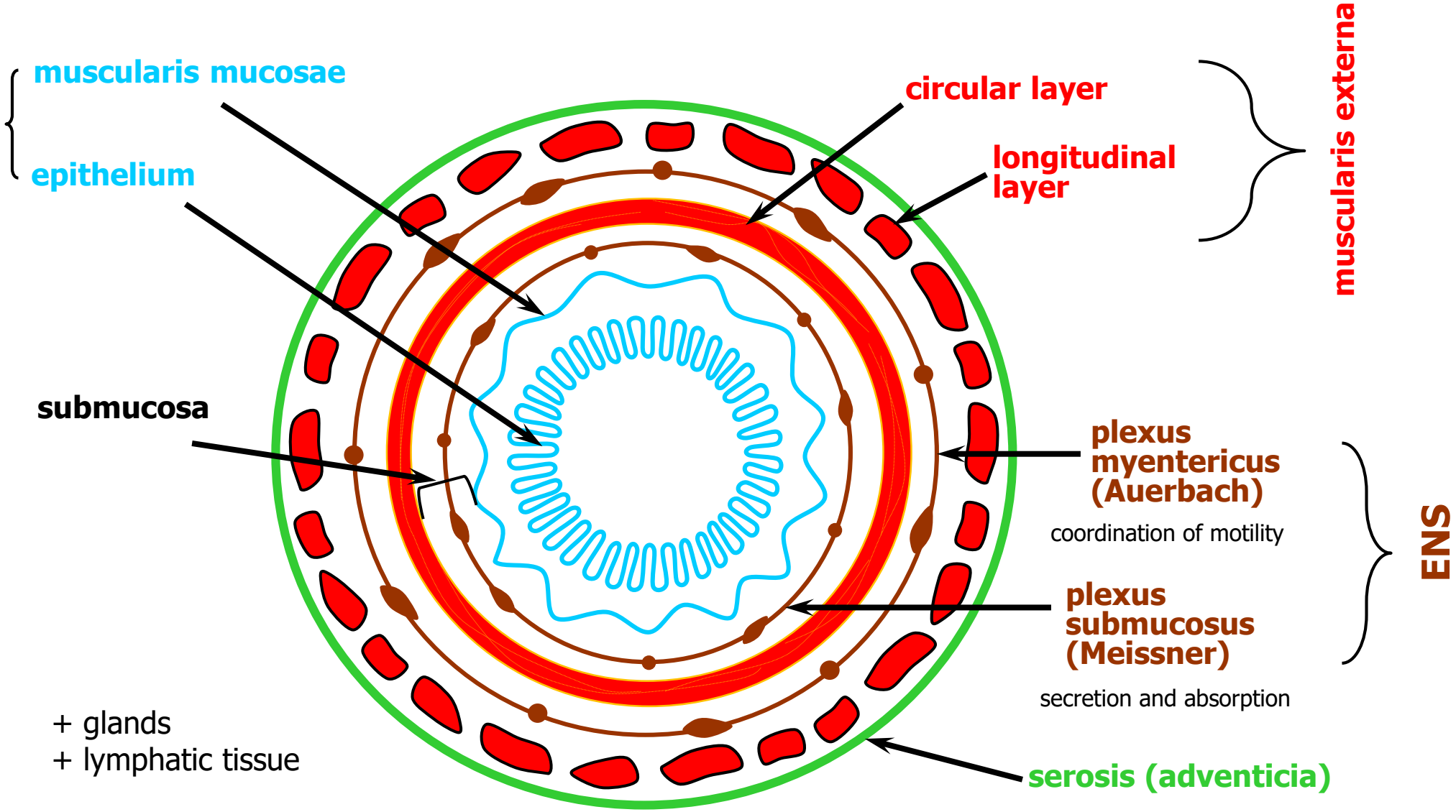
MUNI
MED

GASTROINTESTINAL TRACT



Modified according to: J. Švíglerová: Fyziologie gastrointestinálního traktu, LF UK Plzeň, 2012

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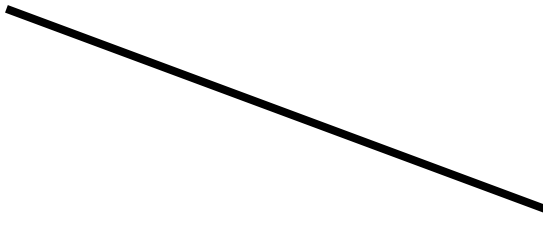
GIT **motility** – mainly nervous control

Secretion in GIT – mainly humoral control



+

PARASYMPATICUS

(preganglionic cholinergic fibres)

n.VII, n.IX, n.X, nn.pelvici (S2-S4)

-

SYMPATICUS

(postganglionic adrenergic fibres)

Th5-L2

(tonus and motility –)

(vasoconstriction)

(musc.mucosae, sphincters +)

Circular muscle layer: inhibitory fibers, contraction – gut is longer and smaller in diameter

Longitudinal muscle layer : no inhibitory fibers, contraction – gut is shorter and bigger in diameter

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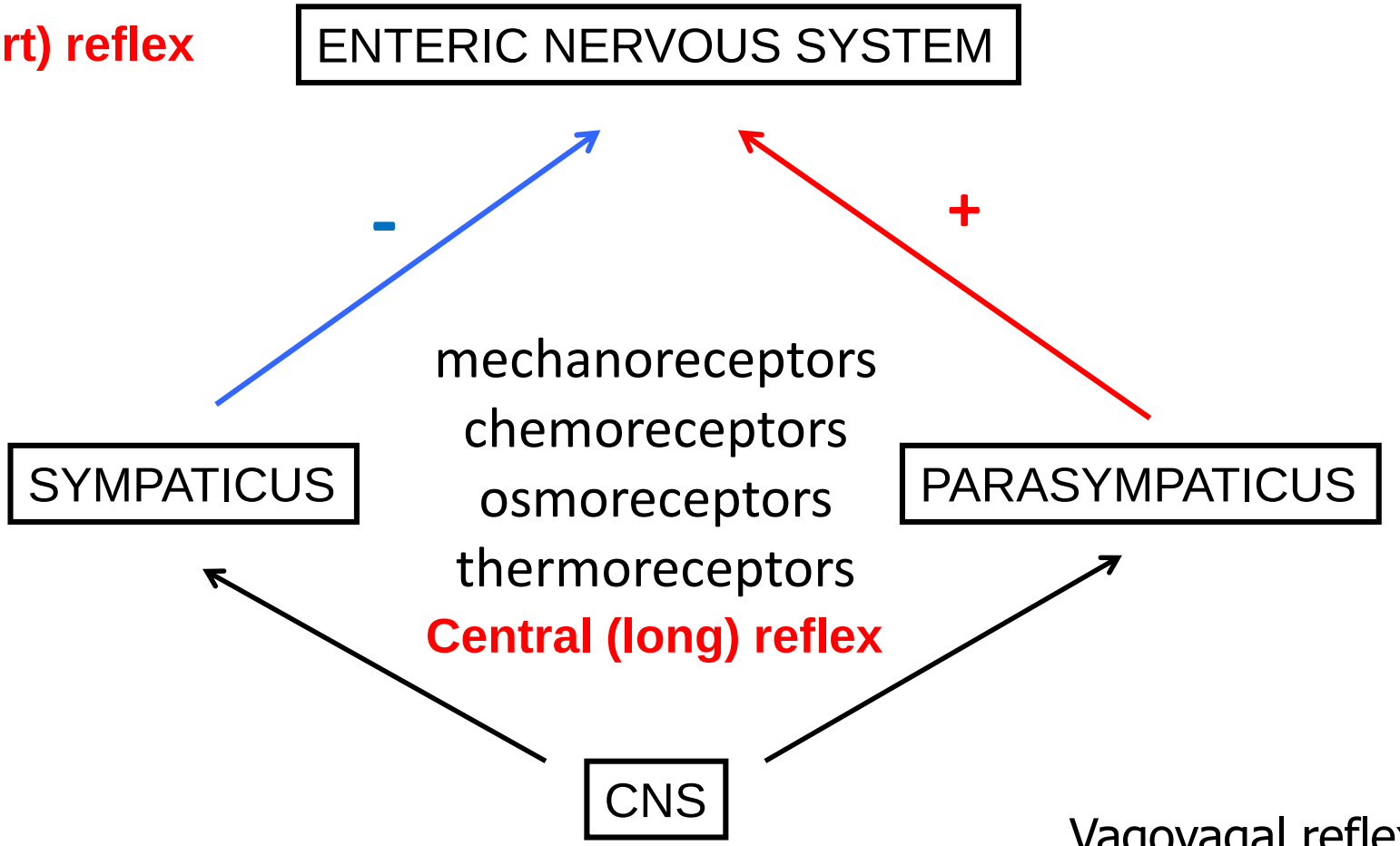
GIT INNERVATION

Local (short) reflex



Vagovagal reflex

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ENTERIC NERVOUS SYSTEM

(plexuses + endings of sympathetic and parasympathetic nervous system + other GIT neurons)

Chemoreceptors, mechanoreceptors, thermoreceptors…
(mucosa, musc. externa)

Local (short) reflexes

Central (long) reflexes

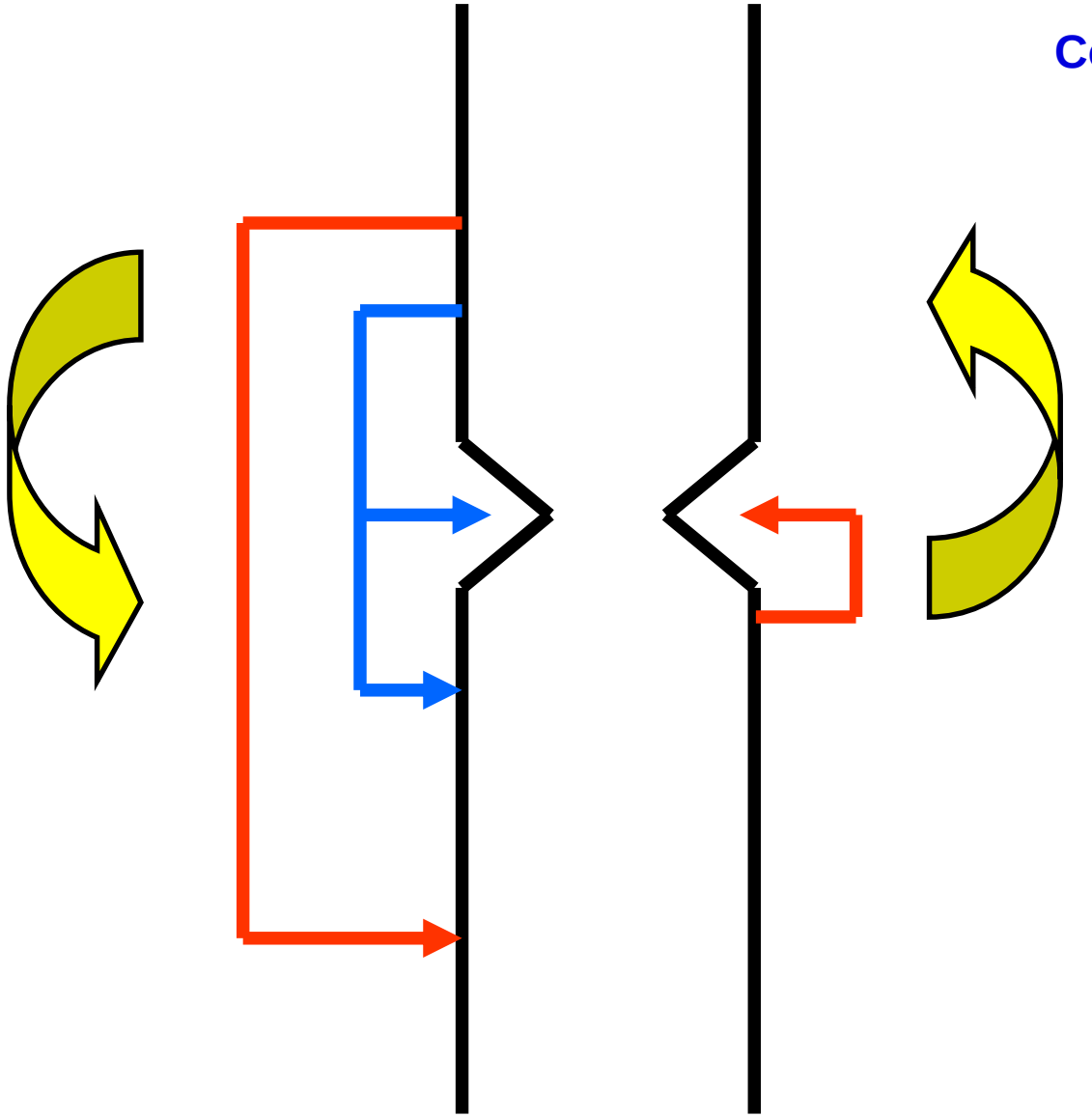
Mediators and modulators: Ach, peptides and bioactive amines

Ach, VIP, NOR, DOPA, serotonin, histamine, AT II, PG
somatostatin, enkephalin, GABA, TRH, neuropeptide Y, substance P
secretin, GIP, glucagon, gastrin, CCK, G-releasing peptide

(Secretin group)
(Gastrin group)

Continuous tonus of
S, PS

FORWARD SIGNALS:
SPEED UP, OPEN THE WAY



BACKWARD SIGNALS:
SLOW DOWN, CLOSE THE WAY

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GIT MOTILITY

CONTRACTIONS

tonic (stomach, colon)

rhythmic

MOVEMENTS

propulsive (peristalsis, myenteric reflex)

mixing

Receptive relaxation.

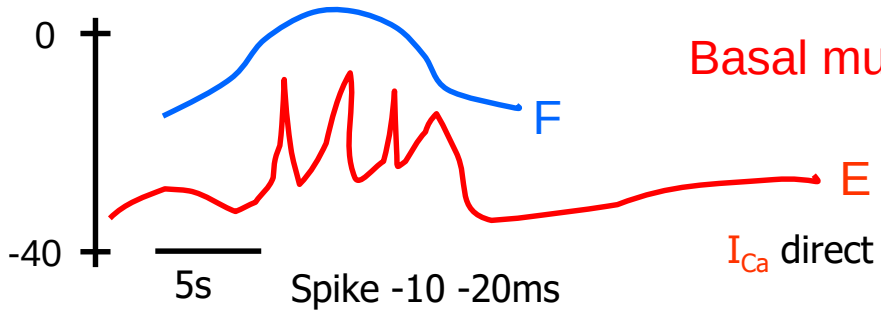
These contractions and movements are responsible for churning, peristalsis and reservoir action in GIT.

