Hypothalamus and adenohypophysis.

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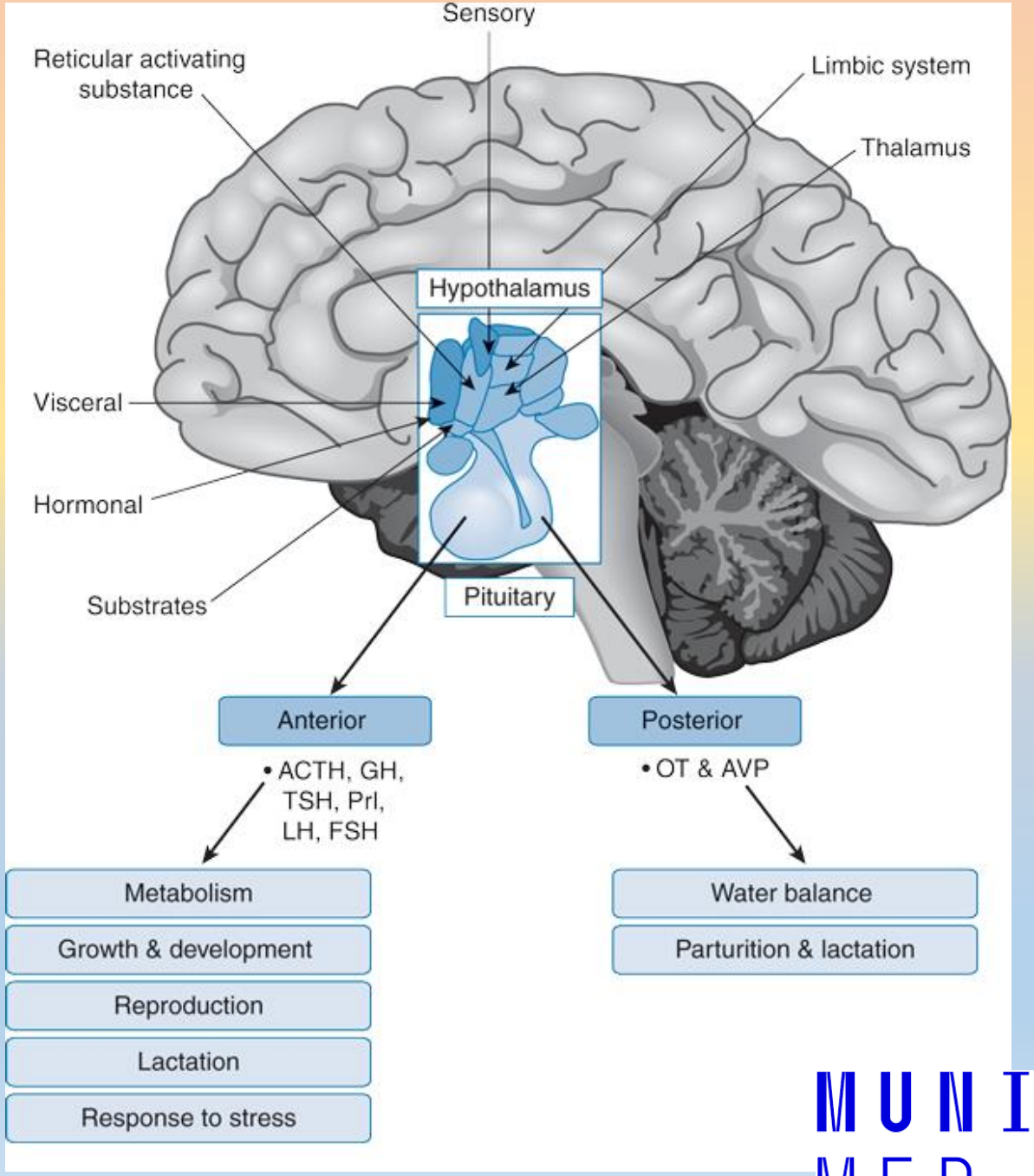
Neuroendocrine regulation

THALAMUS
- NON-SPECIFIC NUCLEI
- SPECIFIC SENSORY NUCLEI
- SPECIFIC NONSENSORY NUCLEI
- ASSOCIATION NUCLEI

HYPOTHALAMUS
- SYSTEM OF SEVERAL DOZENS OF NUCLEI
- PARAVENTRICULAR
- MEDIAL
- LATERAL REGION

HYPOPHYSIS
- PARS DISTALIS (STH, PRL, TSH, FSH, LH,ACTH)
- PARS TUBERALIS (FSH, LH)
- PARS INTERMEDIA (MSH)



Hypothalamus

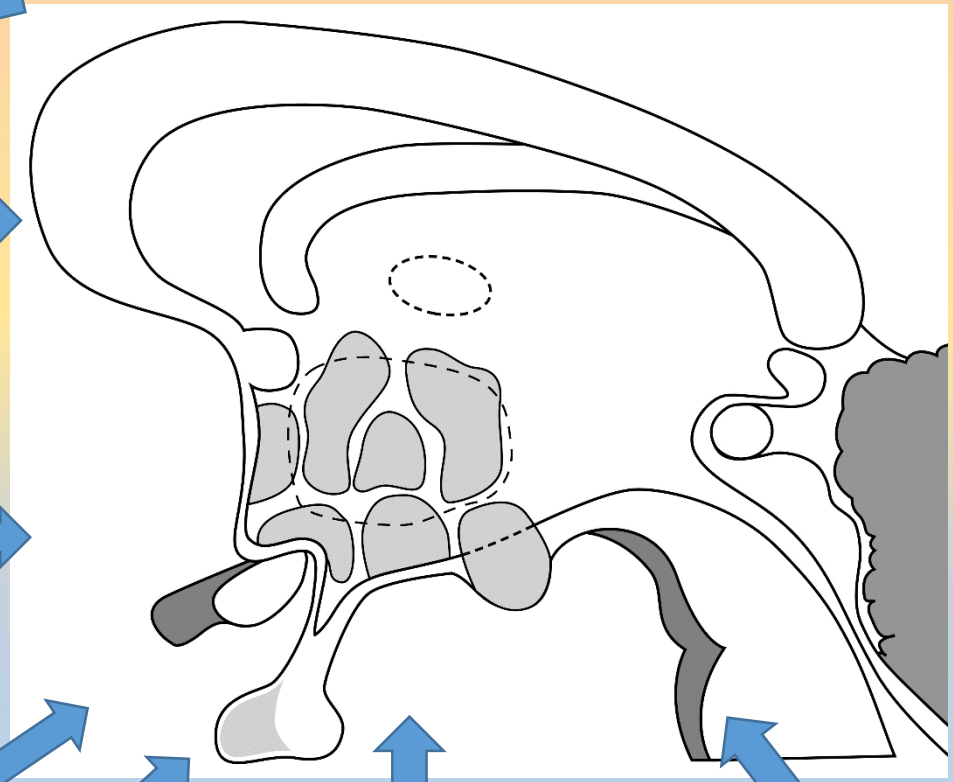
Ventrolateral medulla
(heart, stomach)

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)

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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

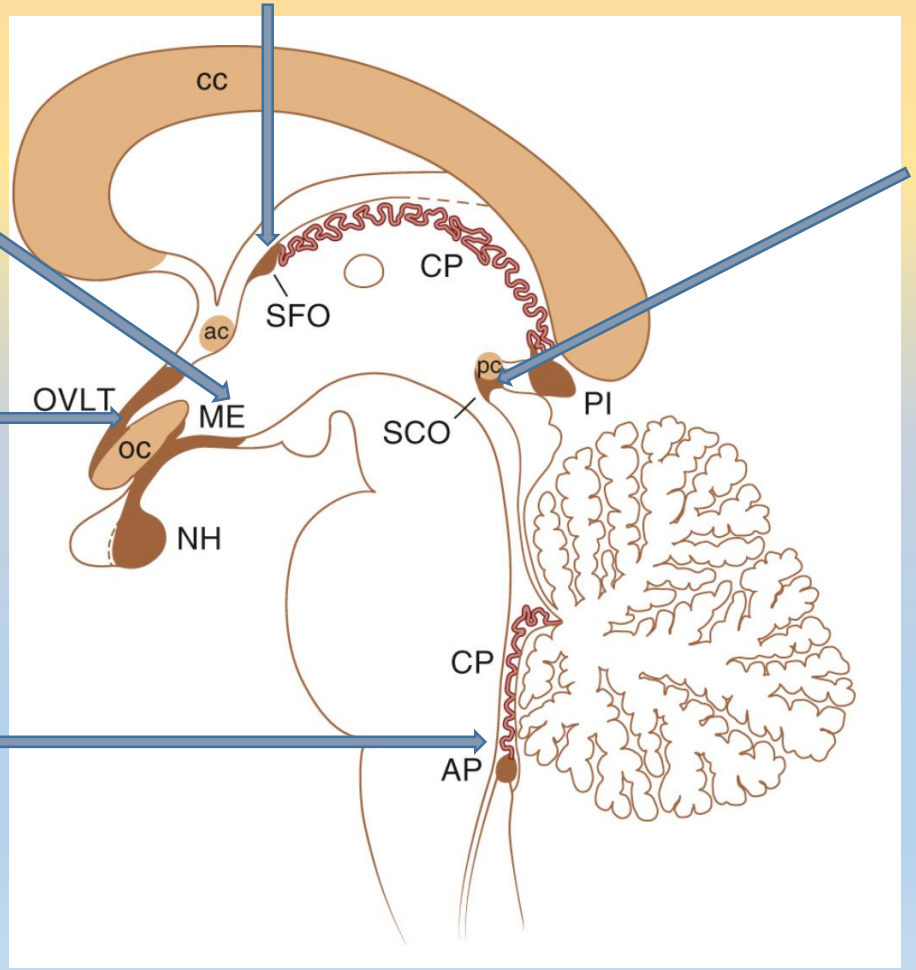
- Regulation of autonomous processes
- Febrile regulation
- Blood osmolality
- Regulation of secretion of GnRH stimulated by estrogens

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

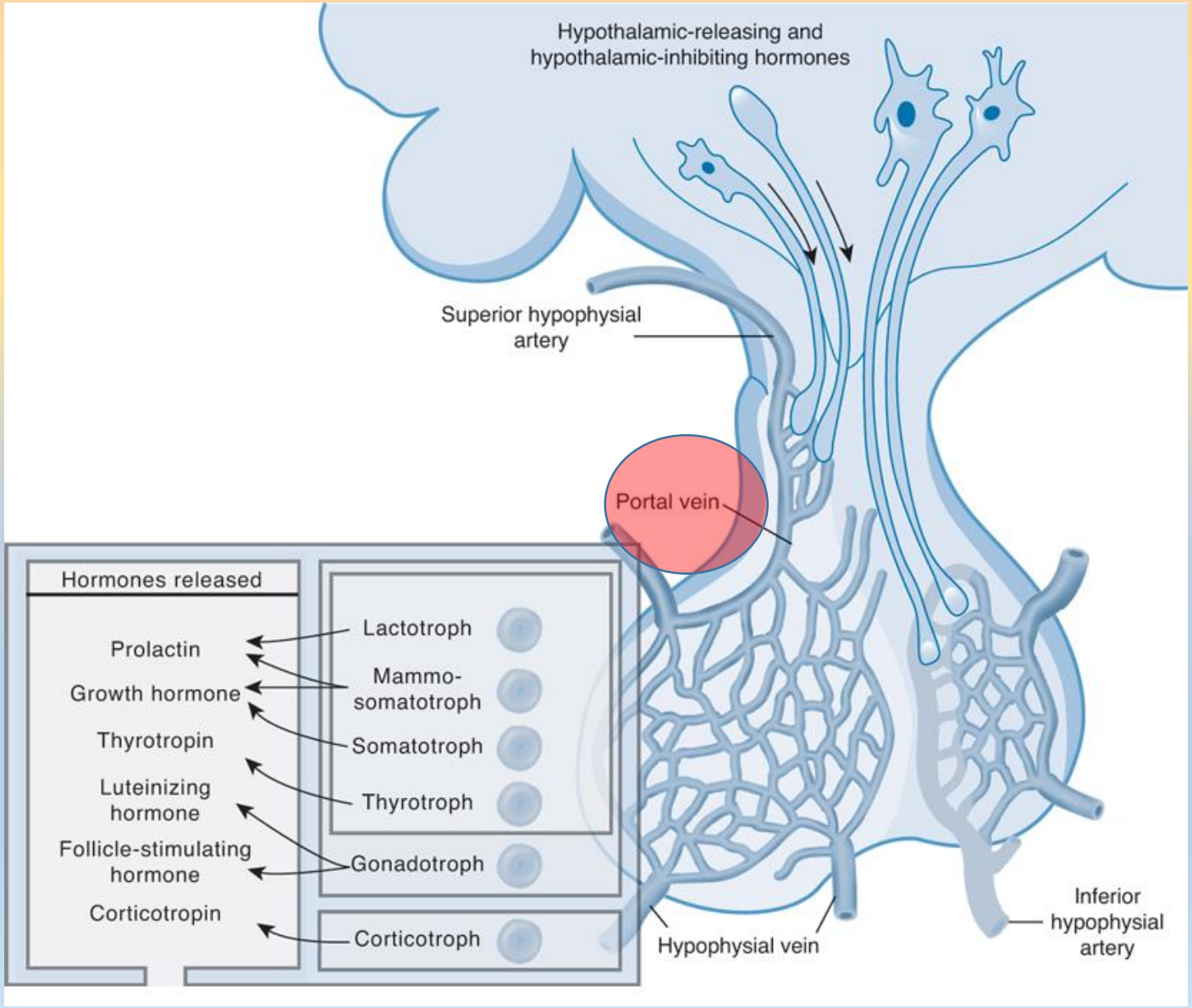


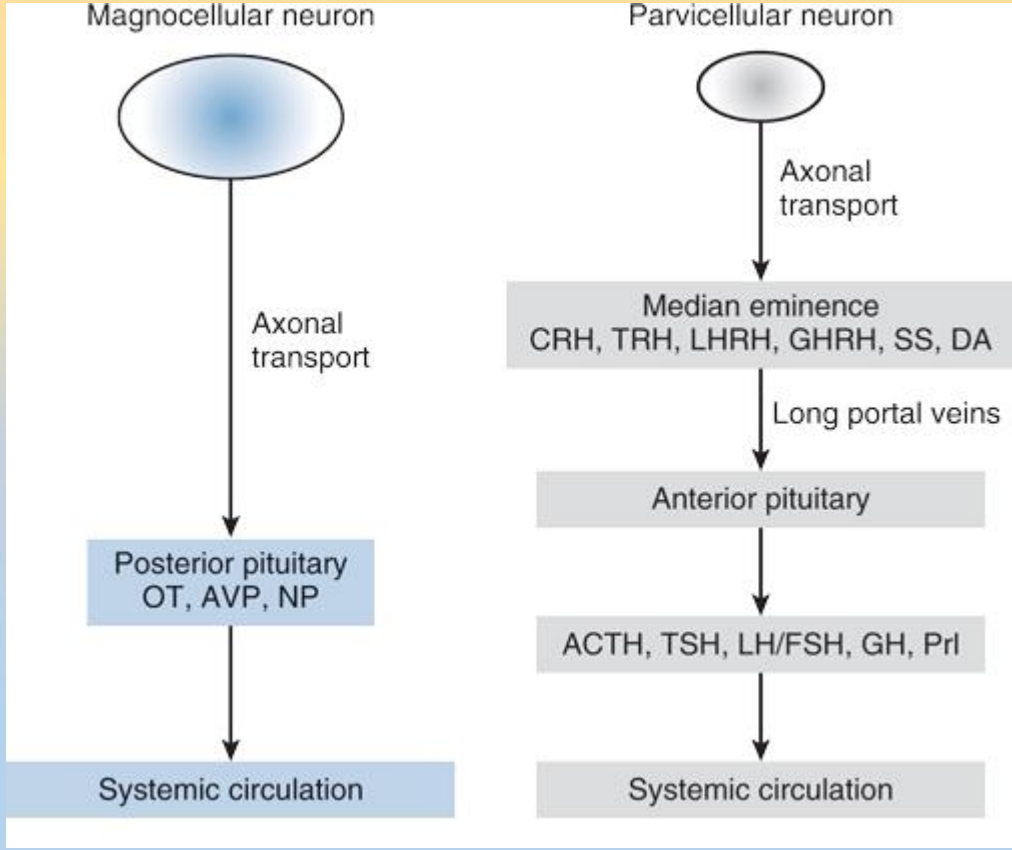
Subcommissural organ

- 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





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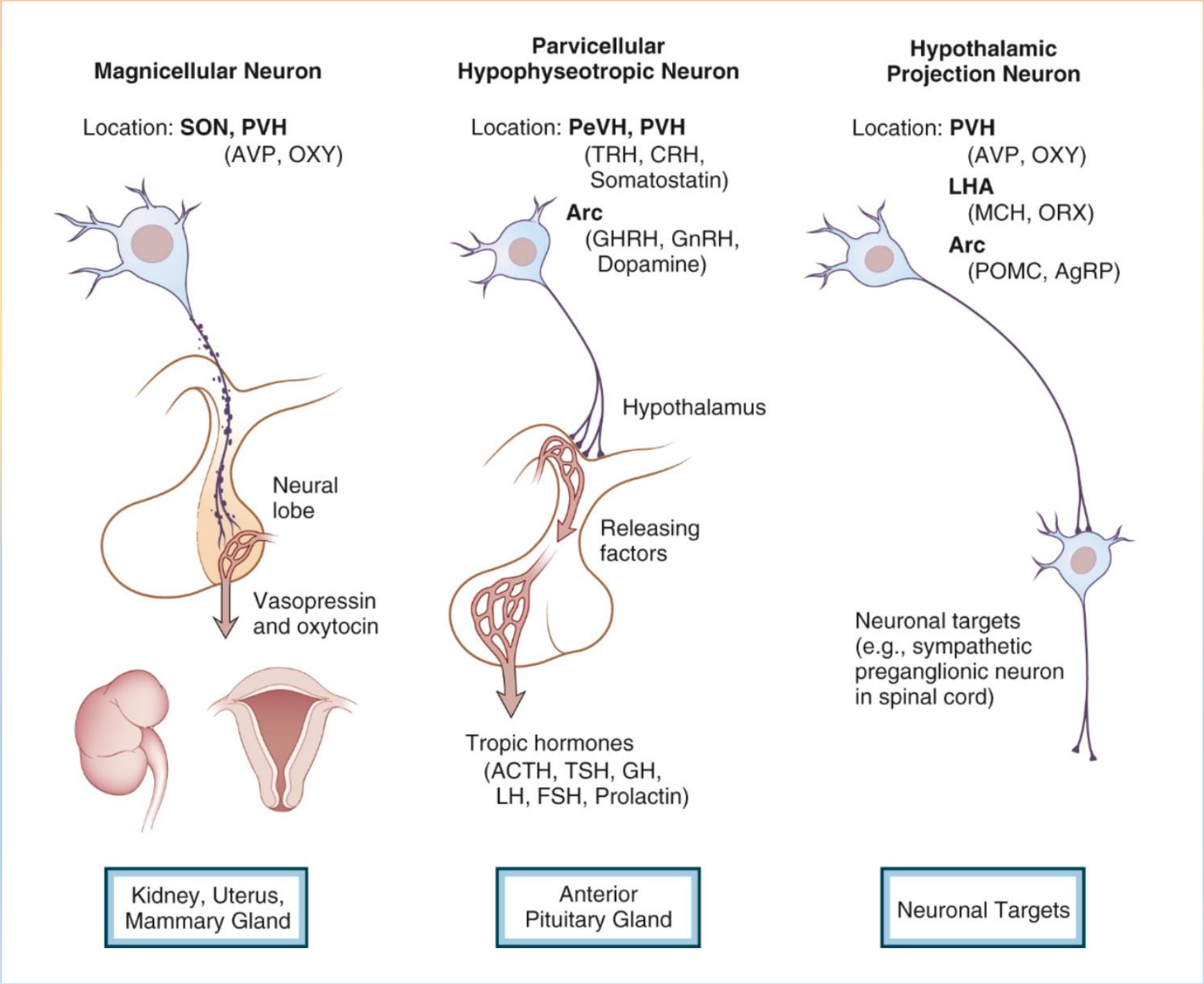
Neurosecretion

