Hypothalamus and adenohypophysis

MUNI MED

Hypothalamus

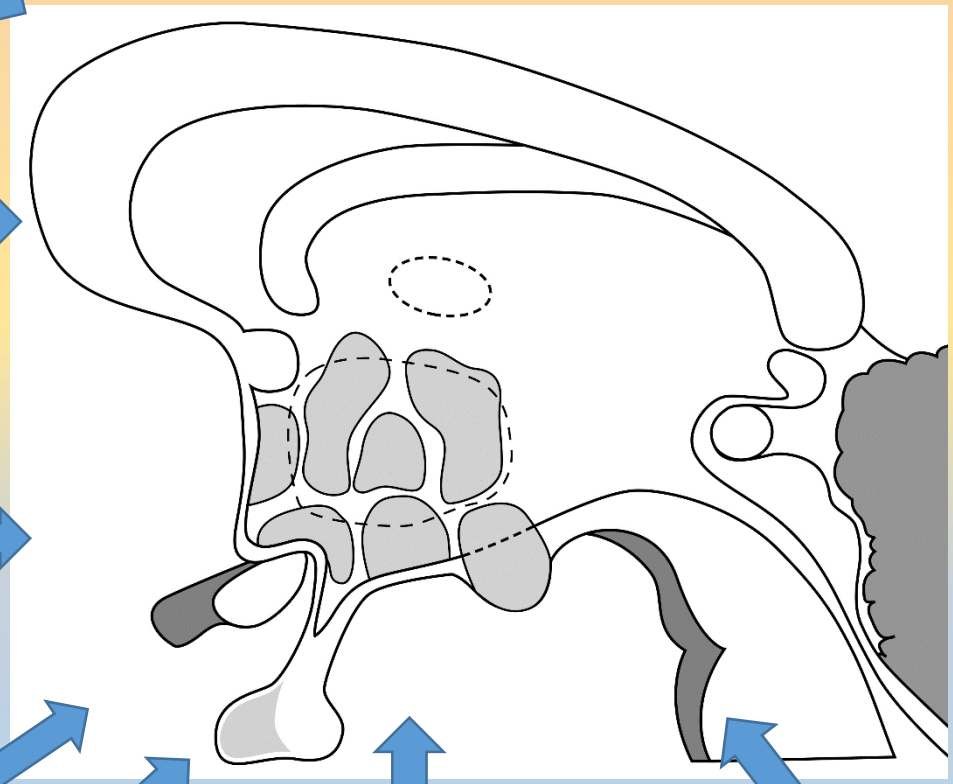
Ventrolateral medulla
(heart, stomach)

Amygdala
(associative regions of neocortex, olfactory bulb, hippocampal formation, subcortical structures including brain stem)

Hippocampus
(associative regions of neocortex, thalamus, reticular formation nuclei, etc.)

Nucleus solitarius
(viscerosensory information– heart, lungs, GIT, blood vessels – baro-/chemoreceptors)

Orbitofrontal cortex
(sensory perception, reaction to reward/punishment)



Locus coeruleus
(prefrontal cortex, N. paragigantocellularis – integration of external and autonomic stimuli – stress, panic)

Lamina terminalis
(blood, blood composition)

- Behavior
- Body temperature regulation
- Neuroendocrine regulation
- Appetitive behavior (hunger, thirst, sexual behavior)
- Defensive reactions
- Biorhythms and their regulation
- Autonomic nervous system (modulation)

Circumventricular organs

Eminentia mediana

- Afferent sensoric organ
- Functional connection of hypothalamus and hypophysis
- Point of entry of some hormones from circulation (fenestration) – leptin
- **CONVERSION - HUMORAL FACTORS – HYPOTHALAMIC REGULATION NEURONS**

OVLT

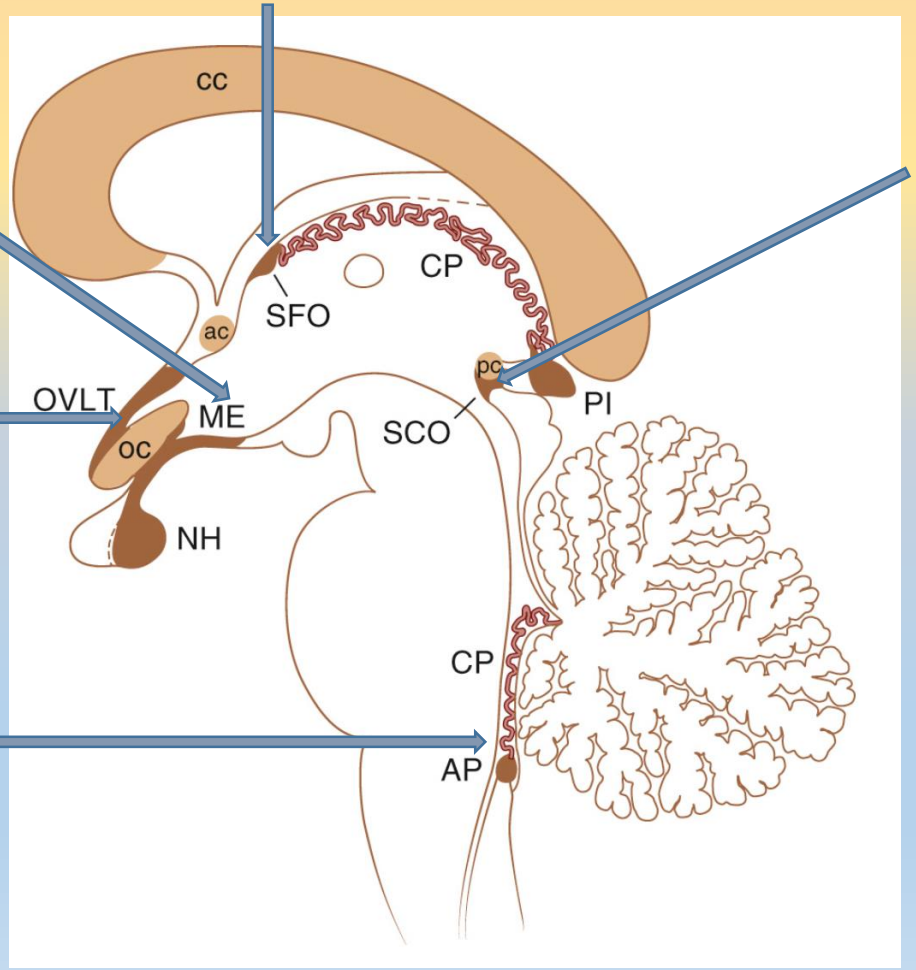
- Regulation of autonomous processes
- Febrile regulation
- Blood osmolality
- Regulation of secretion of GnRH stimulated by estrogens

Area postrema

- Afference (n. vagus, n. glossopharyn-geus)
- R for GLP-1 and amylin
- Chemosensoric neurons with osmoR
- „detection“ of toxins
- coordinated regulation of blood pressure (R for ATII, ADH, ANP)

Subfornical organ

- Body fluid homeostasis
- Blood pressure regulation (R for ANP and ATII)
- Oxytocin secretion regulation

