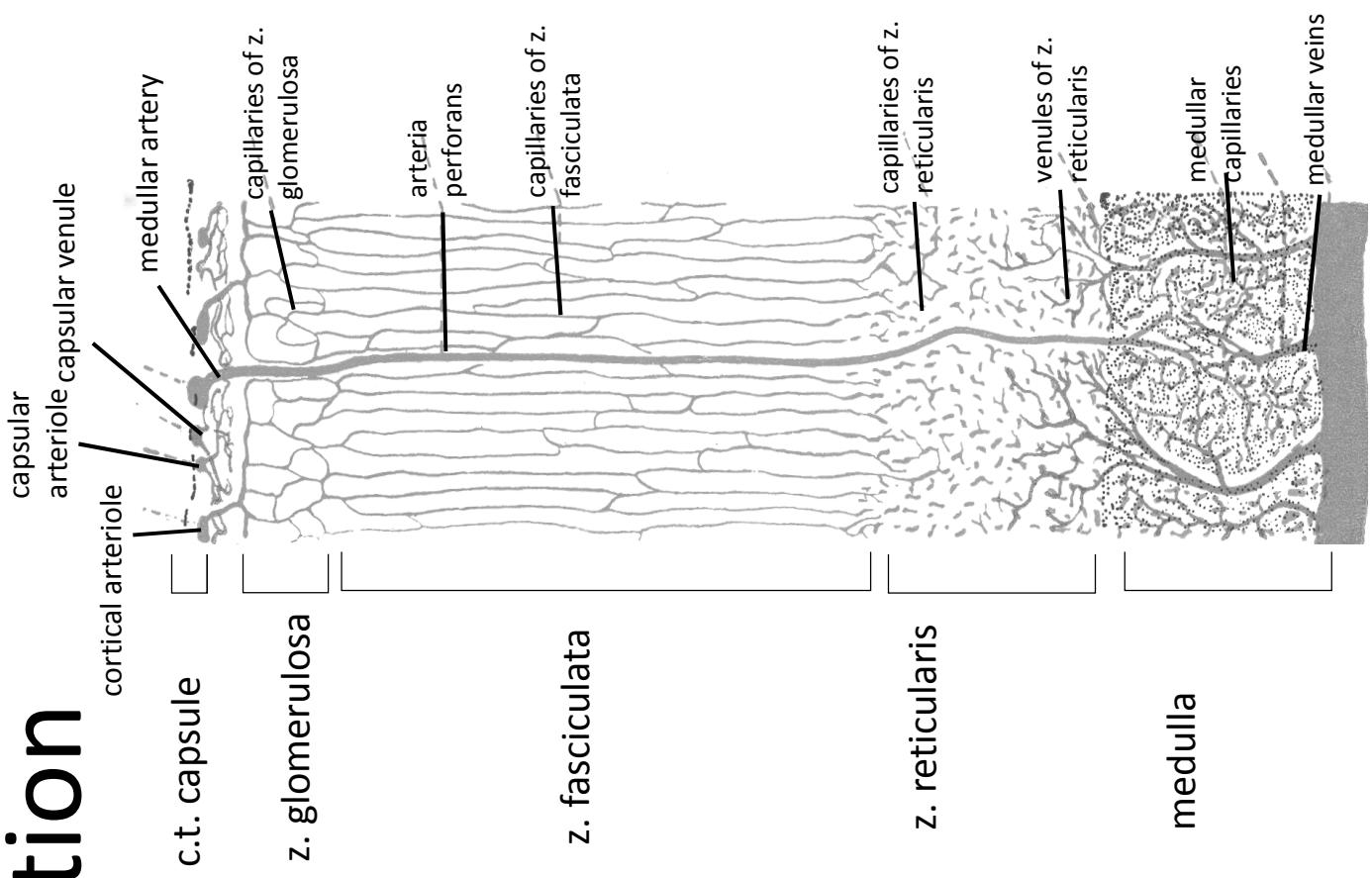


Neural crest origin

Corpus suprarenale – medulla, (HE), objektiv 40x



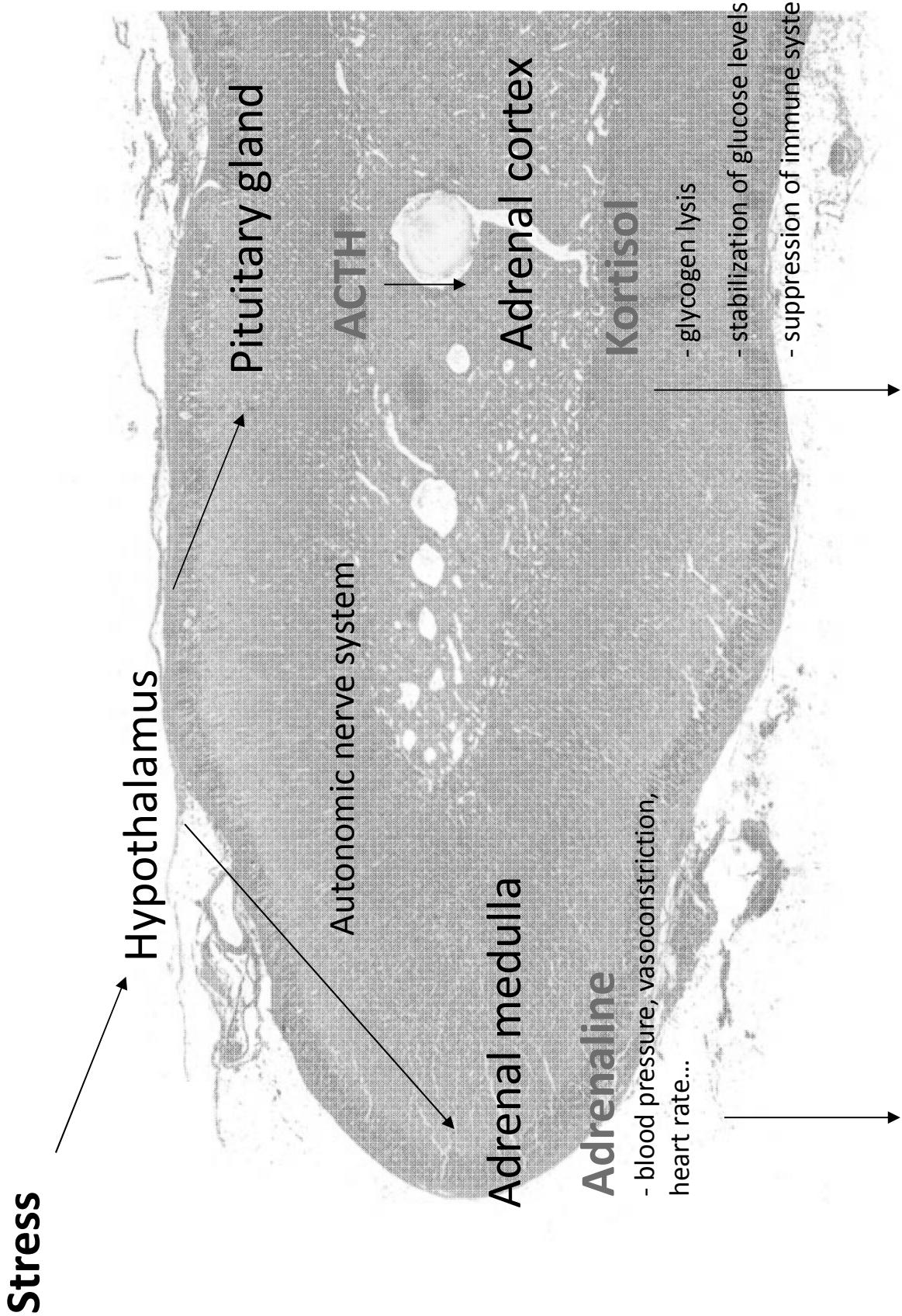
Adrenal vascularisation



arteriae suprarenales (3) → arterial plexus in cortex under c.t. capsule → radially oriented fenestrated sinusoid capillaries continuous with medullar capillaries → medullar veins → v. *suprarenalis*

