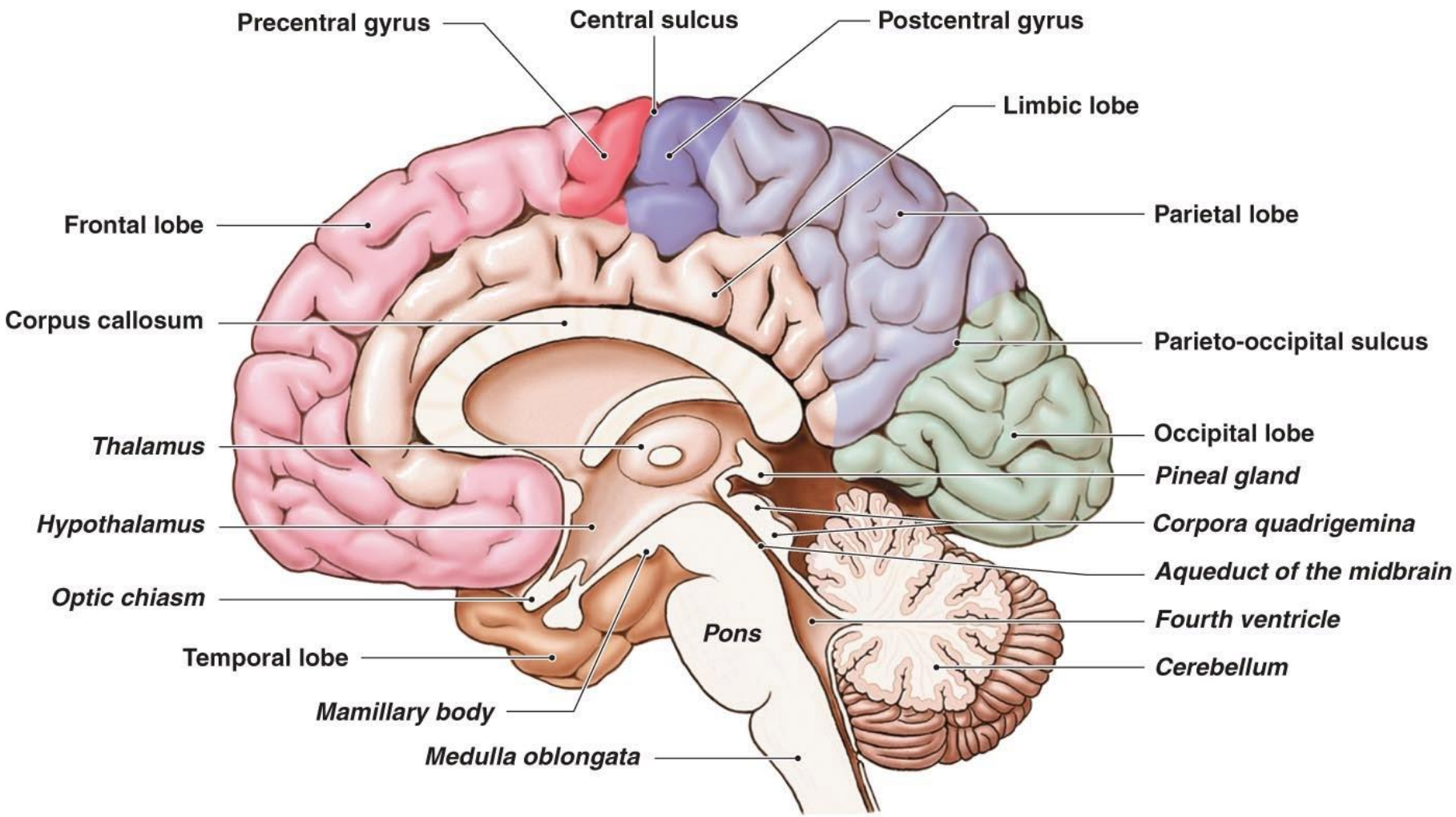
Hypothalamic-pituitary system

Hypothalamic-pituitary system

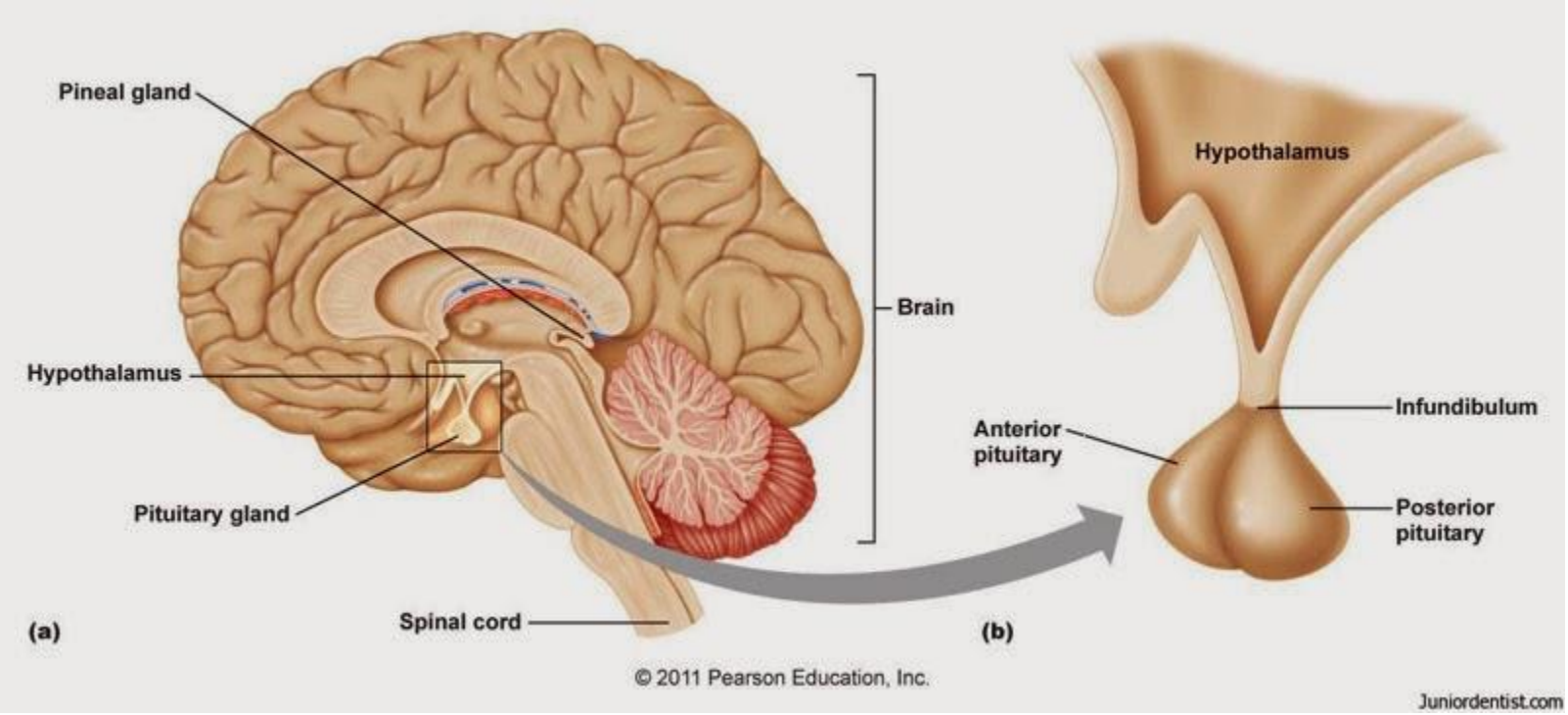
A midsagittal view showing the inner boundaries of the lobes of the cerebral cortex (Structures outside of the cerebrum are labeled in italics.)



Hypothalamo-hypophyseal system

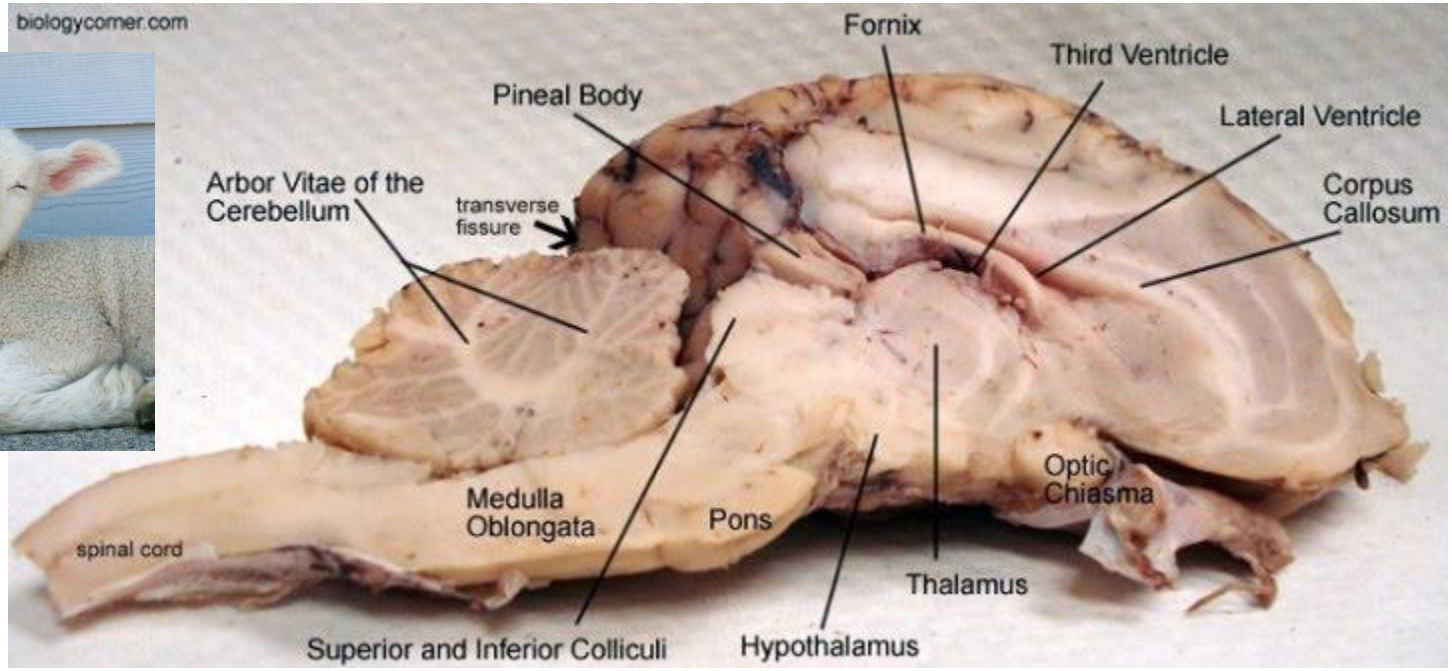
Hypothalamus
Pituitary gland (hypophysis) → **adenohypophysis**
→ **neurohypophysis**

Pineal gland (epiphysis cerebri)