ELECTROPHYSIOLOGY OF GI SMOOTH MUSCLE

Resting potential:	from - 40 to - 80mV (↑gNa : ↓gK)
Lower activity of Na+/K+-ATPase	
Slow waves (oscillation of rest.MP)	3 (stomach) – 12(duodenum)/min – **basal electric rhythm**
Spike (AP)	low voltage, depolarisation – Na^+ and Ca^{2+}, 1-10/sec
Pacemaker cells in ENS	automacy
Variability	neurohumoural regulation

Innervations: nexus, innervations of circular muscle >> longitudinal muscle

No motor endplate Ach, ENS, exceptions

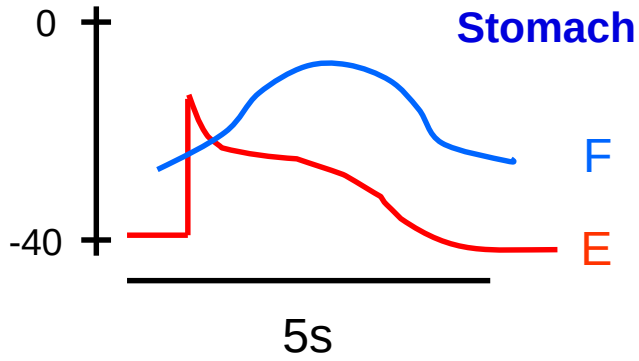


Spike -10 -20ms

Basal muscle tonus, basal rhythm (time summation)

Modulation of slow waves – amplitude (less by frequency)

I_{Ca} direct activation of contraction (binding to calmodulin)



Stomach

Contractions triggered by slow waves (no AP!!!)

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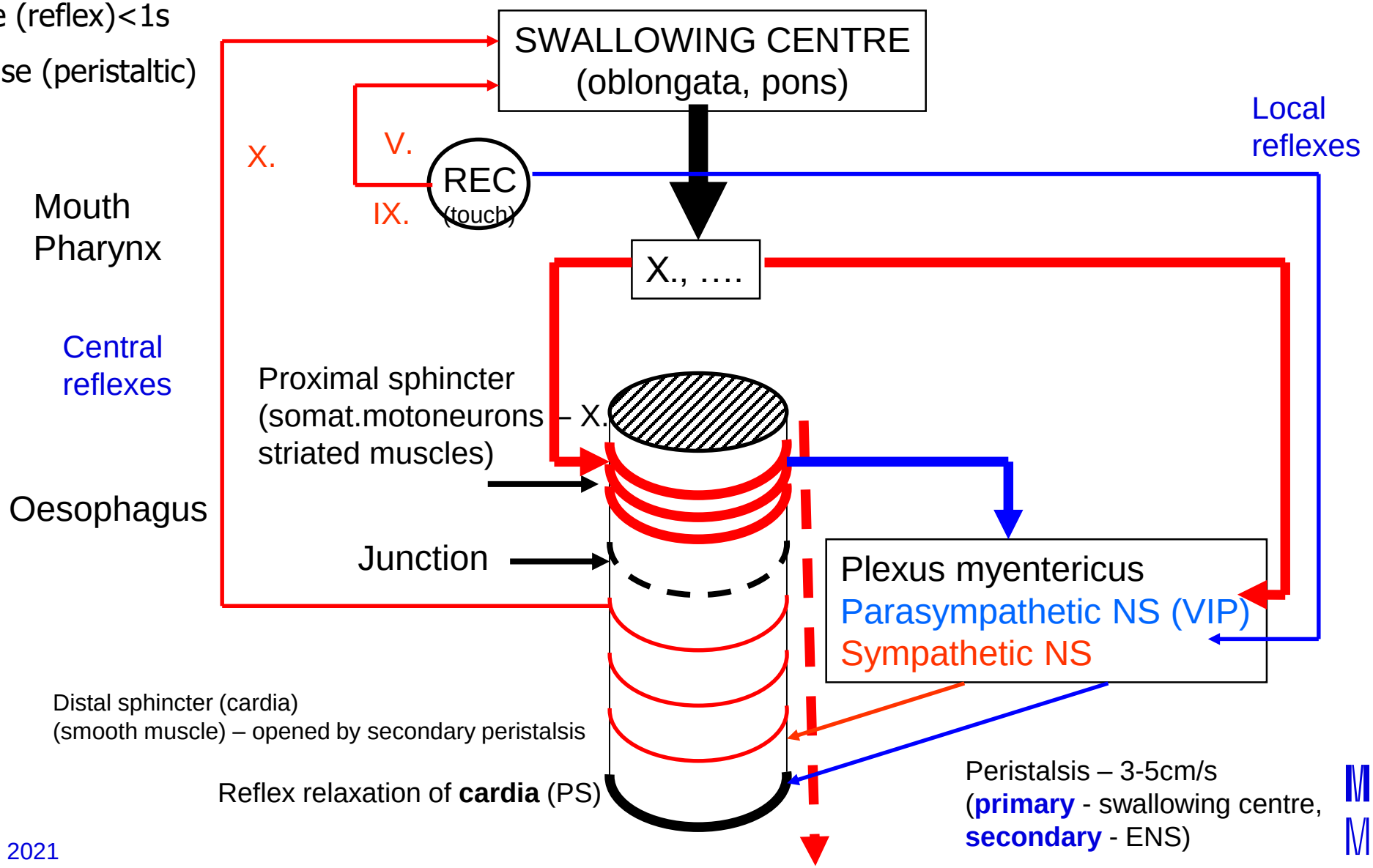
SWALLOWING

- **Oral** phase (voluntary)
- **Pharyngeal** phase (reflex)<1s
- **Oesophageal** phase (peristaltic)

Food – chewing (voluntary and reflex)
Frequency of swallowing – approx. 600x / day
Saliva (1.5 litres / day)



Achalasia (cardiospasmus)
Gastrooesophageal reflux

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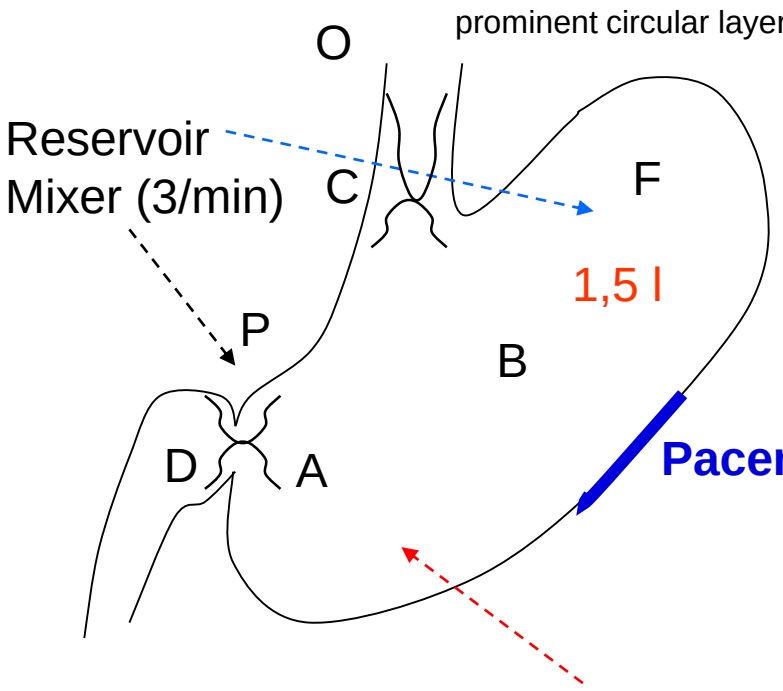
GASTRIC MOTILITY



Reflex relaxation of distal oesophageal sphincter (cardia)

Receptive relaxation of fundus and body
(X. – VIP) (Laplace: P = **T** . R)

Pacemaker zone (3/min)

Motoric gradient
(F <<< A)

Migrating myoelectric complex
(„hungry“ contractions)

Chyme stratification

1-2 hour: rest
10-20 min: activity, during fasting is stronger

PYLORUS = sphincter ???
Common ENS with bulbus duodeni
Smooth muscle
sympaticus +++, n.X. --- (VIP)

N. vagus +
Plexus cealicus -

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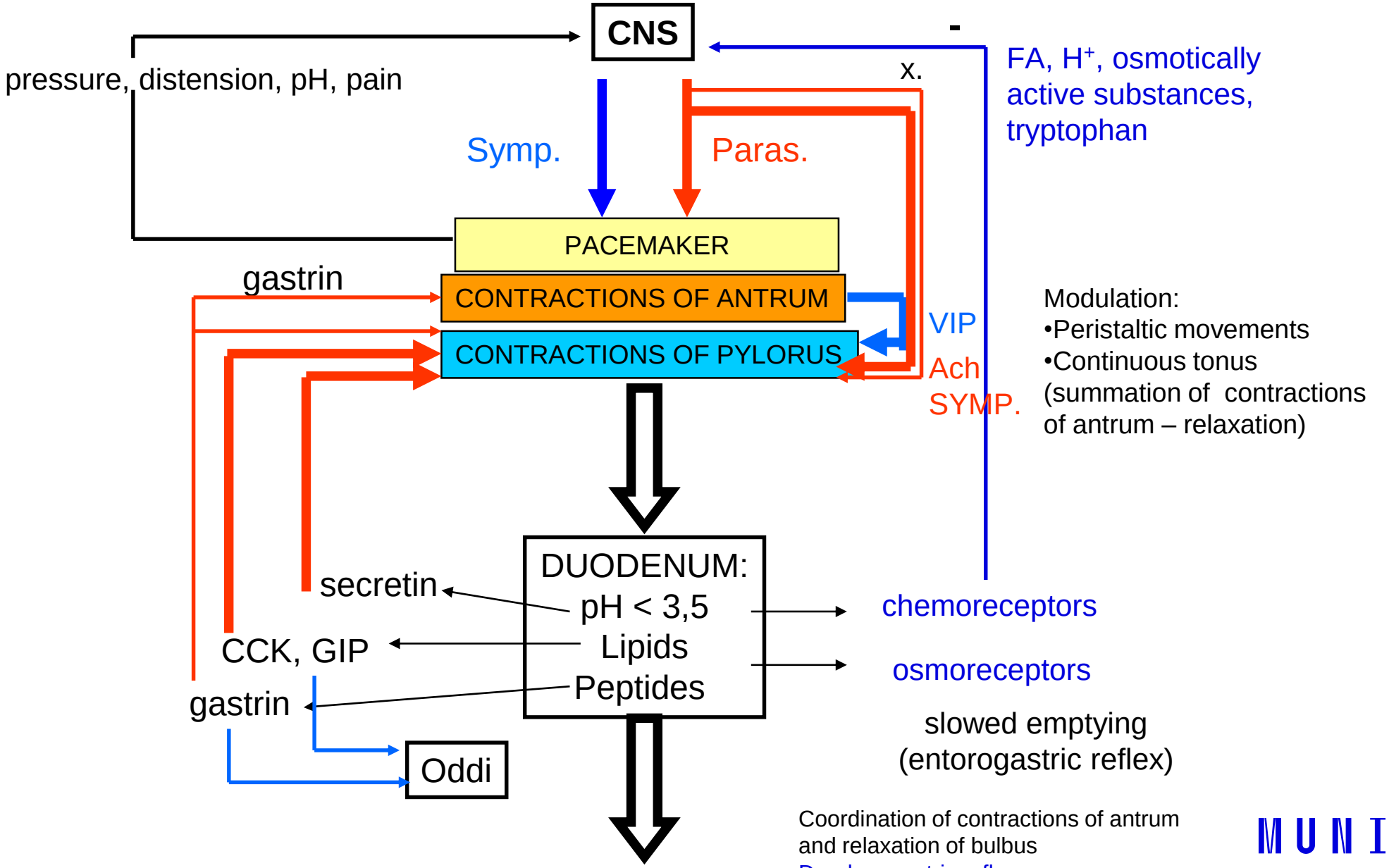
EMPTYING OF STOMACH



A/D reciprocal activity

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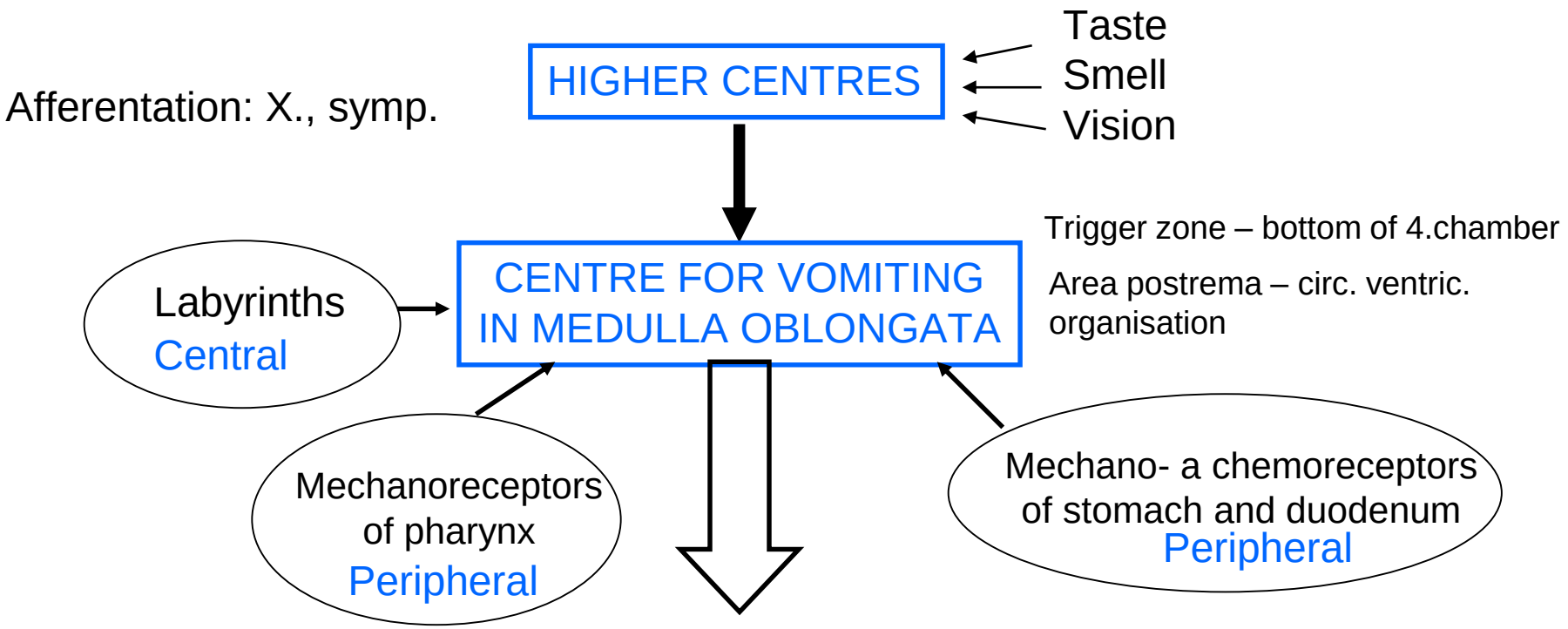
VOMITING (PROTECTION)



- Antiperistalsis in jejunum and duodenum
- Relaxation of pylorus and antrum
- Contractions of diaphragm (increased intraabdominal pressure)
- Inverse Valsalva manoeuvre (decreased intrathoracal pressure)
- Contractions of pylorus and antrum
- Relaxation of cardia
- Relaxation of upper pharyngeal sphincter