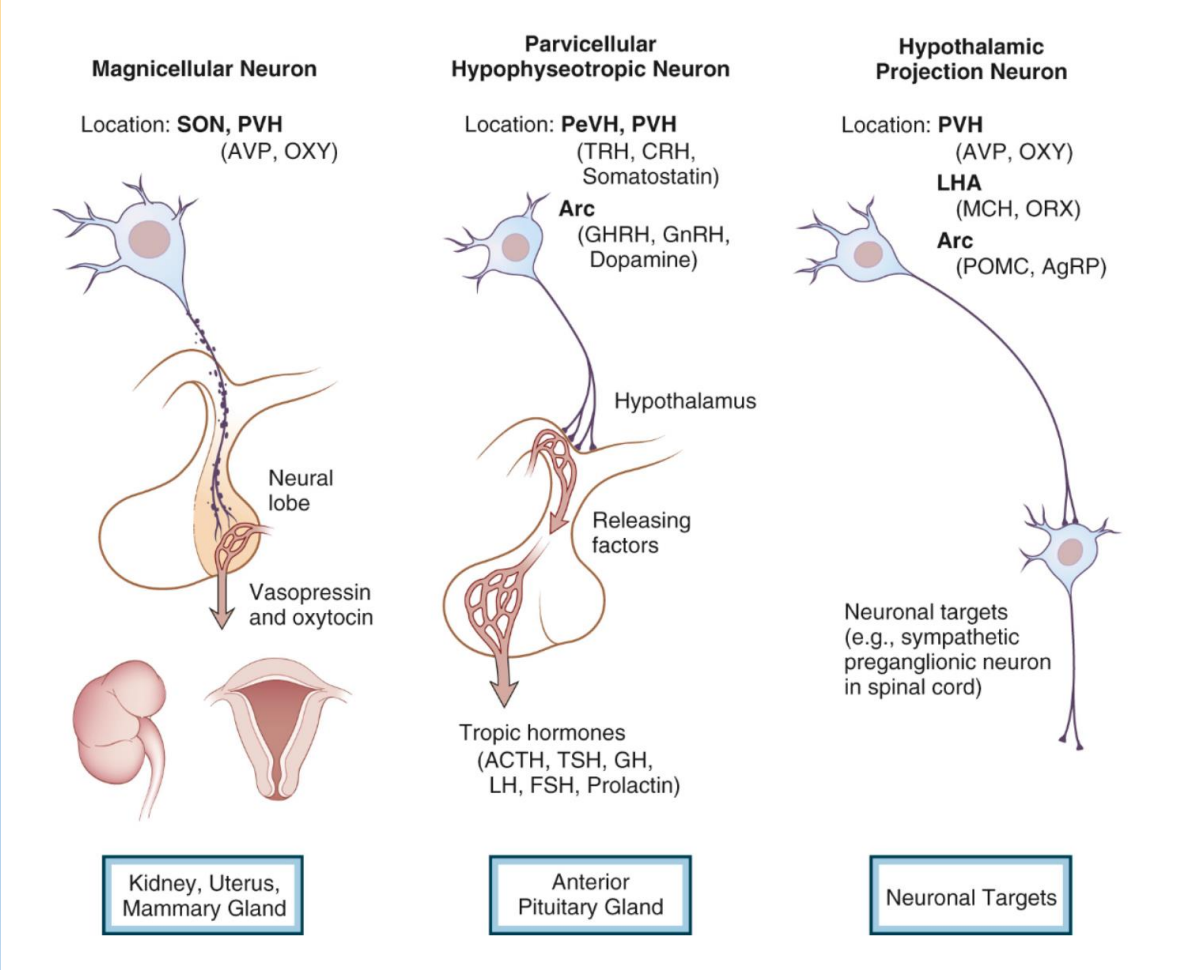


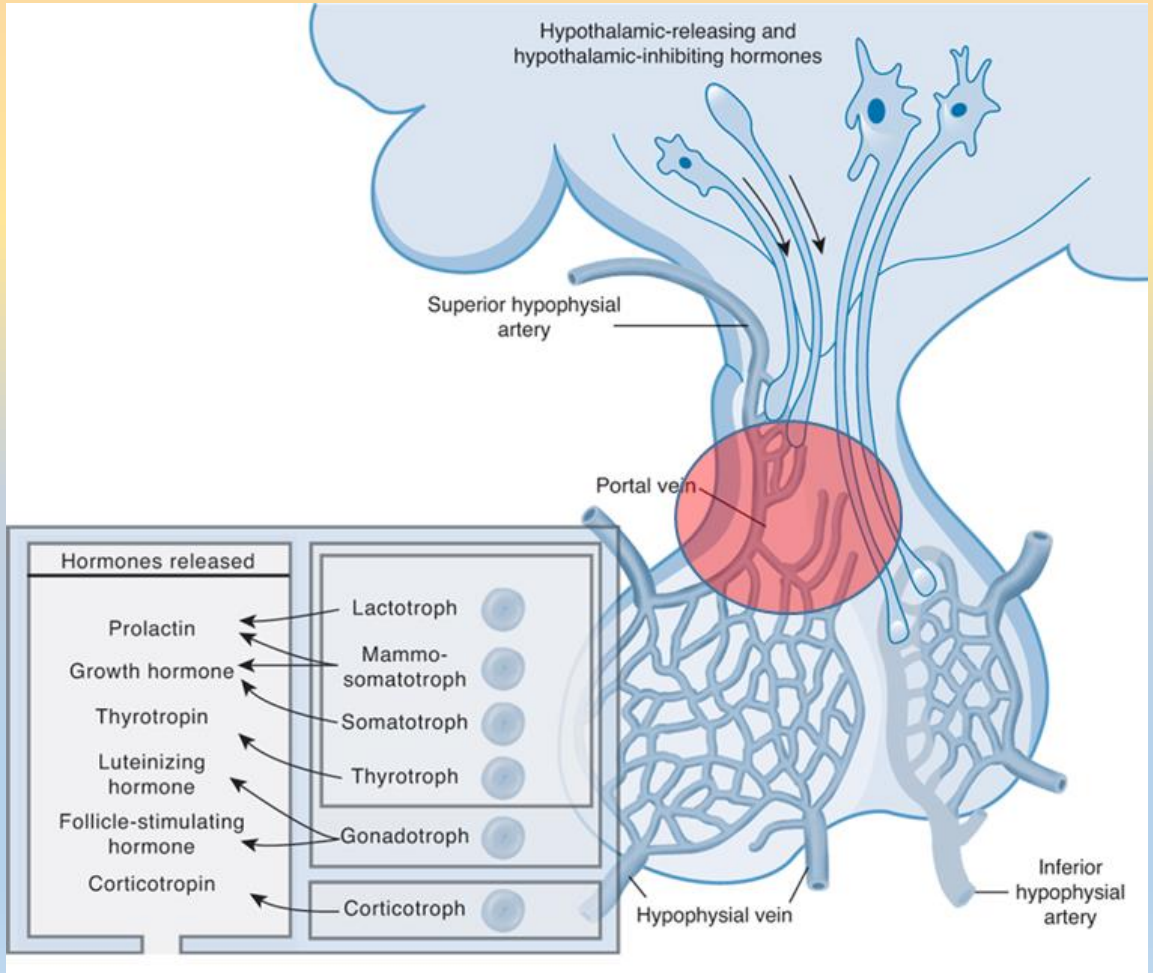
Subcommissural organ

- Mainly unknown function
- R for neuropeptides and neurotransmitters
- ? Production of somatostatin
- „catching“ of monoamines from CSF

CC – corpus calosum
OC – chiasma opticum
ac – commisura anterior
pc – commisura posterior
AP – area postrema
CP – choroid plexus
ME – eminentia mediana
NH – neurohypophysis
OVLT – organum vasculosum laminae terminalis
PI – pineal gland/epiphysis
SCO – subcommissural organ
SFO – subfornical organ

Anatomical and functional connection of hypothalamus and hypophysis, neuroendocrine secretion





Hypothalamic hormones

Hypothalamic hormones are secreted in eminentia mediana region and enter portal circulation via fenestrations

Axons of oxytocin and ADH synthesizing neurons go through eminentia mediana region. Hormones are secreted in neurohypophysis

PIH (prolactin-inhibiting hormone) = dopamine

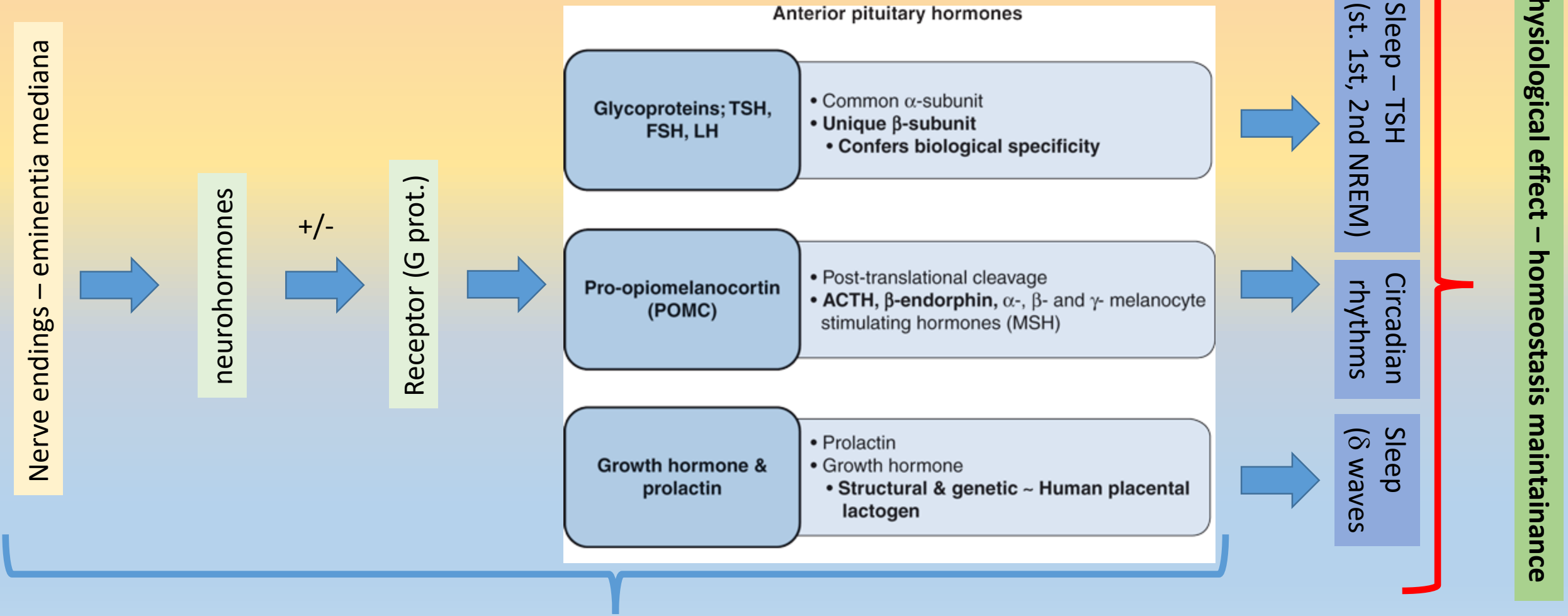
Environmental factors
Neural stimuli
Hormonal stimuli

→ Synthesis and secretion of hypothalamic hormones

Vasopressin
Cys-Tyr-Phe-Gln-Asn-*Cys*-Pro-Arg-Gly-NH_2 (MW = 1084.38)
Oxytocin
Cys-Tyr-Ile-Gln-Asn-*Cys*-Pro-Leu-Gly-NH_2 (MW = 1007.35)
Thyrotropin-Releasing Hormone
pGlu-His-Pro-NH_2 (MW = 362.42)
Gonadotropin-Releasing Hormone
pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2 (MW = 1182.39)
Corticotropin-Releasing Hormone
Ser-Glu-Glu-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Met-Ala-Arg-Ala-Glu-Gln-Leu-Ala-Gln-Gln-Ala-His-Ser-Asn-Arg-Lys-Leu-Met-Glu-Ile-Ile-NH_2 (MW = 4758.14)
Growth Hormone–Releasing Hormone
Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-NH_2 (MW = 5040.4)
Somatostatin
Ala-Gly-*Cys*-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-*Cys* (MW = 1638.12)
Vasoactive Intestinal Peptide
His-Ser-Asp-Ala-Val-Phe-Thr-Asp-Asn-Tyr-Thr-Arg-Leu-Arg-Lys-Gln-Met-Ala-Val-Lys-Lys-Tyr-Leu-Asn-Ser-Ile-Leu-Asn-NH_2 (MW = 3326.26)