Hypothalamus

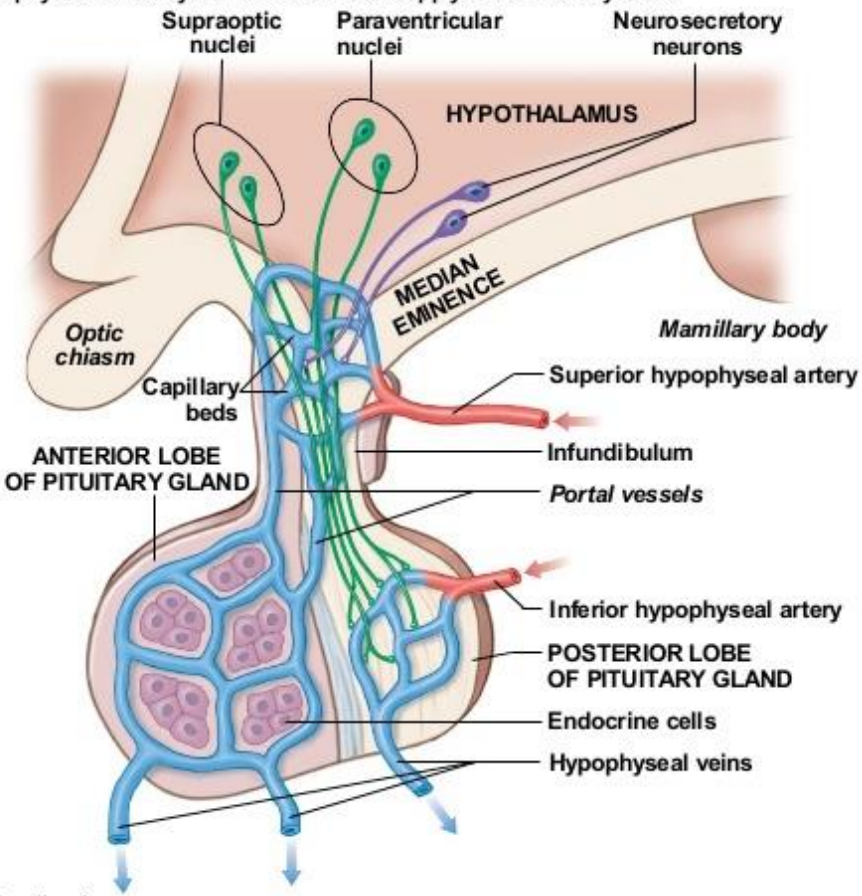
- all vertebrates, human – size of about 4 cm^3
- in the midbrain, in contact with third ventricle
- infundibulum with pituitary gland
- part of the limbic system
- regulation of body temperature, food and water intake (hunger and thirst), reproduction, mood and emotions, circadian rhythms, controls the autonomic nervous system, **mediate communication between nervous and endocrine system**



Endocrine function of hypothalamus

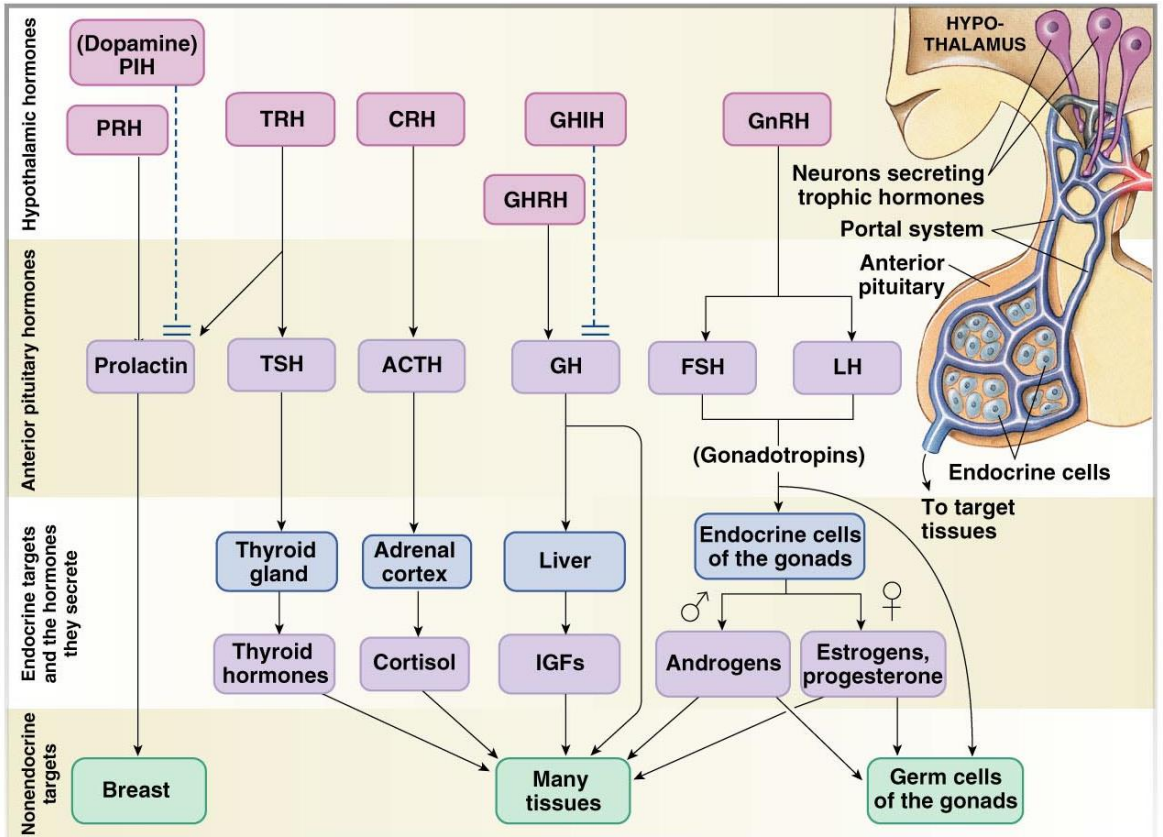
- hypothalamic nuclei > axonal transport > median eminence and transfer to the portal system (releasing factors) > adenohypophysis and other organs
- axonal transport to the neurohypophysis > store and release into the blood (oxytocin, vasopressin)

Figure 18-7 The Hypophyseal Portal System and the Blood Supply to the Pituitary Gland



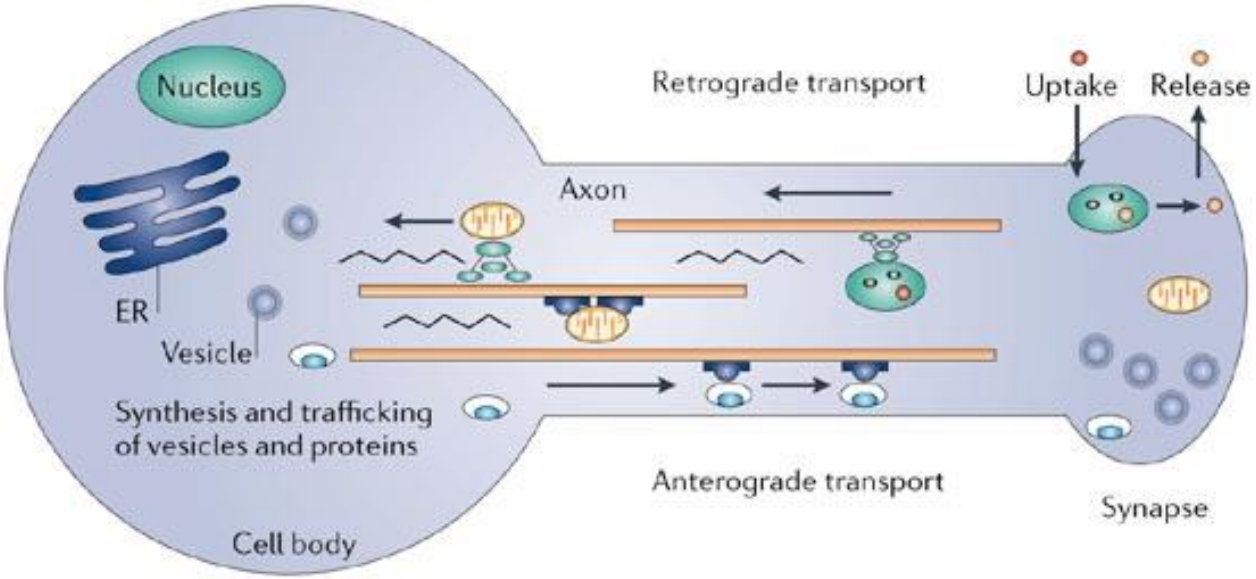
Releasing and inhibiting factors: synthesis

- **liberins (releasing factors)** - thyrotropin-releasing hormone (TRH), corticotropin-releasing hormone (CRH), gonadotropin-releasing hormone (GnRH: LHRH and FSHRH), prolactoliberin (PRH), melanoliberin (MRH), growth hormone–releasing hormone (GHRH)
- **statins (inhibiting factors)** - somatostatin, follistatin, cortistatin
- **dopamine** (derived from tyrosine functions as prolactostatin)



Releasing and inhibiting factors: synthesis

- peptidic hormones
- anterograde axonal transport (kinesins)
- released into the blood in median eminence



Releasing and inhibiting factors: mode of action

- target cells in adenohypophysis
- signal transduction induced by one hormones can use multiple mechanisms, but the mail is usually only one of them

GnRH, TRH:

- binds to G protein-coupled receptors > activation of **IP_3/DAG** pathway > increase of intracellular Ca^{2+} > kinase activation (PKC) and cellular response

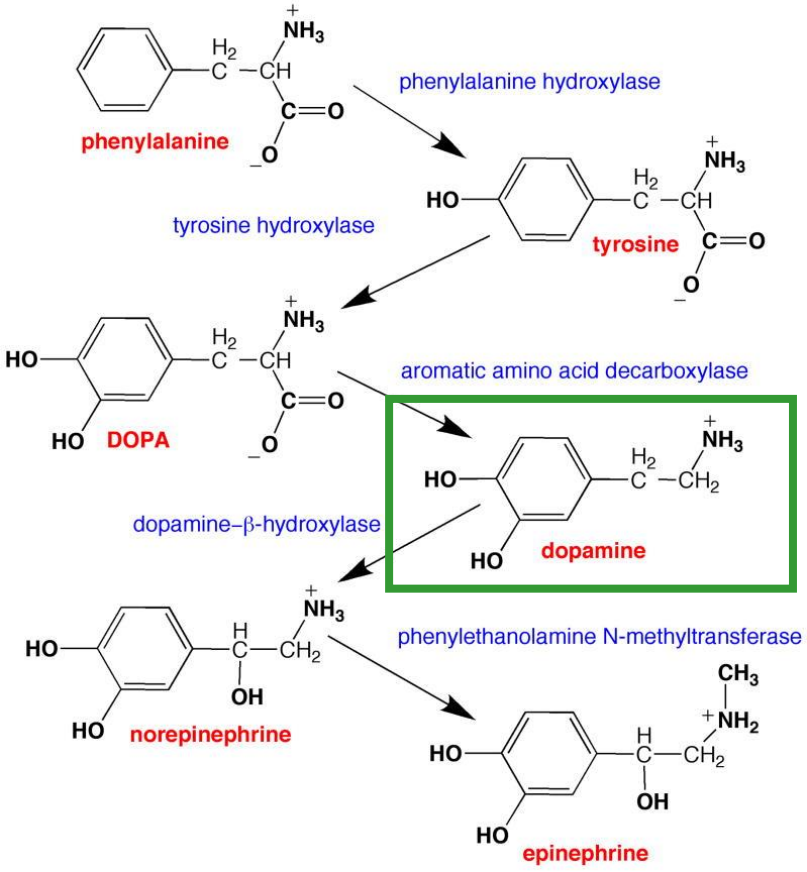
GHRH, GHIH, CRH:

- binds to G protein-coupled receptors > activation of adenylate cyclase > **cAMP** > kinase activation (PKA) > phosphorylation of CREB transcription factors (cAMP response element-binding protein) and cellular response

They stimulate or inhibit cells in the adenohypophysis, which produce tropic hormones > negative feedback loop.