SON – supraoptic nucleus
PVH – paraventricular nucleus
PeVH – periventricular nucleus
Arc – arcuate nucleus
LHA – lateral hypothalamic region



Magnocellular and parvocellular neurons – neurotransmitters and neuromodulators

Paraventricular nucleus

Magnocellular neurons

- Angiotensin II
- Cholecystokinin (CCK)
- Dynorphins
- Glutamate
- Nitric oxide
- Oxytocin
- ADH

Parvocellular neurons

- Angiotensin II
- GABA
- ANP
- CCK
- GRP
- neuromedin B
- CRH
- dopamine
- Endocannabinoids
- Enkephalins
- Galanin
- IL-1
- Neuropeptide Y
- Nitric oxide
- SST, TRH
- VIP

Arcuate nucleus

- Acetylcholin
- GABA
- Agouti-related peptid
- CART
- Dopamine
- Dynorphin
- Endocannabinoids
- Enkephalins
- Galanin, Galanin-like peptid (GALP)
- Glutamate
- GnRH
- GHRH
- Kisspeptins
- Melanocortins, including ACTH
- Neurokinin B
- Pancreatic polypeptide
- Prolactin
- POMC
- SST
- etc.

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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

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Thyreoliberin (TRH, thyrotropin-releasing hormone)

Characteristics
- Phylogenetically very old peptide (primitive vertebrates)
- Central and peripheral effects

Hypothalamo-hypophyseal axis
- Regulation of TSH and PRL secretion (prolactinemia, galactorea)
- No effect on other AH hormones secretion (exception – stimulation of GH secretion during acromegaly, liver diseases, anorexia nervosa, psychotic depression; stimulation of ACTH secretion during Cushing's syndrome)

Other places of TRH synthesis/secretion
- cortex cerebelli
- Circumventricular structures
- Neurohypophysis
- Endocrine pancreatic cells
- GIT
- Heart (positive inotropy and chronotropy)

}
- Neuromodulator function
- Role in central thermoregulation

Clinical significance
- In the past – hyperthyroidis diagnosis (hypothalamic X hypophyseal causes)
- Possible role in depression treatment, spinal muscular atrophy and amyotrophic lateral sclerosis
- Treatment of some syndromes (West, Lannox-Gastaut, early infantile epileptic encephalopathy)

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Thyreoliberin
- regulation of secretion

- Neural control

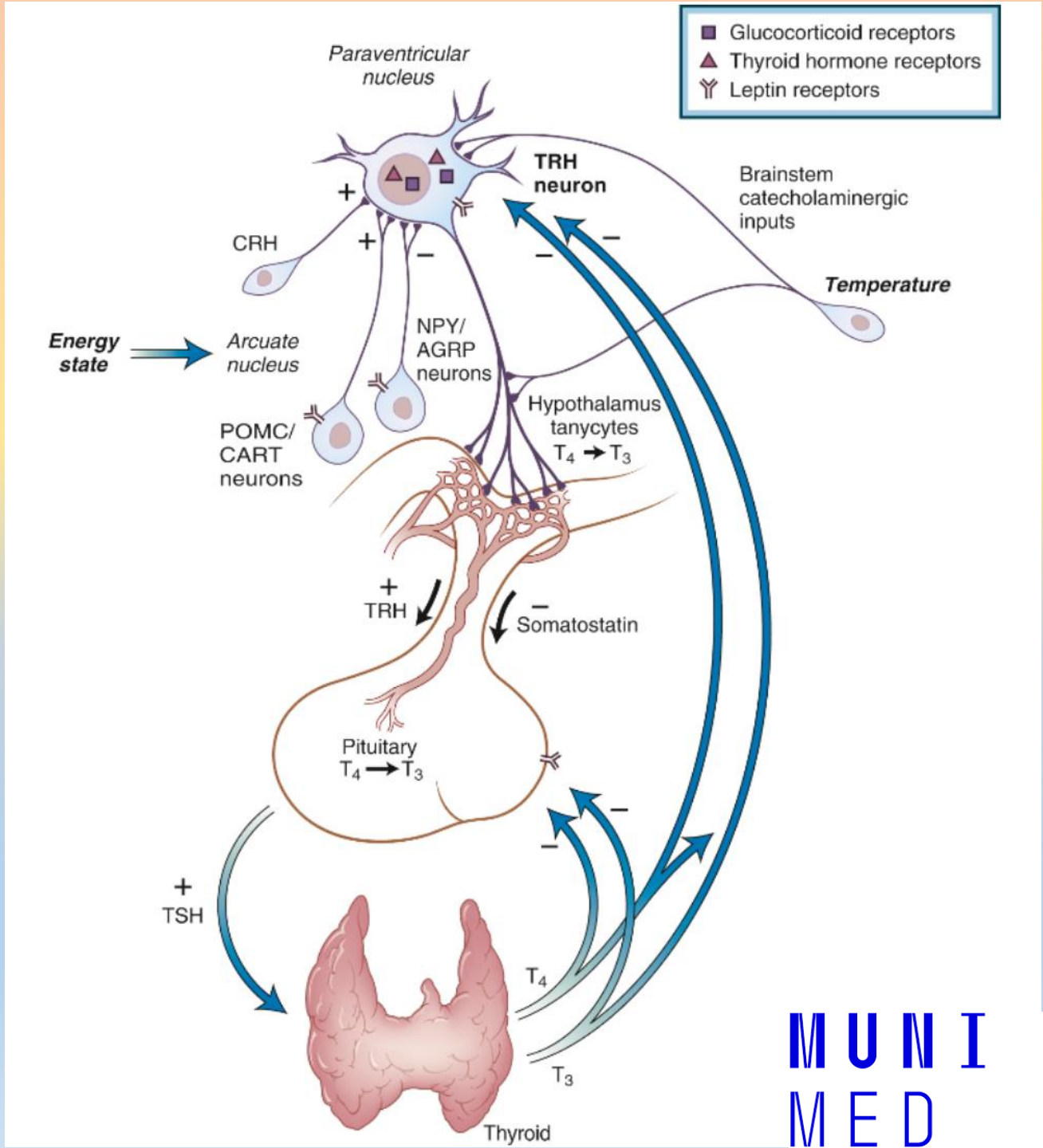
- Circadian rhythm (maximum between 21:00 and 5:00 and between 16:00 and 19:00, peaks in 90–180 min intervals

- Temperature (cold) – higher synthesis among people from colder regions in winter – together with autonomic nervous system (catecholamines)

- Stress – TRH synthesis and secretion inhibition (indirect negative feedback loop between glucocorticoids and effect on hippocampus)

- Starvation – TRH secretion decrease („saving“ energy); effect of leptin

- Body mass – POMC (-) and AGRP (+) system



Cortikoliberin (CRH, corticotropin-releasing hormone)

Characteristics
-Important part of CNS stress response modulation
-Group of related peptides (CRH, urocortin, urocortin II, urocortin III, *urotensin, sauvagin*) with different CNA distribution and CRH-R1 and CRH-R2 affinity
-Exclusively CRH-R1 corticotropic cells (AC)
-CRH-1 – neocortex, cerebellar cortex, subcortical structures of limbic system, amygdala, ovaries, endometrium, skin
-CRH-binding protein

Hypothalamo-hypophyseal axis
- Fast ACTH secretion

Other places of CRH synthesis/secretion
- Limbic system
- Amygdala, substantia nigra
- Nucleus tractus solitarius
- Parabrachial nucleus

→
- Behavior, fear, anxiety regulation
- Anorexigenic factor
- Increased sympathetic tone

- Placenta (3rd trimester)
- Lymphocytes, autonomic nerves, GIT
- Cardiovascular system

→
- Blood pr. regulation (decrease)
- Negative chronotropy
- Immune system, reproduction

Clinical significance
- Potential treatment of obesity
- CRH-R1 antagonists – anxiety and depression treatment

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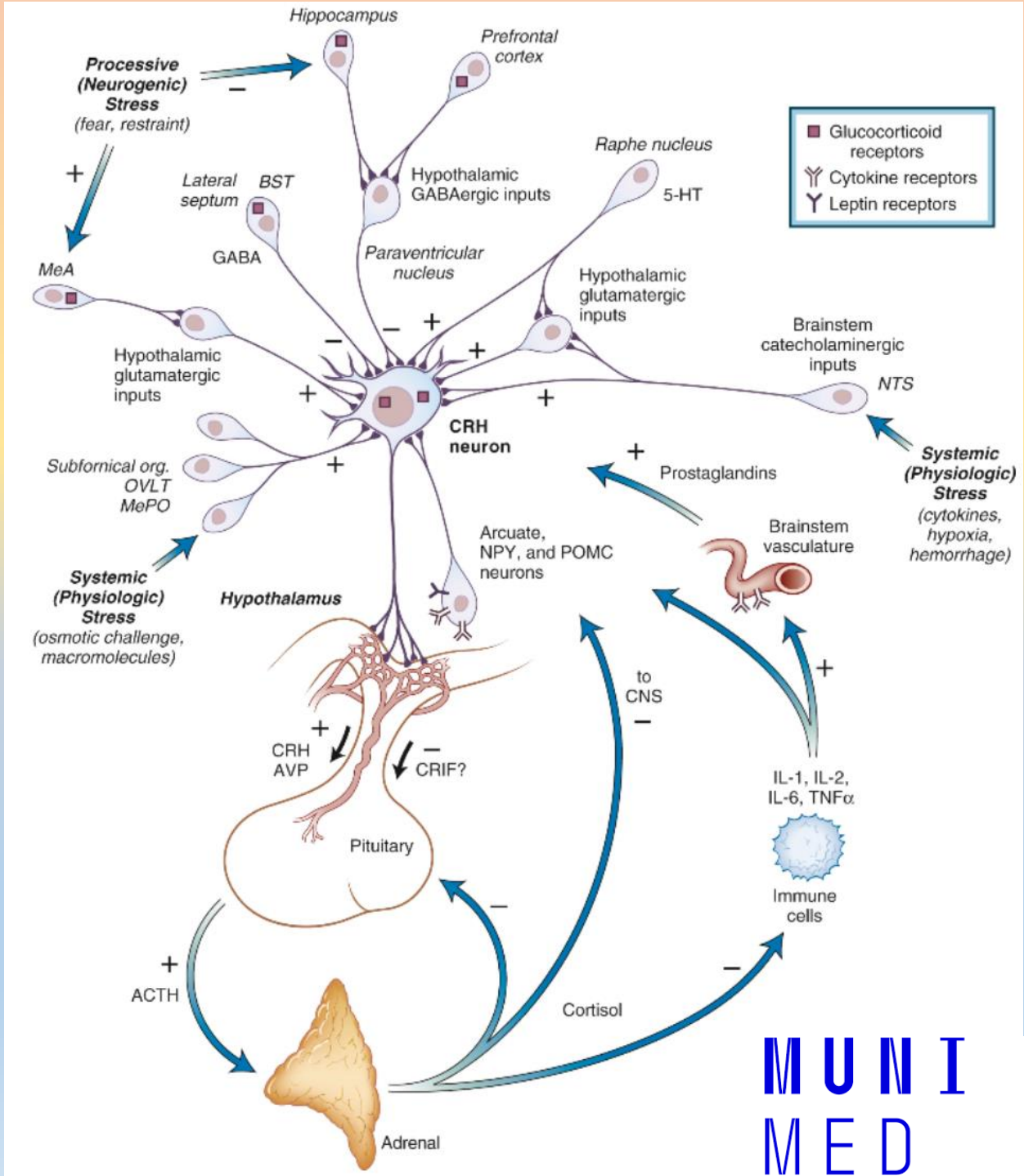
Corticoliberin – regulation of secretion

- Neural control – various stressors
  - Hypothalamo-hypophyseal axis activation
  - Sympathoadrenal axis activation
  - ADH and oxytocin binding
  - *Ensuring requirements in emergency situations*
- Inflammation and cytokines
  - IL-1B and hypothalamo-hypophyseal axis activation
- Circadian rhythms - diurnal rhythms



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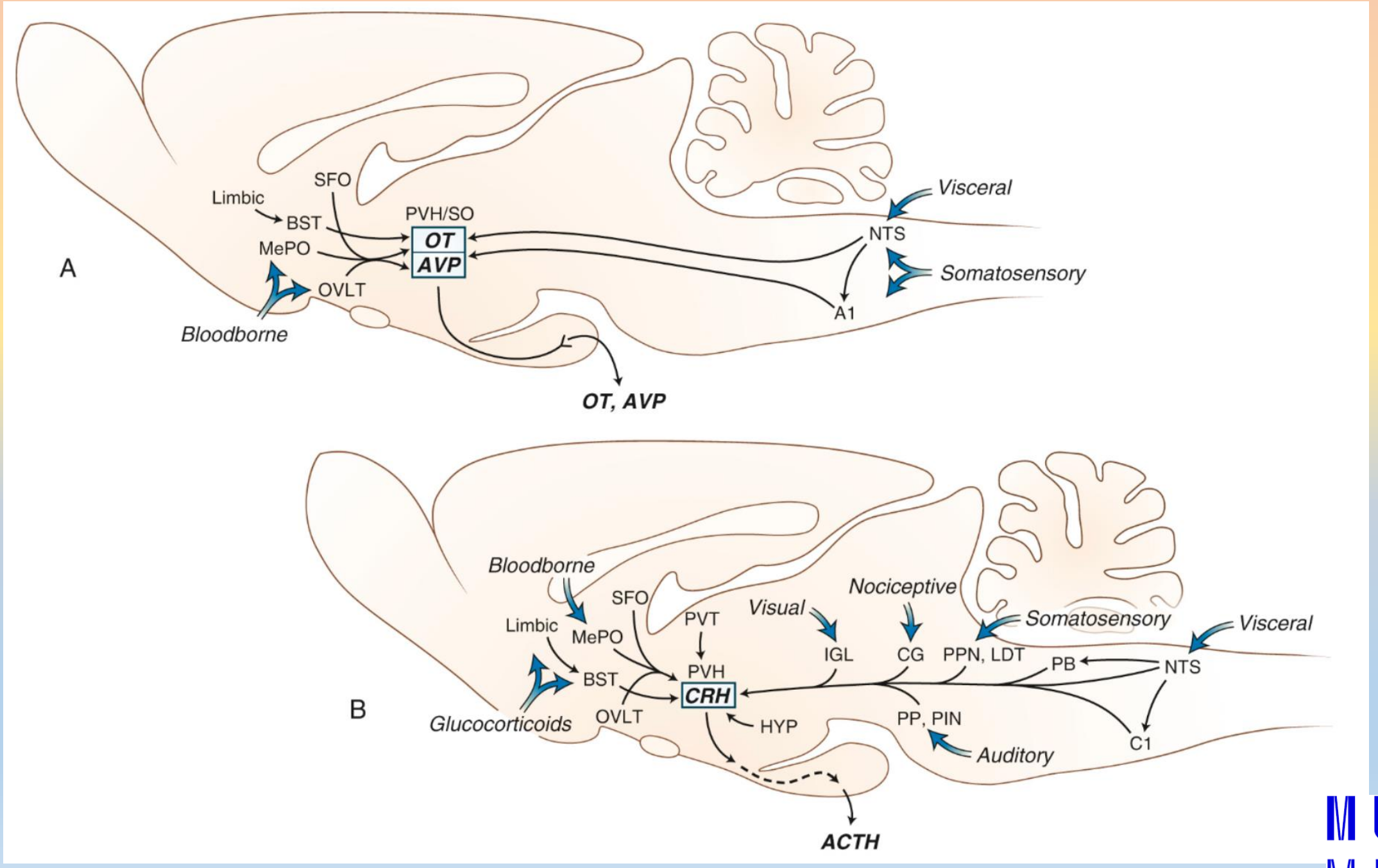