Emetics: central
peripheral

Antiemetics

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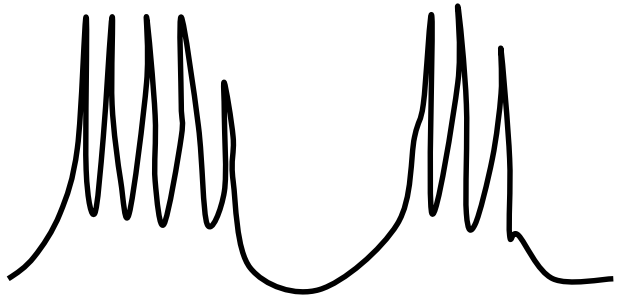
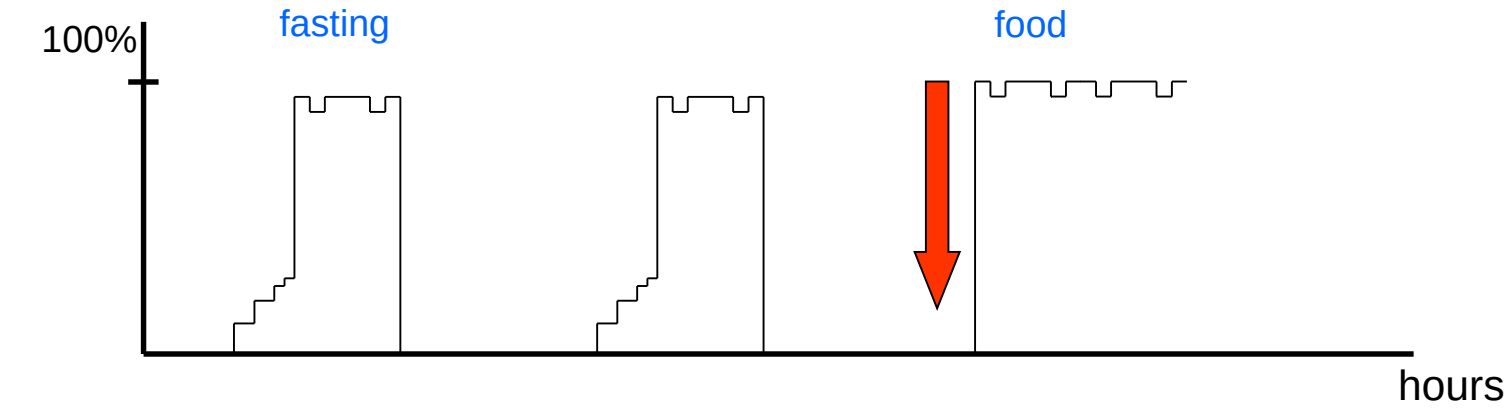
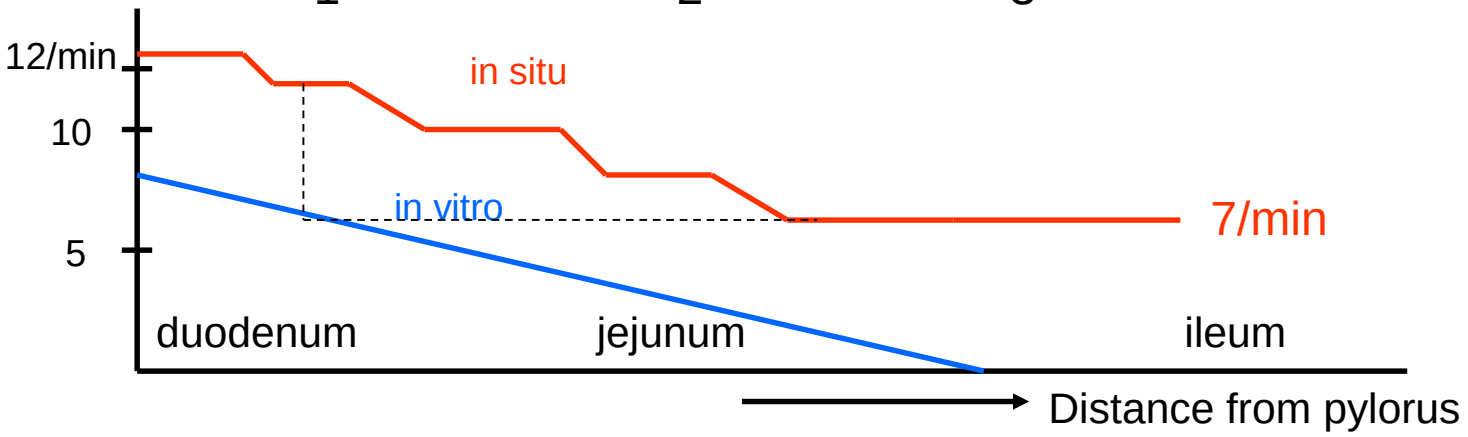
MOTILITY OF SMALL INTESTINE

Segmentation **>>>** peristalsis (up to 10 cm)



- Slow waves – approx.11-13/min in duodenum, 8-9 - ileum
- „Minute“ rhythm (jejunum) – salvos approx. every minute
- Hour rhythm (migrating myoelectric complex, **MOTILIN**)





LAW OF INTESTINE

INTESTINO-INTESTINAL REFLEX
GASTRO-ILEAL R.
GASTRO-COLIC R.

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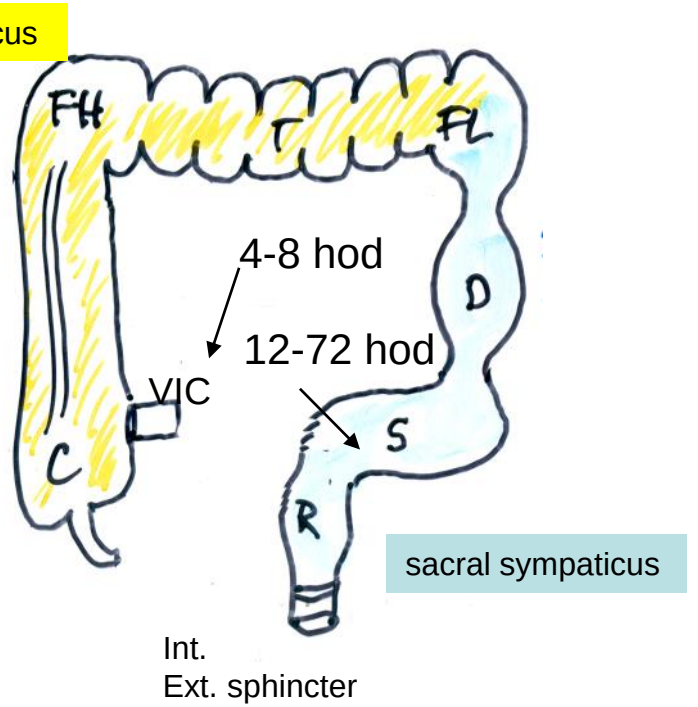
MOTILITY OF COLON

- Slow waves with frequency 4 – 6 / min
- Segmentation = **haustra**; 5-10 cm/hour– **pendulum movements**
- **Mass peristalsis**; 1-3/day – „sweeping"
- Reverse peristalsis – in proximal colon („delay" – absorption of water and ions)
- Control of anal sphincter: int. – reflex, ext. – voluntary (+reflex)
- Defekation: abdominal muscles +++, muscles of pelvic bottom –
- Reflex: colono-colonic, gastro-colic



- Parasympaticus + (X. till FL)
- Sympaticus – (L2 – L4)

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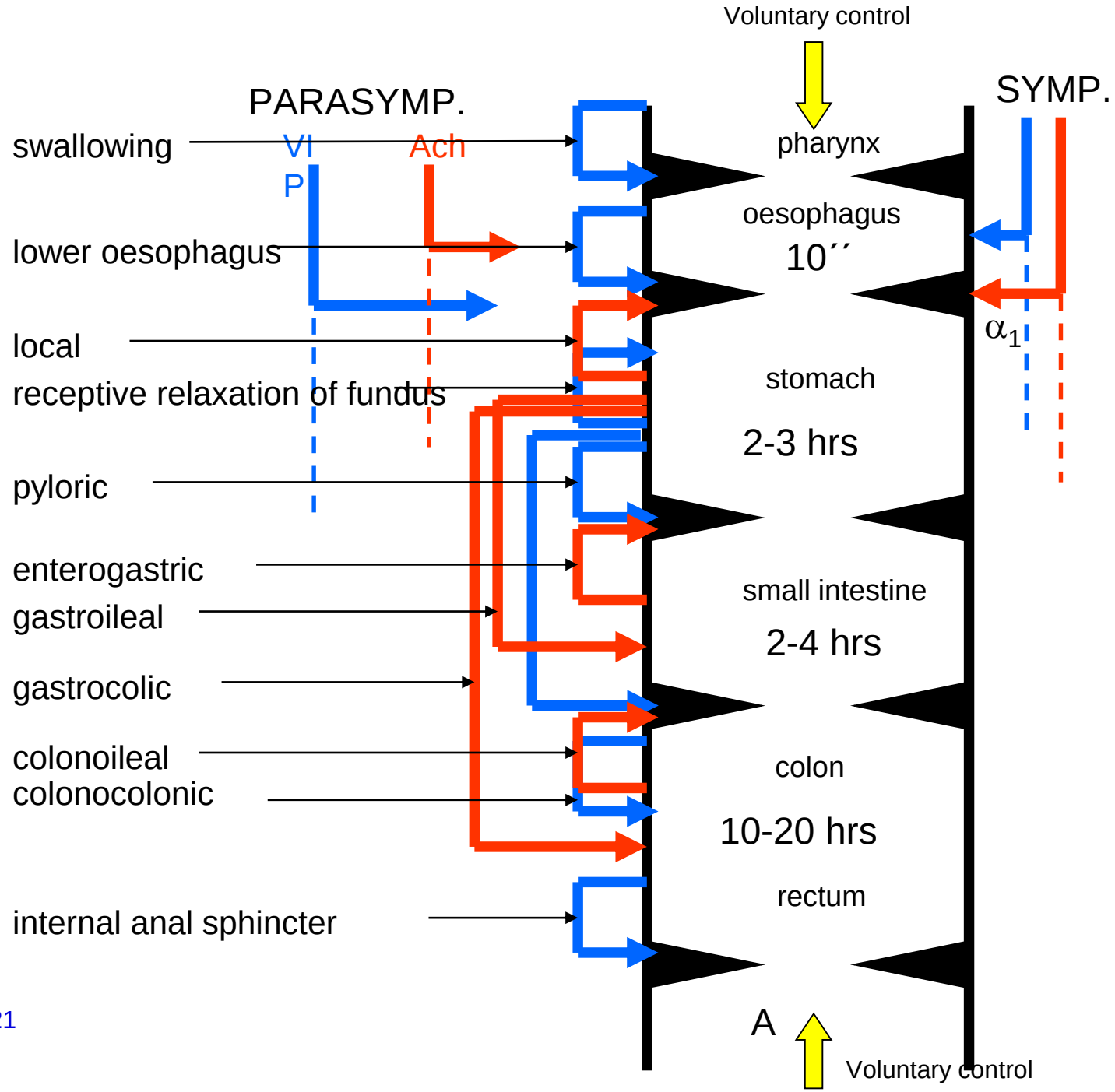
GIT REFLEXES

Superimposed on continuous basal tonus **PS** and **S** (sphincters **S PS**)

Signalling:

↓ relax, move on!

↑ slow down!



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SECRETION in GIT

Common features of GIT secretion:
water, ions, HCO_{3-}, mucin

GIT glands:

- Salivary glands
- Gastric glands
- Small glands of esophagus and intestine
- Exocrine pancreas
- Liver

Function of GIT secretion:

- Lubrication of food
- Swallowing
- Mechanical protection of GIT
- Chemical protection of GIT
- Enzymes
- Immune function(s)
- Articulation

Stimulation of secretory functions in GIT:

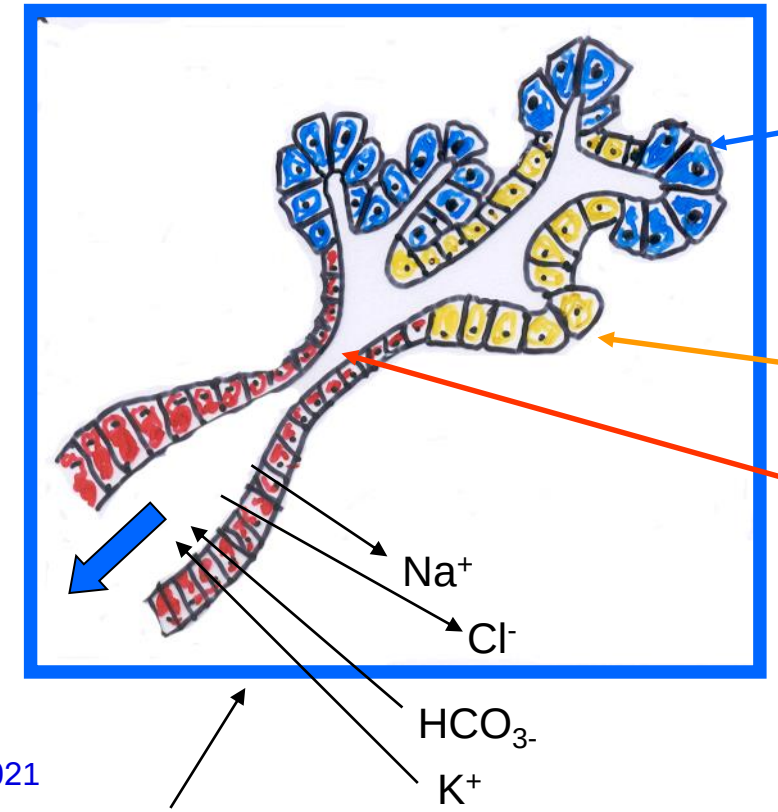
1. Neurocrine
2. Endocrine
3. Paracrine

PRODUCTION OF SALIVA

- **Mucinous** vs. **serous** secretion
- Gl. parotis, gl. submandibularis, gl. sublingualis, small salivary glands in mouth
- 1 liter / day (1ml/min/g)
- High resting blood flow – 10 x contracting muscle, high metabolic exchange
- pH: 7 – 8 (at rest rather acidic, increase in HCO_{3-} - alkalization)
- Parasympathetic stimulation – Ach, VIP, VII. and IX.n.; vasodilatation

Trophic influence of PS

Xerostomia



Resembles exocrine pancreas

PRIMARY SALIVA

ACINES
Serous secretion (H_2O, ions; isotonic)(gl. parotis)
Salivary amylase (zymogenic granules – exocytosis)
Over pH 4!!!