Signal integration to regulate endocrine functions and to maintain hoemeostasis

Adenohypophyseal hormones



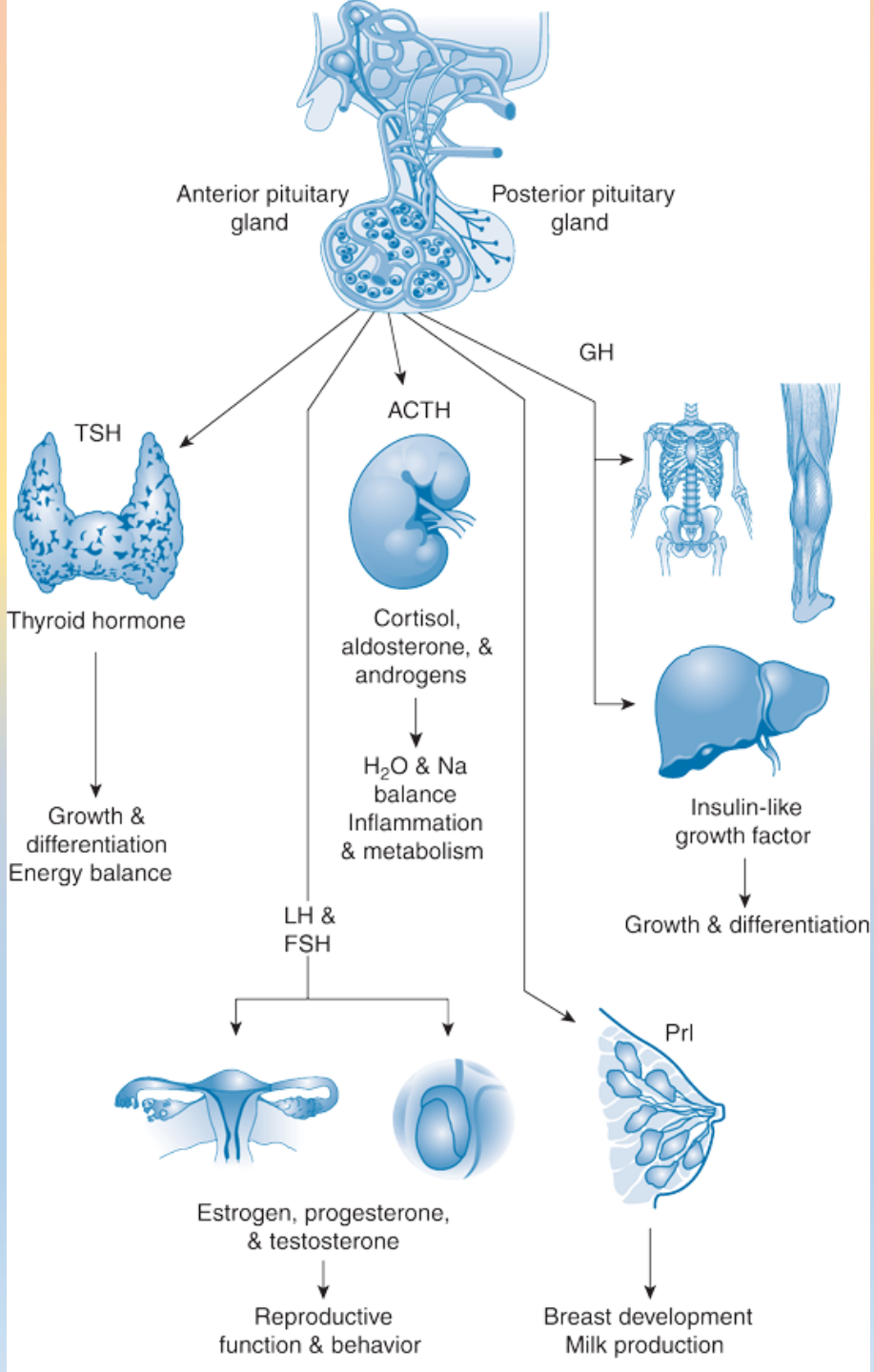
Suprachiasmatic nucleus | Circulating hormones | Feedback system

Adenohypophysis

- ACTH – adrenocorticotropic hormone
- TSH – thyroid-stimulating hormone
- GH – growth (somatotropic) hormone
- PRL – prolactin
- LH – luteinizing hormone
- FSH – follicle-stimulating hormone

Adenohypophyseal cells	Representation	Hypothalamic hormone(s)	Adenohypophyseal hormones	Localization
Lactotropic	Up to 25 %	Dopamine	prolactin	whole AH
Corticotropic	Ca 20 %	CRH	POMC – ACTH, β-LPH, α-MSH, β-end.	Anteromedial region
Thyreotropic	Ca 5 %	TRH	TSH	Anteromedial region
Gonadotropic	Up to 15 %	GnRH	LH/FSH	Posterolateral region
Somatotropic	Ca 40 %	GHRH/GHIH	GH	Posterolateral region

HORMONE PRODUCTION UNDER DIRECT HYPOTHALAMIC CONTROL



Axis GHRH/GHIH-GH-IGF-1

Somatoliberin, (GHIH, growth hormone-releasing hormone)

Characteristics
- Two types present in hypothalamus
- GHRH receptor (cAMP)
- R – homology with R secretin, GLP-1, glucagon, calcitonin, PTH, PTHrP

Hypothalamo-hypophyseal axis
- Fast GH secretion
- + estrogens, glucocorticoids and starvation
- - Somatostatin, age and obesity

Clinical significance
- Nowadays without clinical significance
- GHRP

Regulation of secretion
- stimulation
  - Ghrelin
  - Leptin
  - Galanin
  - GABA
  - α2-adrenergic and dopaminergic input
- inhibition
  - CRH
  - β2-adrenergic input

Somatostatin (GHIH, growth hormone–inhibiting hormone)

Characteristics
- Neurotransmitter – neuromodulator

Hypothalamo-hypophyseal axis
- GH secretion regulation
- TSH inhibition
- PRL and ACTH secretion inhibition

Clinical significance
- Somatostatin analogues (octreotide, lanreotide, vapreotide, seglitide, pasireotide)
- Therapy of acromegaly, TSH producing or neuroendocrine tumors
- ! Negative GIT side effects
- Imaging methods (^{111}In-somatostatin)
- Potential use in tumor treatment

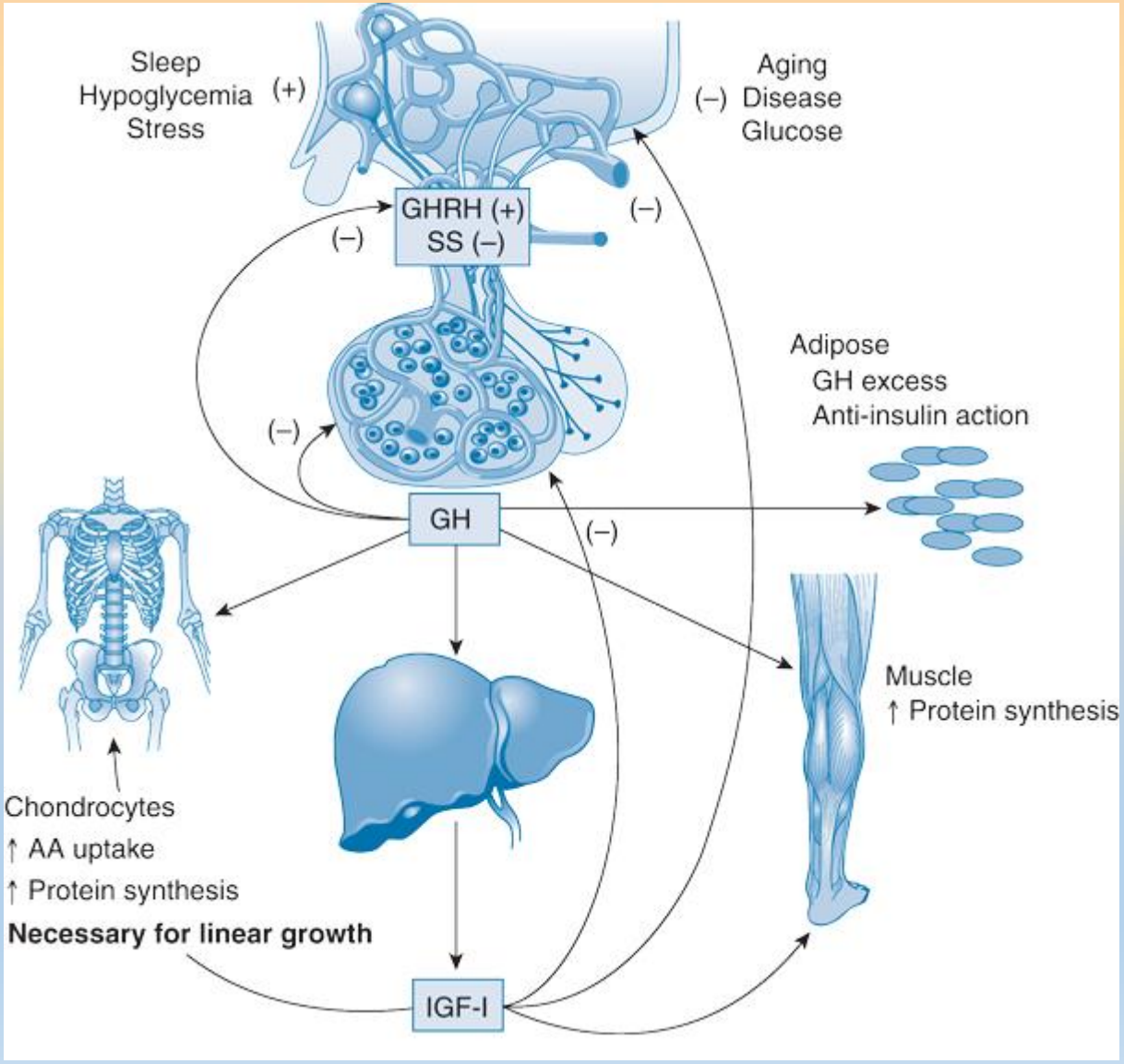
Main effects of somatostatin

Inhibition of hormone secretion	GIT inhibition	Other
Adenohypophysis – TSH, GH, ACTH, PRL	Stomach and duodenal secretion including HCl	Inhibition of activated immune cells
GIT – gastrin, secretin, motilin, GLP-1, GIP, VIP	Stomach emptying	Inhibition of tumor growth (proliferation)
Endocrine pancreas – insulin, glucagon, (somatostatin)	Pancreatic enzymes and bicarbonates secretion	
Kidneys - renin	Bile secretion	
	Decrease of GIT blood flow	
	Stimulation of intestinal water and electrolytes absorption	

Growth hormone (GH)

Characteristics
-hGH genome – 5 products including human chorionic somatomammotropin
-hGH-N – somatotrophs – 20/22 kDA
-hGH-V – placenta – feedback regulation
-Circulating GH:
- 20 (25 %) and 22 kDA (75 %) monomers
- Acetylated 22 kDA form
- Deaminated forms

Regulation of secretion
-GHRH, somatostatin, ghrelin, IGF-1, thyroid hormones, glucocorticoids
-Relatively complicated system of regulation based on:
- Neuropeptides
- Neurotransmitters
- Endogenic opioids