A
SFO
Limbic
BST
MePO
PVH/SO
OT
AVP
OVLT
Bloodborne
Visceral
NTS
Somatosensory
A1
OT, AVP
B
Bloodborne
SFO
Limbic
MePO
PVT
Visual
Nociceptive
Somatosensory
Visceral
IGL
CG
PPN, LDT
PB
NTS
PVH
BST
CRH
OVLT
Glucocorticoids
HYP
PP, PIN
Auditory
C1
ACTH

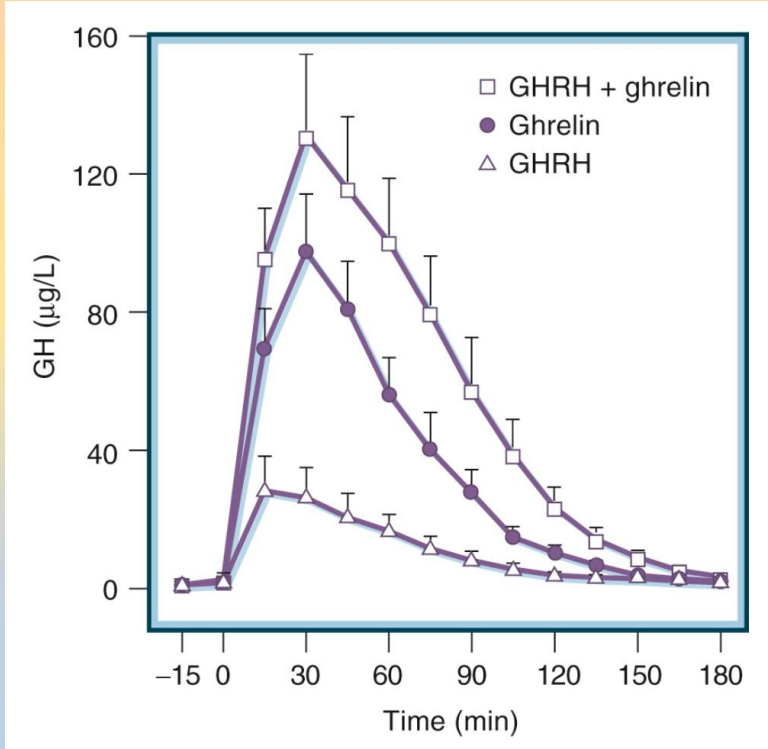
Somatoliberin (GHRH, growth hormone-releasing hormone)

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
- GHRH is not the only GR secretion modulator!
- Synergy with estrogens, glucocorticoids and starvation
- Somatostatin, age and obesity – decreased secretion

Other functions and places of synthesis
-Sleep regulation (SCN)
-Orexigenic factor
-Wound healing - skin
-Ovaries, uterus
-Placenta

} - Unknown role
- Possible alternative splicing



Clinical significance
- Nowadays without clinical significance
- GHRP

Somatostatin (GHIH, growth hormone–inhibiting hormone)

Characteristics
- SST-14 (CNS) and SST-28 (GIT)
- Neurotransmitter – neuromodulator
- SSTR1-SSTR5 (GP – cAMP – PLC, PLA, MAPK, ion channels)
- diverse receptor distribution (mainly CNS)
- SSTR5 – insulin secretion inhibition
- SSTR2 – glucagon secretion inhibition

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

Other functions and places of synthesis
- Myenteric plexus
- Epithelial GIT cells

} - neurotransmitter / - paracrine

- Endocrine pancreas – autocrine and paracrine
- Cortex, lateral septum, amygdala, thalamic reticular nucleus
- Hippocampus, brain stem nuclei
- Cortistatin with SSTR1-5 affinity – neuromodulator (ant. Ach)

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

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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	

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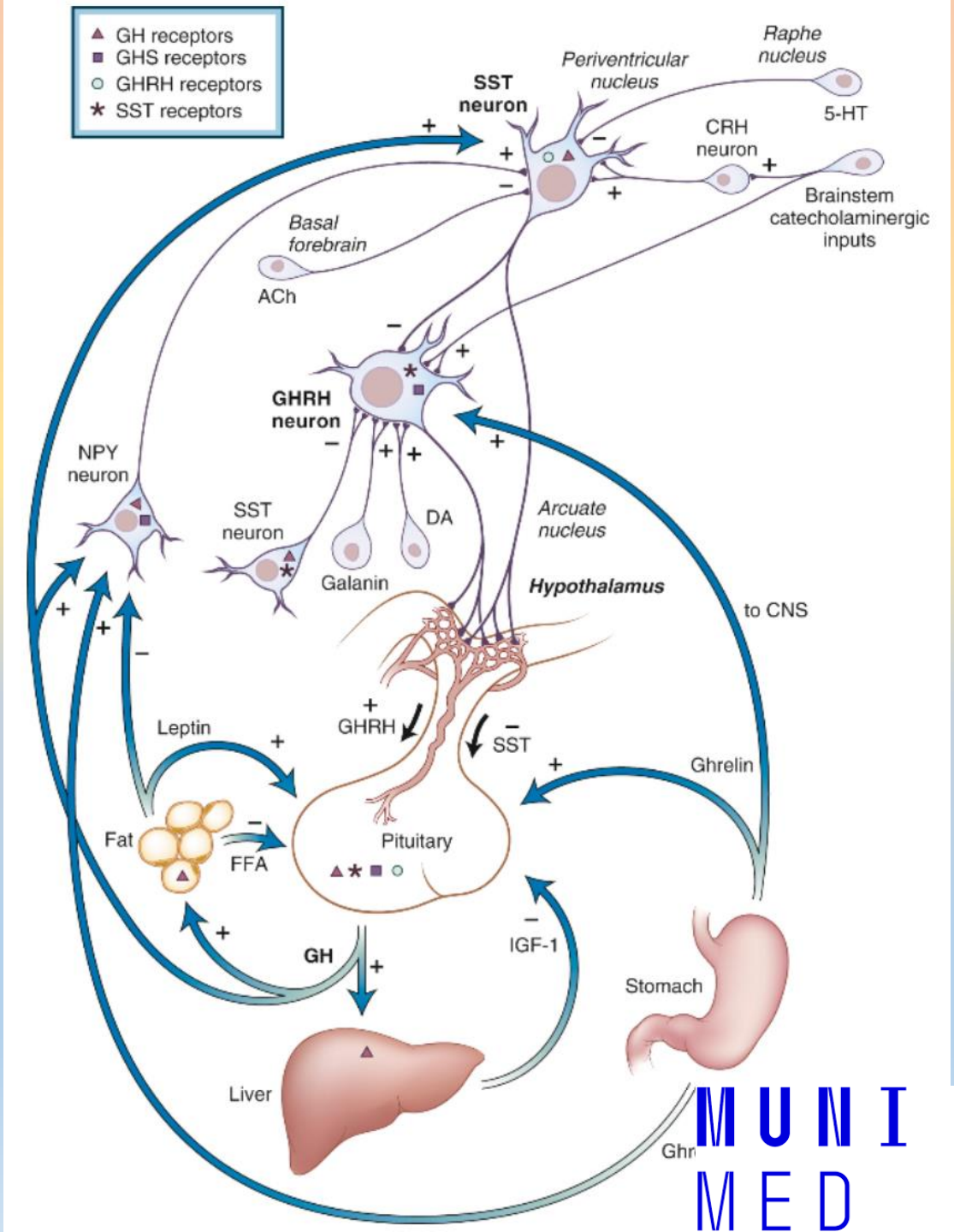
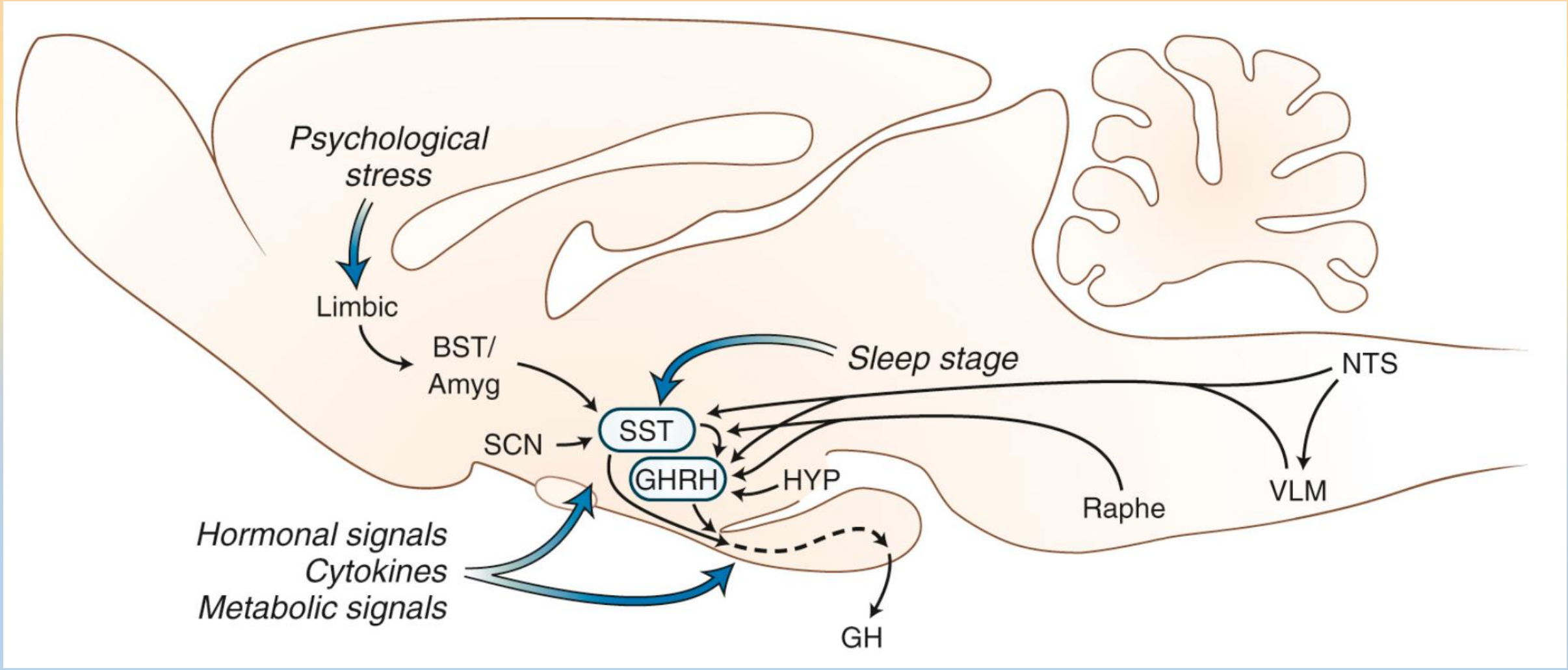
Somatoliberin, somatostatin – regulation of secretion

- GHRH secretion stimulation
  - Ghrelin
  - Leptin
  - Galanin
  - GABA
  - α2-adrenergic and dopaminergic input
- GRHR secretion inhibition
  - CRH
  - β2-adrenergic input
- Somatostatin secretion inhibition
  - Ach
  - 5-HT-1D




Psychological stress
Limbic
BST/ Amyg
Sleep stage
NTS
SST
SCN
GHRH
HYP
Raphe
VLM
Hormonal signals
Cytokines
Metabolic signals
GH

Stimulation of GH secretion

Physiological factors	Hormones and neurotransmitters	Pathological factors
Exercise	Arginin, lysin	Acromegaly
Stress (various causes)	Neuropeptides (ghrelin, RHRH, 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

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Inhibition of GH secretion

Physiological factors	Hormones and neurotransmitters	Pathological factors
Postprandial hyperglycemia, glucosis 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

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Dopamine (PIH, prolactin-inhibiting hormone)

Characteristics
- D2R (G protein inhibition, AC, cAMP decrease, inhibition of shaker type K^+ channels, MAPK, PAK – proliferation!)
- D1R (activation)

Hypothalamo-hypophyseal axis
- Inhibition of PRL (D2R) secretion – lactotropic cells
- ! Lactotrophs with continual high PRL production
- PRL secretion regulated also on adenohypophysis level (paracrine, autocrine)
- Neuroendocrine regulation of PRL secretion – pregnancy, lactation, menstrual cycle, sensoric inputs

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
- Cardial shock
- Neurodegenerative diseases (Parkinson)
- Antipsychotics (antag.)

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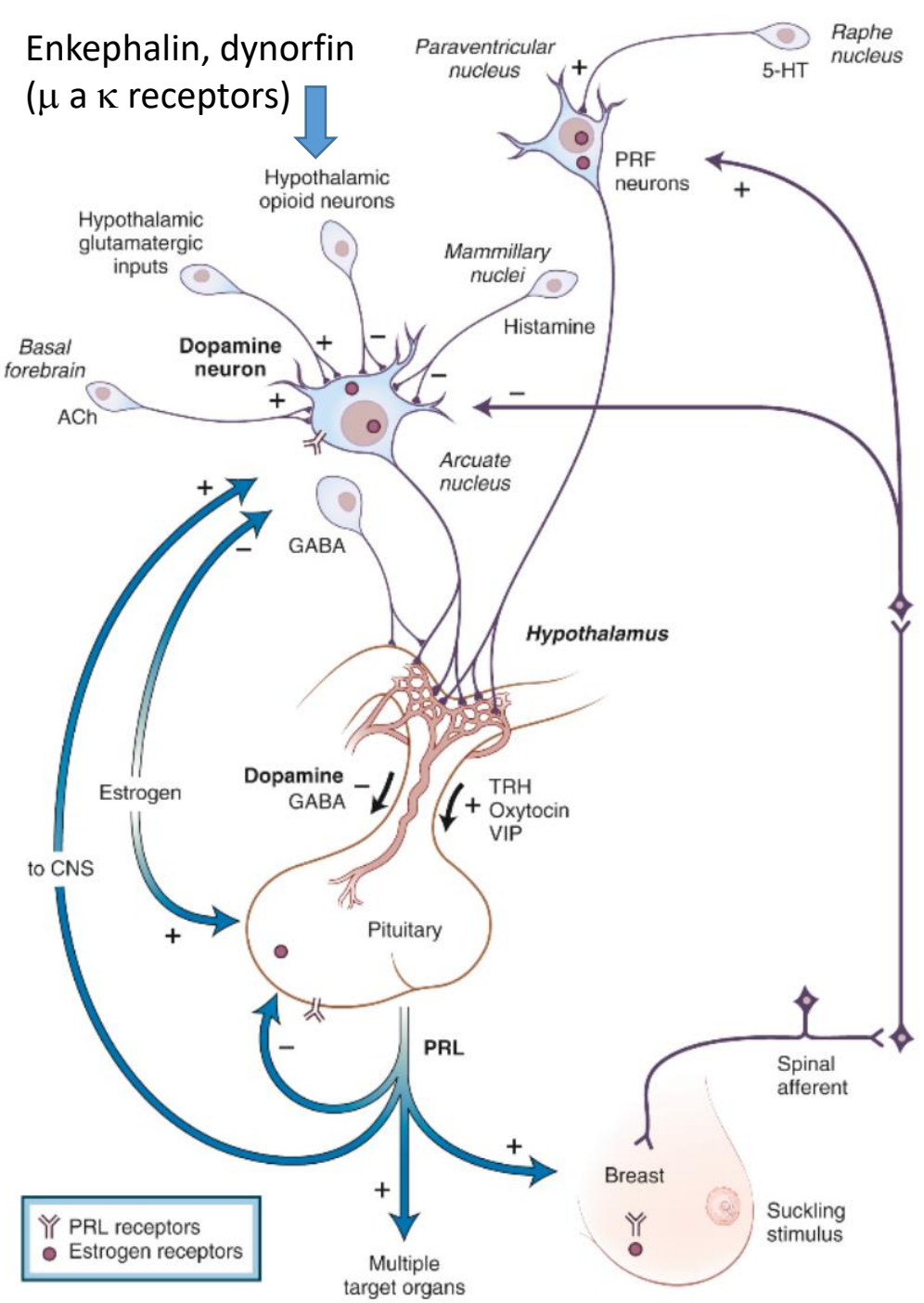
Dopamine – regulation of secretion

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)

- Relevance of studying PRL secretion and its regulation - psychopharmaceutics!