Mucinous secretion (glycoproteins)
(gll. submandibularis and sublingualis)

DUCTUS

SECONDARY SALIVA pH ~ 8

(hypotonic, after stimulation – increased tonus)

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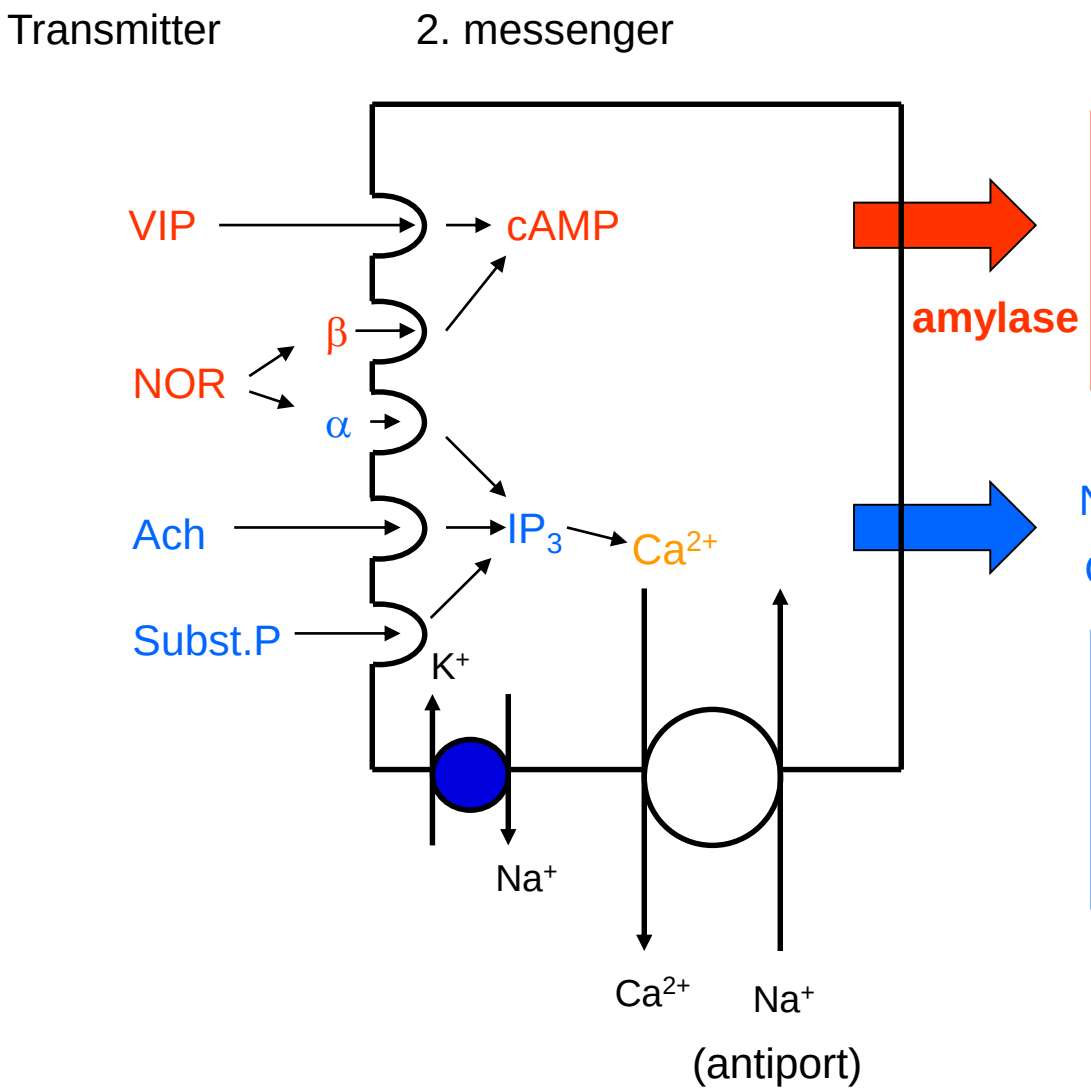
REGULATION OF SALIVA PRODUCTION



SYMPATHETIC NS
Only transient effect !!!
amylase
vasoconstriction
secretion of K^+, HCO_{3-}

PARASYMPATHETIC NS
(dominant) - n.fac.,
n. glossoph.
amylase, mucin
vasodilatation

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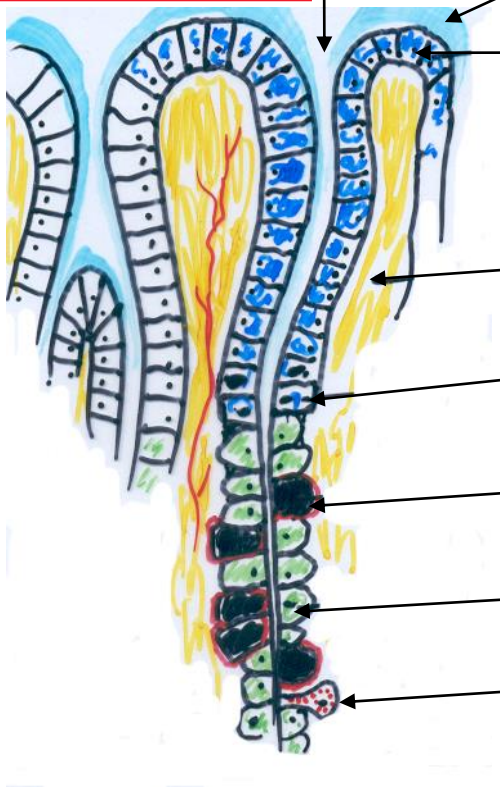
SECRETION OF GASTRIC JUICE

pH 2, high concentration of K^+ (vomiting) a **Cl^-**

Gastric ulcers
Stimulation of α-receptors – decreased secretion of HCO_3^-
NSA – decreased secretion of HCO_3^- and mucus

Area:

- Subcardial (mucus)
- Fundus (HCl)
- Pyloric (mucin, G)



Mucus (pH 7-8)

Gastric mucinous barrier

Gastric pits (glands)

Surface epithelia

Lamina propria

Mucous neck cells

Parietal cells (**HCl, intrinsic factor**)
(individual number!!!)

Main cells - zymogenic granules (pepsinogen)

G cells (gastrin)

\+

Ach, G, CCK, secretin

Gastric juice: water, salts, HCl, pepsin, intrinsic factor, mucus
Production increases after meal
Higher secretion – lower pH, lower secretion – more Na^+, (**always more K^+ than in plasma**)

pepsinogen → pepsin

HCl

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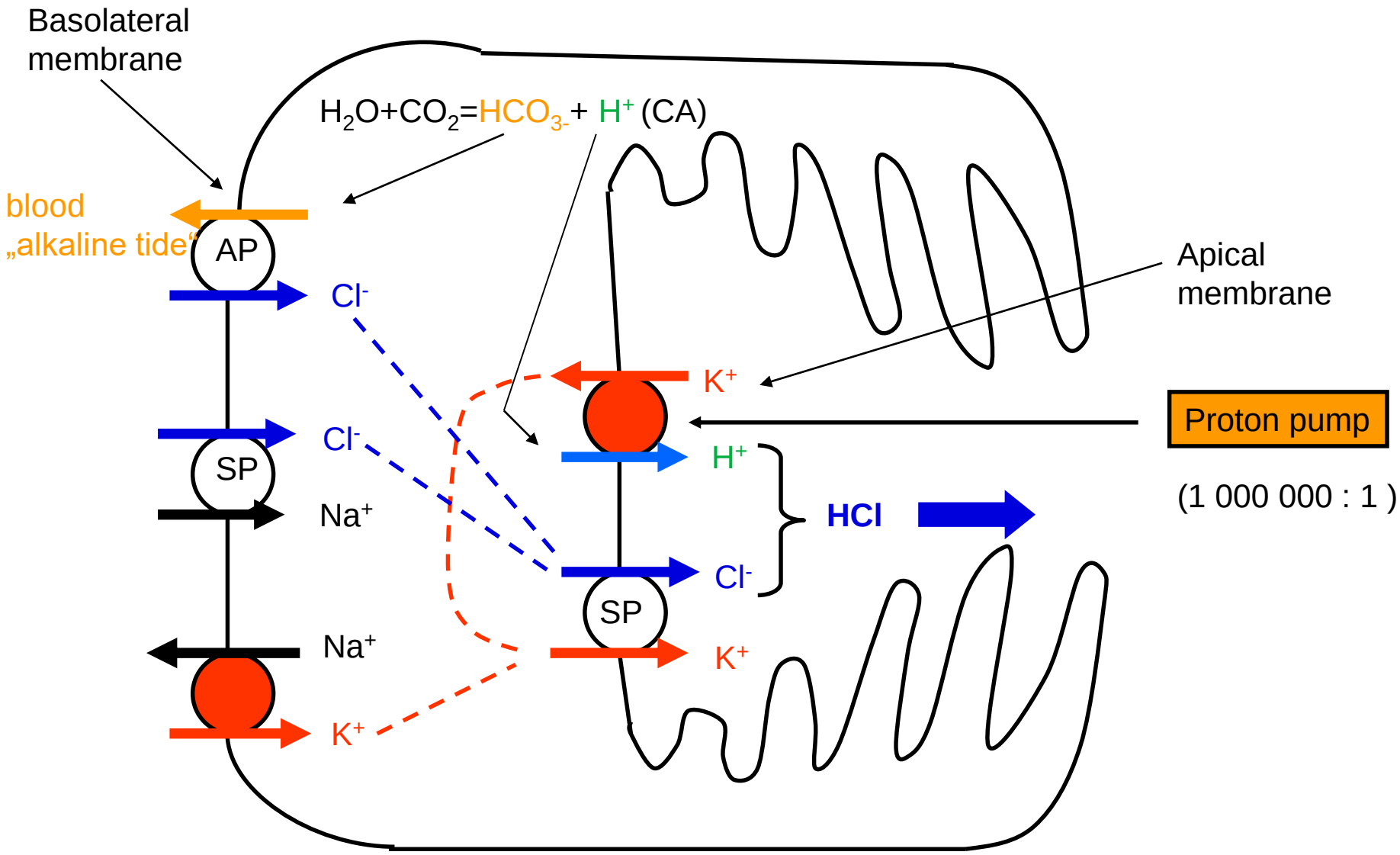
HCl PRODUCTION IN PARIETAL CELL



Tubulovesicular system (rest, 10% – secretion)

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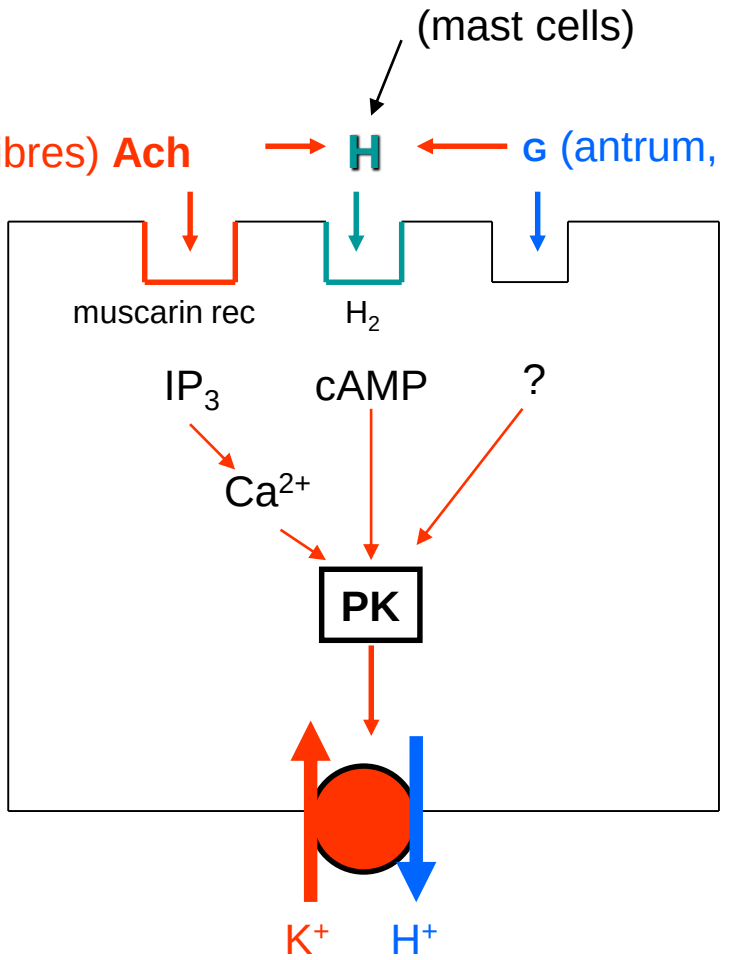
CONTROL OF HCl PRODUCTION IN PARIETAL CELL

Potentiation of stimulation!!!



PGE, somatostatin – **inhibition** of HCl secretion

Phases of gastric secretion:

- Cephalic (vision, smell, taste)(X.)(directly, G, H)
- Gastric (distension of stomach; peptides, AA)(mechanorec.-local and central reflexes; tryptophan, phenylalanine, caffeine, alcohol – G)
- Intestinal (distension of duodenum, peptides, AA)(G from duodenum and jejunum)

Inhibition of gastric secretion:

Low pH, FA, hypertonia v duodenum and jejunum; secretin, bulbogastron, GIP, CCK

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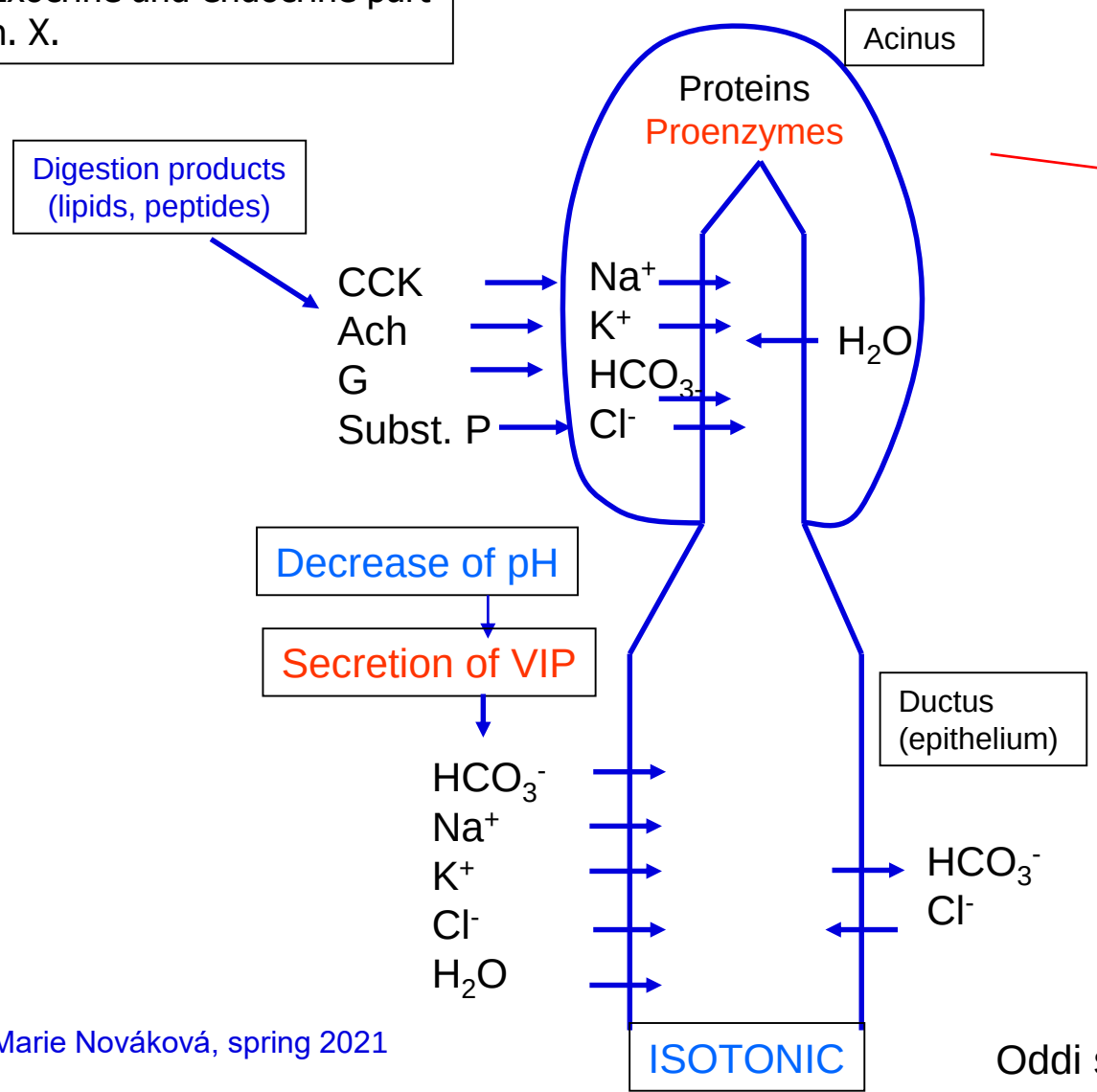
CONTROL OF PANCREATIC JUICE SECRETION

PANCREAS:
100 gr
Exocrine and endocrine part
n. X.