Dopamine (DA, PIH)

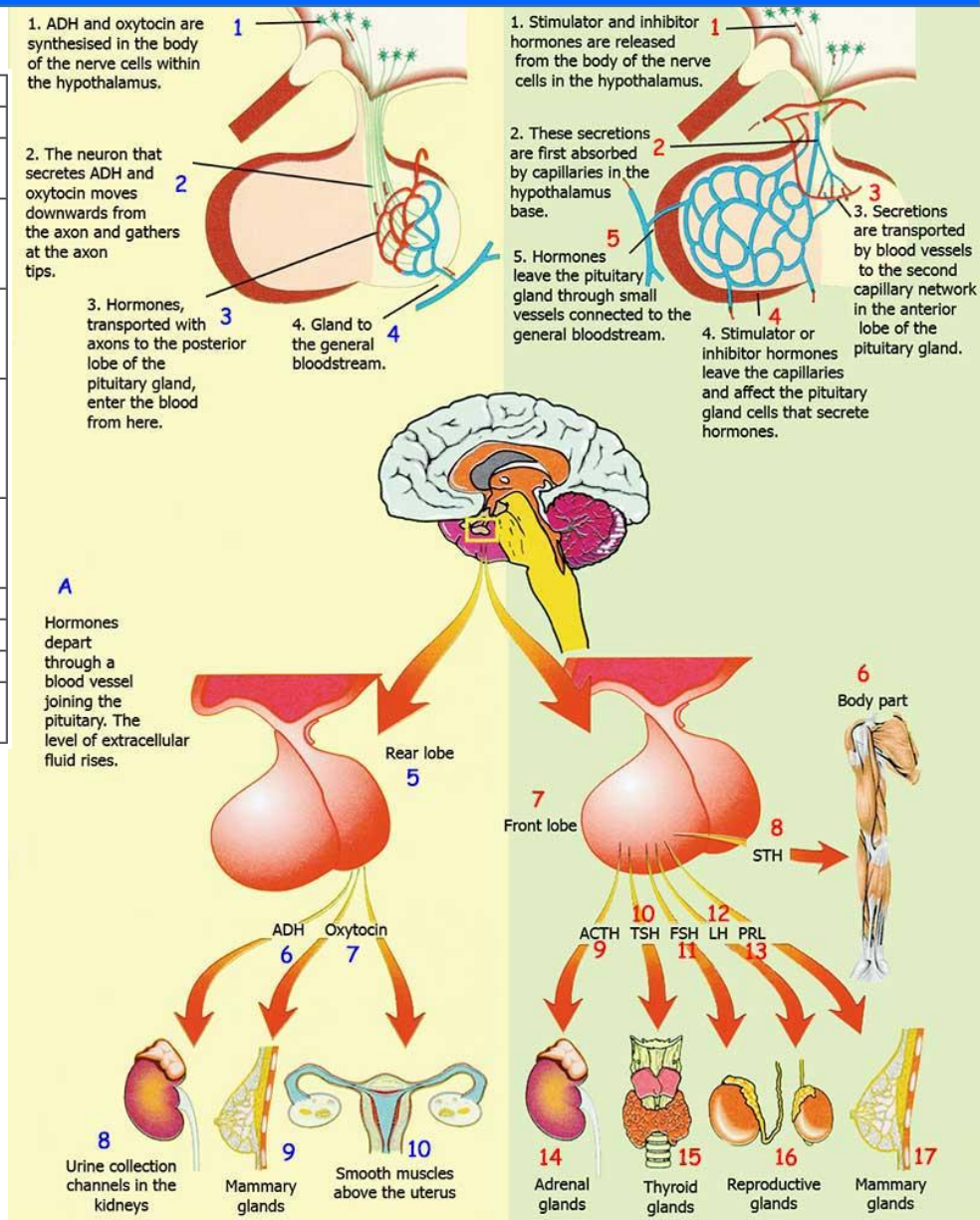
- synthesis in hypothalamic neuron nuclei and partly in the adrenal glands
- catecholamine, tyrosine derivative
- binds to dopamine receptors and increases concentration of cAMP
- acts as a neurotransmitter and neurohormone that inhibits release of prolactin in the adenohypophysis



Pituitary gland (hypophysis)

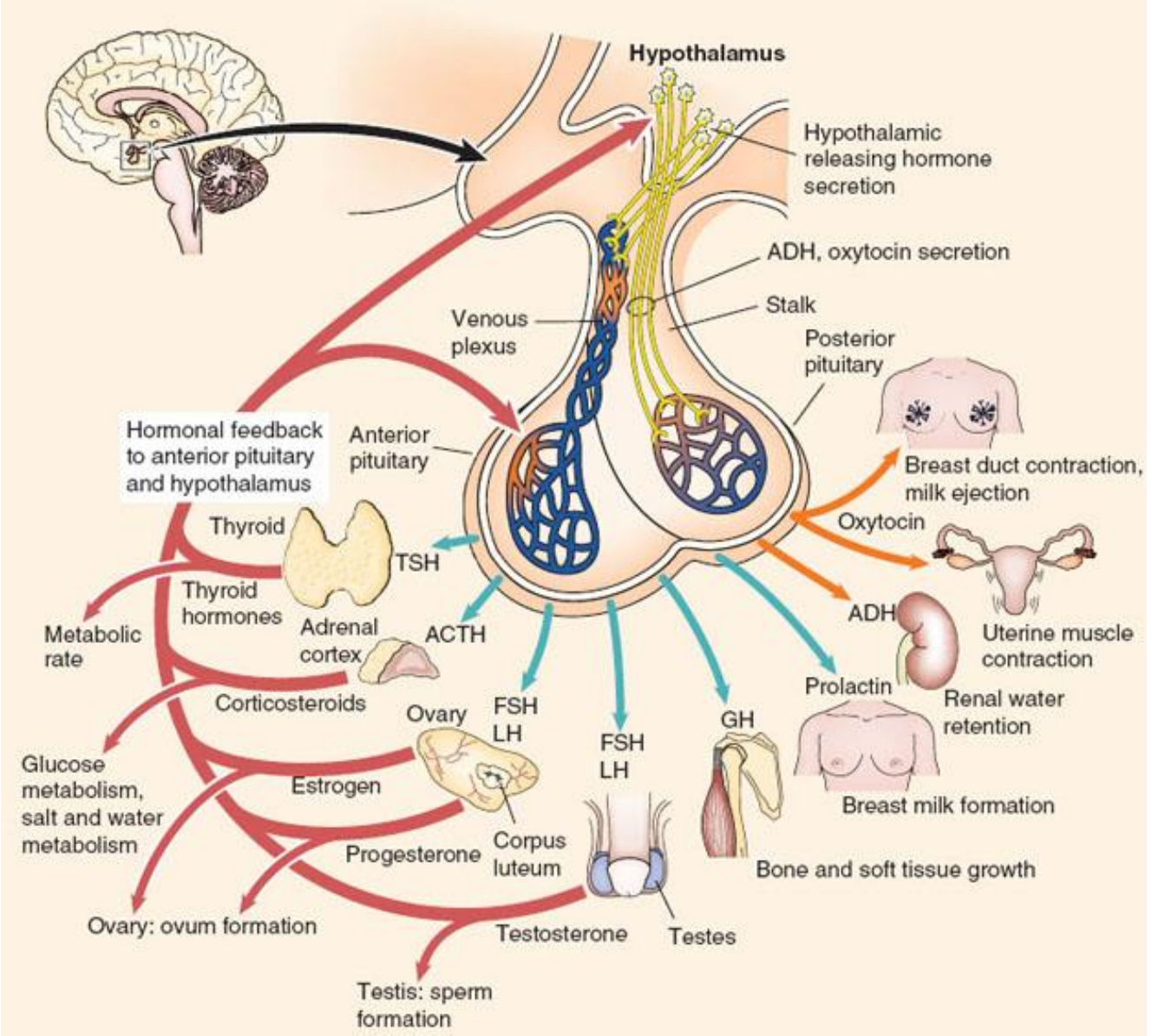
Hormone	*Actions*
Anterior Pituitary *(adenohypophysis)*	
Growth hormone (GH, GRH, somatotropin, STH)	Promotes body growth; other metabolic effects
Adrenocorticotropic hormone (ACTH, corticotropin) – *trophic hormone*	Promotes secretion of cortisol and related glucocorticoids from the adrenal cortex
Thyroid-stimulating hormone (TSH, thyrotropin) – *trophic hormone*	Promotes synthesis and release of thyroid hormones and thyroid hypertrophy
Luteinizing hormone (LH) (gonadotropin) – *sex hormone*	Females: promotes ovulation and luteinization of ovarian follicles Males: promotes testosterone secretion
Follicle-stimulating hormone (FSH) (gonadotropin) – *sex hormone*	Females: promotes ovarian follicle growth and maturation Males: promotes spermatogenesis
Prolactin (PRL)	Females: stimulates milk secretion
Posterior Pituitary *(neurohypophysis)*	
Antidiuretic hormone (ADH, Vasopressin)	Promotes water retention in the kidney
Oxytocin	Causes uterine contraction in pregnancy; promotes milk ejection

- glandotropic hormones (ACTH, TSH, FSH, LH)
- aglandotropic hormones (prolactin, GH)



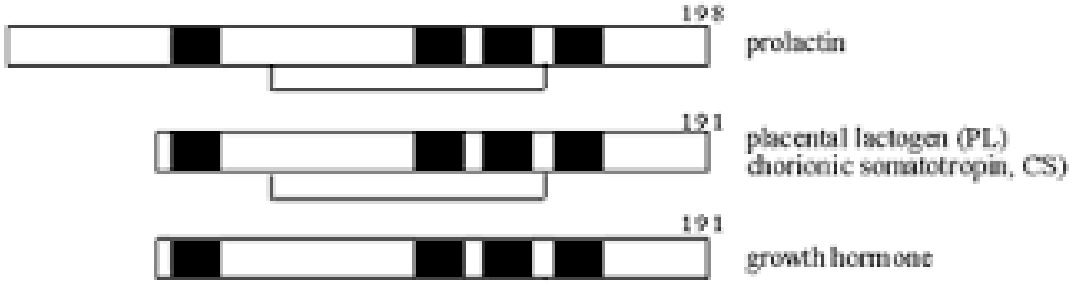
Tropic hormones (tropins): regulation

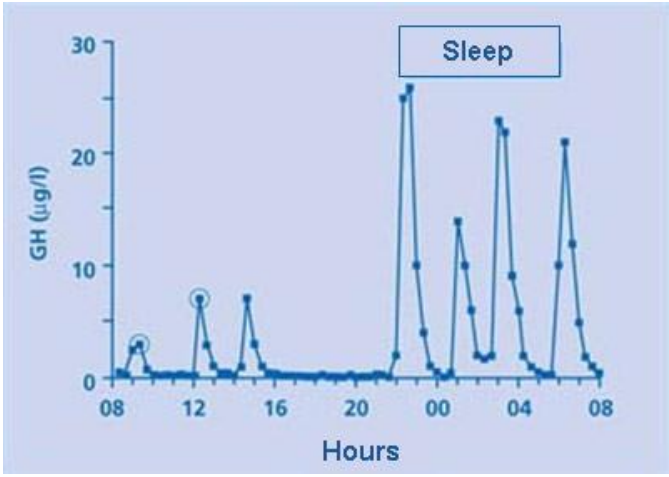
- half-life and degradation
- hypothalamic hormones (RH, IH)
- negative feedback (hormones produced by endocrine glands signal back to hypothalamus and hypophysis)