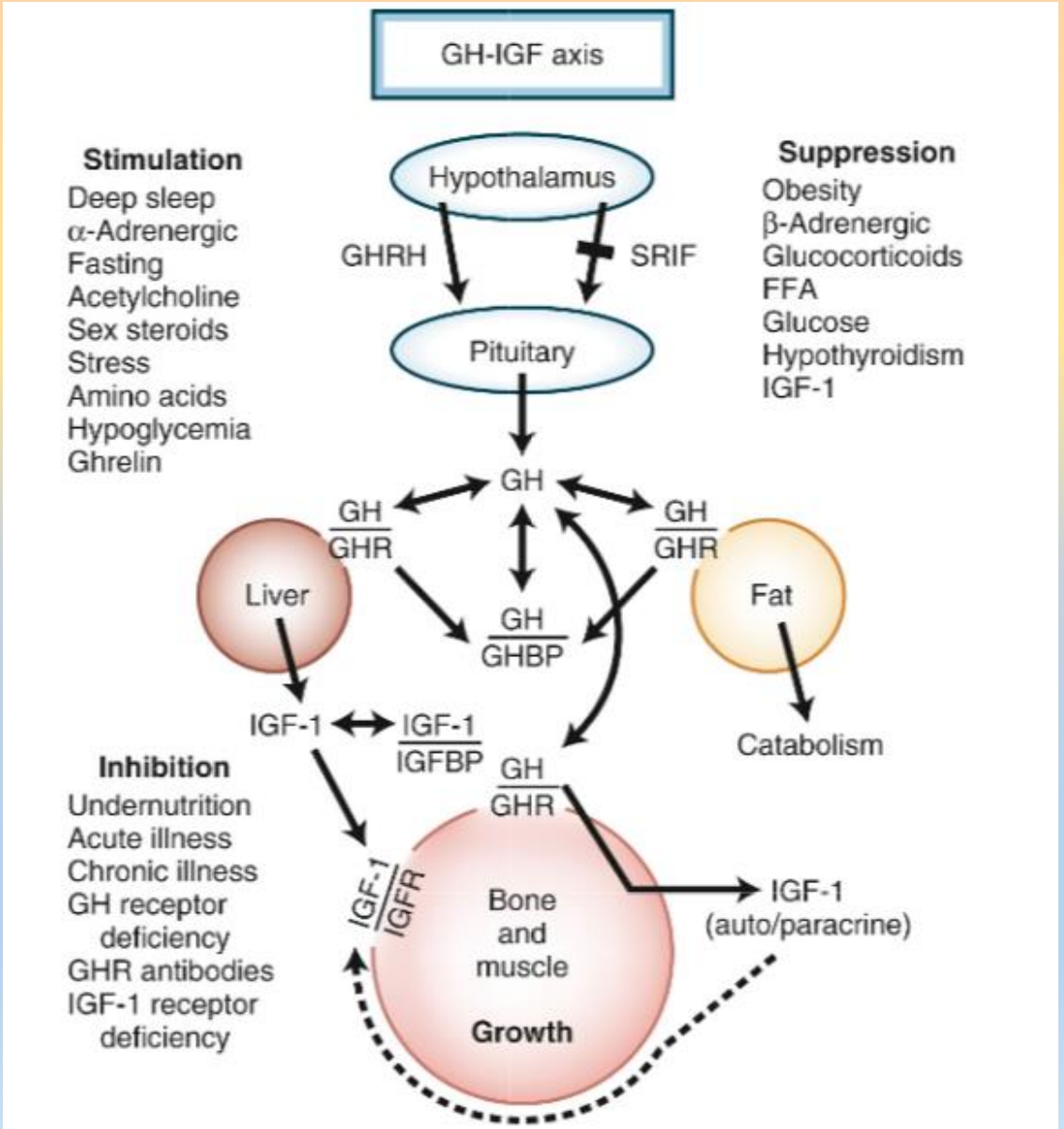
Growth hormone (GH) – regulation of secretion

- GHRH (continual), somatostatin (pulsatile secretion)
- Desensitization of R for GHRH
- IGF-1 - somatostatin

- Ghrelin
  - GHS receptors – stimulation of GHRH secretion
  - Synthesis – stomach and CNS, regulation of food intake

- Diurnal rhythm with maximum during sleep (first episode of slow-wave sleep)
- Very low basal secretion, decrease with age (peak in puberty, then decrease)

Interval	Young Adult	Fasting	Obesity	Middle Age
24-h secretion (μg/24 h)	540 ± 44	2171 ± 333	77 ± 20	196 ± 65
Secretory bursts (number in 24 h)	12 ± 1	32 ± 2	3 ± 0.5	10 ± 1
GH burst (μg)	45 ± 4	64 ± 9	24 ± 5	10 ± 6



Stimulation of GH secretion - overview

Physiological factors	Hormones and neurotransmitters	Pathological factors
Exercise	Arginin, lysin	Acromegaly
Stress (various causes)	Neuropeptides (ghrelin, GHRH, galanin, opioids – μ receptors, melatonin)	TRH, GnRH
Sleep	Neurotransmitters (agonists α2-AR, antagonists β-AR, M1 agonists, 5-HTD1 agonists, H1 agonists)	Glu, Arg
Decrease in postprandial glycemia	GABA	IL-1, 2, 6
Starvation	Dopamine (D2R)	Protein depletion
Insulin-induced hypoglycemia	Estrogens	Starvation, anorexia nervosa
	Testosterone	Kidney failure
	Glucocorticoids (acute, not chronic)	Liver cirrhosis
		DM 1st type

Inhibition of GH secretion

Physiological factors	Hormones and neurotransmitters	Pathological factors
Postprandial hyperglycemia, glucose infusion	Somatostatin	Acromegaly
Increased FAA in plasma	Calcitonin	L-DOPA
Increased GH concentration in plasma	Neuropeptide Y	D2R agonists
Increased IGF-1 concentration in plasma	CRH	Phentolamin
REM sleep	Neurotransmitters (α1,2-AR antagonists, β-AR agonists, H1 antagonists, serotonin receptor antagonists, nicotine cholinergic receptor agonists)	Galanin
Aging	Glucocorticoids (chronic)	Obesity
		Hypothyroidismus
		Hyperthyroidismus

GH and interaction with other hormonal axes

ACTH – Glucocorticoids
- Acute (+) – effect after ca 3 hours
- Chronic (-)

TRH – TSH – thyroid hormones
- Necessary for GH secretion
- Hypothyroidismus (-)

GnRH – FSH a LH – sex hormones
- Testosterone (+)
- Estrogens (+) – only p.o. – decreased inhibition of IGF-1 + feedback
- aromatization of androgens affects GH synthesis and secretion (paracrine effect of estrogens in CNS)

GH and its effects

METABOLIC

-Energetic metabolism

-Together with insulin (metabolism of sugars, fats, proteins)

-Lipolysis and FA oxidation(+) (hormone-sensitive lipase, + LDL)

-Glucose – direct or indirect effect,

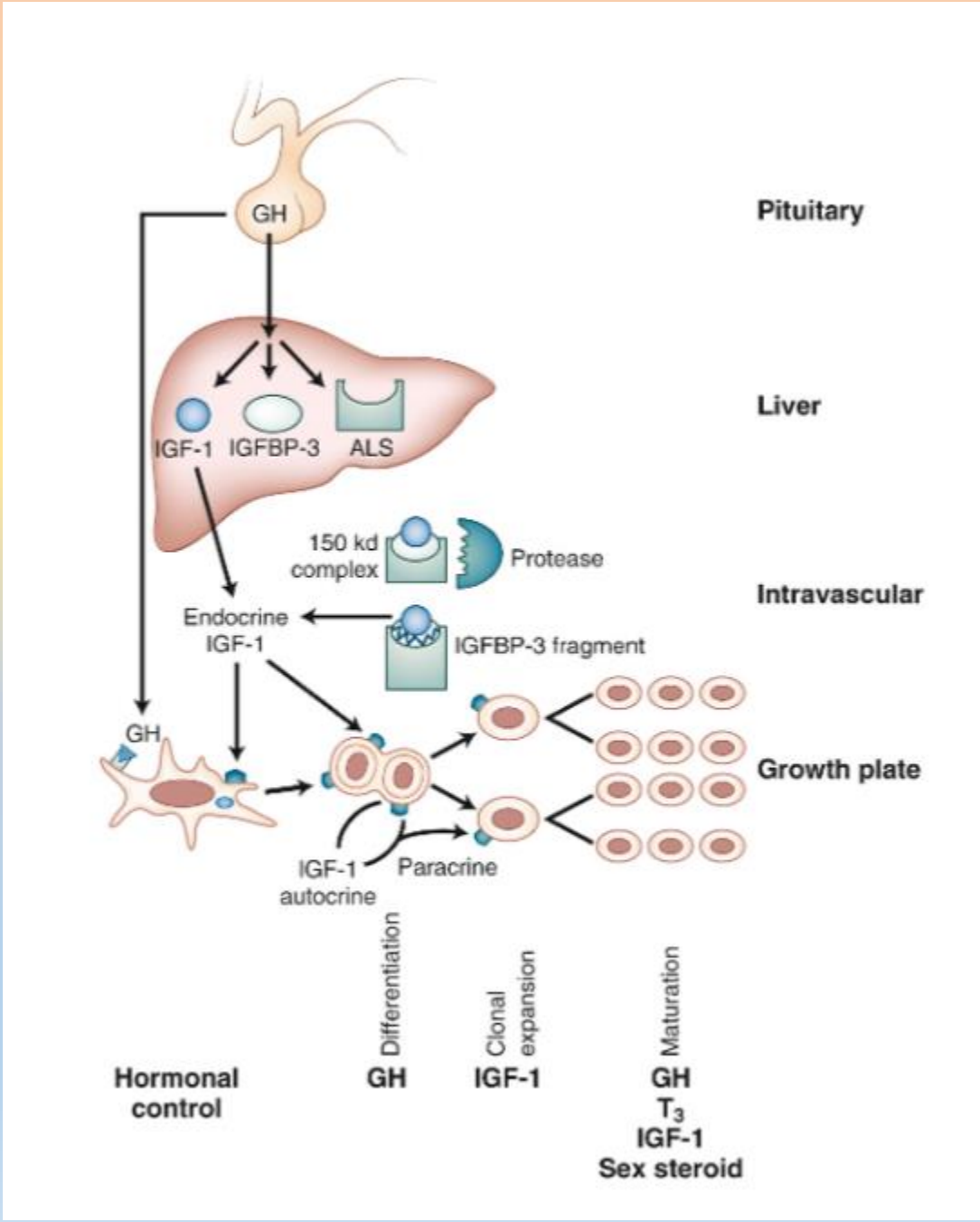
- (+) uptake of Glu
- (-) Glu oxidation
- (+) gluconeogenesis

-Proteins

- (+) anabolism, (-) urea
- (+) AA transport
- (+) incorporation of AA to proteins
- (-) protein oxidation

GROWTH

-Mediated by IGF-1 (auto-/paracrine)



GH – clinical aspects

GH deficiency – gained or congenital – often tumors or inflammation

- nonspecific symptoms (i.e. loss of energy, social isolation, loss of focus)
- myocardium changes (left ventricle)

GHR – mutation

Significance of **markers** (IGF-1, IGFBP3)

Substitution therapy – wide array of side-effects, contraindication – cancer

Experimental indications:

- catabolic states (i.e. extensive burns)
- osteoporosis
- HIV/AIDS
- sport medicine, aging

Axis PIH-prolactin

PIH, prolactin-inhibiting hormone

Characteristics
- dopamine

Hypothalamo-hypophyseal axis
- Inhibition of PRL (D2R) secretion – lactotropic cells
- ! Lactotrophs with continual high PRL production
- Paracrine and autocrine regulation of PRL secretion

Other functions and places of synthesis
- Blood vessels – vasodilatation (physiological concentrations)
- Kidneys – sodium secretion
- Endocrine pancreas – decrease in insulin secretion
- GIT – lower motility
- Effect of dompamine on immune system

Clinical significance
- Effect of medication on dopamine and PRL secretion
- Neurodegenerative diseases (Parkinson)
- Antipsychotics (antag.)