PANCREATIC JUICE: approx. 1 l/day

1. Water phase (HCO_3^-) – secretin; ductal cells
2. Enzymatic phase - CCK



1. Trypsinogen (trypsin activates 1, 2, 3)
2. Chymotrypsinogen
3. Prokarboxypeptidase
4. Trypsin-inhibitor
5. α-amylase
6. Pancreatic lipases

- Enterokinase – activates trypsinogen

Acute pancreatitis

Regulation of secretion

1. Phase cephalic (n.X. – gastrin)
2. Phase gastric (distension of stomach – gastrin)
3. Phase intestinal (acid in duodenum and jejunum – secretin; peptides, AA = tryptophan., phenylalanine, FA – CCK)

Oddi sphincter (X. – relaxation, secretin - contraction)

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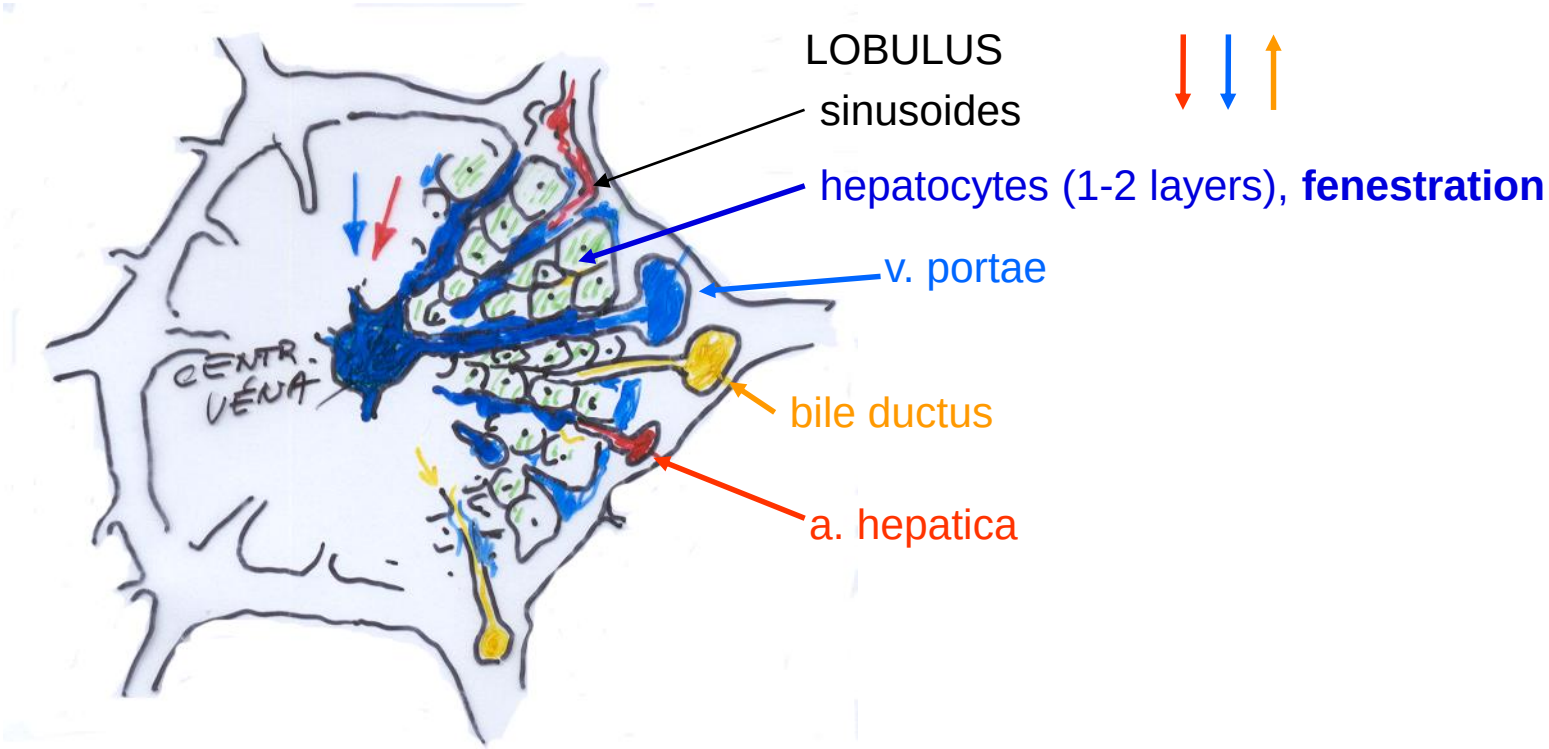
LIVER FUNCTION

- **Regulation of metabolism** (saccharides – glycogenolysis, gluconeogenesis; lipids – chylomicrons, lipoprotein lipase, VLDL, cholesterol and triglycerides; ketone bodies; proteins – synthesis of urea)
- **Proteosynthesis** (non-essential AA, lipoproteins, albumins, globulins, fibrinogen and other proteins of blood clotting cascade)
- **Storage** (glycogen, vitamins – A, D, B_{12}, iron)
- **Degradation** (hormones – epinephrine, norepinephrine, steroids, polypeptide hormones)
- **Inactivation and excretion** (remedies, toxins) – detoxication by conjugation with glucuronic acid, glycine and glutathione

BILE PRODUCTION

Secretion resembles exocrine pancreas



Bile

- 250-1500ml/day, isotonic, **primary secretion –** resembles plasma, **CCK**; modification - **secretin**
- bile acids (salts – Na^+) – conjugated (glycin, taurin) – soluble in H_2O, 50% of dry, micels
- cholesterol (crystals, lithiasis)
- lecithins
- bile pigments (bilirubin – glucuronid) – **yellow colour of bile** (lithiasis)
- Na^+, K^+, Cl^-
- H_2O, HCO_3^- (secretin)

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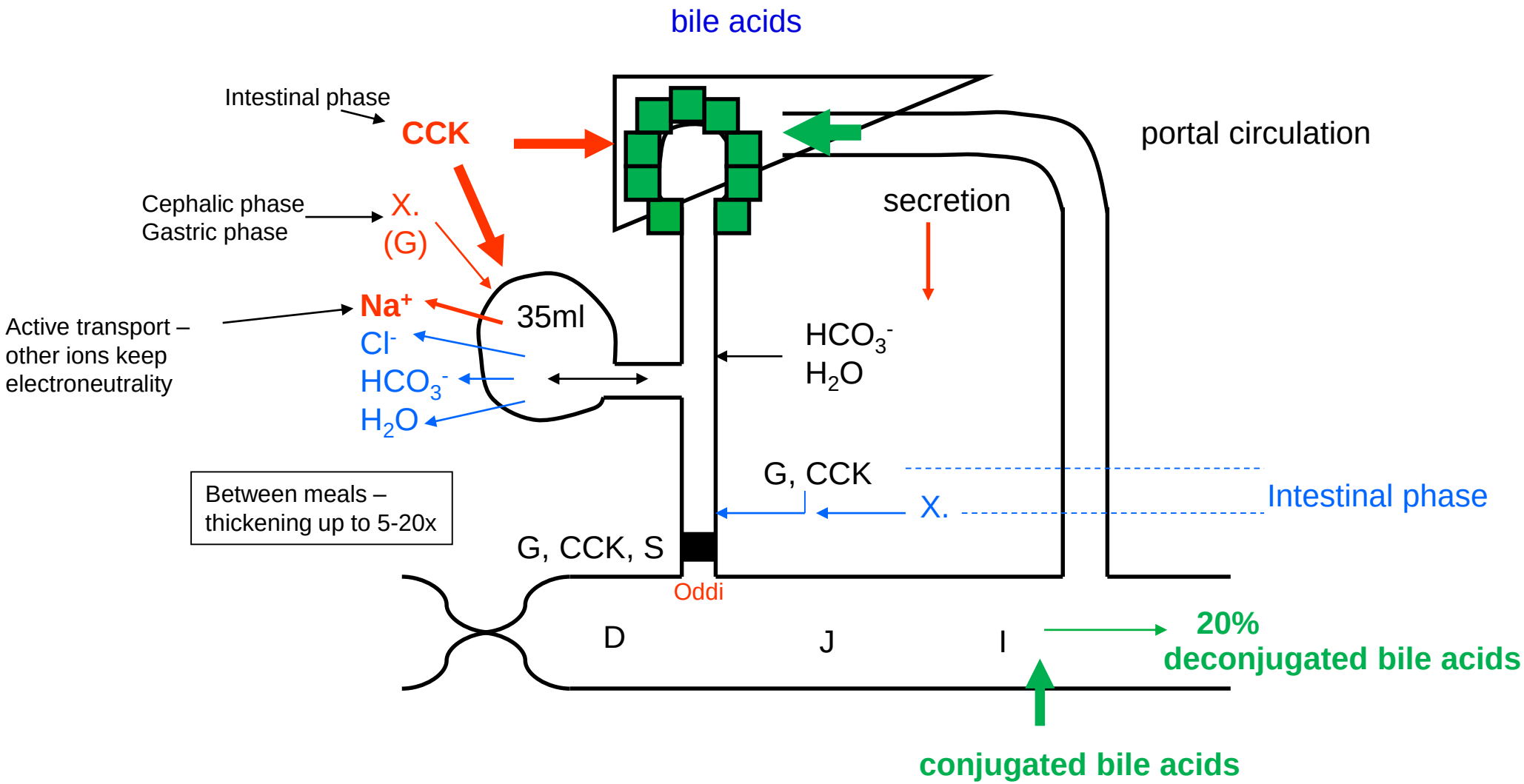
ENTEROHEPATIC CIRCULATION of BILE ACIDS



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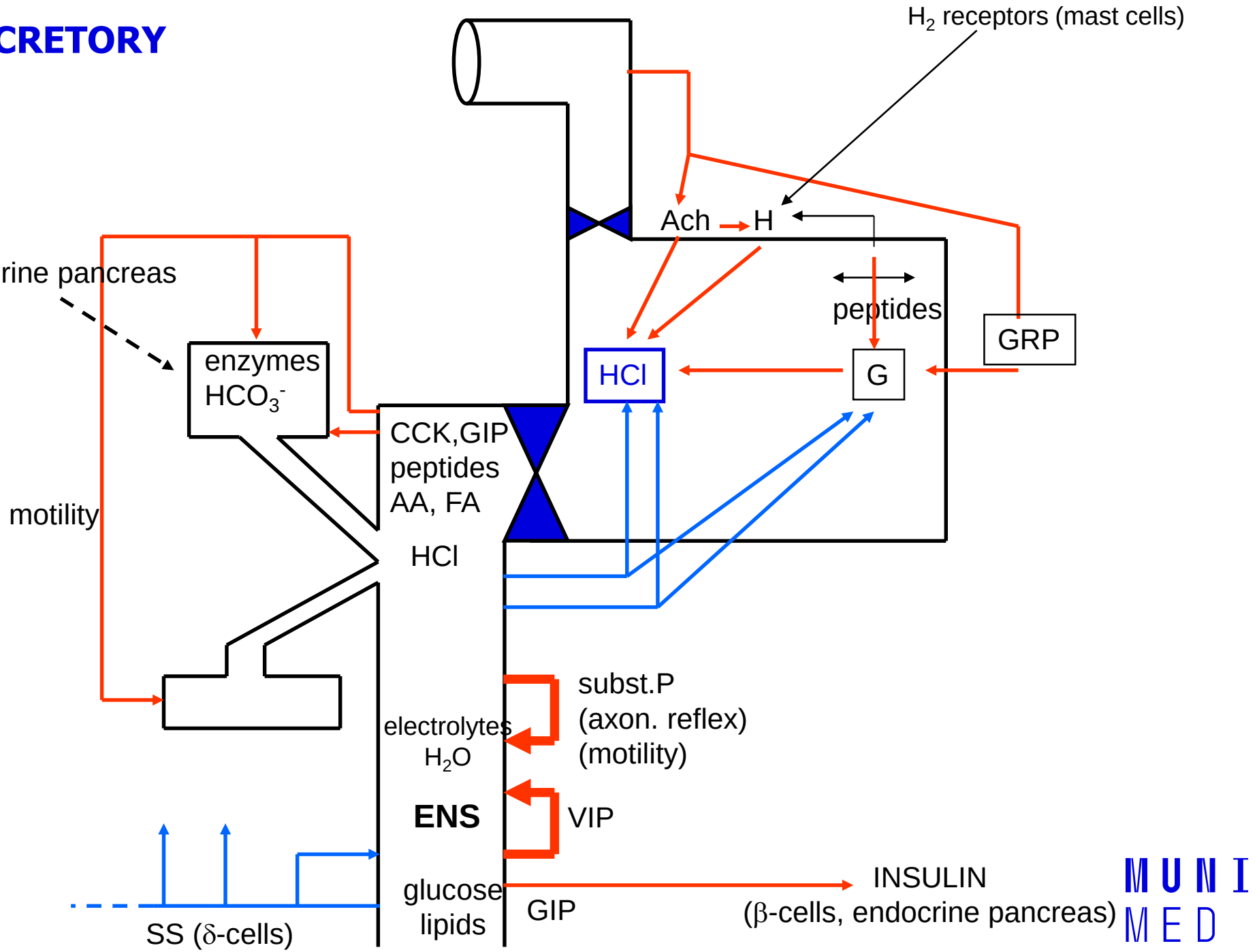
REGULATION OF SECRETORY FUNCTIONS IN GIT

*** CEPHALIC PHASE**
(taste, smell…)

*** GASTRIC PHASE**
(Ach, H, S, G, CCK - stimulation of production

INTESTINAL PHASE OF SECRETION

*** mediated by gastrin**



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SELECTED QUESTIONS – related to ABSORPTION, IONS AND WATER