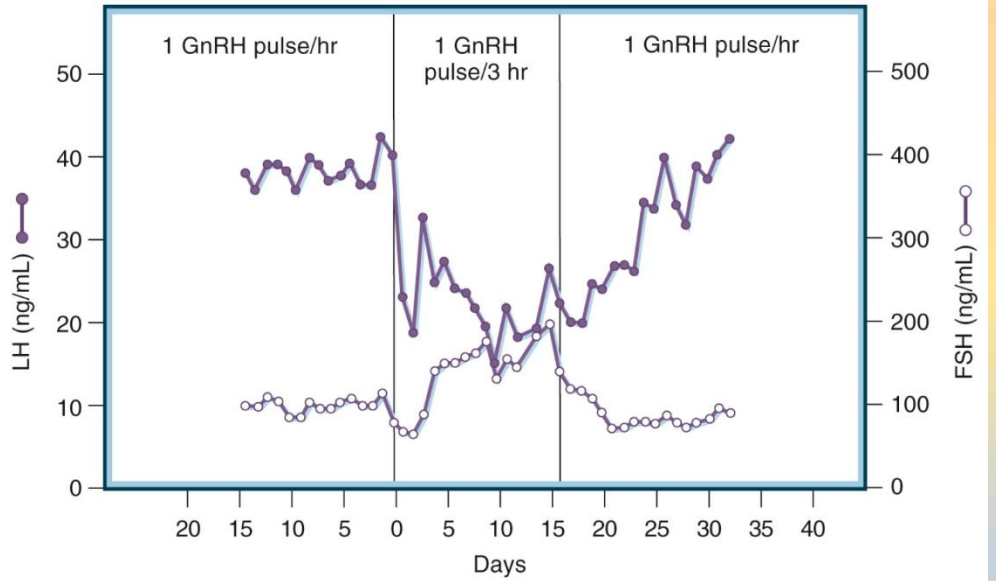
Gonadoliberin (GnRH, Gonadotropin-Releasing Hormone)

Characteristics
- Specific origin of GnRH neurons outside of CNS
- GnRH-I, GnRH-II, (GnRH-III) – $G_{q/11}$ (PKC, MAPK)
- Important up- and down- regulation (steroid hormones, gonadotropic hormones)
- Downregulation – malnutrition, lactation, seasonal effects, aging, continual GnRH
- Upregulation – effect of GnRH on gonadotrophs (menstrual cycle)
- *GNRH1* – hypothalamus; *GNRH2* – other parts of CNS

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

Other functions and places of synthesis
- CNS – neurotransmitter (preoptic region)
- Placenta
- Gonads
- Tumor tissue (prostate, endometrium)

} - Unknown function



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

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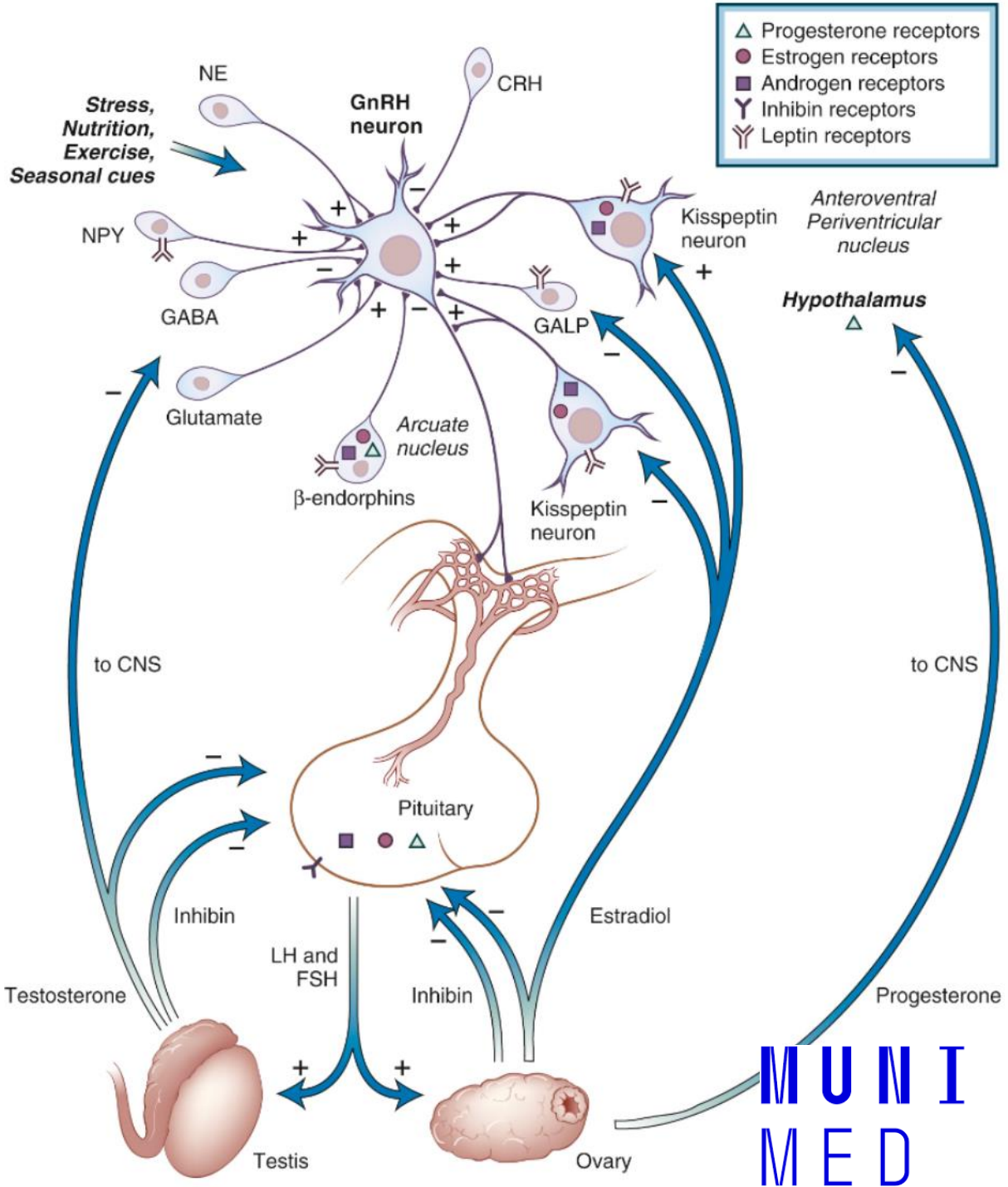
Gonadoliberin – regulation of secretion

- Inputs from various CNS regions (brain stem, limbic system)
- Predominant 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



Neurohypophysis

Synthesis - magnocellular neurons (SON, PVN)

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

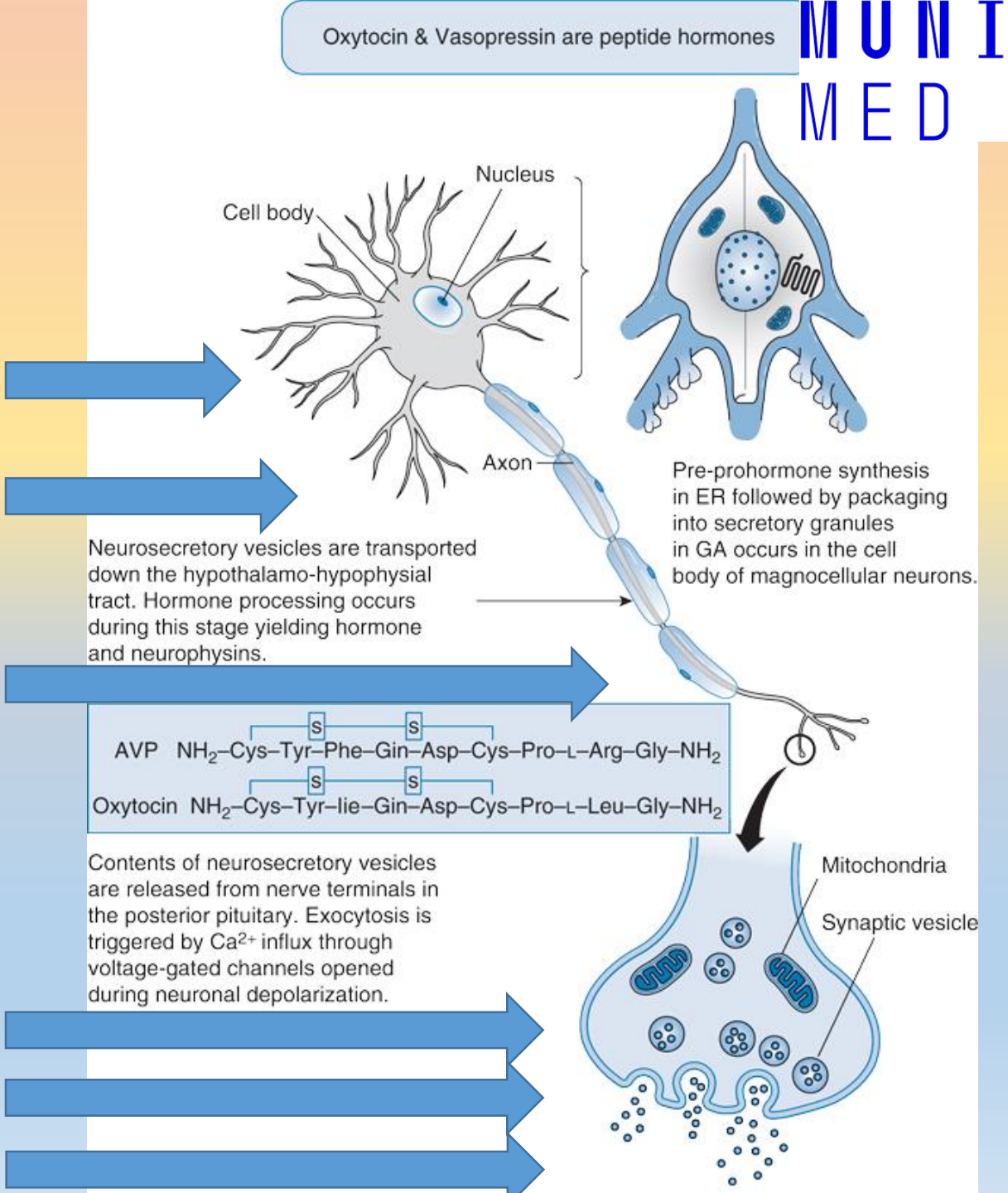
Posttranslational modification – ADH/OT + neurophysins + copeptin

Neurophysins – importance – ADH transport and secretion

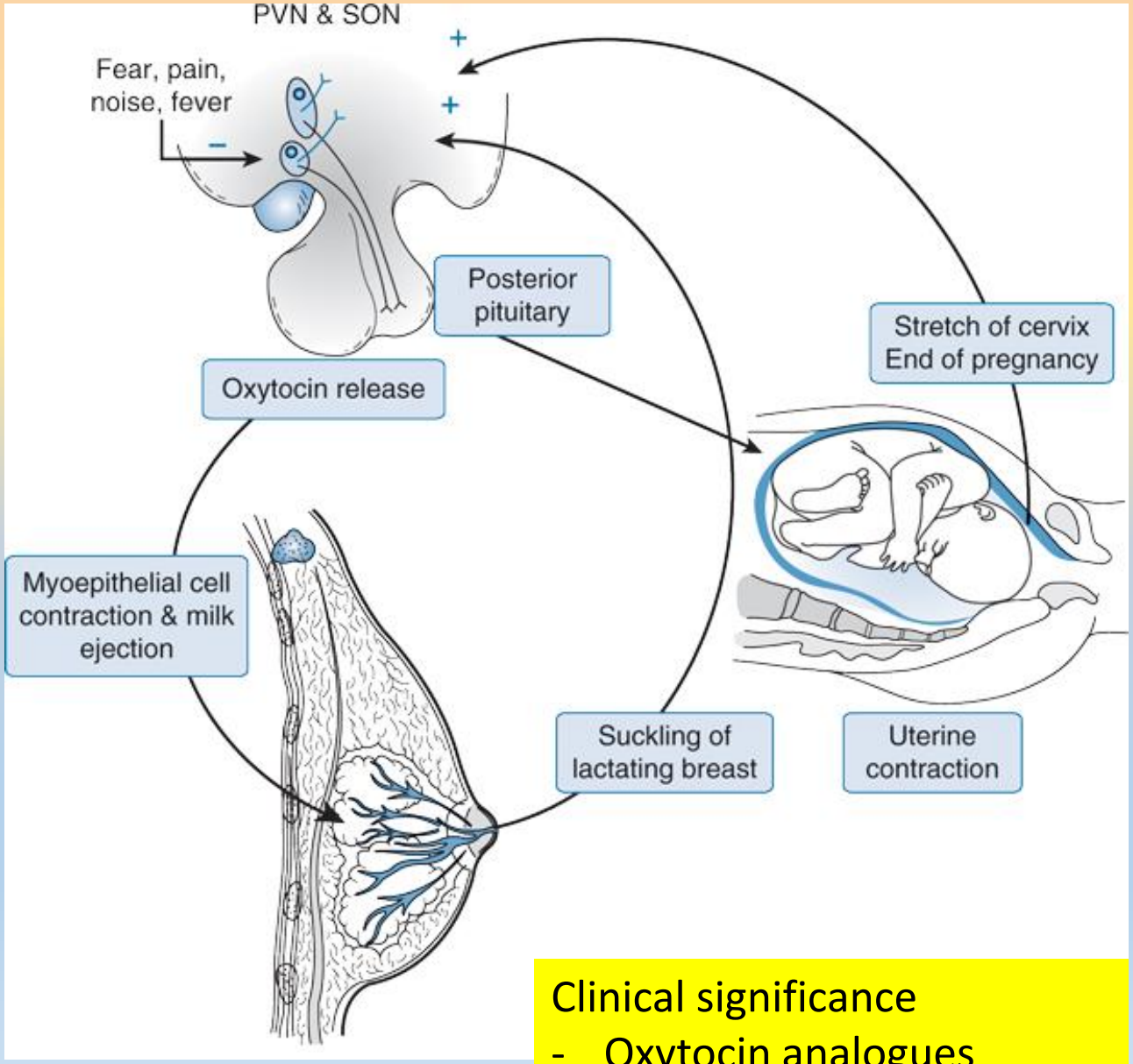
Termination (neurohypophysis, eminentia mediana)

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

Circulation – free, elimination – kidneys, liver



Oxytocin



Clinical significance
- Oxytocin analogues

Characteristics
- Mechanoreceptors/tactile receptors
- Magnocellular neurons (PVN, SON)
  - inhibition by endogenous opioids, NO, GABA
  - Autocrine (+ ZV)
  - Prolactin, relaxin (-), Estrogens (+)
- OXT receptors ($G_{q/11}$) – effect of up/down regulation
- 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

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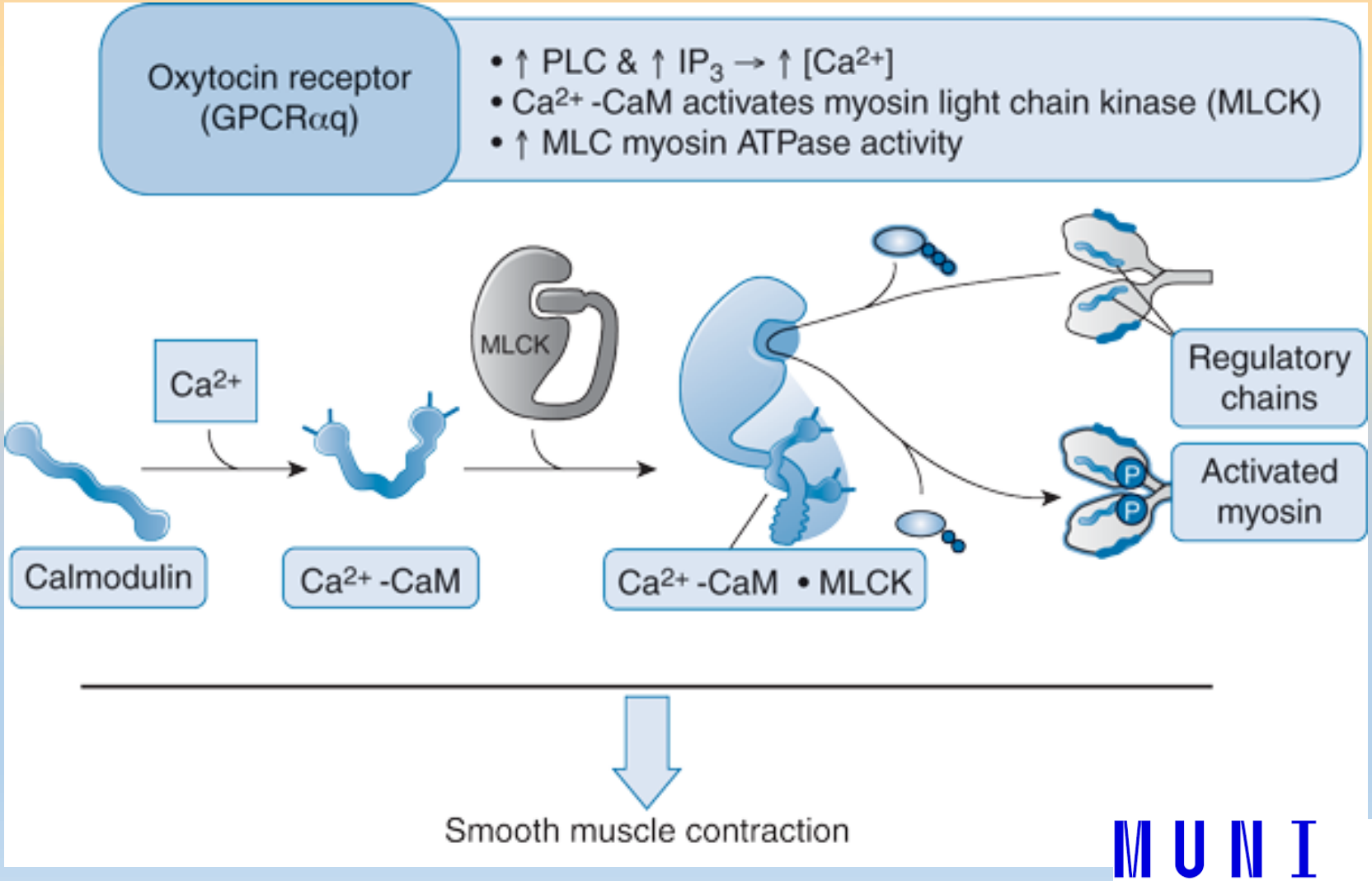
OT receptors

- OXT receptors ($G_{q/11}$)
  - Myoepithelial cells
  - Myometrium
  - Endometrium
  - CNS
- PLC, IP_3, Ca^{2+}
- Target molecule – MLCK (myosin light chain kinase)