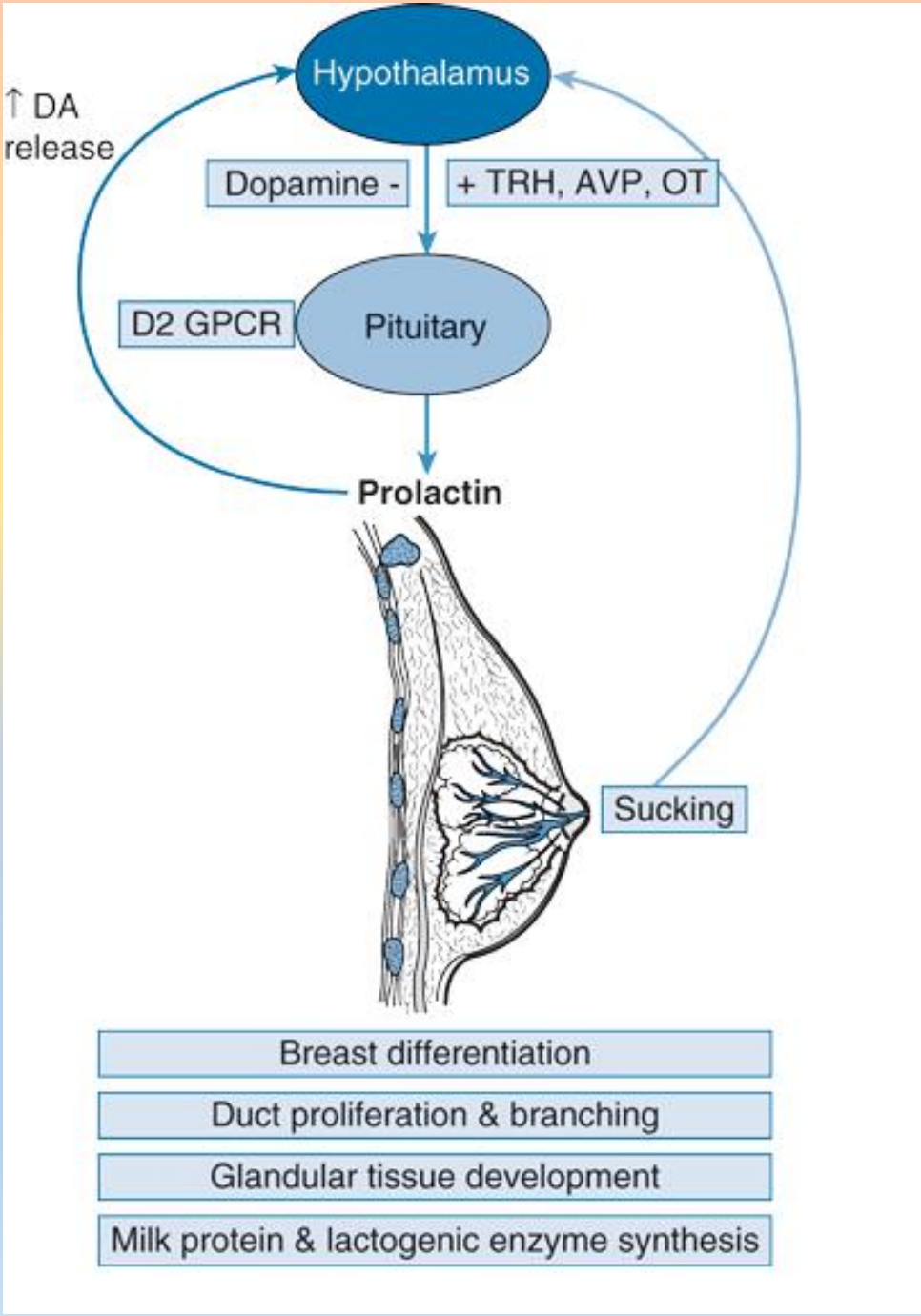
PROLACTIN-RELEASING FACTORS (PRF)
- TRH, oxytocin, VIP
- under specific conditions ADH, ATII, NPY, galanin, substance P, GRP, neurotensin
- *prolactin-releasing peptide* (PrRP) – stress, satiety (other parts of CNS)

- Important feedback mechanism (short loop) of PRL secretion regulation
  - Circadian rhythm (maximum in the morning)
  - Nipple stimulation (1-3 min, peak 10 – 20 min)

Prolactin - PRL

Characteristics
- Lactotropic cells (only PRL)
- Mammosomatotropic cells (PRL and GH)
- Hyperplasia – pregnancy and lactation
- Expression regulated by estrogens, dopamine, TRH, thyroid hormones
- PRLR – mammary gl., adenohypophysis, adrenal gl., liver, prostate, ovaries, testicles, small intestine, lungs, myocardium, SNS, lymphocytes

Regulation of secretion
- Pulsatile secretion – 4 – 14 pulses/day
- Highest levels during sleep (REM, nonREM)
- Lowest between 10:00 and 12:00
- Lower secretion with aging
- TIDA cells – dopamine Paracrine – endothelin-1, TGF-β1, calcitonin, histamine (-)
- FGF, EGF (+)
- TRH, estrogens, VIP, serotonin, GHRH in higher concentrations (+)
- Cholecystokinin - ?



Prolactin - functions

Production of breast milk during pregnancy and lactation = function necessary for survival

Other functions – metabolic, melatonin synthesis, maternal behavior

Development of mammary gland and lactation

- Puberty – development of mammary gland due to GH and IGF-1
- Effect of estrogens and progesterone
- At age 8 – 13
- During pregnancy proliferation of alveoli and production of breast milk proteins and colostrum
- During third trimester – colostrum production (PRL, estrogens, progesterone, GH, IGF-1, placental hormones)
- Lactation – increase of PRL after birth, without breast-feeding decrease after ca 7 days
- Accumulation of breast milk stops further production
- Role of OT

Reproductive function of PRL

- Lactation = amenorrhea and secondary infertility
- Inhibition of GnRH secretion
- Role of kisspeptin neurons (PRLR)
- Possible role of metabolic factors

Immune function of PRL

- Antiinflammatory effect ?

Clinical significance

- hyperprolactinemia – drugs including some antihypertensives, chronic kidney failure
- Macroprolactinemia
- Galactorrhea – role of GH (acromegaly)
- PRL deficiency

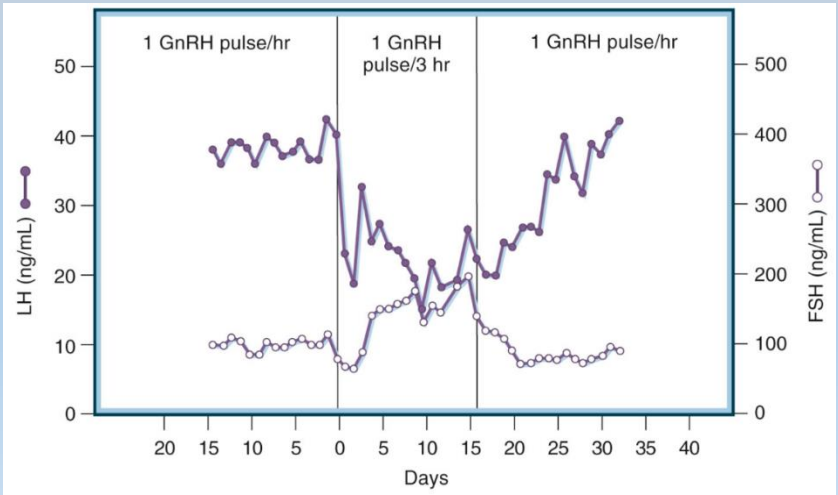
Axis GnRH-LH/FSH-gonads

GnRH, Gonadotropin-Releasing Hormone, GnIH

Characteristics
- Specific origin of GnRH neurons outside of CNS
- Downregulation – malnutrition, lactation, seasonal effects, aging, continual GnRH
- Upregulation – effect of GnRH on gonadotrophs (menstrual cycle)

Hypothalamo-hypophyseal axis
- FSH, LH
- Importance of GnRH pulses frequency (glycosylation)
- Menstrual cycle, puberty and its onset

Clinical significance
- Continually distributed analogues of GnRH – treatment of estrogen/steroid-dependent tumors of reproductive system
- Premature puberty treatment (leuprorelin – agonist!)



Regulation of secretion

- Inputs from various CNS regions (brain stem, limbic system)
- Inhibitory effect of sex-hormones with exception of estradiol (negative/positive feedback)
- Importance of kisspeptin for females
- Inhibitory effect of PRL
- Effect of circulating substrates (FA, Glu)
- Leptin (NPY, kisspeptin)

- Stress (various causes)
  - Acute – disruption of MC without effect on fertility
  - Chronic – disruption of fertility, lowering of circulating sex-hormones levels