Growth hormone (GH, somatotropin)

- peptide (191 AA) encoded by genes GH1 and GH2
- homolog of prolactin and placental lactogen
- alternative splicing produces several GH isoforms
- released at intervals of 3 to 5 hours (maily after falling asleep)
- induced by GHRH, hypoglycemia, exercise, sleep
- transported by growth hormone binding proteins (**GHBP**)

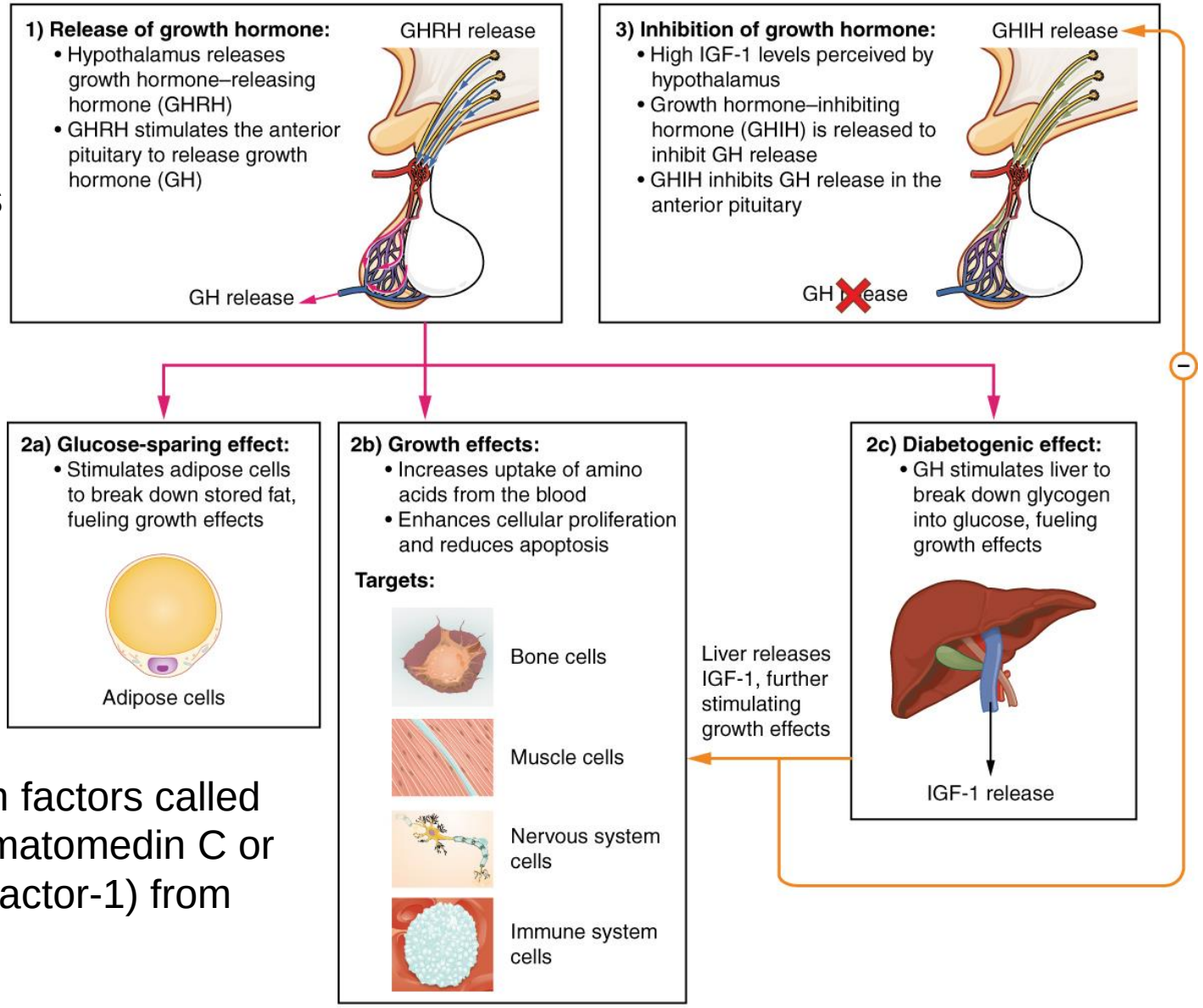




- growth (anabolic) and stress hormone
- increases the concentration of glucose and free fatty acids in the blood, promotes the production of IGF-1 like growth factor (somatomedin C) in the liver

Growth hormone (GH, somatotropin)

- targets all body organs
- especially the liver, bones and muscles
- growth, cell proliferation (mitogen), regeneration
- promotes erythropoietin production

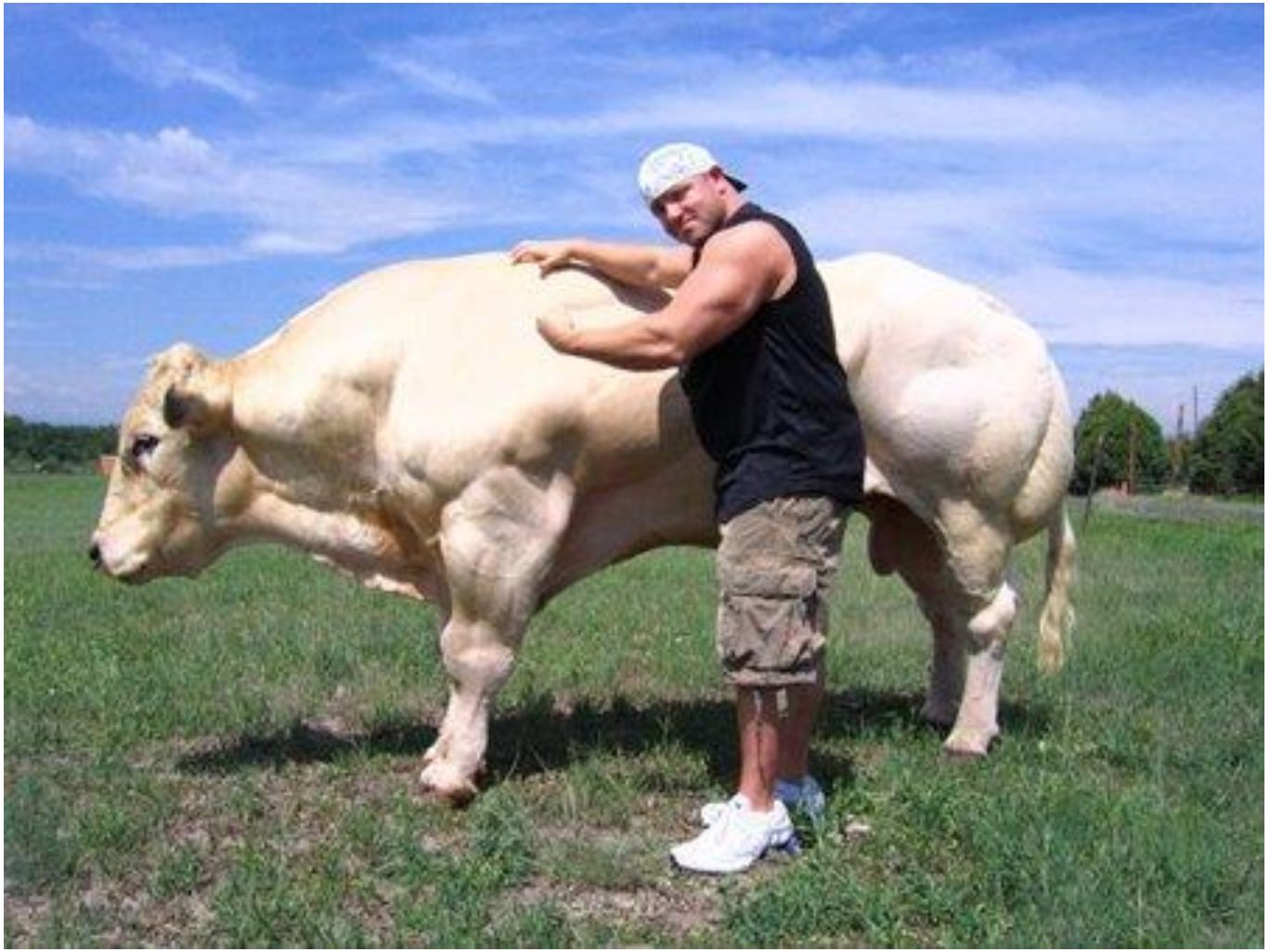


- acts through growth factors called somatomedins (somatomedin C or insulin-like growth factor-1) from the liver

Growth hormone (GH, somatotropin): pathophysiology

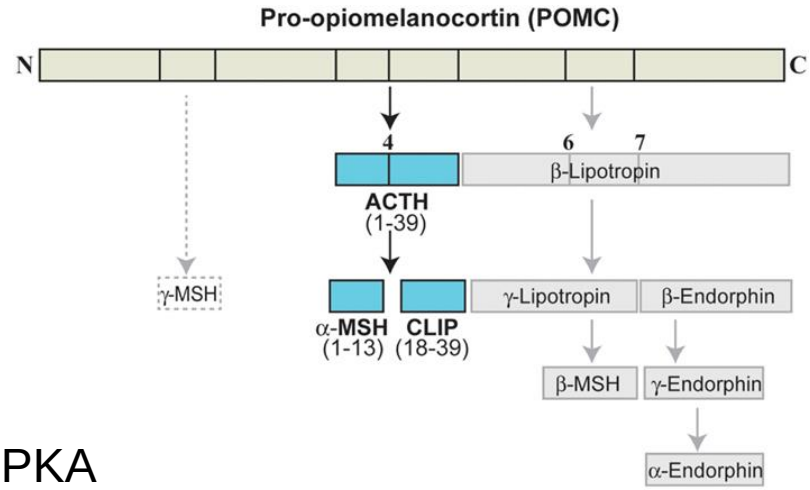
- gigantism
- acromegaly
- dwarfism
- metabolic inbalance (diabetes)

Growth hormone (GH, somatotropin): recombinant hGH



Corticotropin (Adrenocorticotropic hormone, ACTH)

- pre-pro-**opiomelanocortin** (285 AA) > proteolysis > pro-opiomelanocortin (**POMC**, 241 AMK) is the precursor of ACTH, melanotropin (MSH), β-lipotropin, β-endorphin and others
- tissue specific posttranslational processing of POMC
- glycosylation, phosphorylation, acetylation, **proteolysis** by subtilisin-like enzymes