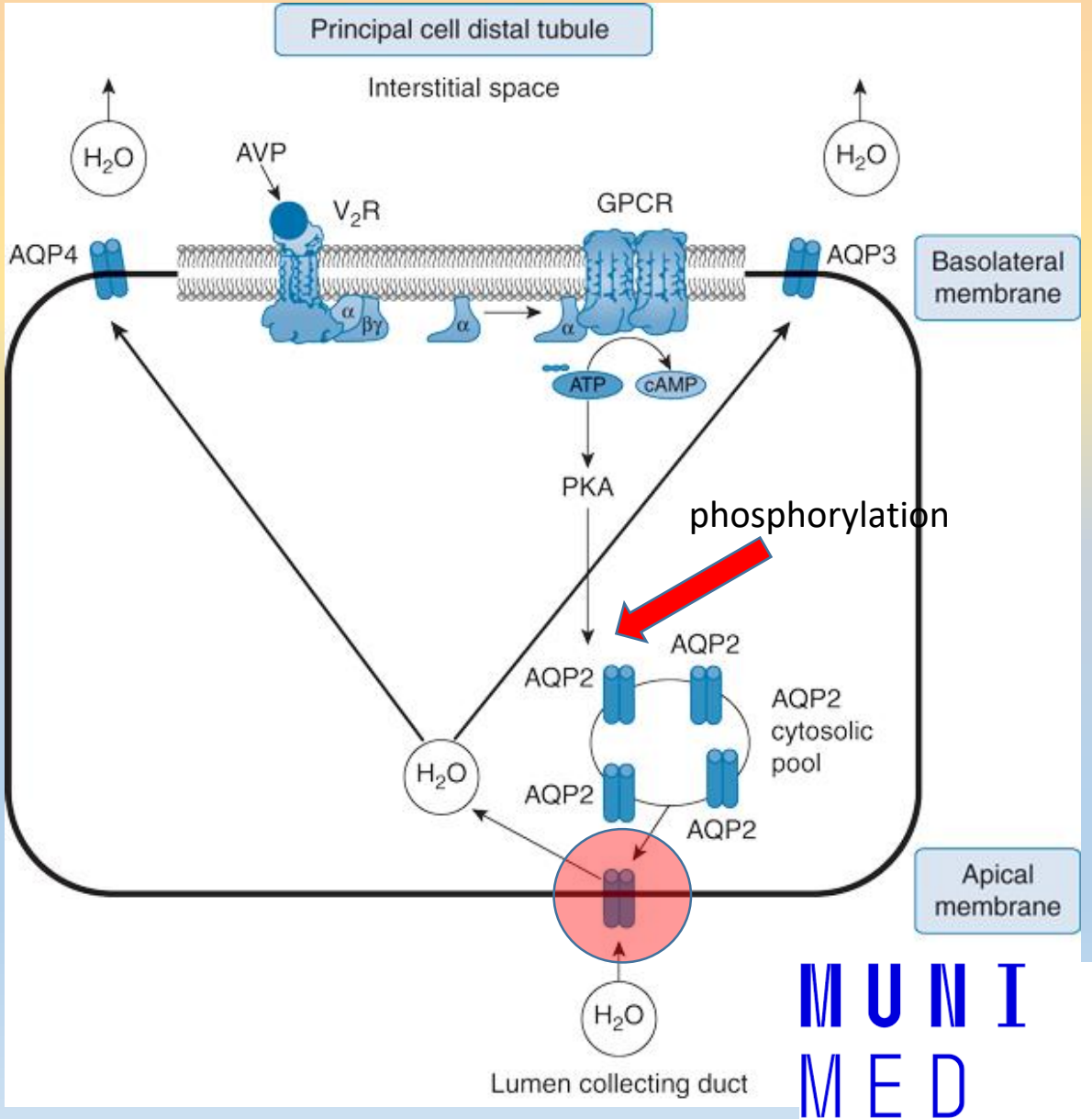


Antidiuretic hormone (ADH, vasopresin, AVP)

Characteristics
- Magnocellular neurons (PVN, SON)
- AVP 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

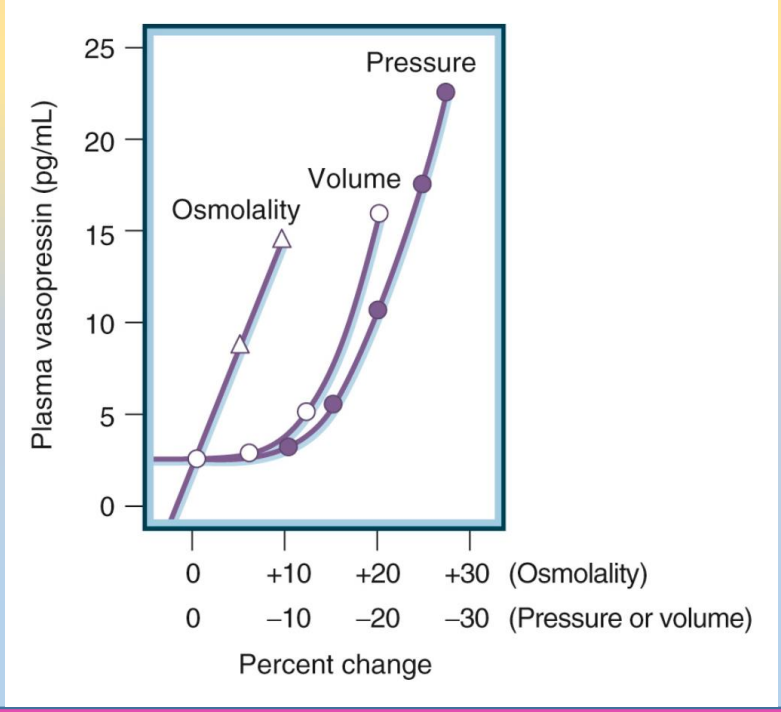
Function
- Water reabsorption (distal tubule, collecting tubule) – tubular system with different water permeability in different parts
  - AQP1 – proximal tubule, HL descending limb HK – 90 % of water reabsorption
  - AQP2 – collecting tubule (only ADH; acute X chronic effect)
  - AQP3, AQP4
- Vasoconstriction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

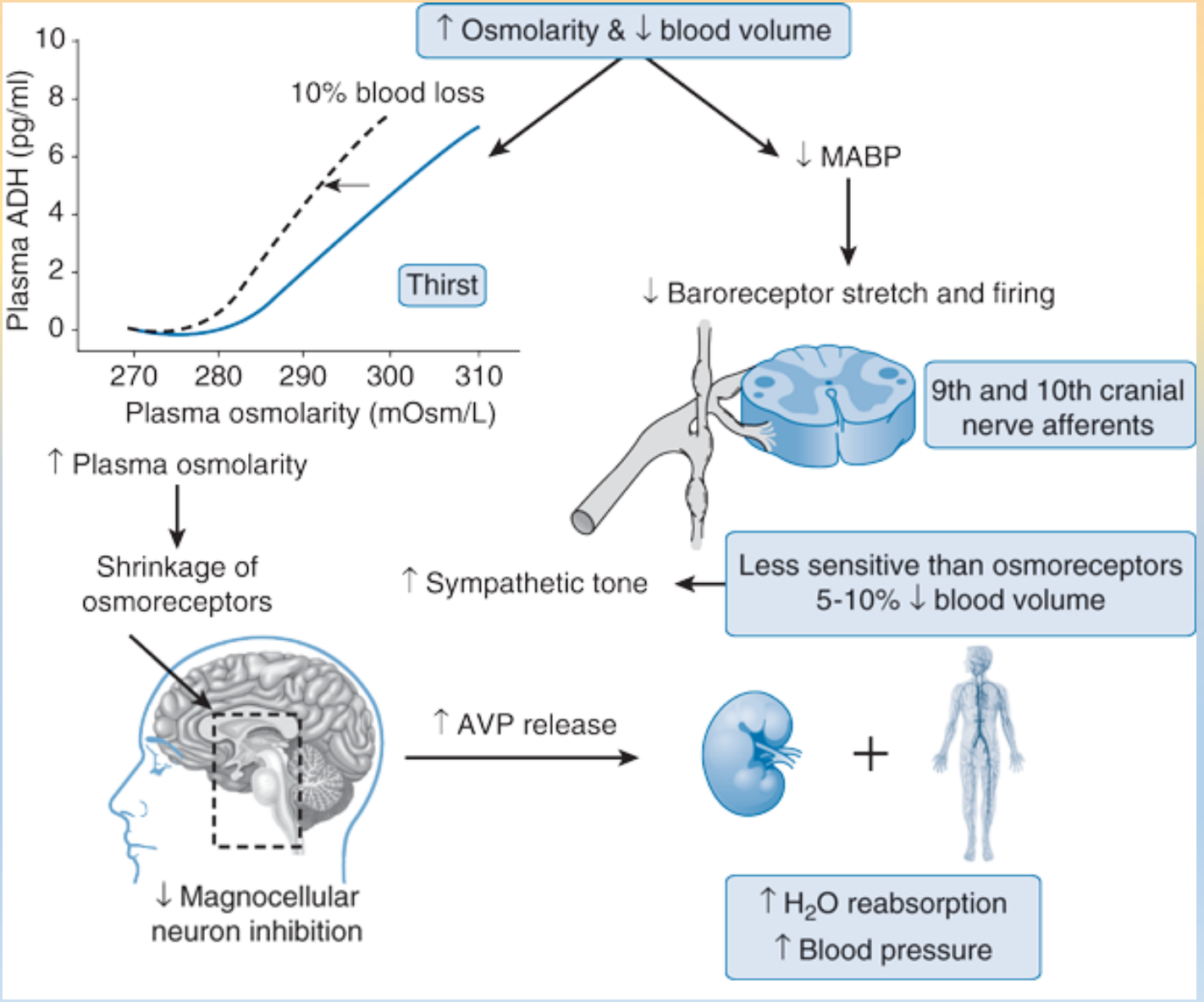


ADH - regulation of secretion

- 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 – osmotic regulation of secretion

- Organum vasculosum laminae terminalis (OVLT) – „Osmostat“
- Insensitivity to urea and glucose
- AQP2
  - Acute effect (min.)
  - Chronic effect – circulating ADH (together with AQP3) – stays up to 24 hours

Thirst

- Increase of plasma osmolality (2 – 3 %)
- Lower IVF volume (over 10 %, usually 20 – 30 %)
  - Frontal region of hypothalamus – osmoreceptors
  - Low- and high-pressure baroreceptors
  - Together with ATII

Pregnancy – RESET OSMOSTAT

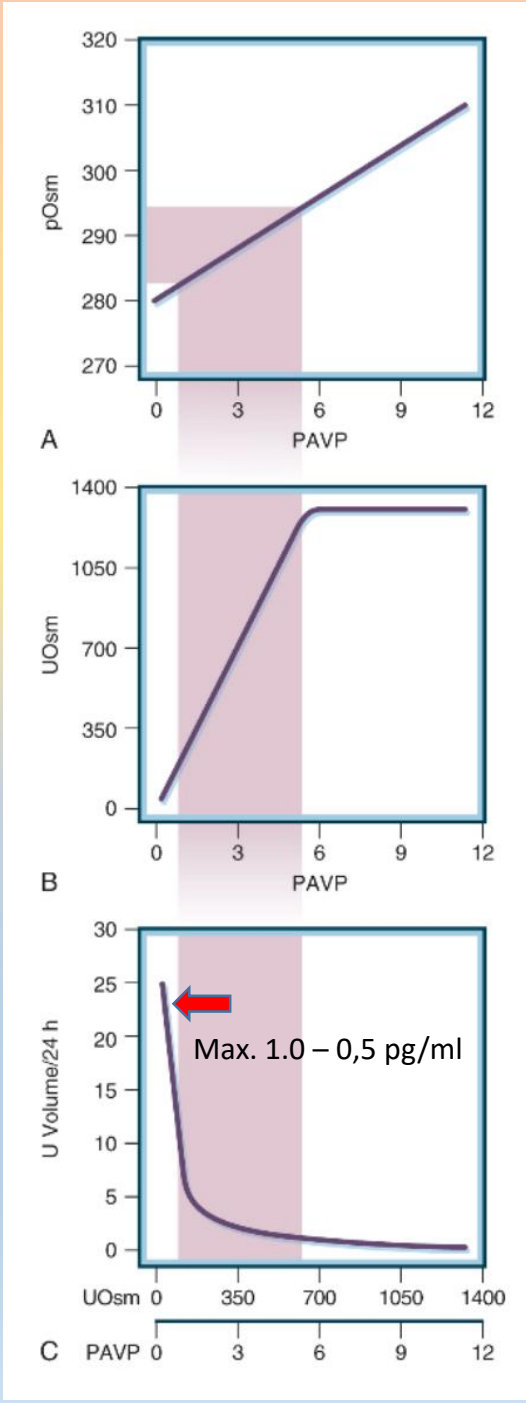
- Decresed osmolality, increased IVF volume
- from 5th – 8th week to 2nd week after birth
- Vasodilatation
- Effect of relaxin (+) and estrogens (+ NO)

Old age – lower sensitivity to ADH, hypo-/hypernatremia

plasma

urine

urine



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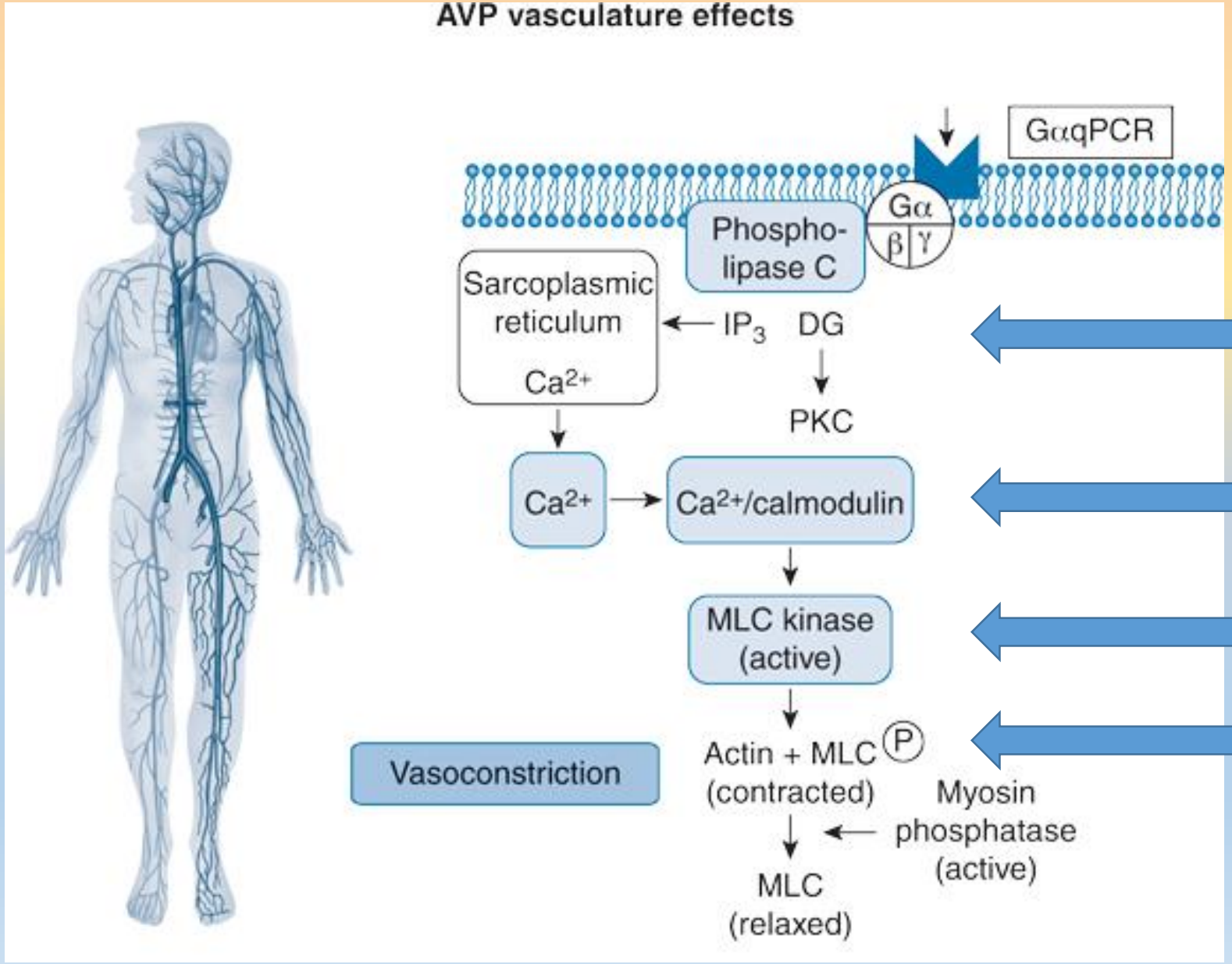
Vasoconstrictive effect of ADH