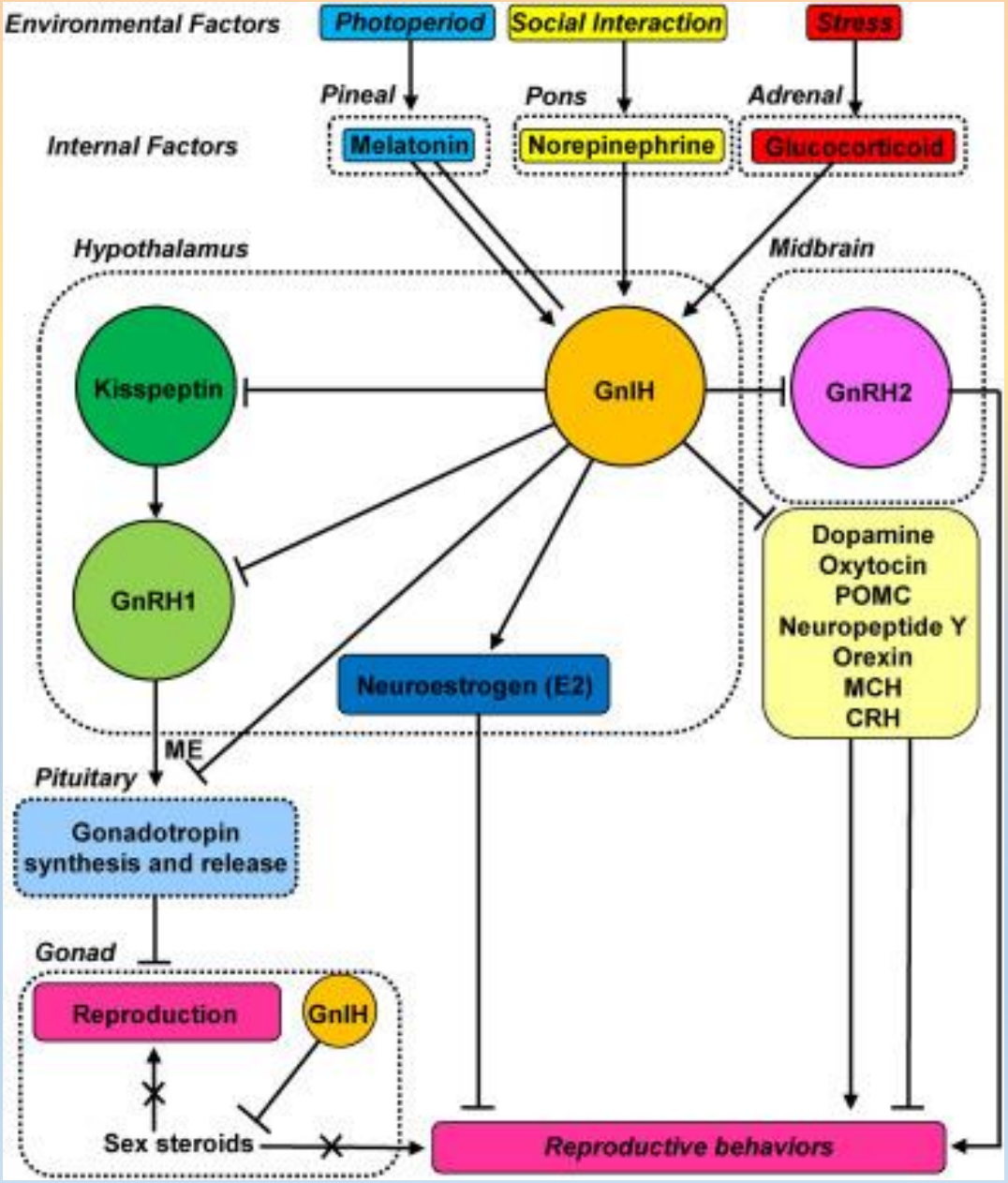
GnIH, Gonadostatin

Characteristics

- Discovered in 2000
- Dorsomedial nucleus of the hypothalamus
- Projection to the eminentia mediana
- Binding to GnIH receptor (hypothalamus, adenohypophysis, ovary)
- Differential secretion during the ovarian cycle

Functions

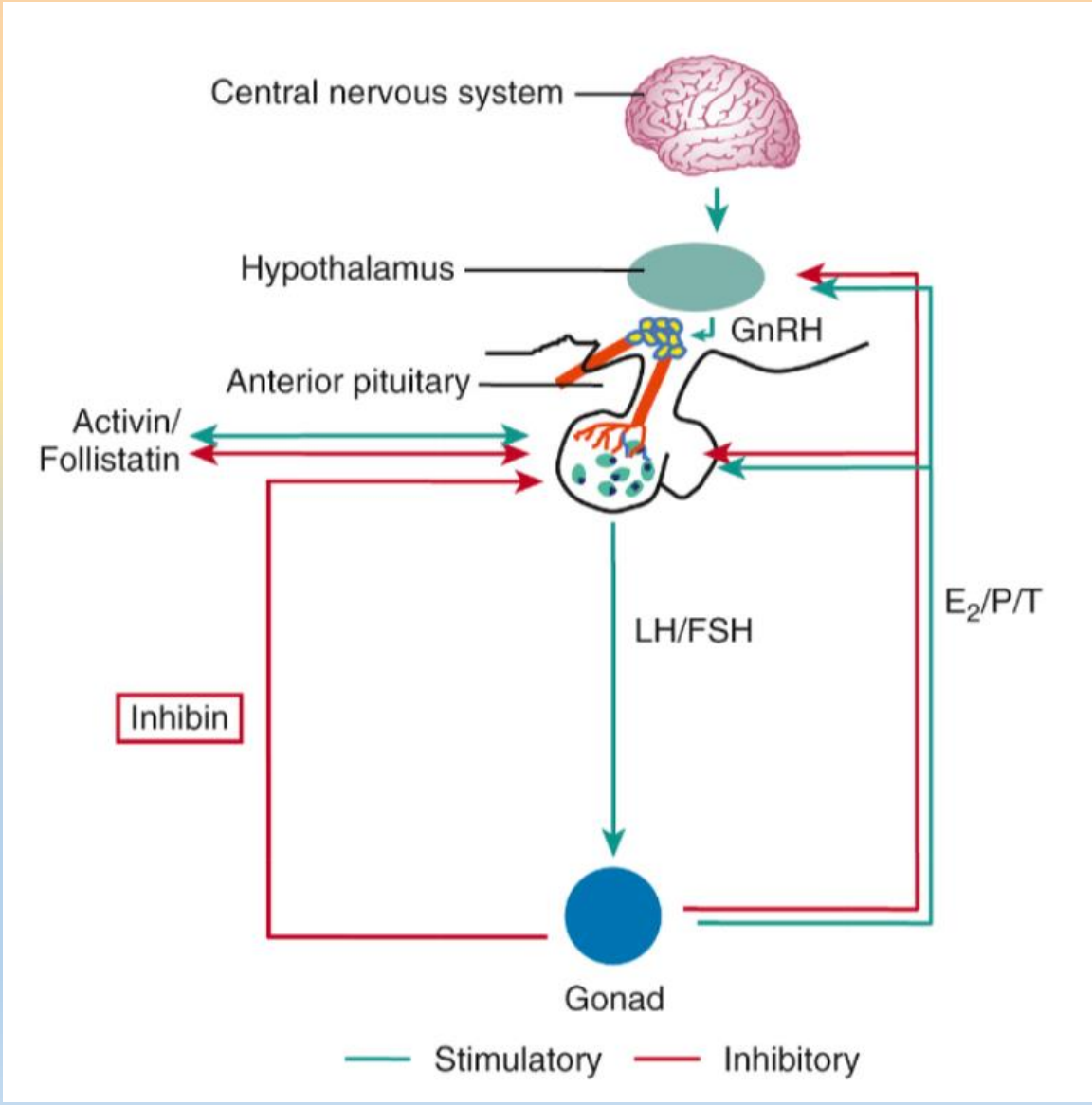
- Regulation of the reproduction axis, including the onset of puberty
- Regulation of the reproduction behaviour
- Regulation of some CNS functions (neurotransmitter synthesis)



Glycoproteins – FSH a LH

Characteristics
- Heterodimer, different expression of subunits, glycosylation
- Structurally close to hCG (placenta)

Regulation of secretion
- sex hormones, local factors – paracrine (activins, inhibins, follistatin)
- (+) – glutamate, noradrenaline, leptin
- (-) – GABA, opioids
- Key role of kisspeptins, neurokinin B and substance P in GnRH secretion – FSH/LH
- Estrogens, progesterone, androgens – direct effect on gonadotrophs, indirect through GnRH
  - Estrogens (-) – inhibition of transcription (α)
  - Kisspeptin – stimulation of LH/FSH, GnRH
  - Estrogens (+) shift
  - Progesterone (-) – influences pulsatile secretion of GnRH
  - Testosterone, estradiol (-) – males, kisspeptin neurons and AR
- GnRHR – Ca^{2+} mobilization
- Different half-life for circulating LH and FSH



FSH and LH functions

FEMALES
- FSH
  - Growth and development of follicular cell (maturation)
  - Biosynthesis of estradiol
  - Regulation of inhibin synthesis during follicular phase
  - Upregulation of LH receptors (preovulatory follicles)
  - Selection of dominant follicle
  - Recruitment of follicles for next cycle
- LH
  - Stimulation of estrogen synthesis (theca)
  - Oocyte maturation (preovulatory follicle)
  - Rupture of ovulatory follicle, ovulation
  - Conversion of follicle wall to corpus luteum

MALES
- LH
  - Intratesticular synthesis of testosterone (Leydig cells)
- FSH
  - Spermatogenesis (Sertoli cells)

Clinical significance
- Possible deficiency of gonadotropins
- Hypogonadotropic hypogonadism
- Kallmann syndrome
- Syndrome Prader-Willi
- Reproductive dysfunction

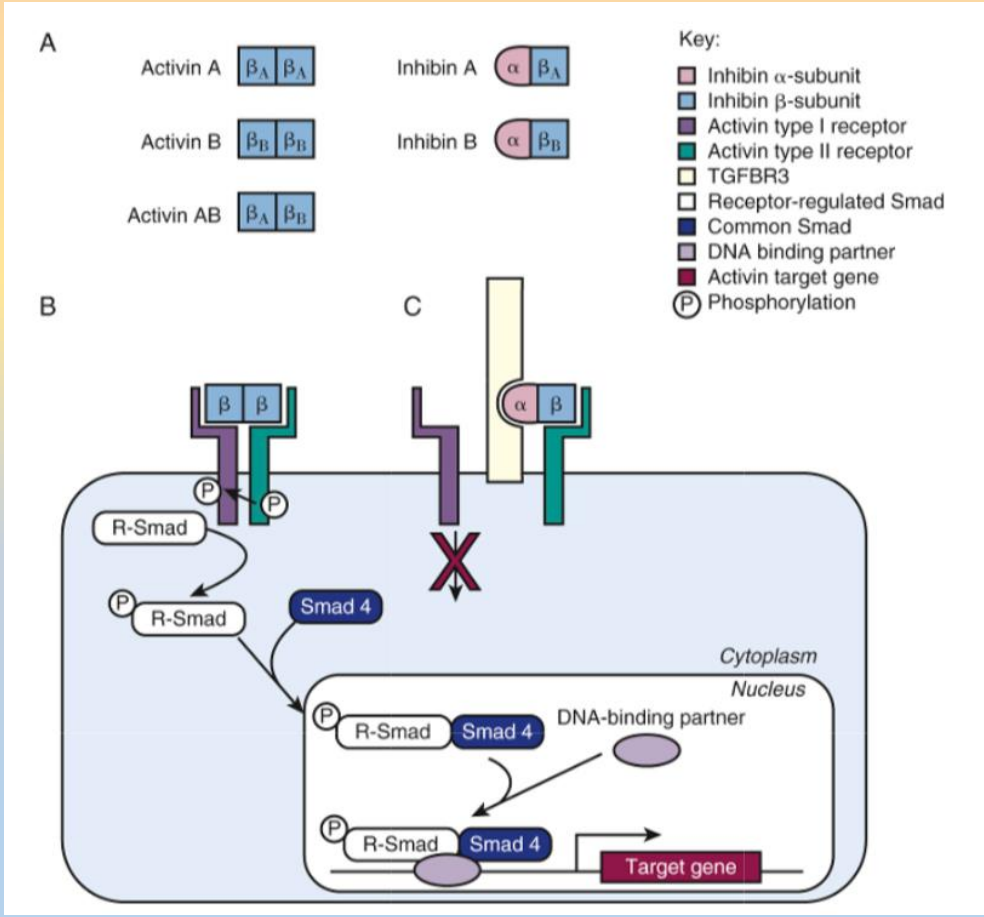
Activins and inhibins

Inhibins – dimeric peptides ($\alpha + 1$ or two β_A or β_B)
– inhibin A – dominant follicle, corpus luteum
– inhibin B – testes, luteal and early follicular phase of MC
- FSH inhibition