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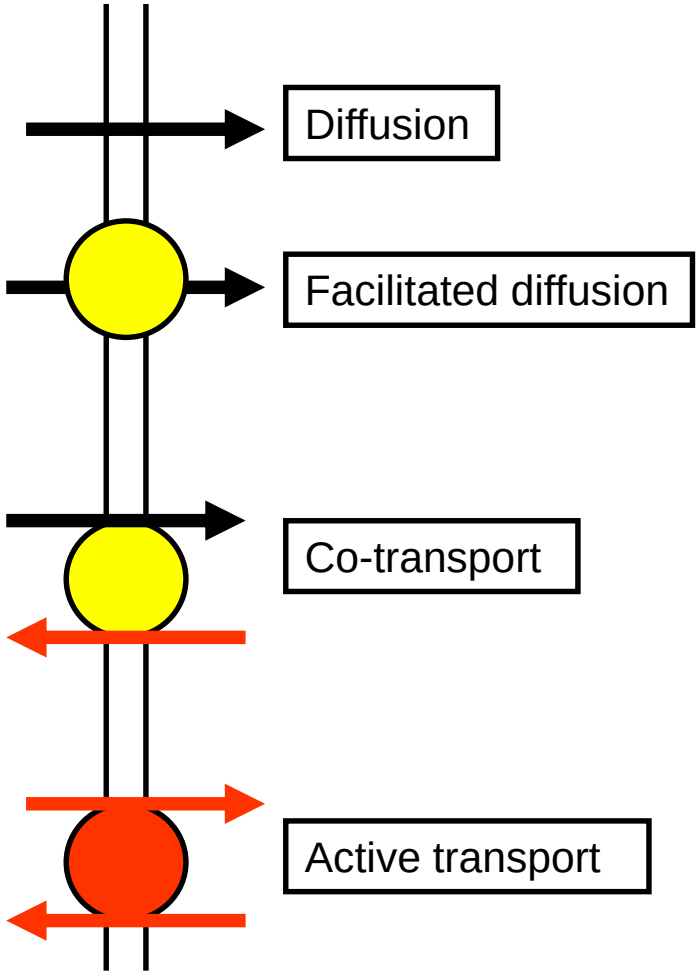
- Both active and passive mechanisms participate in GIT absorption
- Both paracellular and transcellular movements are involved
- Absorption area is enlarged by folds, villi and microvilli (mostly in small intestine)
- Absorption of water and electrolytes occurs in both small and large intestine, absorption of nutrients occurs only in small intestine
- Small intestine absorbs water and electrolytes and secretes HCO_3^-, large intestine absorbs water and electrolytes and secretes potassium and HCO_3^-
- Water „follows" electrolytes, eventually is „drafted" by osmotically active substances
- **Numerous absorption mechanisms depend on sodium gradient**

TRANSPORT MECHANISMS in GIT



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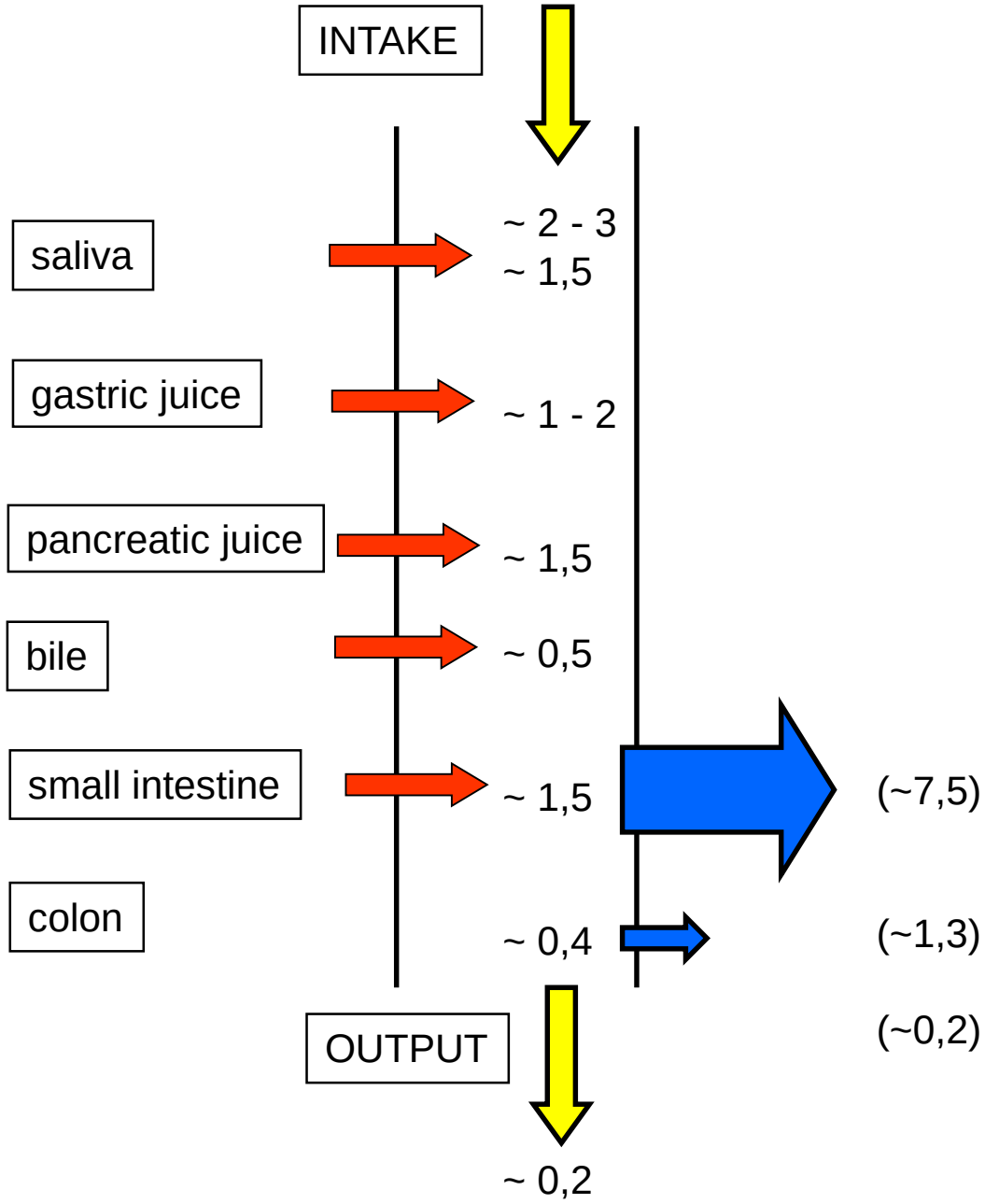
DAILY WATER BALANCE



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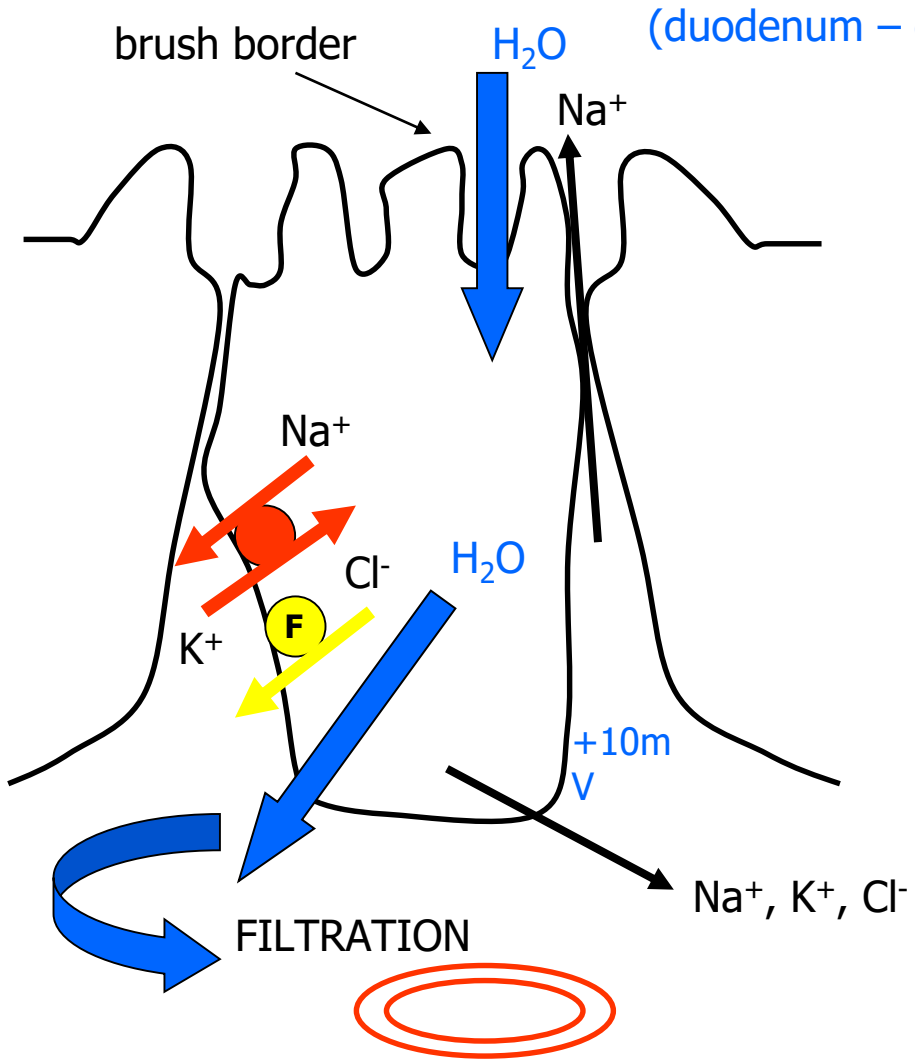
WATER ABSORPTION

(small intestine, gallbladder, stomach, colon)

STIMULATION: digestion products (AA, sugars)

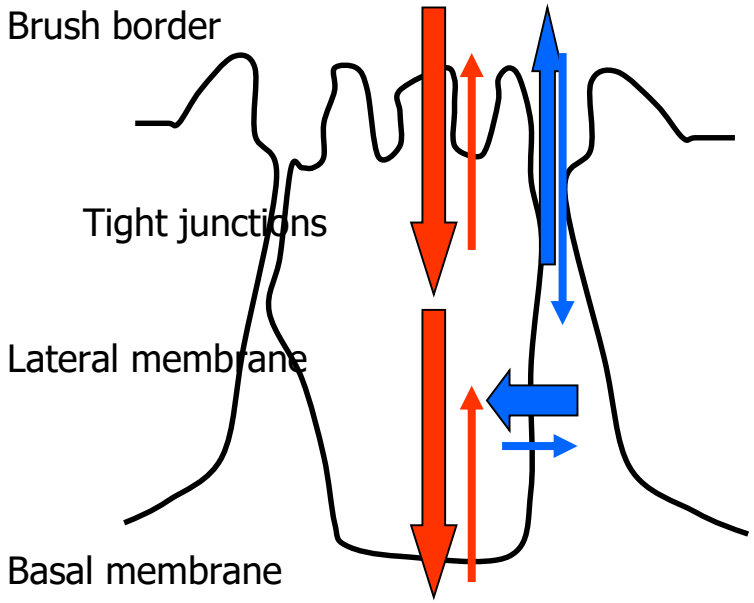


(duodenum – osmotic draft of H_2O)

Continuous osmotic gradient

TRANSPORT

- Transcellular
- Paracellular



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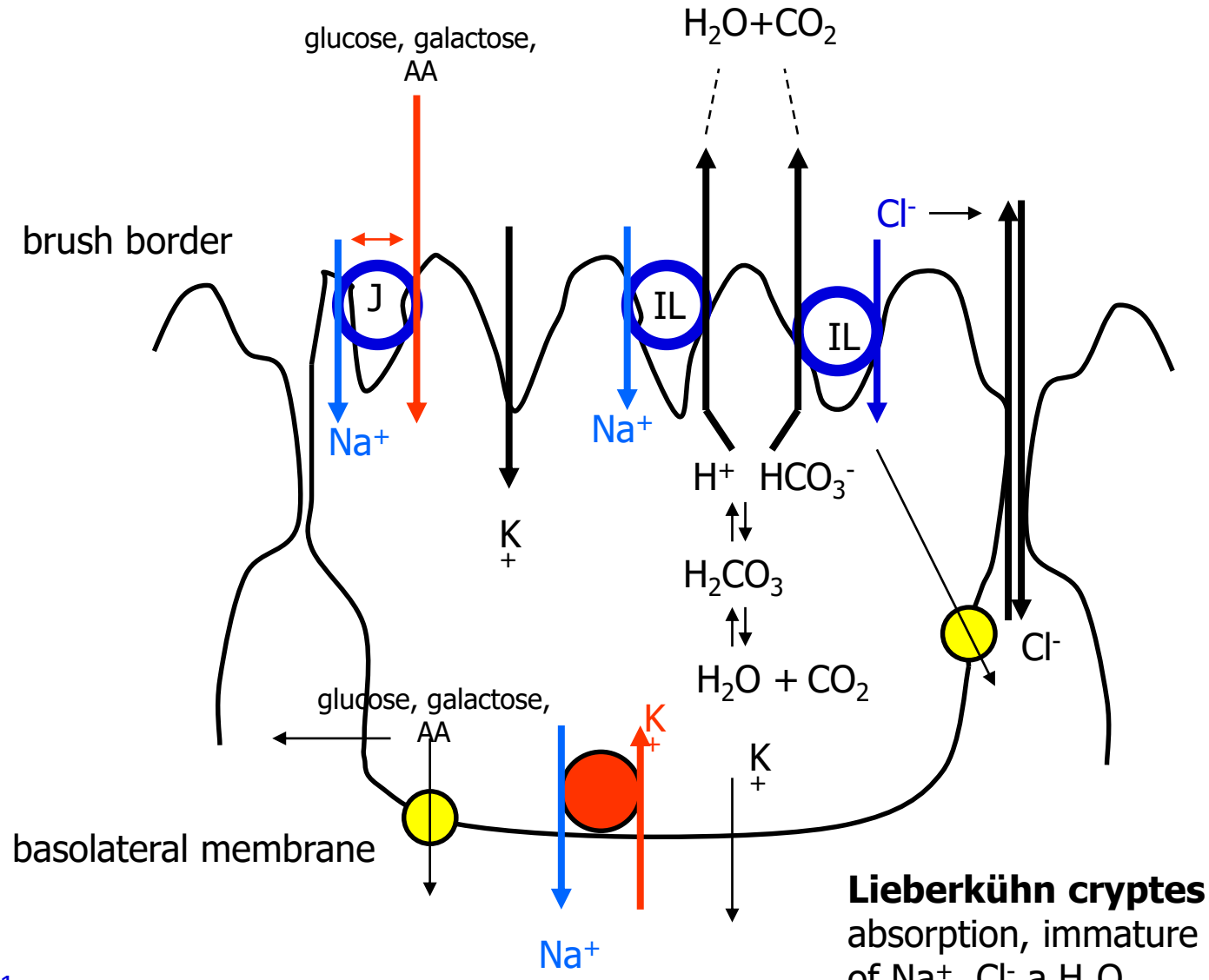
TRANSPORT OF IONS