IP_3 and mobilization of Ca^{2+}

Ca^{2+}.CaM

MLCK activation

Increased activity of myosin ATPase

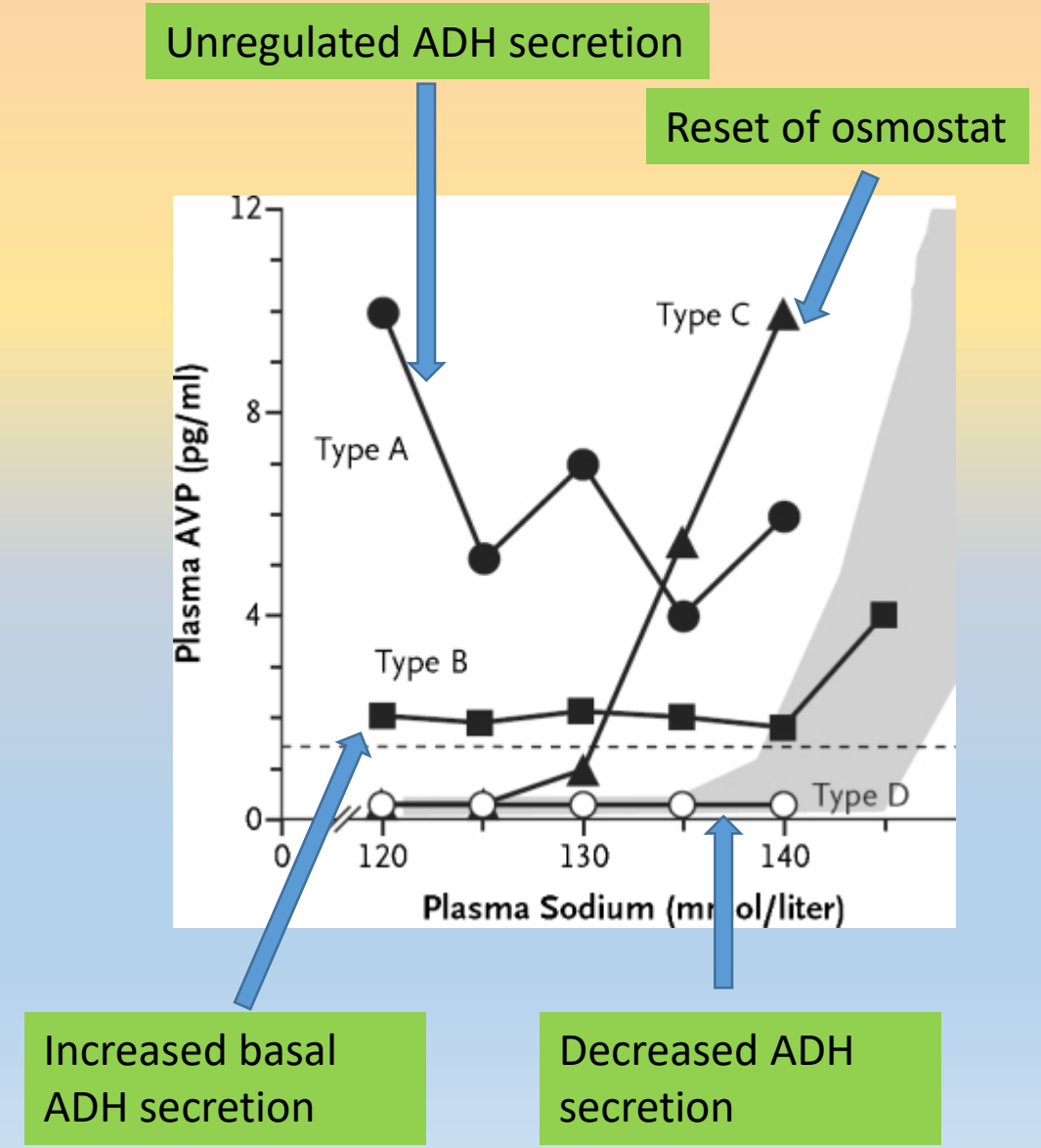
ADH – clinical aspects

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

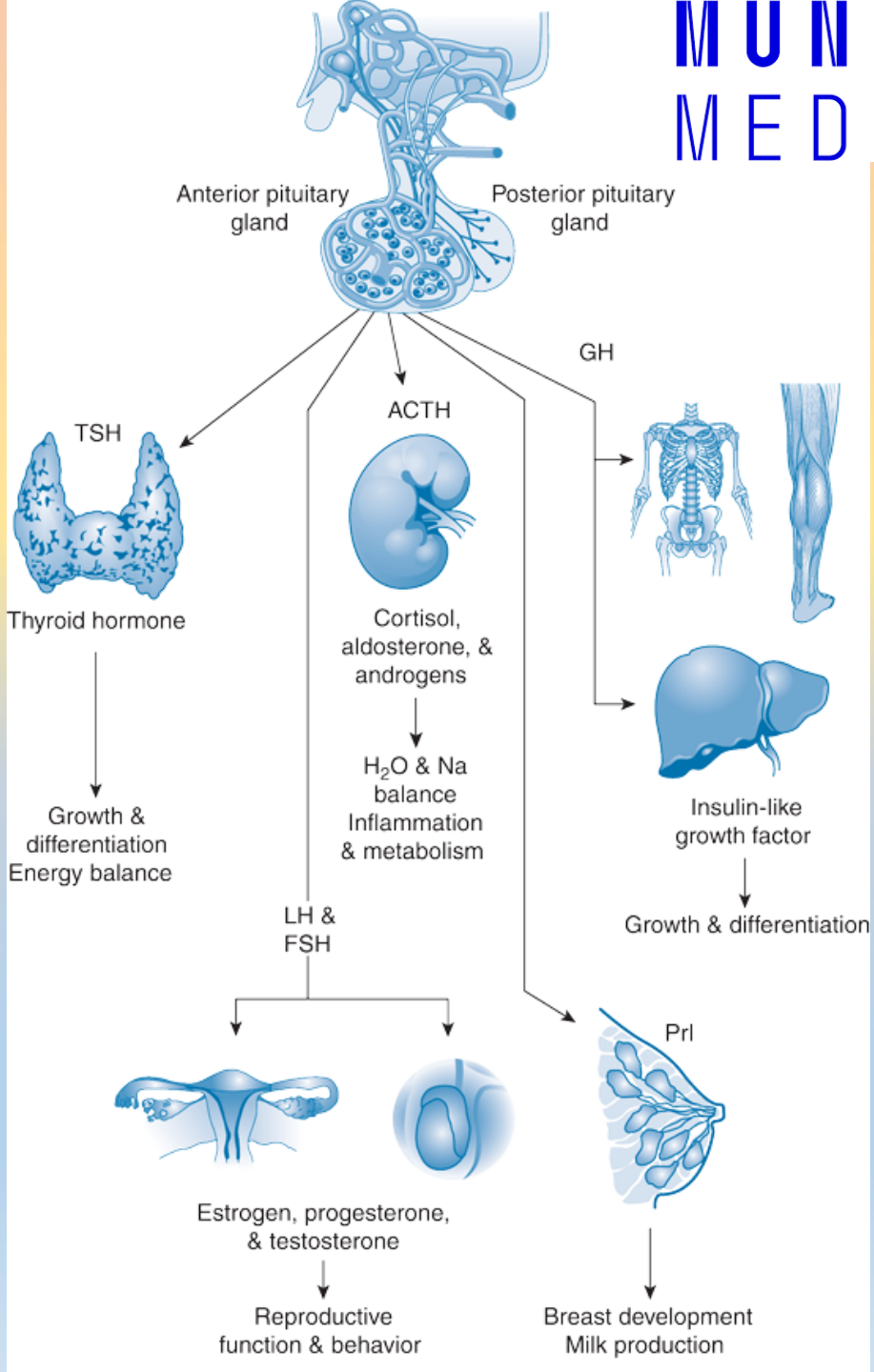


Adenohypophysis

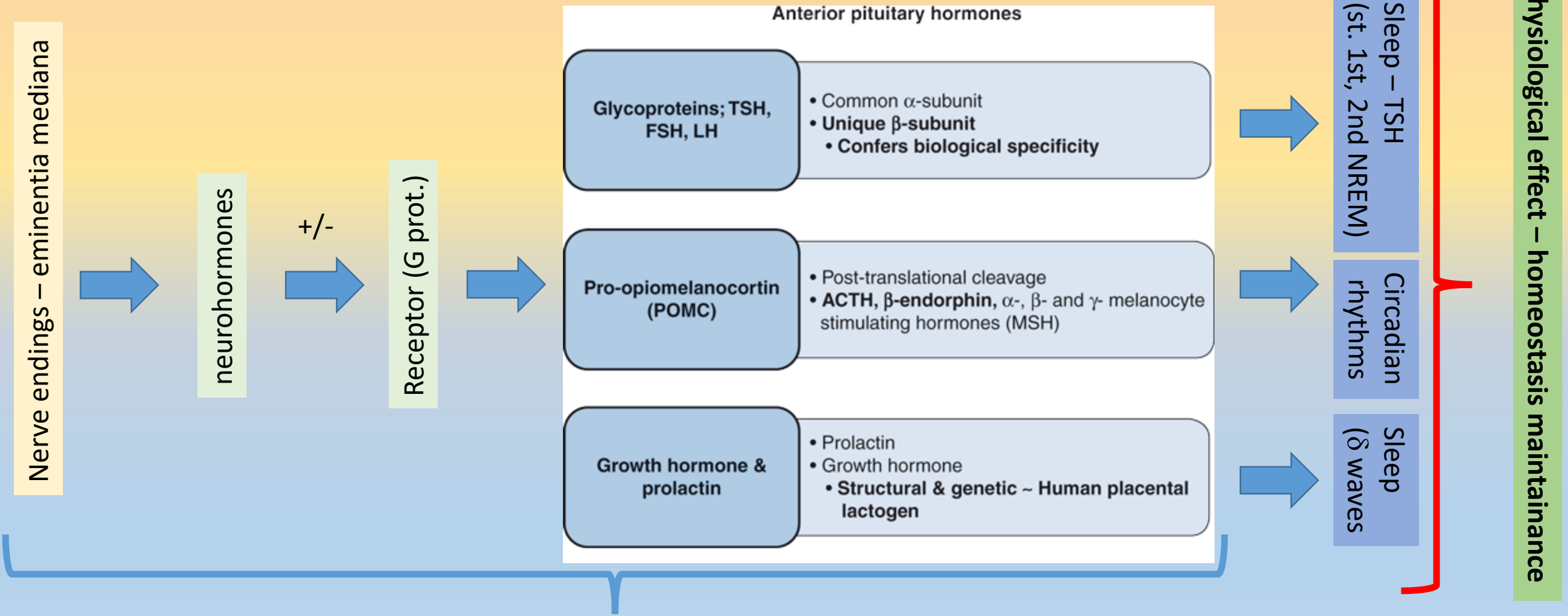
- ACTH – adrenocorticotropic hormone
- TSH – thyreotropic hormone
- GH – growth (somatotropic) hormone
- PRL – prolactin
- LH – luteinizing hormone
- FSH – follicle-stimulating hormone

Adenohypophyseal cells	Representation	Hypothalamic hormone(s)	Adenohypophyseal hormones	Localization
Lactotropic	Up to 25 %	Dopamine	prolactin	whole AH
Cortikotropic	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

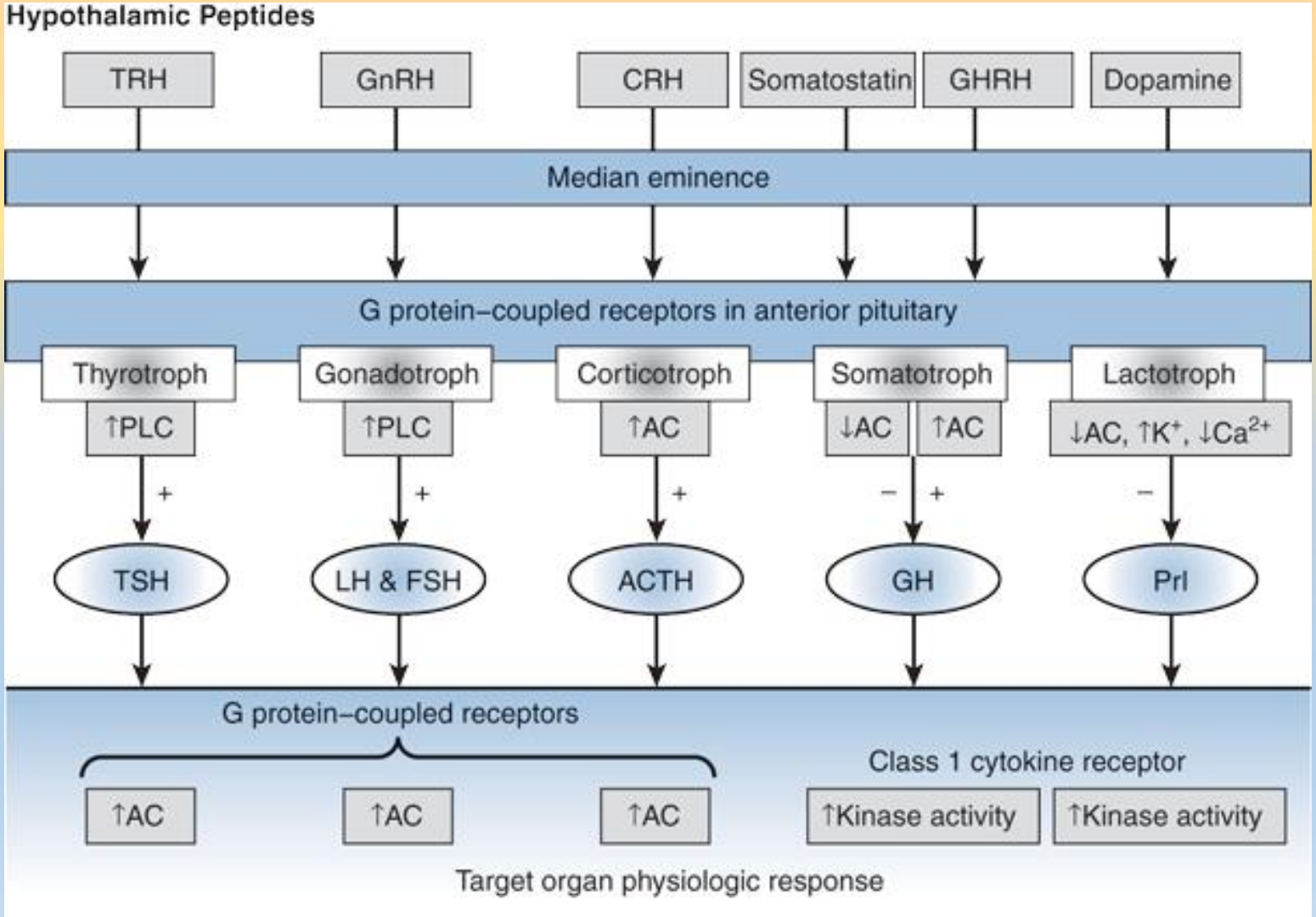


Adenohypophyseal hormones



Suprachiasmatic nucleus | Circulating hormones | Feedback system

Adenohypophyseal hormones



G protein-coupled receptors

JAK/STAT signaling

Glycoproteins - TSH

Characteristics
- Heterodimer
- β subunit – transcriptional factors GATA2 and Pit1
- Negative feedback T3 – inhibition of α subunit transcription; dopamine (α and β)
- Positive feedback – TRH
- Co-translational glycosylation and folding (- T3, + TRH)

Secretion regulation
- 2-3 h pulse + tonic non-pulsatile secretion
- Peak between 23:00 and 5:00
- Stable for 24 hrs. Secretion without other factors (gender, BMI, etc)
- TRH (paracrine), transporters OATP and MCT
- T3 – deiodinases 2 (+T3) and 3 (-T3) with different expression
- Catecholamines – increased of setpoint for TRH inhibition
- Somatostatin (-), glucocorticoids (-), NSA (-)
- Dopamine (-)

Function
- Stimulation of thyroid hormones synthesis
- Growth hormone for thyroid gland

Clinical significance
- TSH deficiency (mutation in genes coding TRH and TSH receptors)
- Analogues of somatostatin
- ! (+) cortisol metabolism

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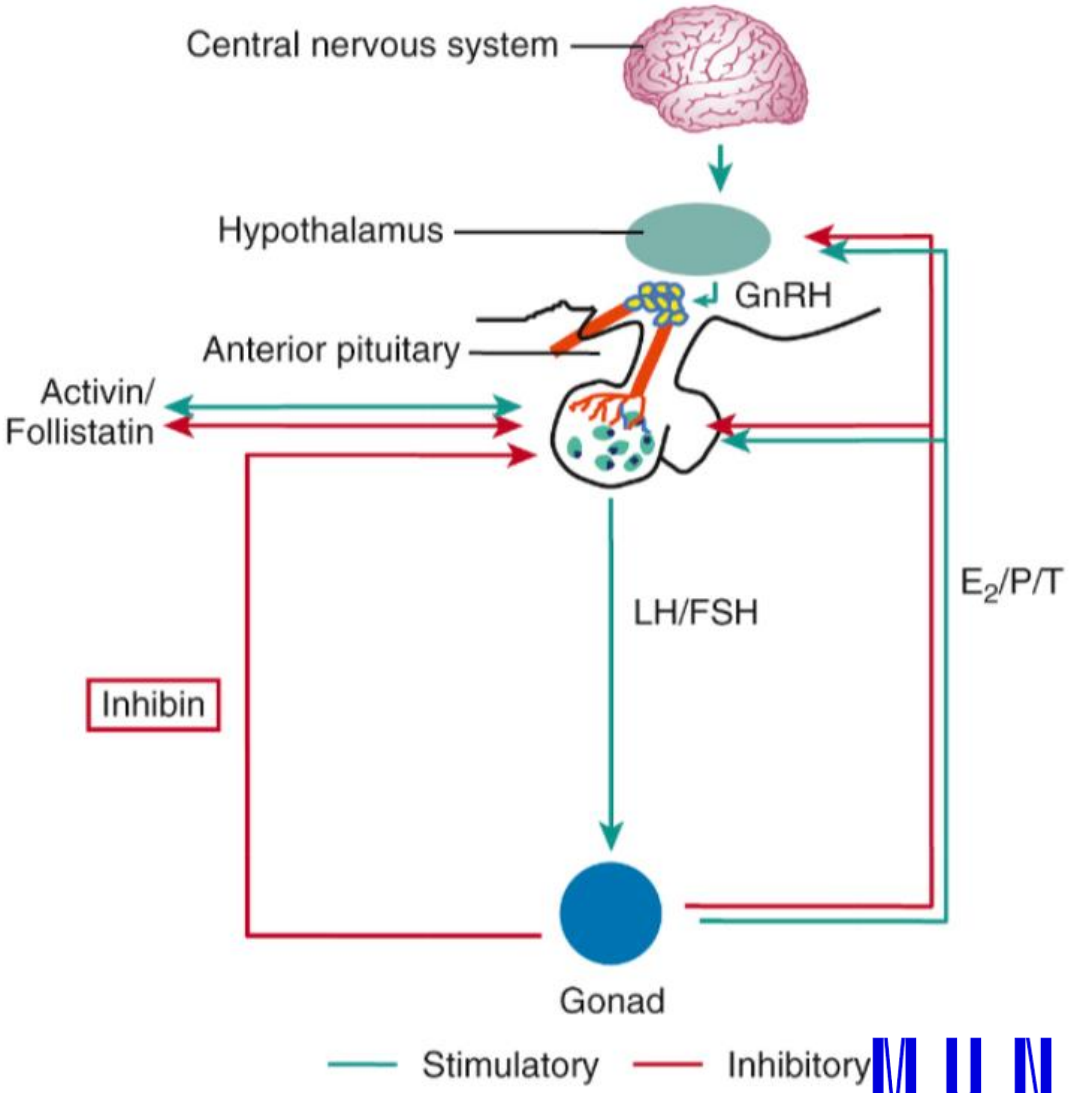
Glycoproteins – FSH a LH

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 influence on gonadotrophs, indirect influence through GnRH
  - Estrogens (-) – inhibition of transcription (α), kisspeptin – NEG
  - 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