- half-life in blood approx. 10 min
- G protein-coupled receptors > **cAMP** > PKA
- rapid effect (minutes) - stimulation of cholesterol transfer to mitochondria (StAR, $P450_{SCC}$)
- slow effect (hours) – stimulates the transcription of steroidogenic enzymes (e.g. $P450_{SCC}$) and mitochondrial genes involved in oxidative phosphorylation
- ACTH is produced together with CRH in response to biological stress

Thyrotropin (Thyroid-stimulating hormone, TSH)

- glycoprotein (201 AA; 26kDa):

α subunit (92 AA)

- related to human chorionic gonadotropin (hCG), follitropin and lutropin
- stimulates adenylate cyclase and synthesis of **cAMP**

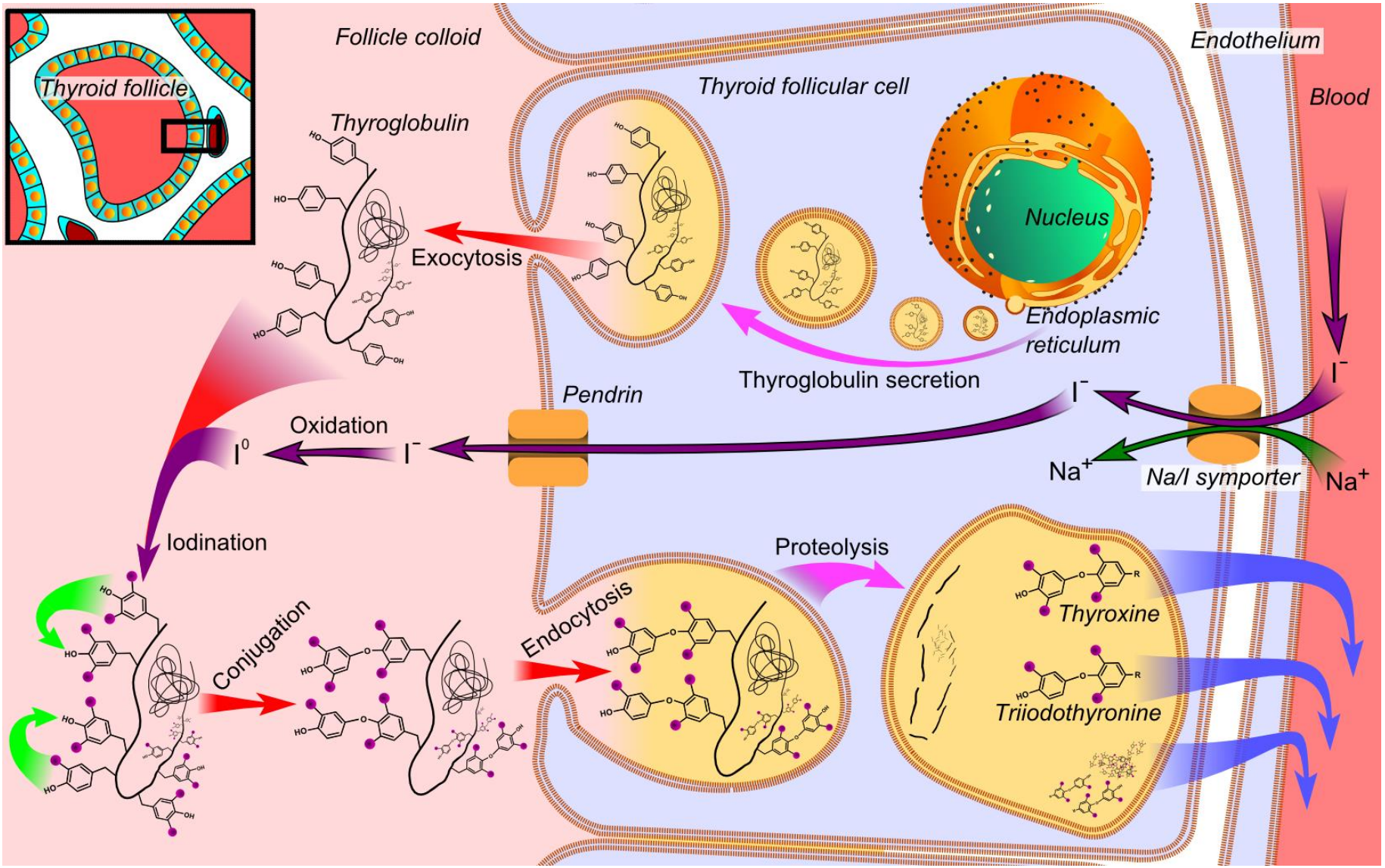
β subunit (118 AA)

- specific for TSH > receptor specificity

Carbohydrate side chains

- half-life about one hour
- released in pulses and especially during a period of rapid growth and development
- receptors found primarily on thyroid follicular cells
- increases blood flow and metabolism in thyroid gland, stimulates synthesis of thyroxine and triiodothyronine

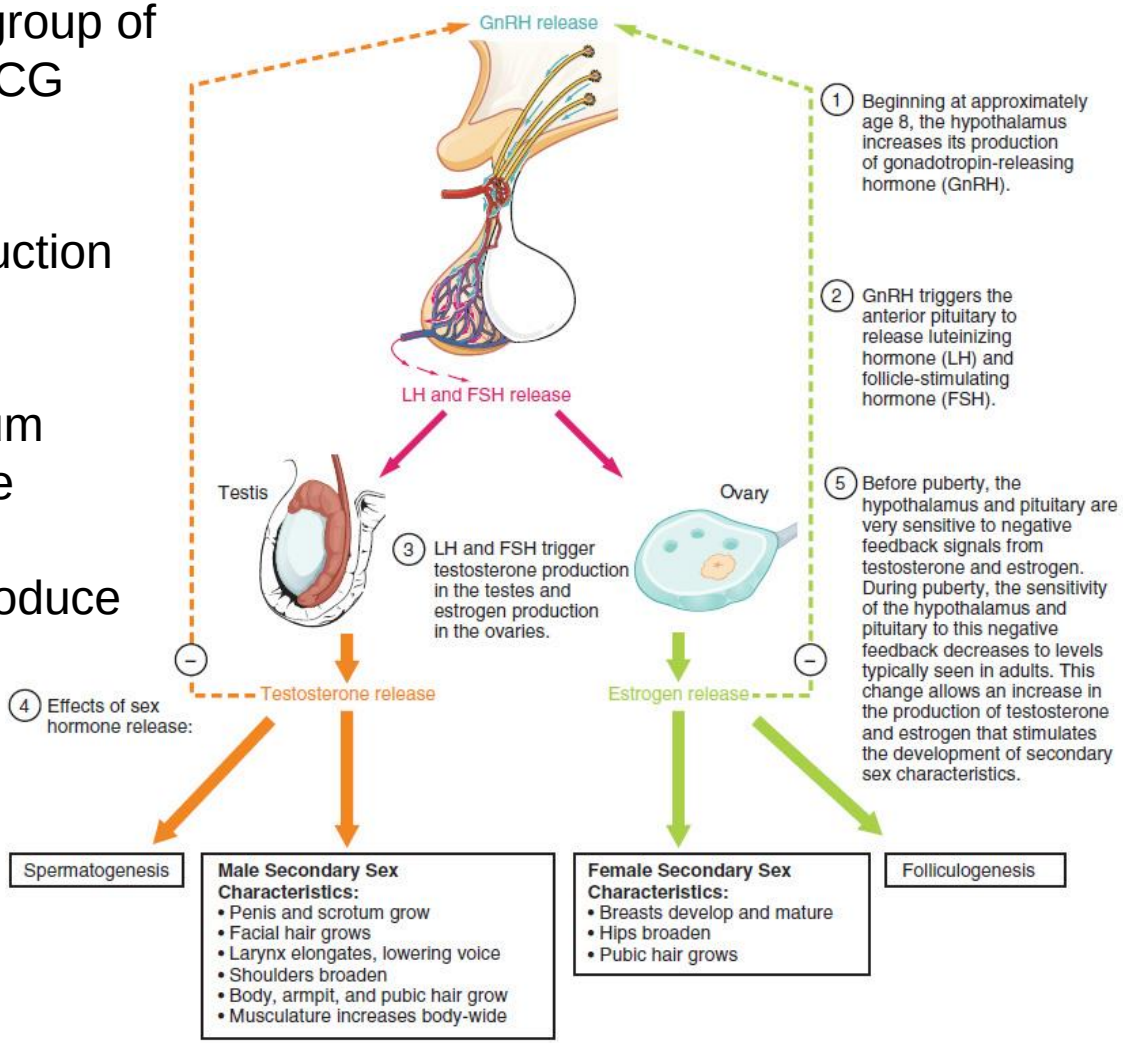
Thyrotropin (Thyroid-stimulating hormone, TSH)



Lutropin (Luteinizing hormone, LH)

- gonadotropic hormone
- belons to the same structural group of hormones as TSH, FSH and hCG
- released in pulses
- half-life app. 20 minutes
- sex steroids suppress its production
- acts through cAMP

- triggers ovulation, corpus luteum development and progesterone production in women
- stimulates in Leydig cells to produce testosterone
- synergy with FSH



Follitropin (Follicle-stimulating hormone, FSH)

- glycoprotein (35.5 kDa)
- structurally similar to LH, TSH and hCG (identical α subunit)
- half-life 3 to 4 hours
- gonadotropin interacting with LH

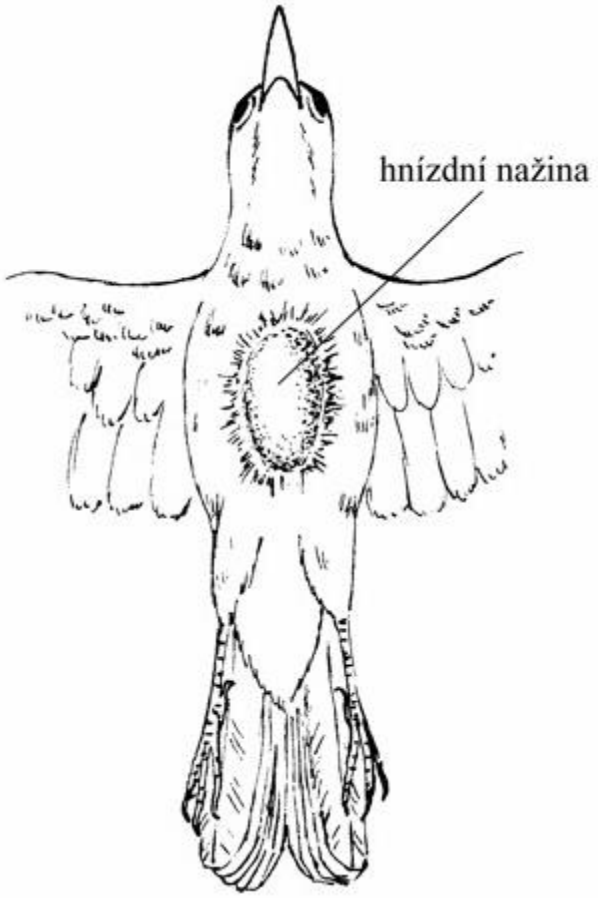
- acts through cAMP
- regulation of growth and development, sexual maturation and reproductive processes
- stimulates germ cell maturation in both males and females
- in Sertoli cells induces secretion of androgen-binding protein
- initiates growth of ovarian follicles (mitosis and production of follicular fluid)