JEJUNUM
ILEUM



Lieberkühn cryptes: matured cells – absorption, immature cells – secretion of Na^+, Cl^- a H_2O

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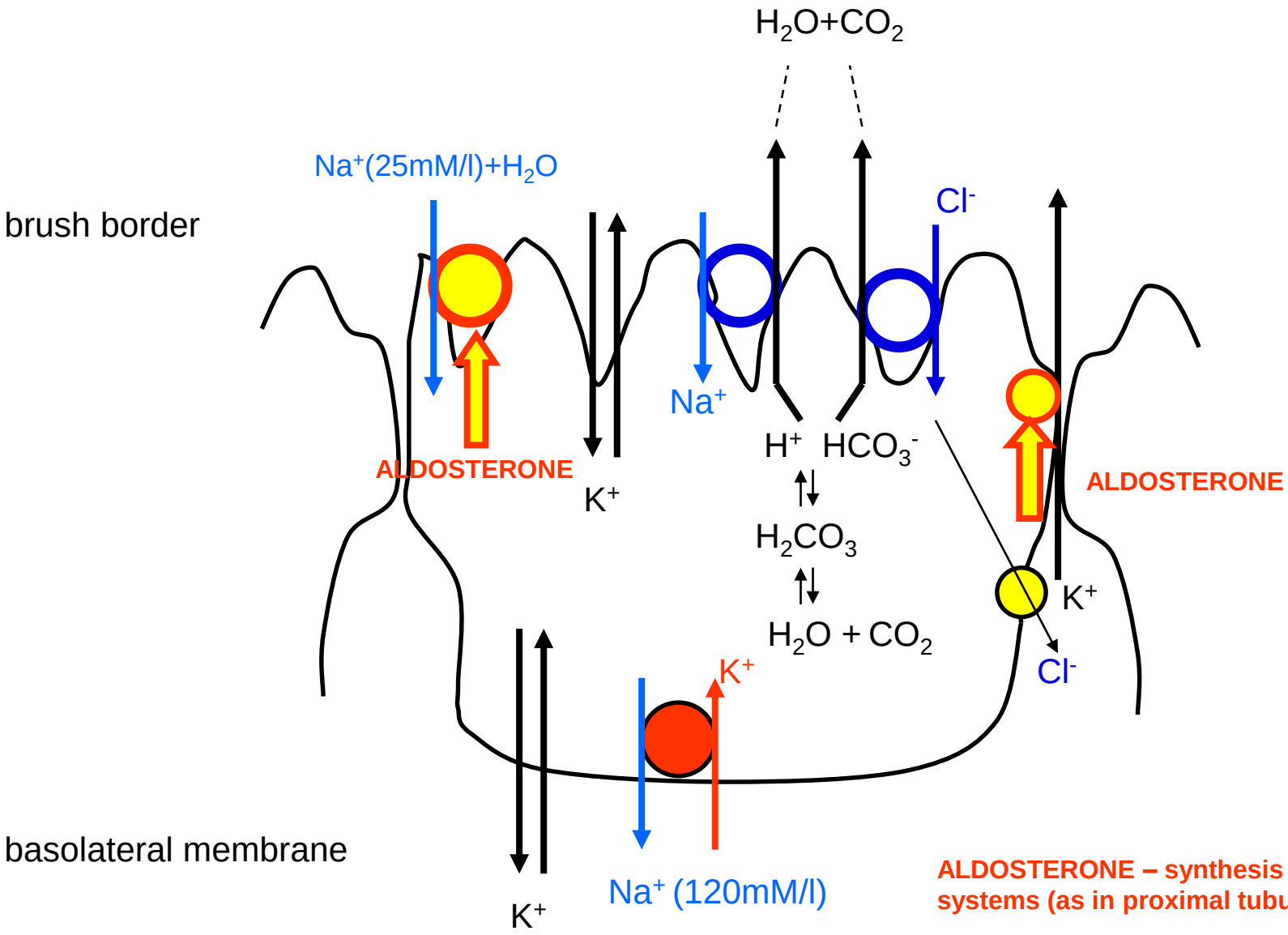
TRANSPORT OF IONS

COLON



ALDOSTERONE – synthesis of transport systems (as in proximal tubule)

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REGULATION OF TRANSPORT OF WATER AND IONS

1. **Autonomous nervous system**: **SYMP** (noradrenaline, enkefalins) + **somatostatin** – increase of absorption of water, sodium and chlorine

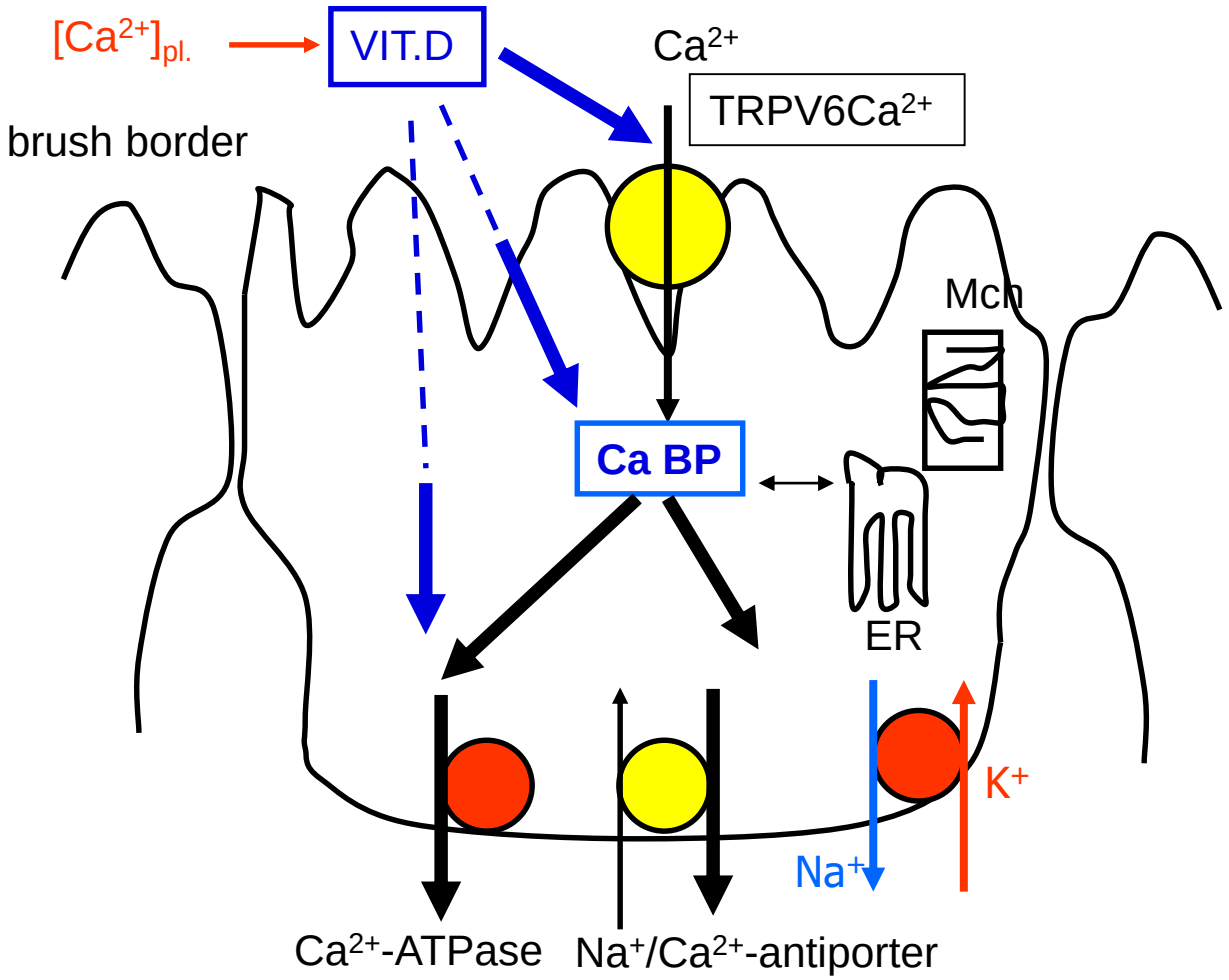
2. **Aldosterone:** colon – stimulation of secretion of potassium and absorption of sodium and water (up-regulation of Na/K-ATPase, Na-channel)

3. **Glucocorticoids:** small intestine and colon - absorption of sodium, chlorine and water (up-regulation of Na/K-ATPase)

ABSORPTION OF Ca^{2+}

INTAKE: 1000mg/day
ABSORPTION: 350mg/day

Absorption against concentration gradient (1:10) in all GIT (D, J), 50x slower than absorption of Na^+



1,25-dihydrocholecalciferol

Calbindin – prevention of formation of insoluble salts (phosphates, oxalates)

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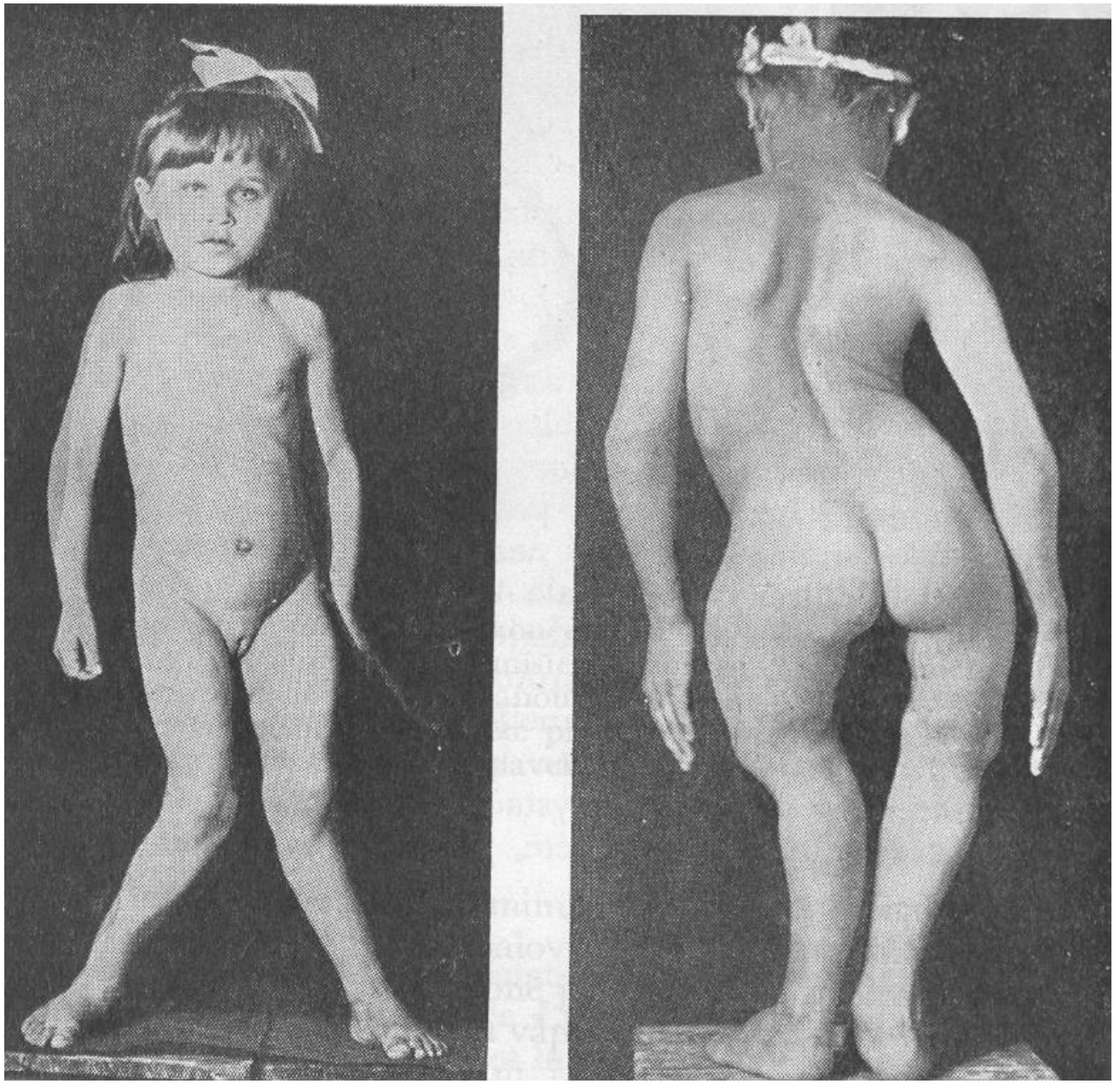
RACHITIS
(rickets)