Activins
– dimeric peptides – dimers of β subunits
– FSH stimulation
– autocrine/paracrine factors
– other tissues – growth and differentiation

Folllistatin
– monomeric polypeptide
– FSH inhibition

- „supplementary “ regulation of FSH and LH secretion



Hormones of hypothalamus secreted by neurohypophysis

Neurohypophysis

Synthesis - magnocellular neurons (SON, PVN)

Precursor protein (signal peptide, hormone, neurophysin 2, glycopeptide copeptin)

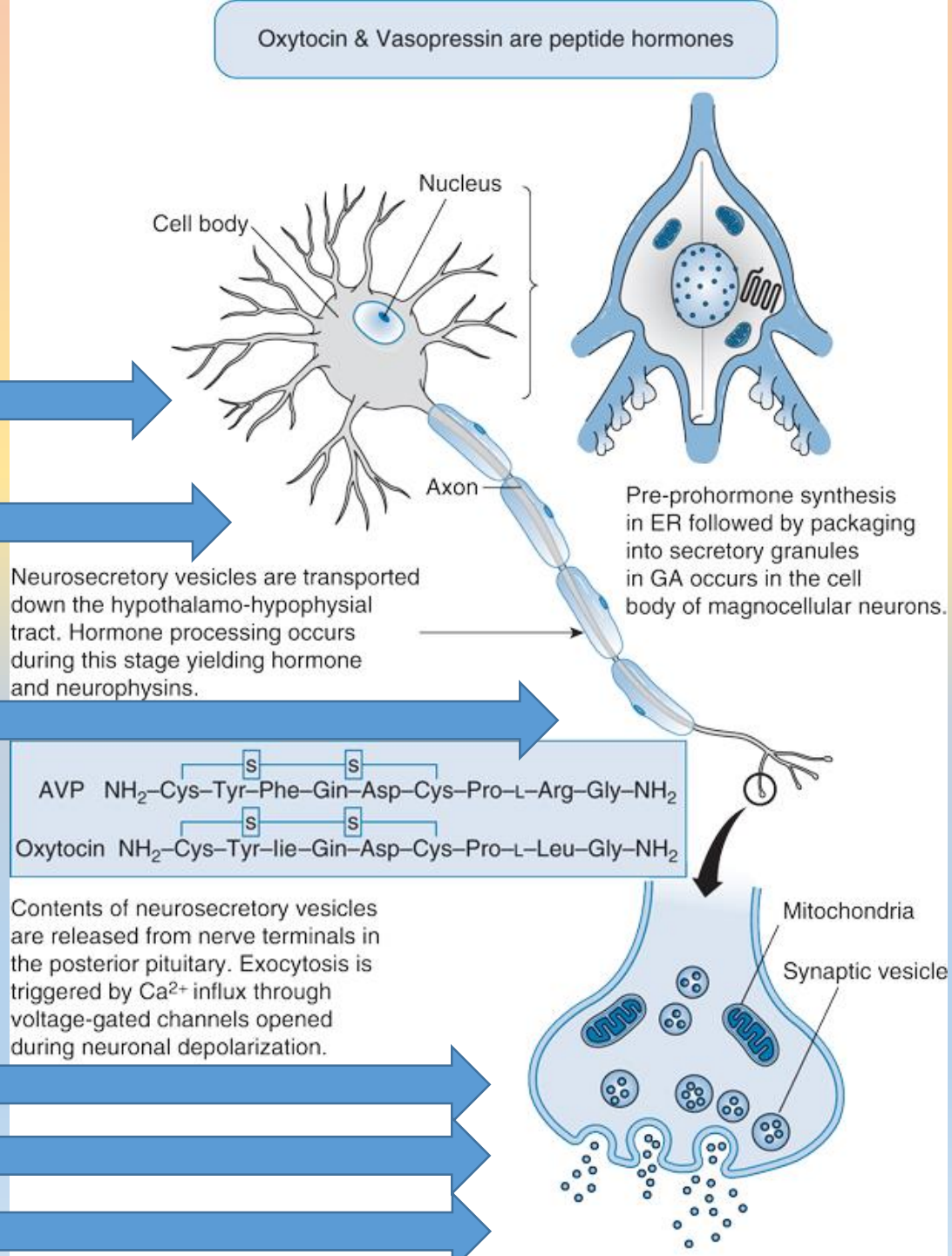
Posttranslational modification – ADH/OT + neurophysins + copeptin

Neurophysins – importance – ADH transport and secretion

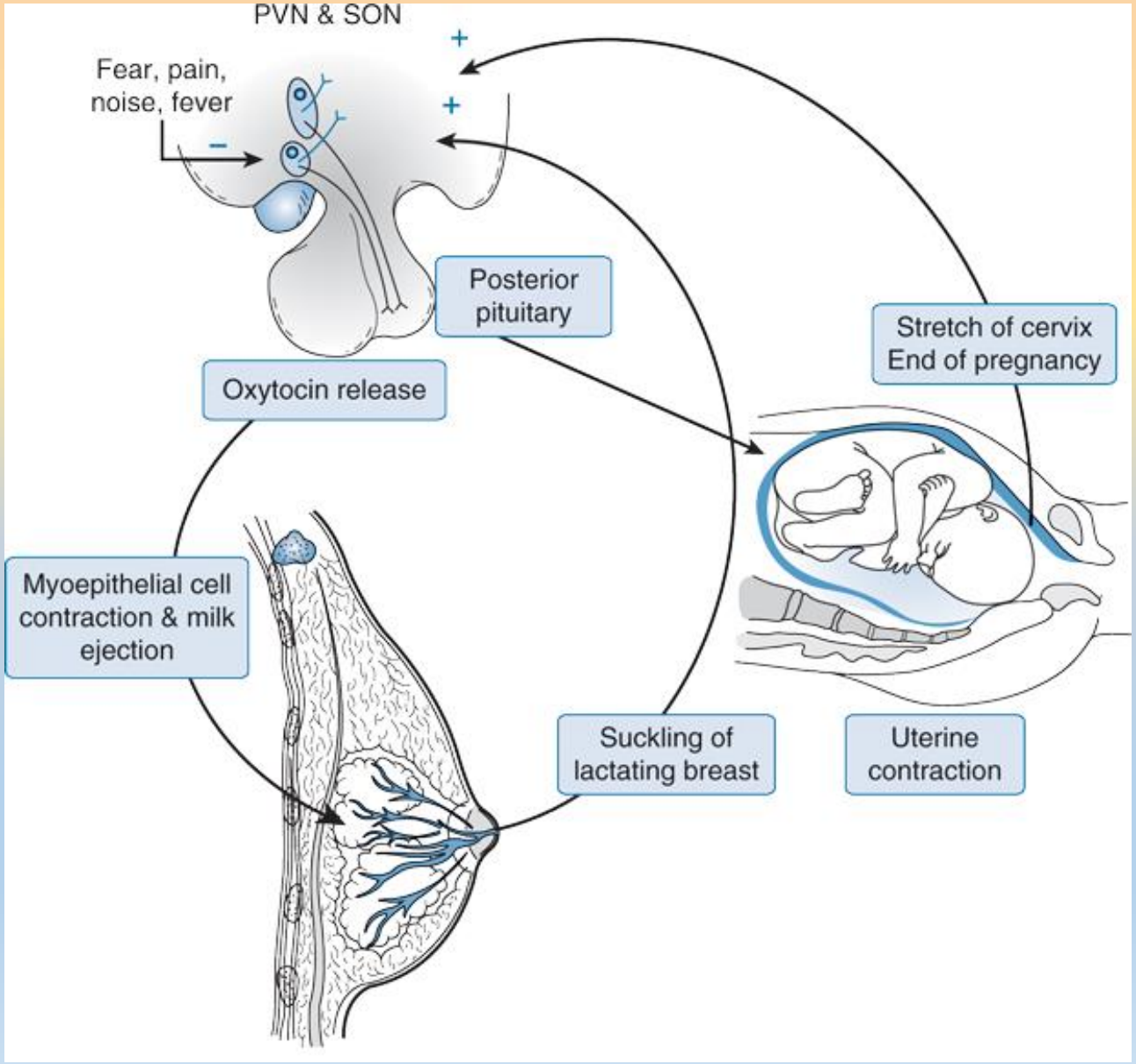
Termination (neurohypophysis, eminentia mediana)

Secretion – voltage-gated Ca^{2+} channels

Circulation – free, elimination – kidneys, liver



Oxytocin



Characteristics
- Mechanoreceptors/tactile receptors
  - endogenous opioids, NO, GABA (-)
  - Prolactin, relaxin (-), Estrogens (+)
- Works together with prolactin and sex hormones

Functions
- Lactation (under 1 min)
- Childbirth
  - rhythmical contractions of smooth muscles (gap-junction, stimulation of prostaglandin synthesis – extracellular matrix)
  - postpartum bleeding, uterus involution
- Ejaculation (males)
- Behavior

Other functions and places of synthesis
- CNS
  - Stimulation of ACTH secretion through CRH
  - Stimulation of ADH/induced vasoconstriction
  - Stimulation of prolactin secretion
  - Memory traces recollection inhibition
  - Maternal behavior