Prolactin (PRL, lactotropin)

- homolog of growth hormone and placental lactogen
- peptide hormone with three disulfide bridges
- several isoforms (different molecular weight and glycosylation) > larger forms have lower biological activity
- secreted in pulses after eating, mating, estrogen administration, ovulation or when taking care of an offspring (activation of mechanoreceptors during breastfeeding + oxytocin)
- **primarily inhibitory regulation by dopamine** (PIH) secreted in hypothalamus

- endocrine, paracrine and autocrine effect (cytokine-like, hematopoiesis, angiogenesis)
- triggers mammary gland growth and lactation, modulates immunity, regulates growth and development in general
- maternal behavior, sexual refractory period, weak gonadotropin

Prolactin (PRL, luteotropin): action and function



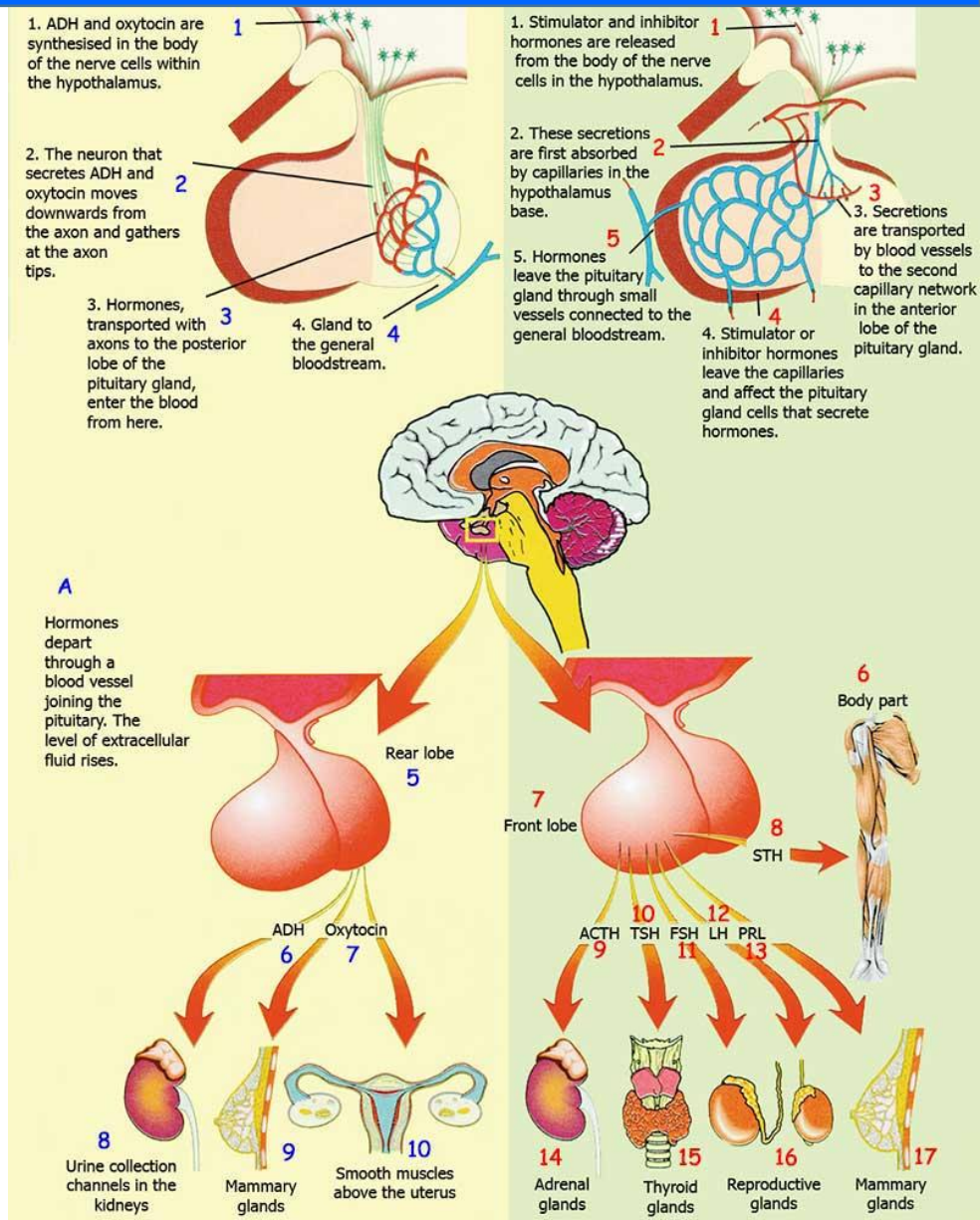
- stimulates parental behavior, production of so-called pigeon milk in crop (pigeons), or esophagus (flamingos, penguins)
- together with estrogens involved in the physiological changes before nesting

Neurohypophysis (posterior pituitary)

Hormones synthesized in hypothalamus and released to the blood in neurohypophysis.

Secreted hormone	Abbreviation	Produced by
Oxytocin	OXY or OXT	Magnocellular neurosecretory cells of the paraventricular nucleus and supraoptic nucleus
Vasopressin (antidiuretic hormone)	ADH or AVP	Magnocellular and parvocellular neurosecretory cells of the paraventricular nucleus, magnocellular cells in supraoptic nucleus

Effect
Uterine contraction Lactation (letdown reflex)
Increase in the permeability to water of the cells of distal tubule and collecting duct in the kidney and thus allows water reabsorption and excretion of concentrated urine



Superfamily of oxytocin and vasopressin neuropeptides

Vertebrate Vasopressin Family		
Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly-NH_2	Argipressin (AVP, ADH)	Most mammals
Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Lys-Gly-NH_2	Lypressin (LVP)	Pigs, hippos, warthogs, some marsupials
Cys-Phe-Phe-Gln-Asn-Cys-Pro-Arg-Gly-NH_2	Phenypressin	Some marsupials
Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Arg-Gly-NH_2	Vasotocin†	Non-mammals
Vertebrate Oxytocin Family		
Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH_2	Oxytocin (OXT)	Most mammals, ratfish
Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Pro-Gly-NH_2	Prol-Oxytocin	Some New World monkeys, northern tree shrews
Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Ile-Gly-NH_2	Mesotocin	Most marsupials, all birds, reptiles, amphibians, lungfishes, coelacanths
Cys-Tyr-Ile-Gln-Ser-Cys-Pro-Ile-Gly-NH_2	Seritocin	Frogs
Cys-Tyr-Ile-Ser-Asn-Cys-Pro-Ile-Gly-NH_2	Isotocin	Bony fishes
Cys-Tyr-Ile-Ser-Asn-Cys-Pro-Gln-Gly-NH_2	Glumitocin	skates
Cys-Tyr-Ile-Asn/Gln-Asn-Cys-Pro-Leu/Val-Gly-NH_2	Various tocins	Sharks
Invertebrate VP/OT Superfamily		
Cys-Leu-Ile-Thr-Asn-Cys-Pro-Arg-Gly-NH_2	Diuretic Hormone	Locust
Cys-Phe-Val-Arg-Asn-Cys-Pro-Thr-Gly-NH_2	Annetocin	Earthworm
Cys-Phe-Ile-Arg-Asn-Cys-Pro-Lys-Gly-NH_2	Lys-Connopressin	Geography & imperial cone snail, pond snail, sea hare, leech
Cys-Ile-Ile-Arg-Asn-Cys-Pro-Arg-Gly-NH_2	Arg-Connopressin	Striped cone snail
Cys-Tyr-Phe-Arg-Asn-Cys-Pro-Ile-Gly-NH_2	Cephalotocin	Octopus
Cys-Phe-Trp-Thr-Ser-Cys-Pro-Ile-Gly-NH_2	Octopressin	Octopus

†Vasotocin is the evolutionary progenitor of all the vertebrate neurohypophysial hormones.[37]

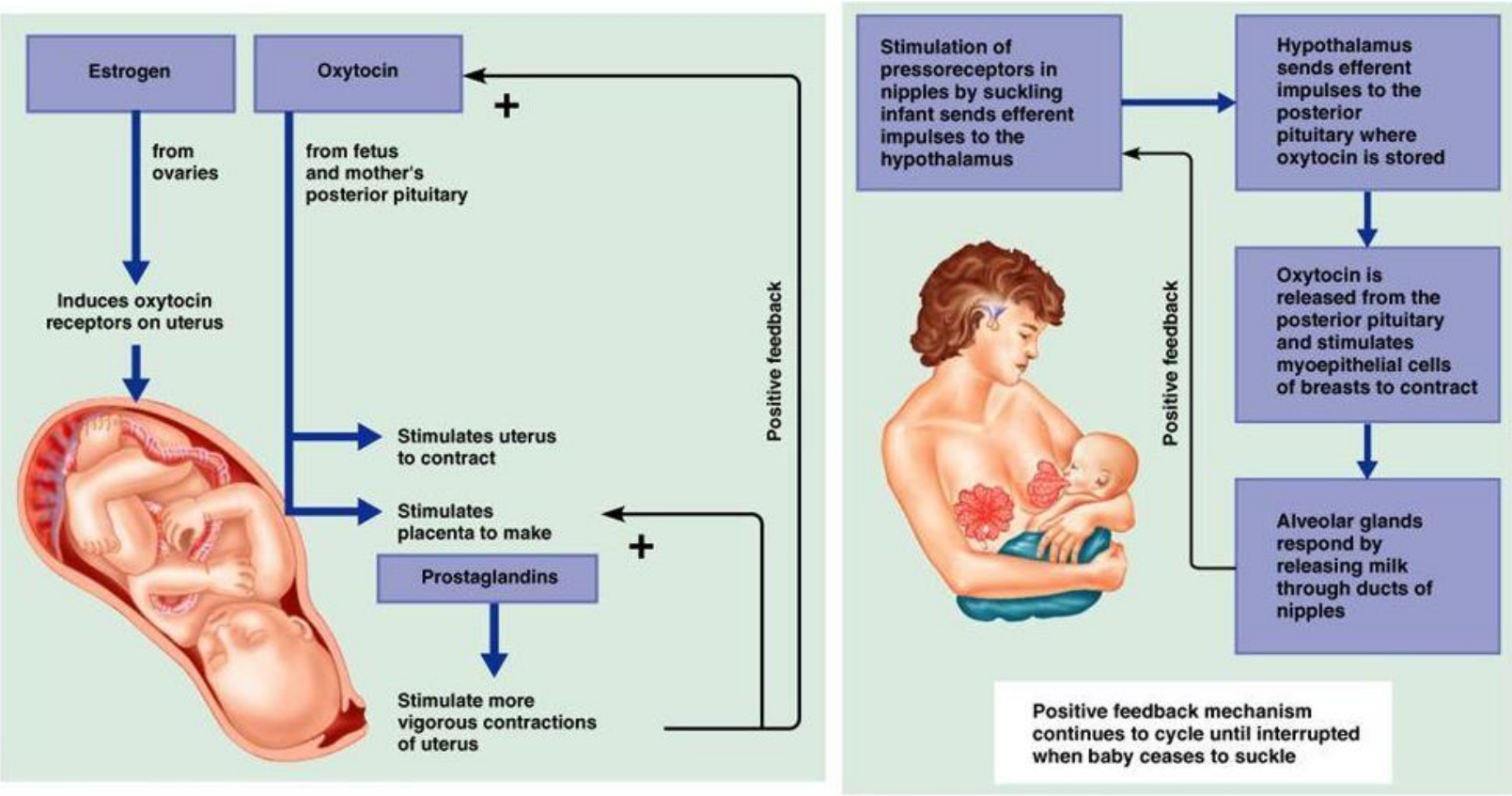
Oxytocin

- produced in hypothalamus (**nucleus paraventricularis and supraopticus**), minor synthesis in corpus luteum, placenta, Leydig cells, retina, adrenal medulla, thyroid gland and pankreas
- production induced by cervical and uterine dilation during childbirt and stimulation of nipples during breastfeeding
- gene *OXT* encodes oxytocin/neurophysin I prepropeptide > enzymatic hydrolysis to end products
- nonapeptide with disulfide bridge: Cys-Tyr-Ile-Glu-Asp-Cys-Pro-Leu-Gly