three arterial regions

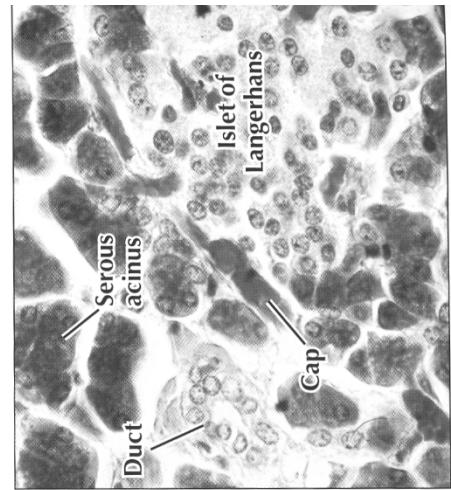
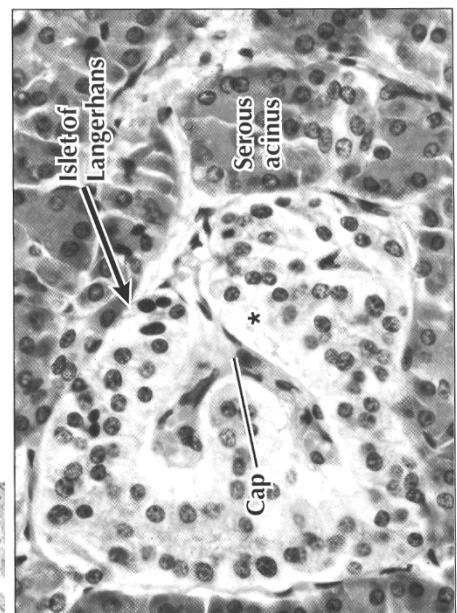
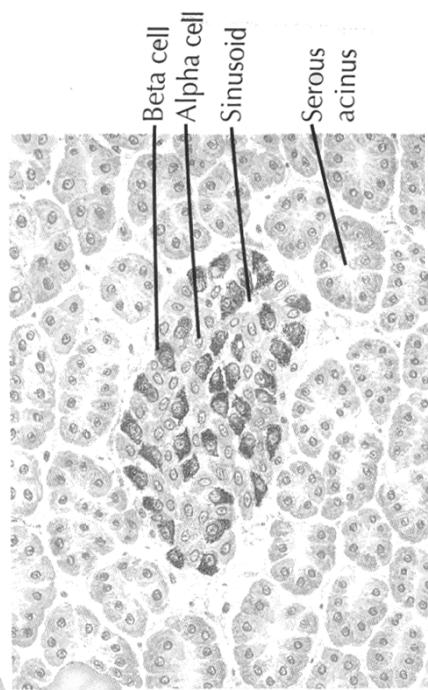
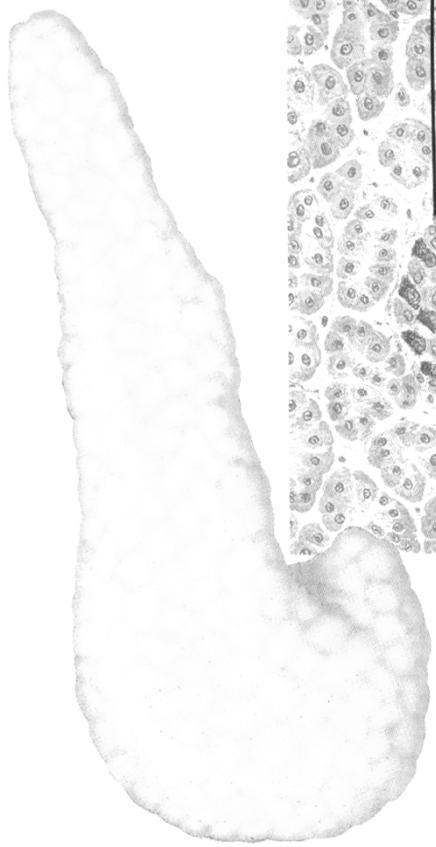
- 1) c.t. capsule and superior parts of cortex
- 2) radial capillaries of cortex continuing to medulla
- 3) medullar capillaries from *aa. perforantes*



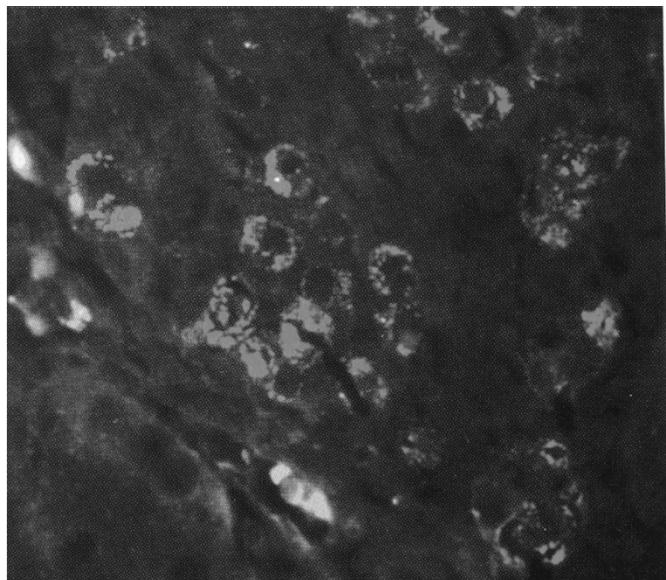
Fight or Flight

Adaptation, regeneration

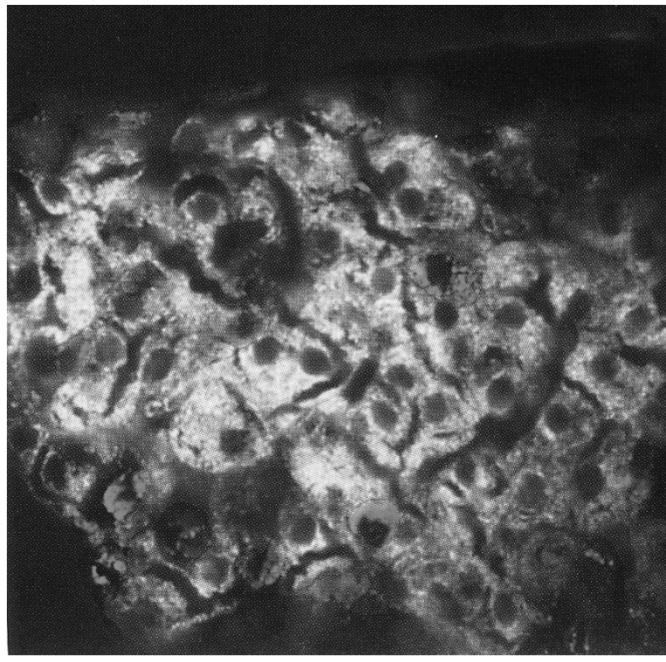
Langerhans islet of pancreas



Langerhans islets of pancreas



B-cells producing insulin
Ab-anti insulin -Alexa Fluor



A-cells producing glucagon
Ab-anti glukagon -Texas Red

Thank you for attention