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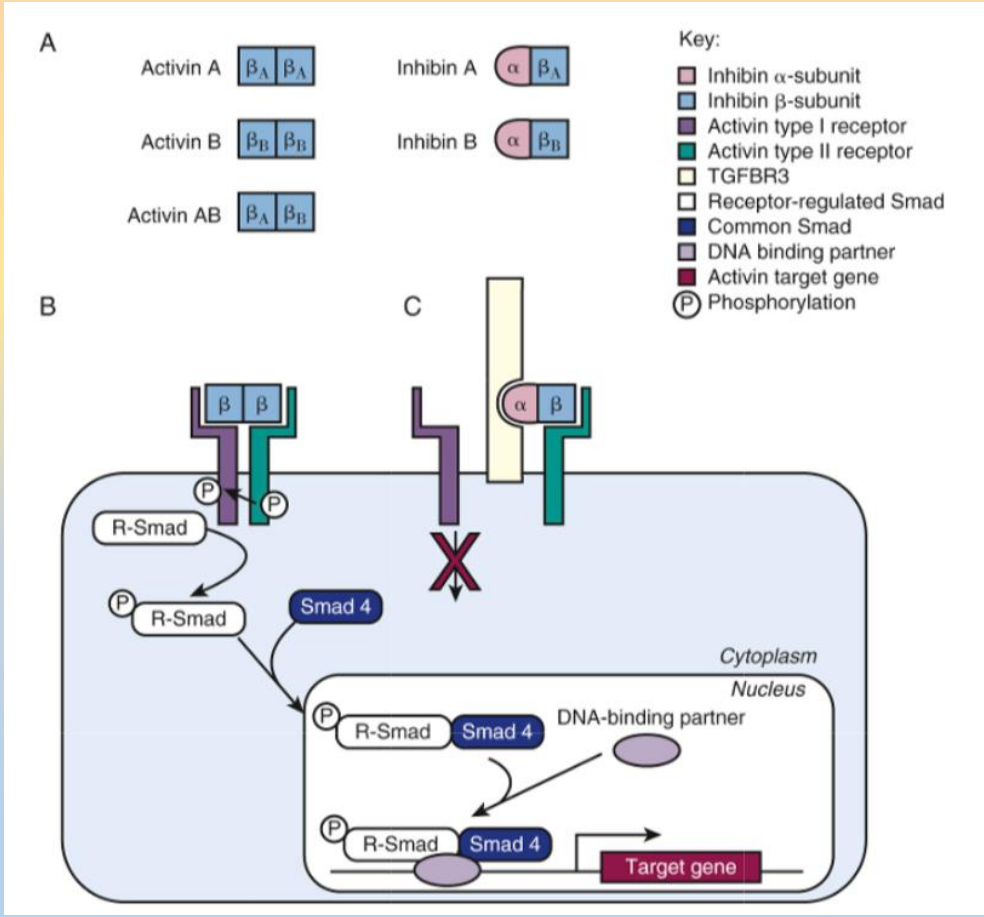
Activins and inhibins

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

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
- activins = regulation of transcription, follistatin and inhibins = inhibition of activins through appropriate activin-receptor binding



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 on various levels (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

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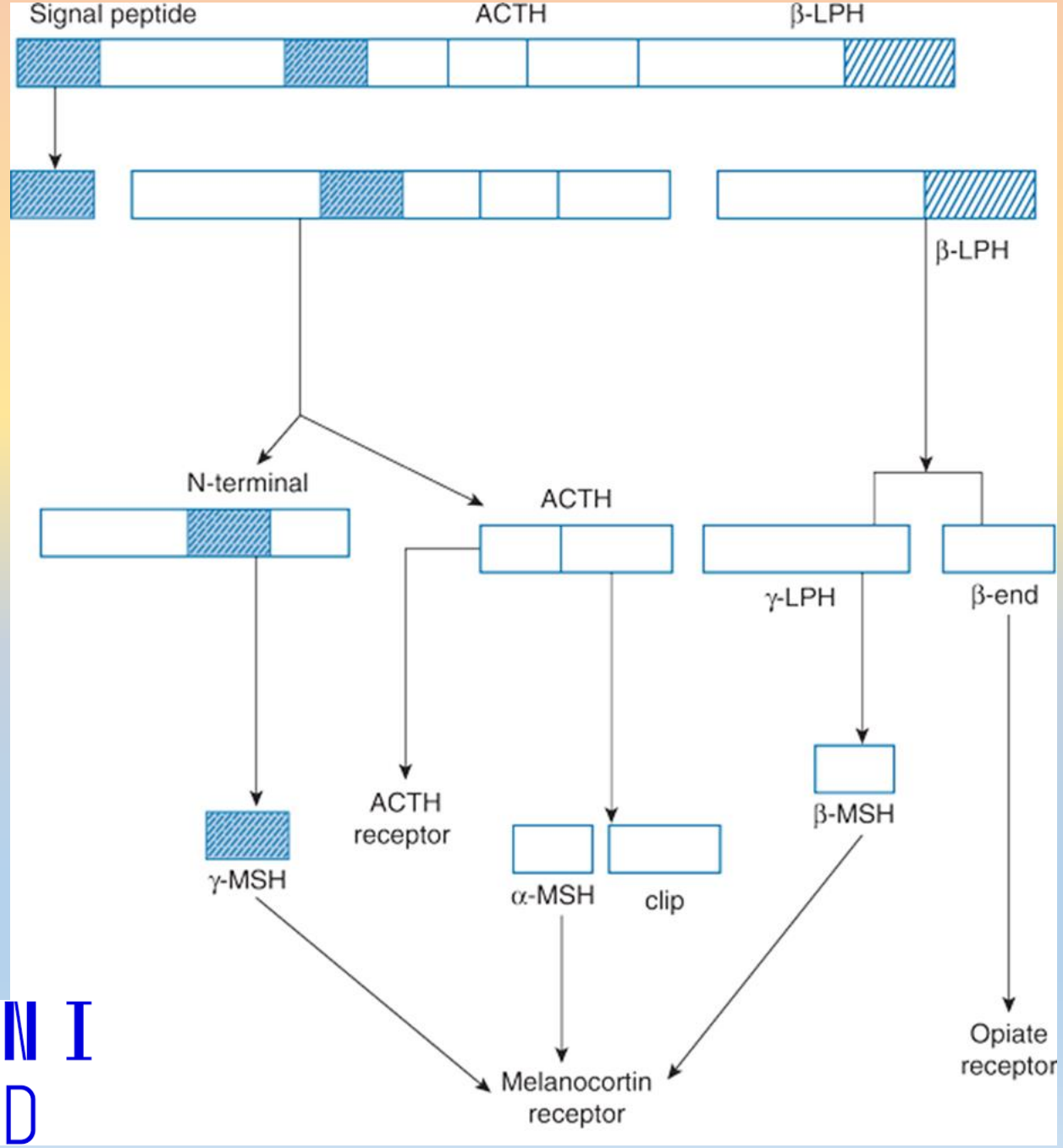
Proopiomelanocortin - POMC

Characteristics
-Adenohypophysis - short transcript
-CNS
-Placenta
-Skin
-Gonads
-GIT
-Liver
-Kidneys
-Adrenal medulla
-Lungs
-Lymphocytes

long transcript with synthesis of products regulating energetic metabolism

Stimulation of expression
-CRH, cytokines, ADH, catecholamines, VIP

Posttranslational modification
- Role of prohormone convertases (PCs)



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Functions of POMC-derived peptides

Adrenal glands - ACTH
- the only POMC hormone with effect on adrenal glands
- MC2R receptor for melanocortin)
- Glucocorticoids, androgens, (mineralocorticoids)
- Mitogennic effect on adrenal glands (N terminal peptide)

Skin pigmentation – ACTH, β-LPH, γ-LPH
- MC1R
- Paracrine regulation (melanocytes, keratinocytes)

Regulation of appetite – α-MSH
- Inhibition of inhibitory effect of leptin
- Activation of MC3R and MC4R (hypothalamus)

Immune functions – α-MSH
- Inhibition of leukocyte migration
- Inhibition of macrophage functions
- Modulation of antigen-presenting and T cells

Analgesia – β-endorphin
- Circulating probably without effect on CNS

Placental POMC
- 2nd trimester
- Decrease 3 days after birth
- No correlation to ACTH/cortisol of mother
- Unknown physiological function

Ectopic synthesis of POMC/ACTH
- Mainly tumors with ability of posttranslational changes

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ACTH

Secretion
-Circadian and ultradian rhythms
-Rise from 16:00 with peak before 19:00
-Lowest levels between 23:00 and 3:00
-pulsatile secretion (ca 40/day, higher in males)

Function
- Adrenal glands size, structure and function
- Steroidogenesis stimulation

Secretion regulation
- Very complex - neuroendocrine control of stress response and homeostasis
- Regulatory molecules – CNS, hypothalamus (CRH, ADH, dopamine) – corticotropic cells
- Cytokines (IL-6, LIF), growth factors – adenohypophysis – local control (paracrine)
- Glucocorticoids
  - Negative feedback mechanism – inhibition of CRH secretion, decrease of basal ACTH secretion
  - Modulation of somatostatin inhibitory effect (downregulation of R)
- Dopamine
- Physiological regulation of secretion – exercise (athletes – hypercortisolism)

Clinical significance
- Deficiency ACTH
- Hypersecretion of ACTH
- Testing - insulin

ACTH and stress
- Complex – peripherial and central stress adaptors
- Vasovagal and sympathetic activation (catecholamines), cytokine secretion
- Pain, infection, inflammation, bleeding, hypovolemia, trauma, hypoglycemia, psychological stress
- Higher amplitude of ACTH pluses

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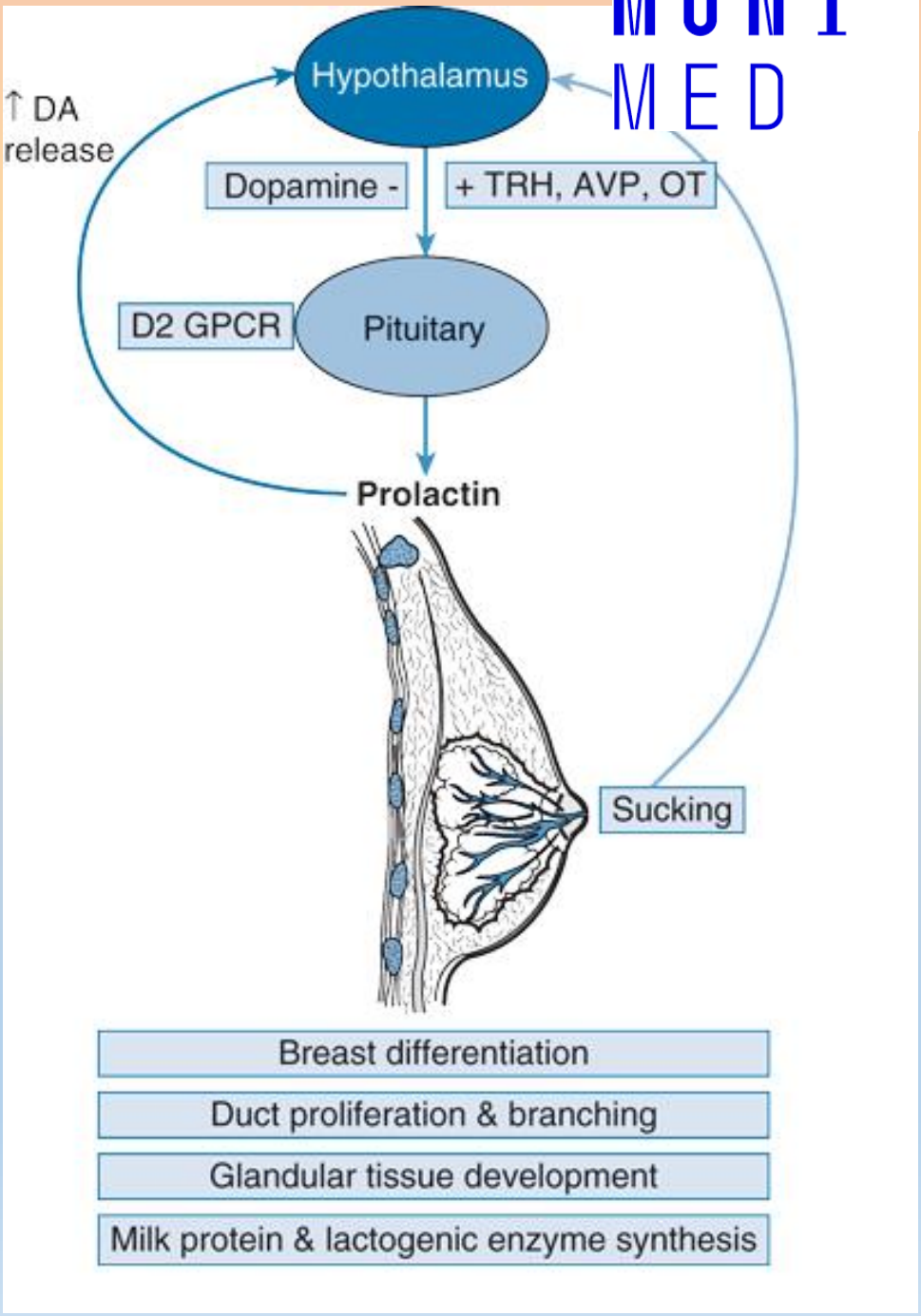
Prolactin - PRL

Characteristics
- Lactotropic cells (only PRL)
- Mammosomatotropic cells (PRL and GH)
- Hyperplasia – pregnancy and lactation
- Expression regulated by estrogens, dopamine, TRH, thyroid hormones
- Polypeptide circulating in three forms (mono-, di-, polymer)
- Monomeric PRL with highest biological activity
- Monomeric prolactin further spliced (8/16 kDA)
- 16 kDA PRL – antiangiogenic function
- 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 (-, D2R)
- 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, melanin 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

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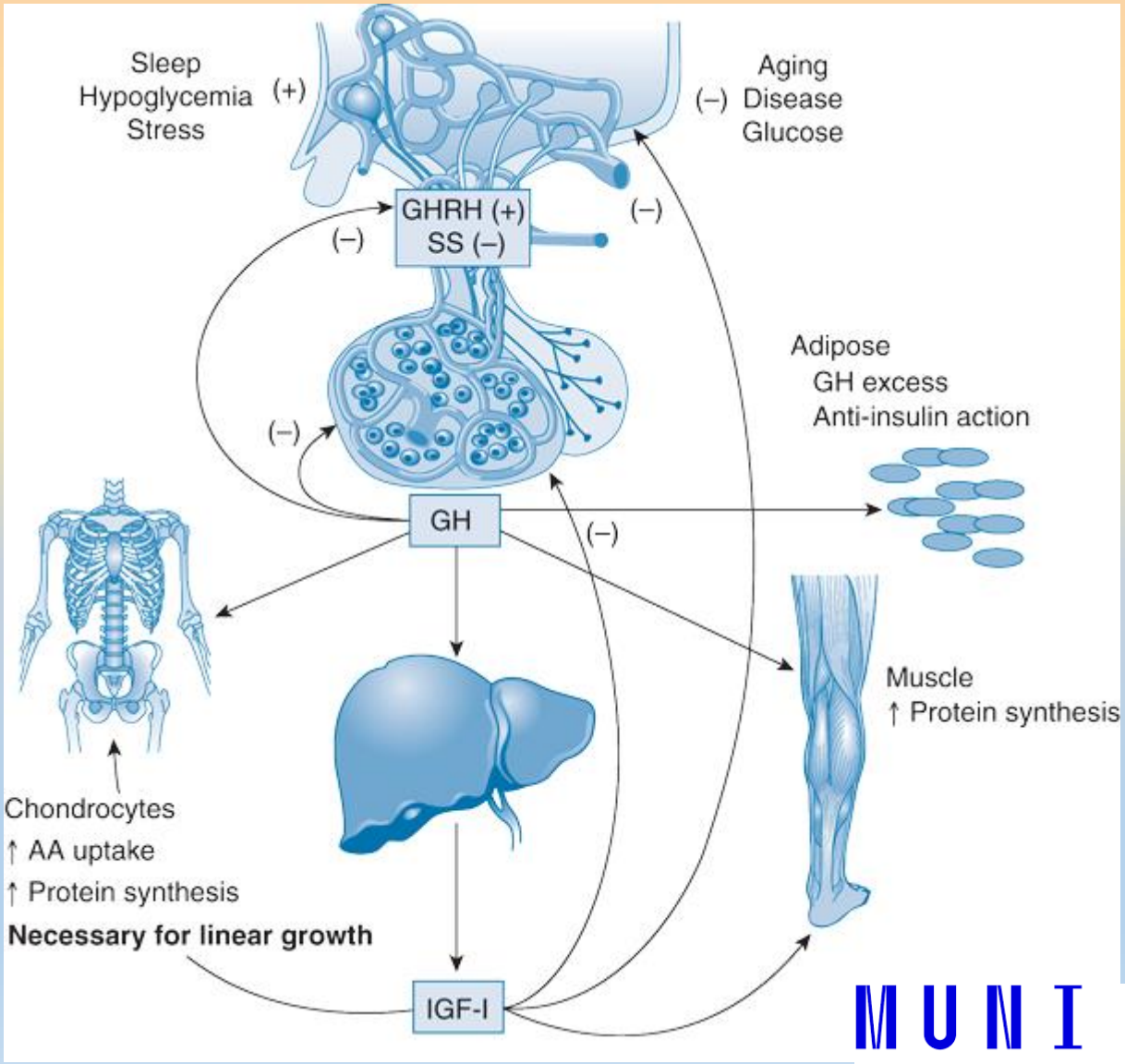
Growth hormone (GH)

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, IGH-1, thyroid hormones, glucocorticoids
-Relatively complicated system of regulation:
- Neuropeptides
- Neurotransmitters
- Endogenic opioids