- axonal transport to the neurohypophysis, where it is stored in vesicles (Herring bodies) with **neurophysin I** (10 kDa, 90-97 AA) and ATP
- stimulus > action potential in producer neuron > axonal depolarization > exocytosis of vesicles with oxytocin

Oxytocin

- high affinity G protein-coupled receptors (rhodopsin-type, class I), e.g. on smooth muscle cells > IP_3/DAG pathway > Ca^{2+} release > musle contraction
- sucking infant stimulates mother‘s mechanoreceptors > spinal nerves > hypothalamus > higher frequency of action potentials in oxytocin producing cells > release of oxytocin into the blood > mammary gland stimulation
- acts through peripheral nerves in the brain (**hematoencephalic barrier**)



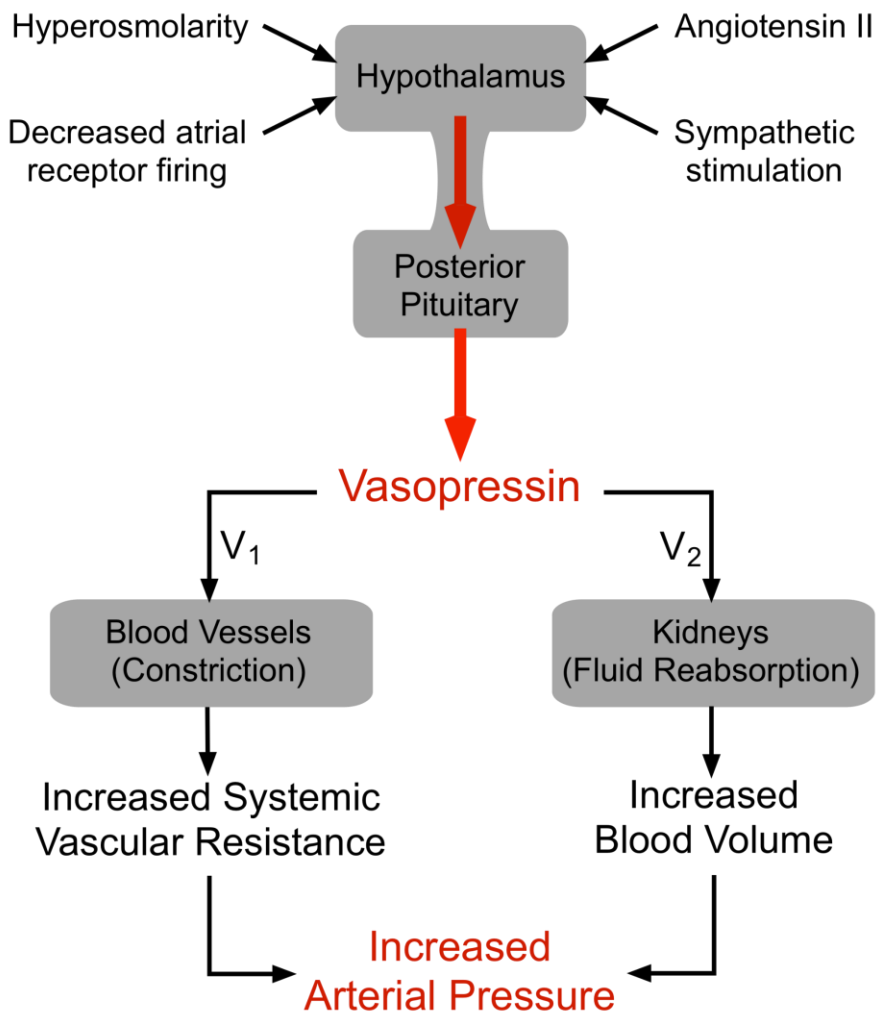
Vasopressin / antidiuretic hormone (ADH)

- also referred to as arginine vasopressin (AVP) and argipressin
- differs from oxytocin in two AA (isoleucine/**phenylalanine** at position 3, leucine/**arginine** at position 8)
- **supraoptical** and paraventricular nuclei in the hypothalamus
- released during a decrease of blood pressure and blood volume, stimulated by angiotensin II through its receptors in the hypothalamus

- stored at the ends of axons (Herring bodies) separately from oxytocin and bound to the polypeptide **neurophysin II** (19.6 kDa, 95 AA)
- released in the neurohypophysis
- half-life 16-24 minutes

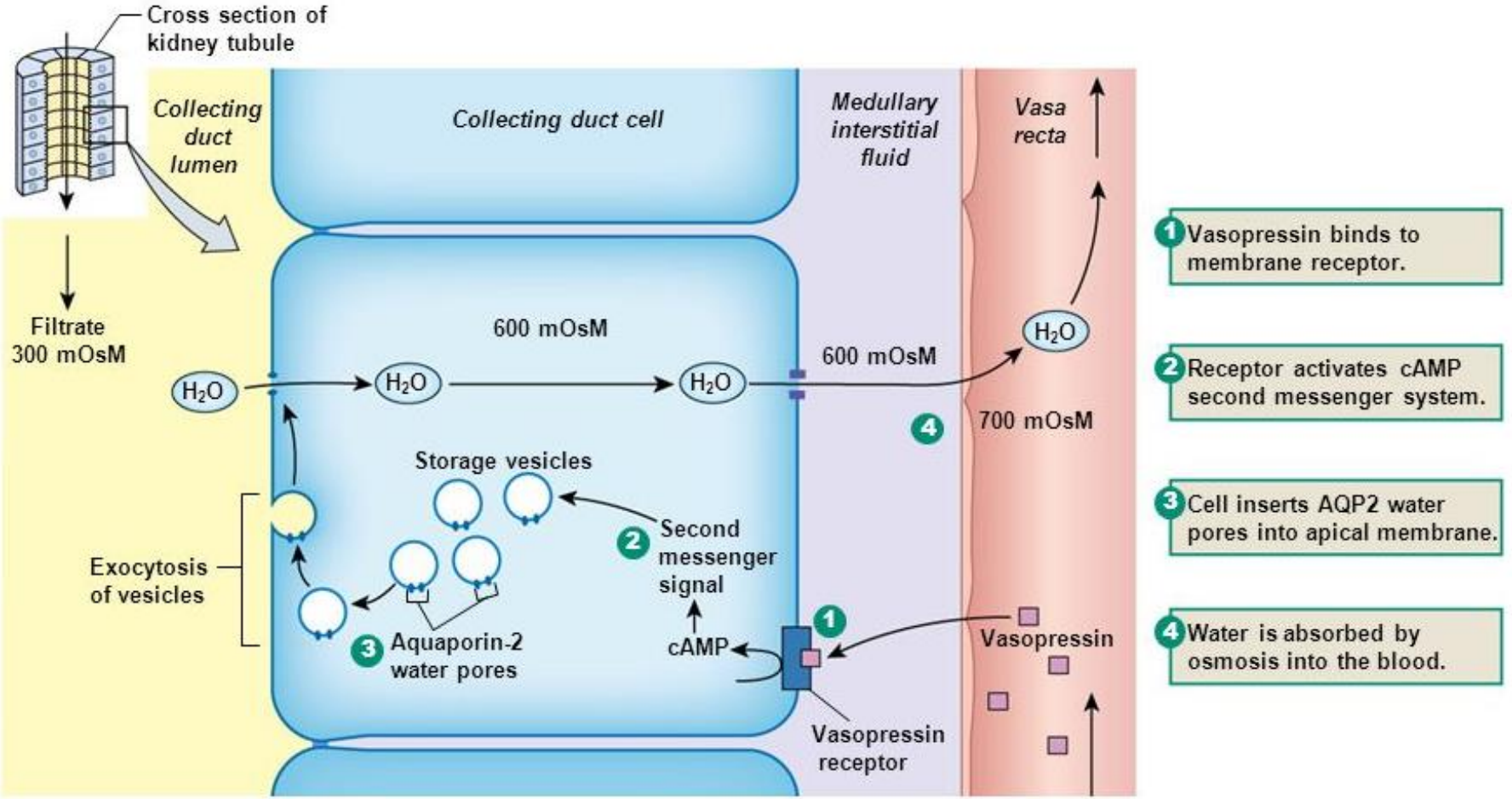
Vasopressin / antidiuretic hormone (ADH)

- targets **vasomotor activity and kidneys**, (and brain > changes in behavior)
- V_1 receptors (vascular smooth muscle) and V_2 receptors (collecting ducts)



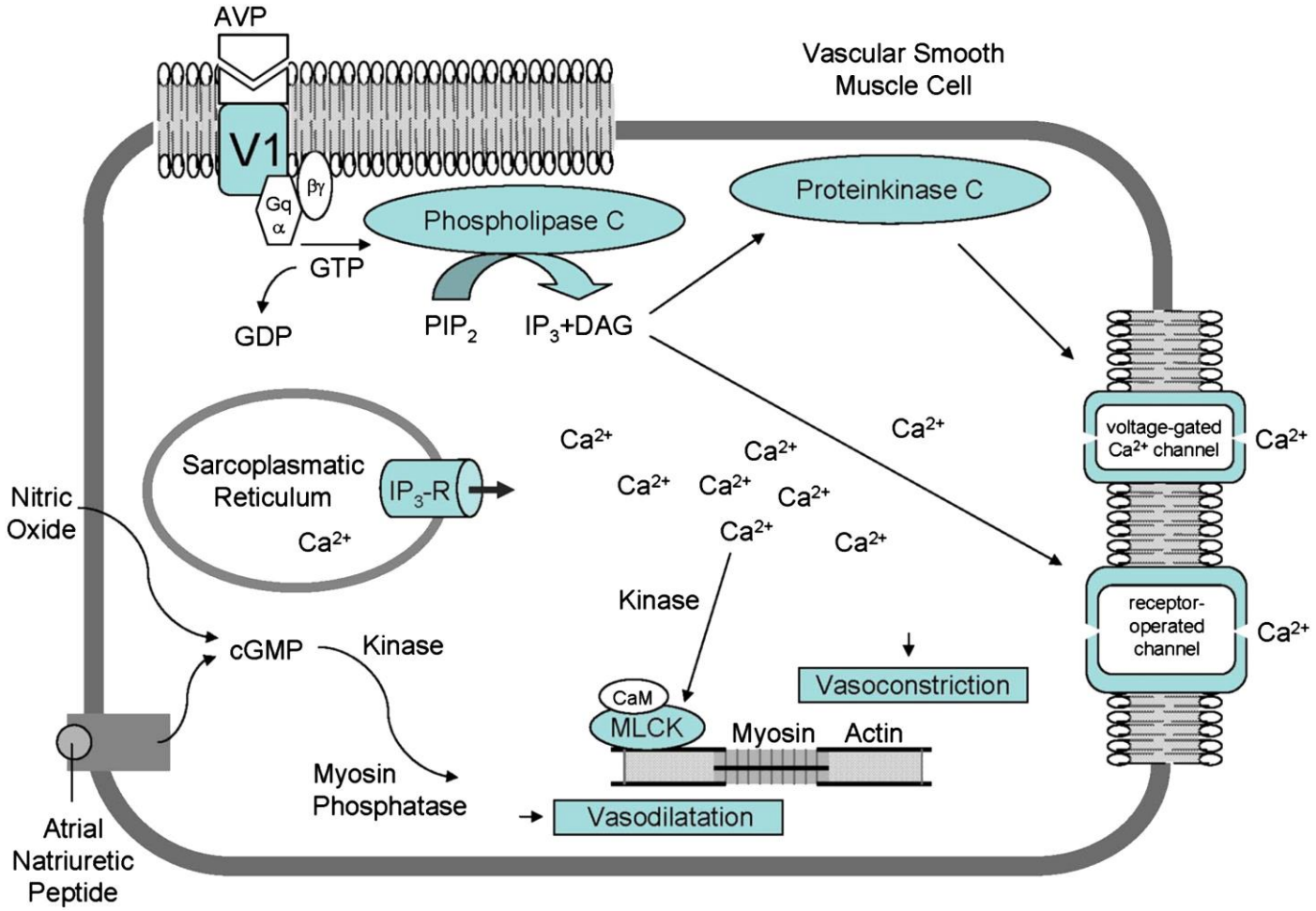
Vasopressin / antidiuretic hormone (ADH)