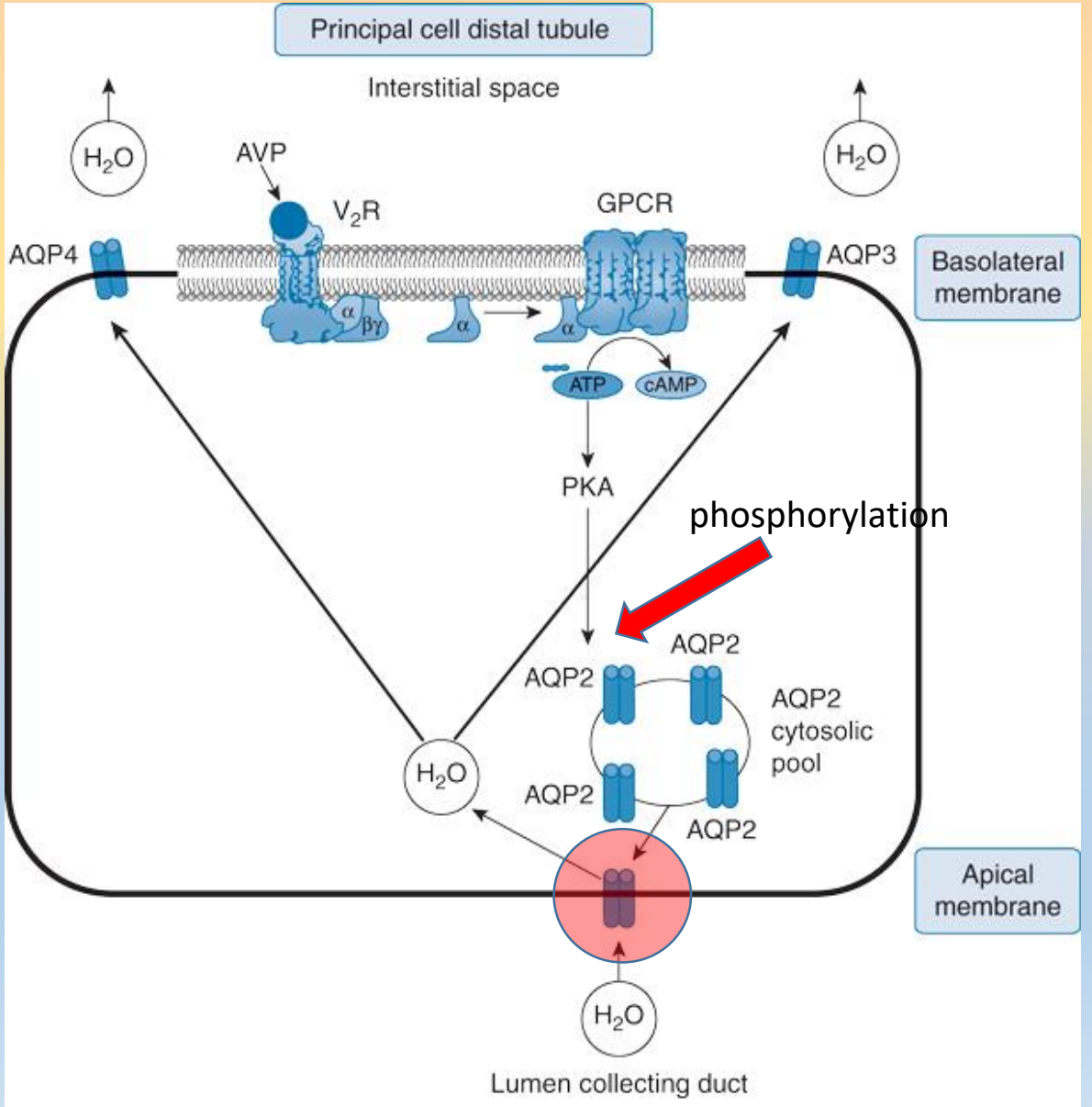
Clinical significance
- Oxytocin analogues

Antidiuretic hormone (ADH, vasopresin, AVP)

Characteristics
- receptors (G protein)
  - V_1R - V_{1a} ($G_{q/11}$) – liver, smooth muscles, CNS, adrenal glands – only ligand ADH
  - V_2R (G_s) – kidneys
  - V_3R - V_{1b} ($G_{q/11}$) – corticotropic cells (CNS), kidneys, thymus, heart, lungs, pancreas, uterus

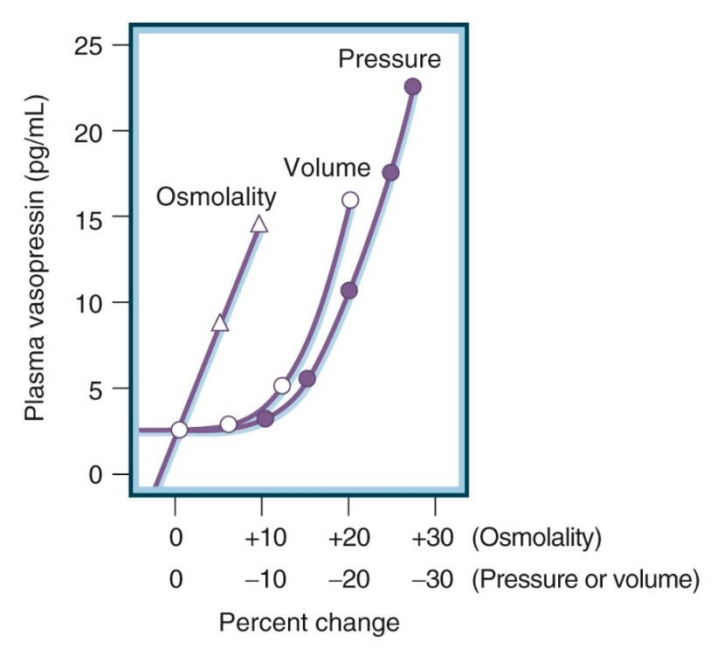
Function
- Water reabsorption (distal tubule, collecting tubule) – tubular system with different water permeability in different parts
  - AQP1 – proximal tubule, HL descending limb HK – 90 % of water reabsorption
  - AQP2 – collecting tubule (only ADH; acute X chronic effect)
  - AQP3, AQP4
- Vasoconstriction (hemorrhagic shock, sepsis)

Other functions and places of synthesis
- CNS – increased recollection of memory traces
- Periphery – stimulation production of factor VIII and von Willebrand factor

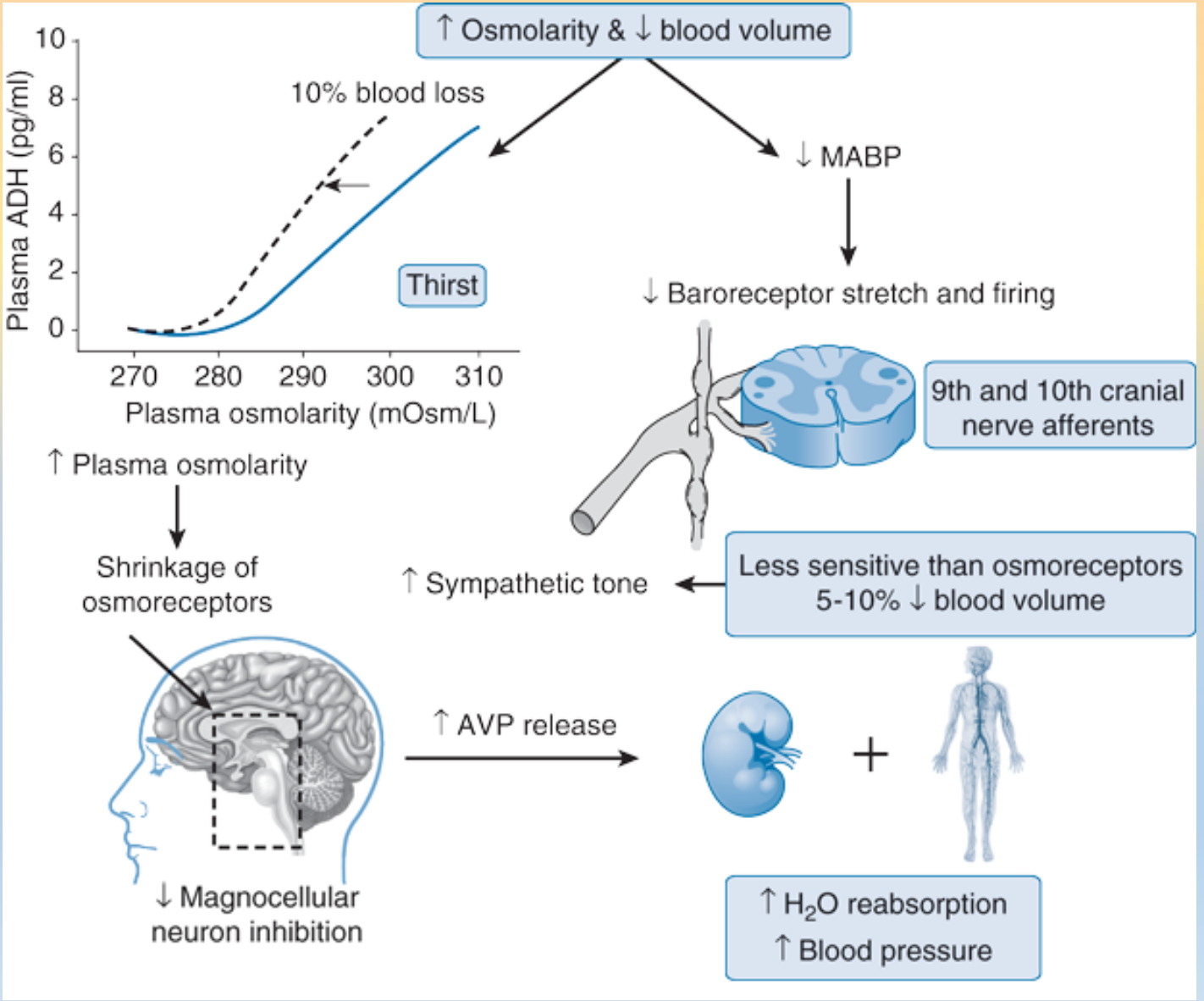


ADH - regulation of secretion

- Osmotic regulation
- Regulation volume-pressure
- Predominantly inhibitory effect of R on magnocellular N



ADH is the main hormone regulating water homeostasis and osmolality, RAAS is the main regulatory system of blood volume and pressure.



ADH – clinical aspects

Diabetes insipidus (DI)

- Primary polydipsia
- Decreased ADH synthesis/secretion (ADH gene) (neurogenic)
- Decreased kidney sensitivity (nephrogenic)

SIADH – Syndrome of Inappropriate Antidiuretic Hormone Secretion

- Increased ADH synthesis/secretion
- Absence of physiological ADH secretion stimuli

Absence of thirst after osmotic stimulation

Ethanol lowers ADH secretion