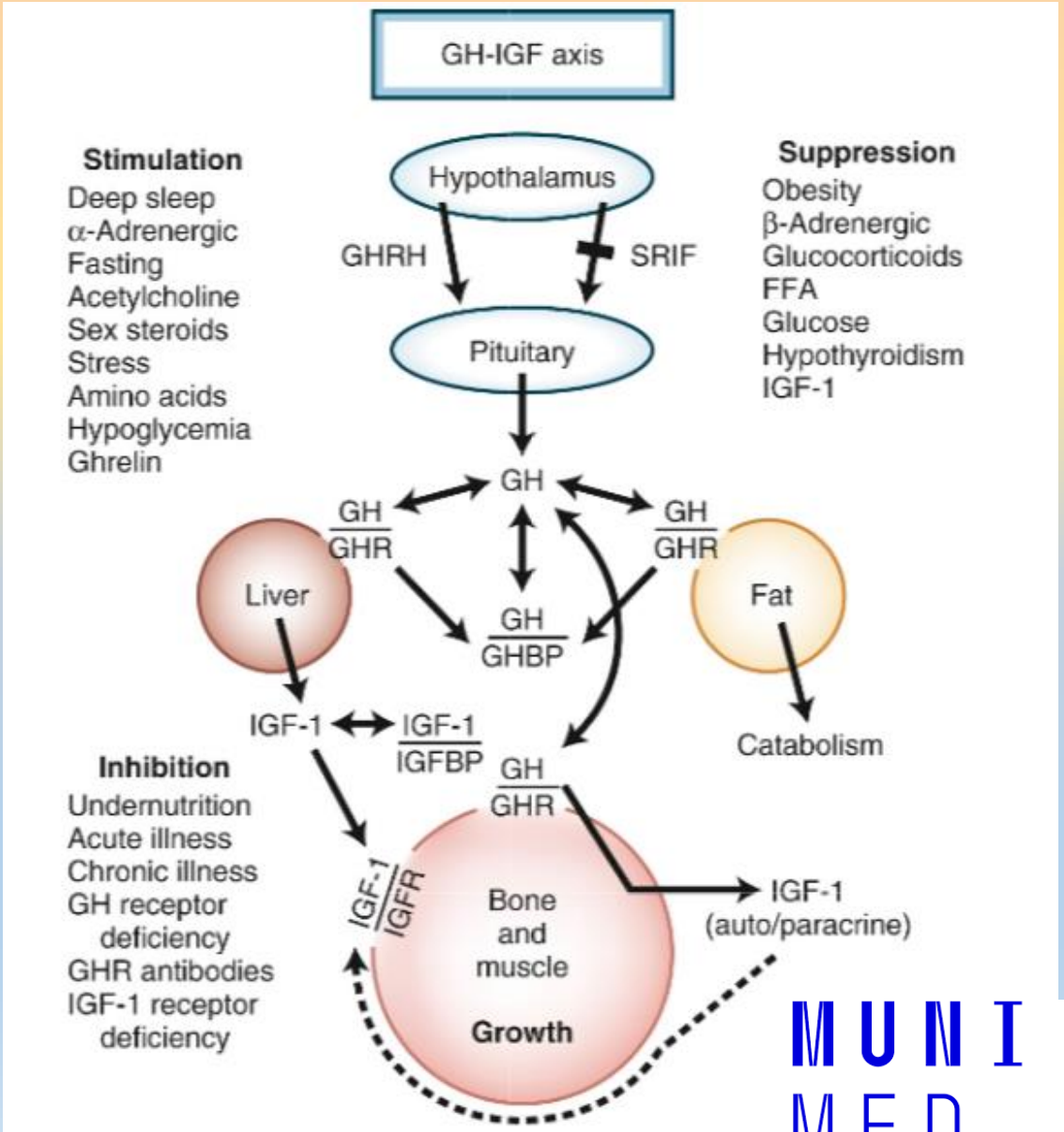
Growth hormone (GH) – regulation of secretion

- 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



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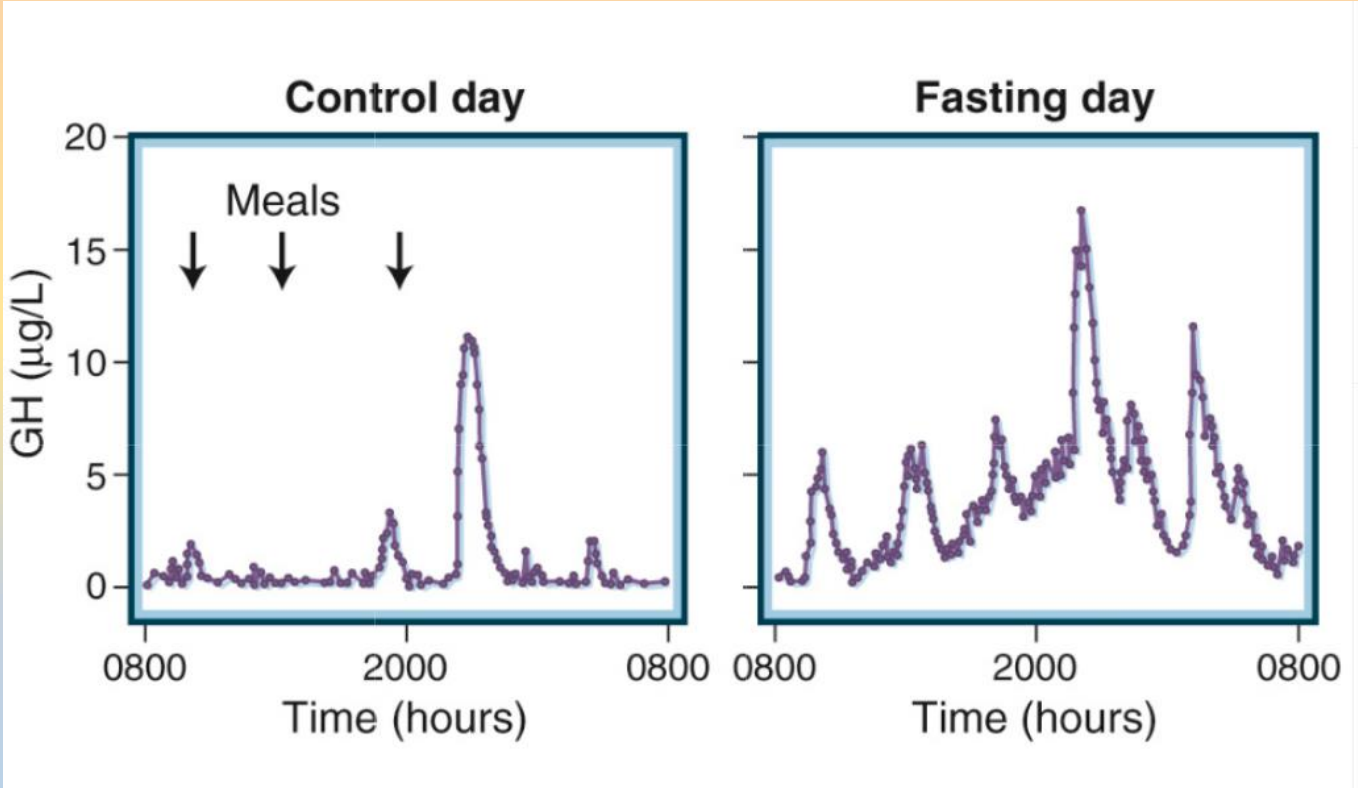
Growth hormone (GH) – regulation of secretion



- Malnutrition (+)
- Obesity (-)
- Glucose (-)
- Arginine, leucine (+)
- FFA (-)
- leptin

- „jet lag“
- exercise
- physical stress including infection, sepsis

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GH and interaction with other hormanal 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)

TRANSPORT
-GHBPs
-20 kDA with low affinity
-60 kDa with high affinity
-Obesity (+)
-Pregnancy (+)
-p.o. estrogens (+)
-Malnutrition (-)
-Cirrhosis (-)
-Hypothyroidism (-)
-Androgens (-)
-Glucocorticoids (-)

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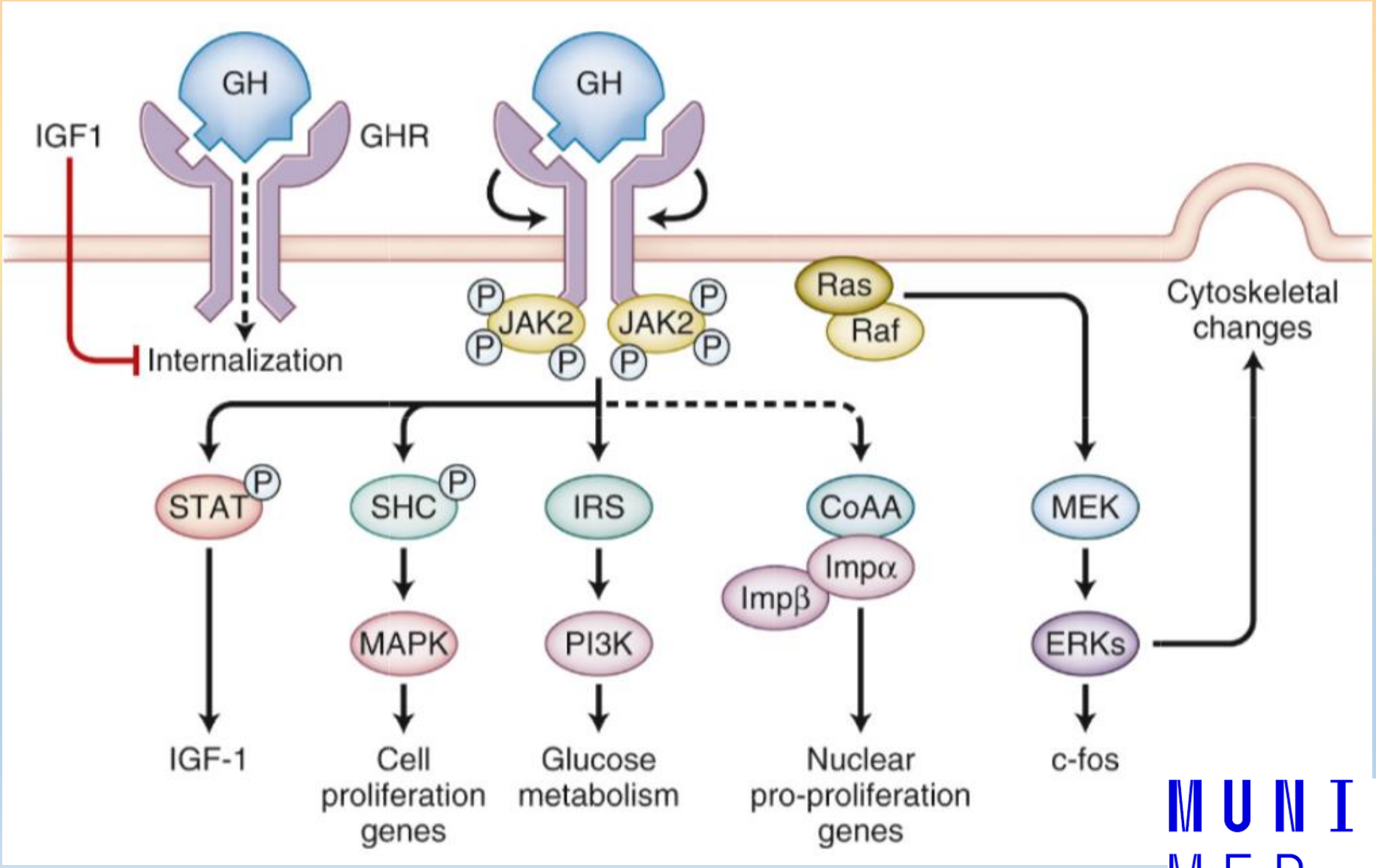
GH – receptors and cell signaling

- GHR (dimer)
- JAK-STAT
- Liver
- Adipose tissue
- Skeletal muscles

- Mutual integration of signaling pathways?



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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,

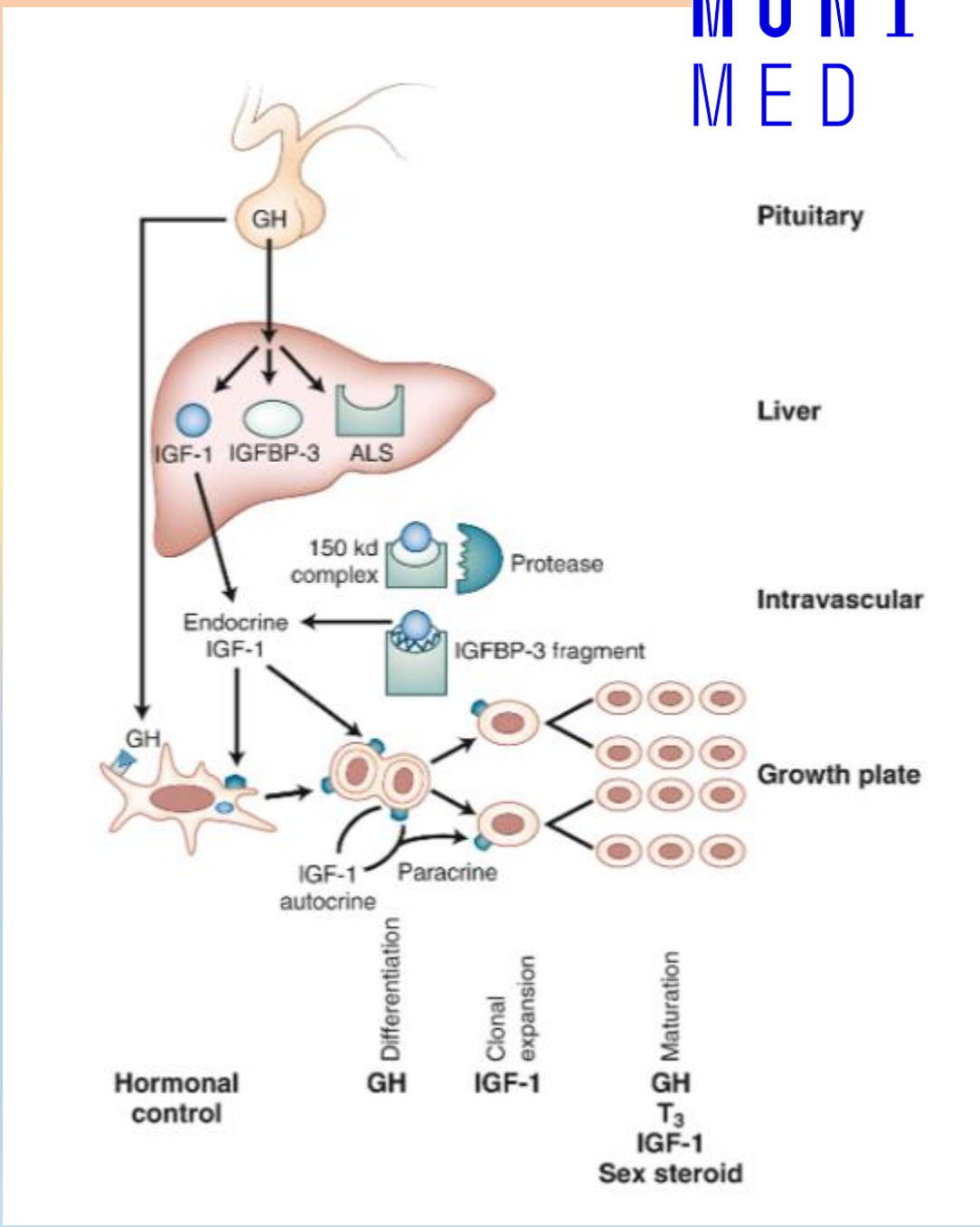
- (+) uptake of Glu
- (-) Glu oxidation
- (+) gluconeogenesis

-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

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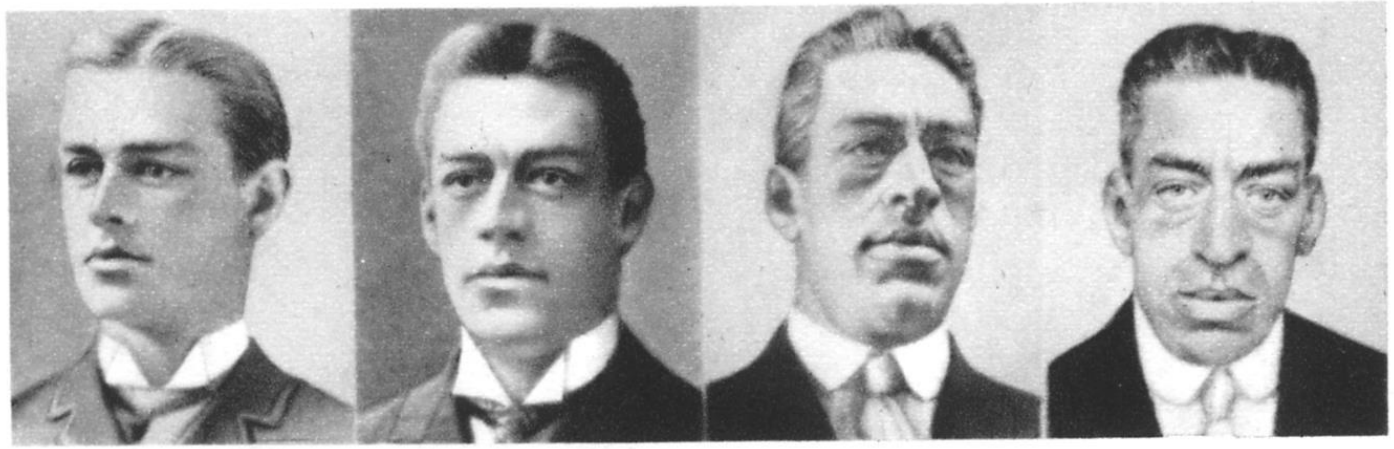

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MSH – melanotropins

α-MSH: Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val
β-MSH: Ala-Glu-Lys-Lys-Asp-Glu-Gly-Pro-Tyr-Arg-Met-Glu-His-Phe-Arg-Trp-Gly-Ser-Pro-Pro-Lys-Asp
γ-MSH: Tyr-Val-Met-Gly-His-Phe-Arg-Trp-Asp-Arg-Phe-Gly

- Pregnancy (+)
- Adrenal glands (hypofunction)

Clinical significance

-Synthetic analogues

-Afamelanotide – photoprotection

-Melanotan II – increased libido

-Bremelanotide – aphrodisiac effect (MC3R and MC4R)

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