- G protein receptor > cAMP > translocates aquaporins to the membrane of renal ducts (+ regulation of urea transporters) > decreased urine production > increased blood volume > higher arterial pressure



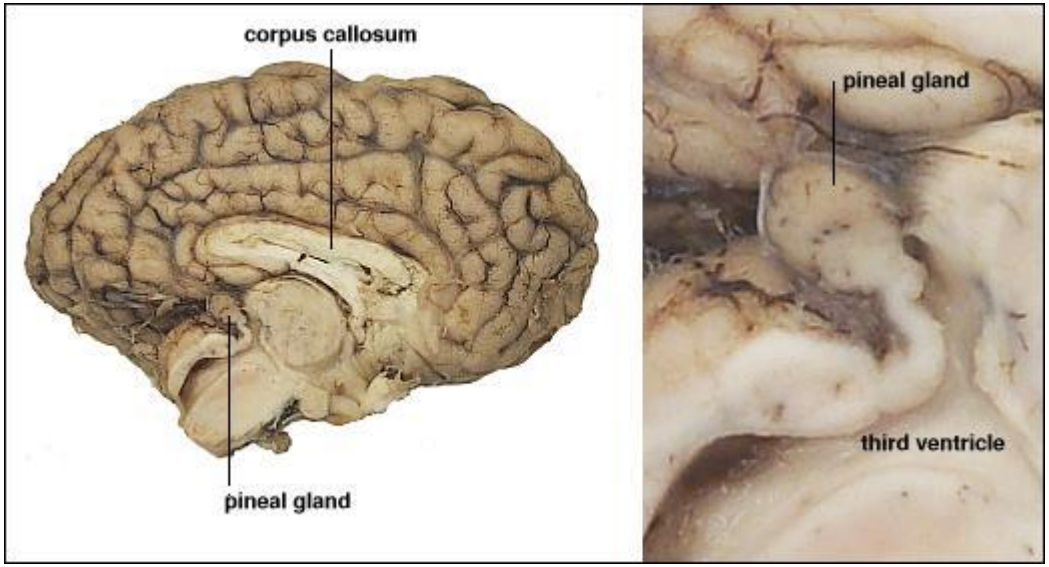
Vasopressin / antidiuretic hormone (ADH)

- G protein receptor > IP_3/DAG pathway > increase in arterial pressure
- physiological concentrations of ADH usually below vasoactive threshold (hemorrhagic shock)



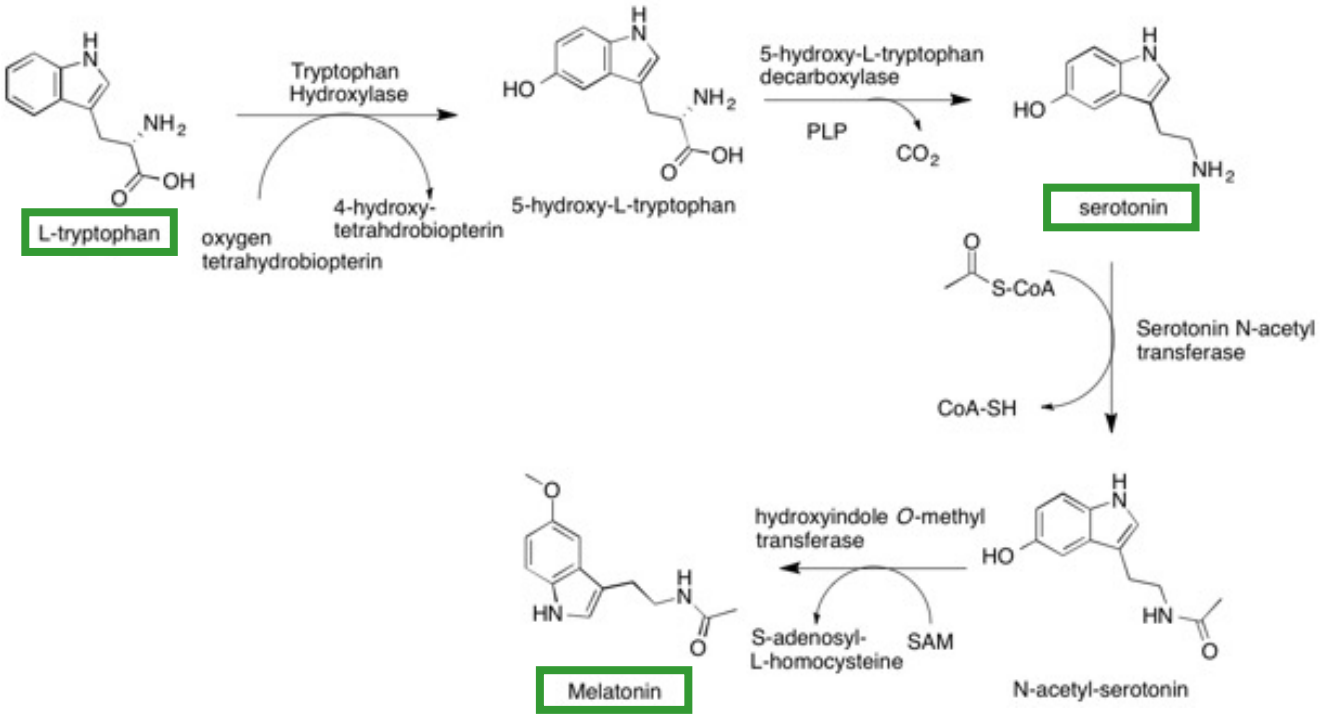
Pineal gland (corpus pineale, glandula pinealis)

- similar to a pine cone
- in epithalamus between the two brain hemispheres in contact with the third cerebral ventricle
- calcificates during aging
- evolutionarily atrophied photoreceptor (in amphibians and reptiles associated with photoreceptor organs, parietal eye of the hateria)
- produces **melatonin**
- main regulator of circadian and seasonal rhythms



Melatonin (MT)

- N-acetyl-5-methoxy-tryptamine
- serotonin N-acetyl transferase
- produced also in plants (formed in response to oxidative stress)
- synchronizing hormone (melatonin receptor) and antioxidant (protection of nuclear and mitochondrial DNA)
- derived from tryptophan, synthesis via serotonin



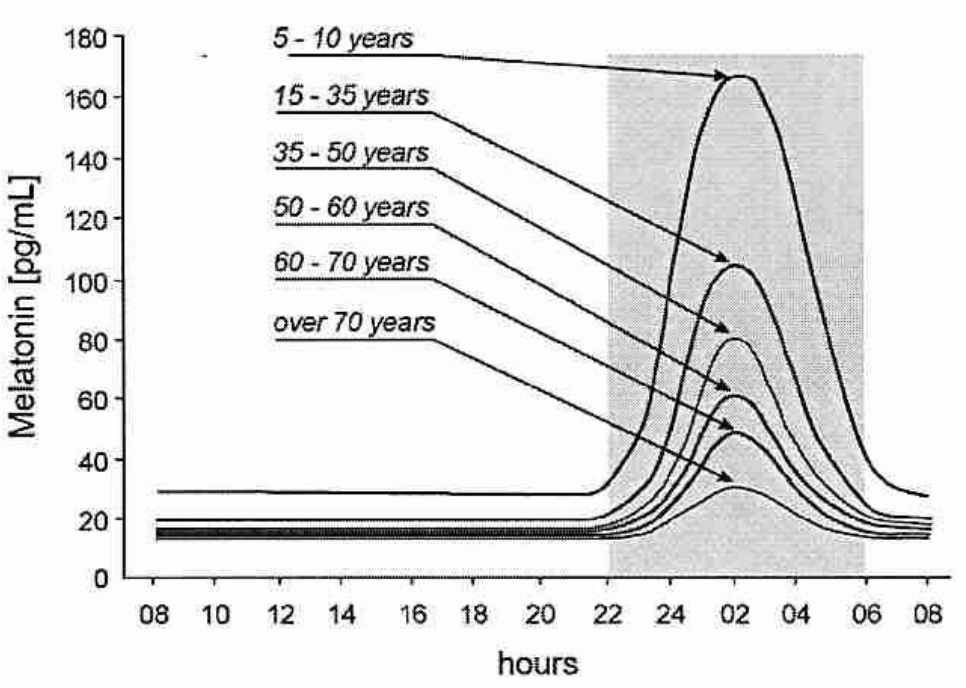
Melatonin (MT)

- passes through cell membranes
- **in the dark:**
  retinal photoreceptors > suprachiasmatic nuclei > spinal cord > sympathetic ganglia > norepinephrine stimulation > pineal gland > cAMP increase in pinealocytes > PKA > phosphorylation of serotonin N-acetyl transferase > conversion of serotonin to melatonin
- **in the light:**
  cessation of noradrenaline stimulation and rapid proteolysis of melatonin
- melatonin formation depends on the wavelength of light:
  blue light (460-480 nm) attenuates melatonin synthesis proportionally to the intensity and length of illumination

Melatonin (MT)

Synchronization of rhythms (circadian and seasonal):

- activity of nocturnal animals and sleep of diurnal species, including humans
- photoperiod and related in seasonal rhythms (behavior, reproduction, growth, color changes, etc.)



Antioxidant:

- cytosolic and nuclear receptors > activation of antioxidant enzymes such as superoxide dismutase, glutathione peroxidase and glutathione reductase)
- effective scavenger of free radicals (cascading effect)
- involved in immune processes

Melatonin (MT)