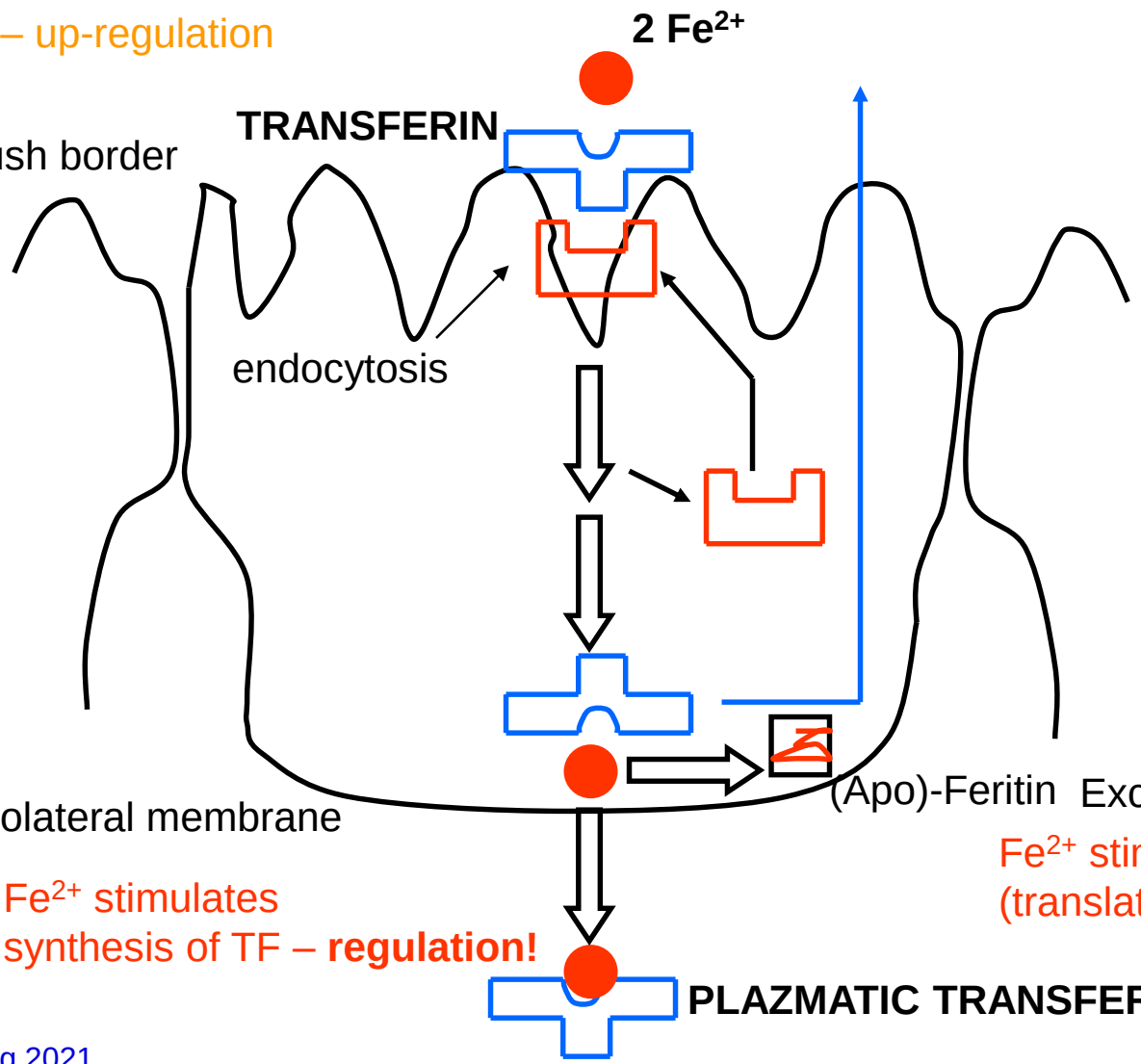


MUNI MED

ABSORPTION OF Fe^{2+}

Insoluble salts and complexes (20:1) – limitation of absorption
Decrease of pH

↓ Fe – up-regulation



↓ Fe^{2+} stimulates synthesis of TF – **regulation!**

Excess of Fe^{2+} – loss with epithelium

Fe^{2+} stimulates synthesis of apoferitin (translation) – **regulation!**

Hemosiderin – deposits of Fe in desmosomes

INTAKE: 15-20mg/day
ABSORPTION:
Men: 0,5 - 1mg/day
Women: 1 – 1,5mg/day
D, J

↓ pH: $Fe^{3+} \rightarrow Fe^{2+}$

70% - Hb
25% - F

MUNI MED

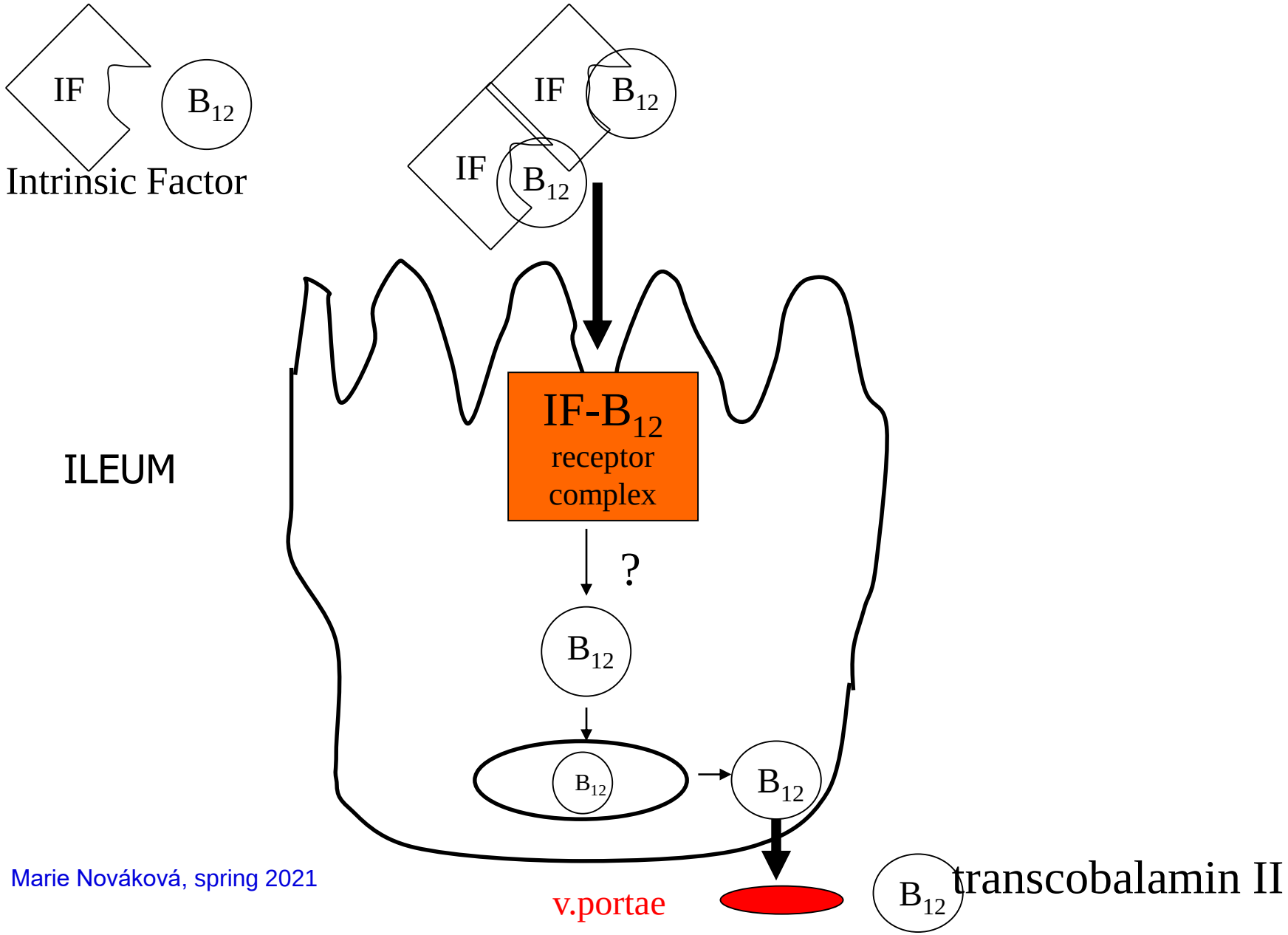
VITAMIN B_{12}

- Daily need is close to its absorption capacity
- Synthesised by bacteria in colon – BUT there is not absorption mechanism
- Store in liver (2-5mg)
- In bile 0.5-5mg / day, reabsorbed
- Daily loss – 0.1% of stores → stores will last for 3-6 years

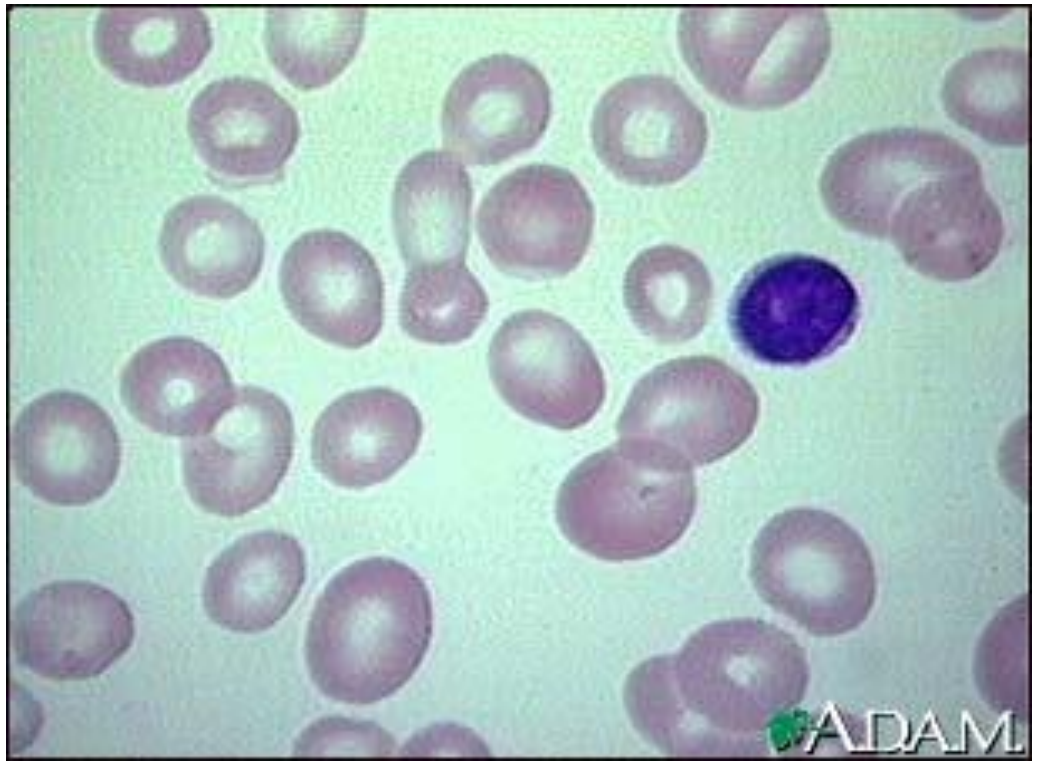
ABSORPTION

1. **Gastric phase**: B_{12} is bound to proteins, low pH and pepsin release it; bound to glycoproteins – **R-proteins** (saliva, gastric juice), almost pH-undependable; intrinsic factor (**IF**) – parietal cells of gastric mucosa; most of vitamin bound to R-proteins
2. **Intestinal phase:** pancreatic proteases, cleavage of R-B_{12}, bound to IF (resistant to pancreatic proteases)

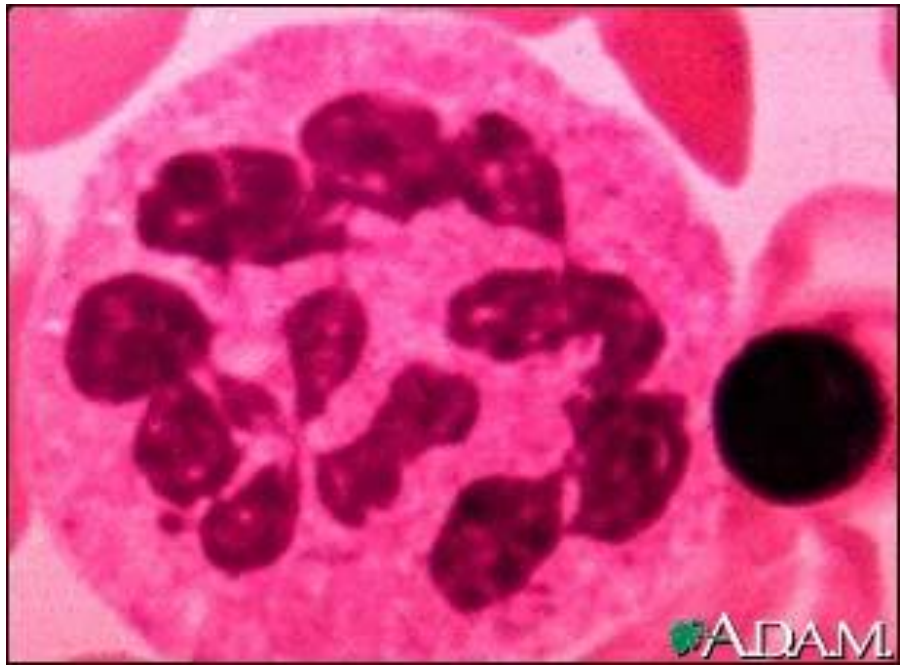
ABSORPTION OF B_{12} VITAMIN



MUNI MED

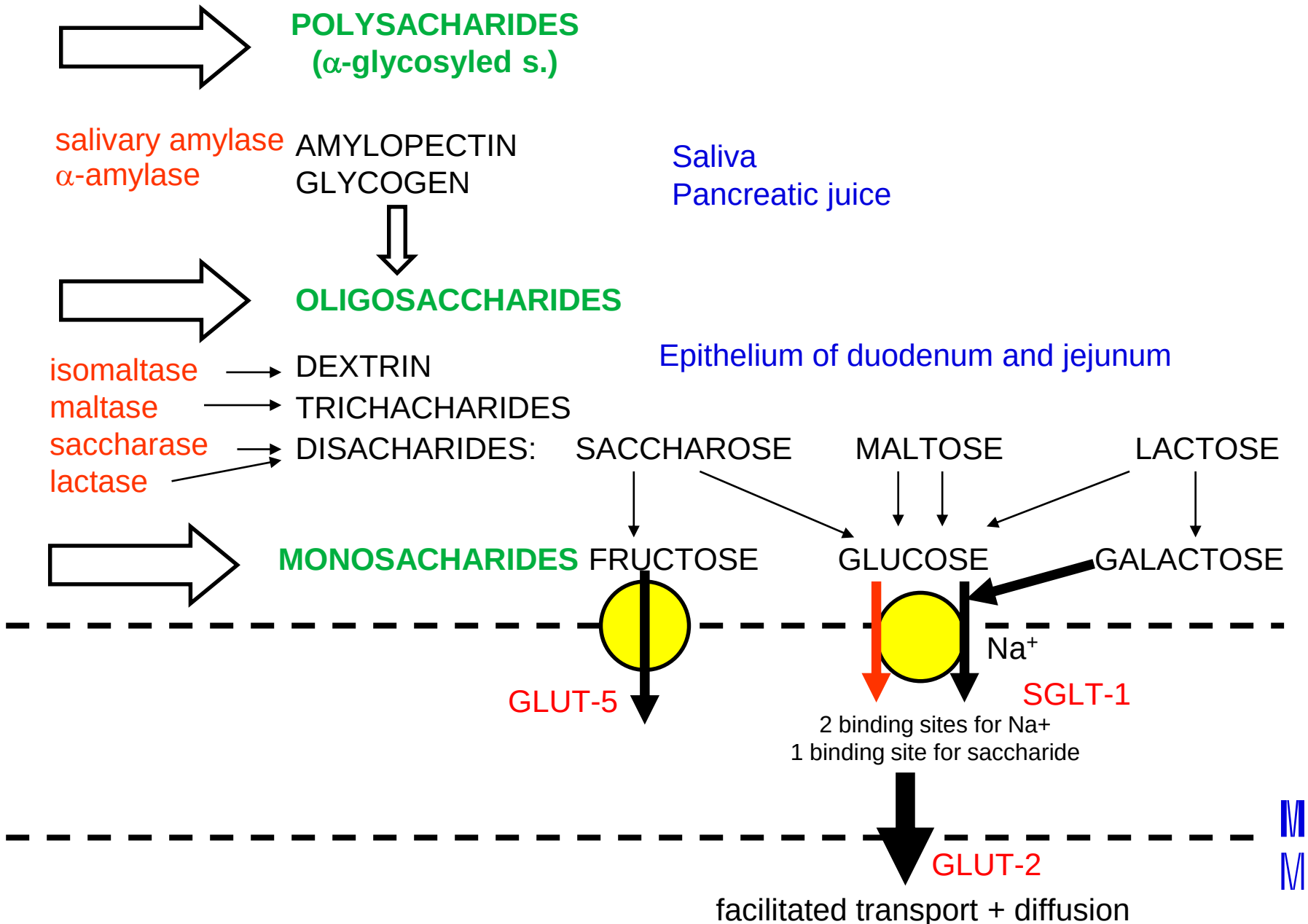


Pernicious anaemia
(megaloblastic)



MUNI MED

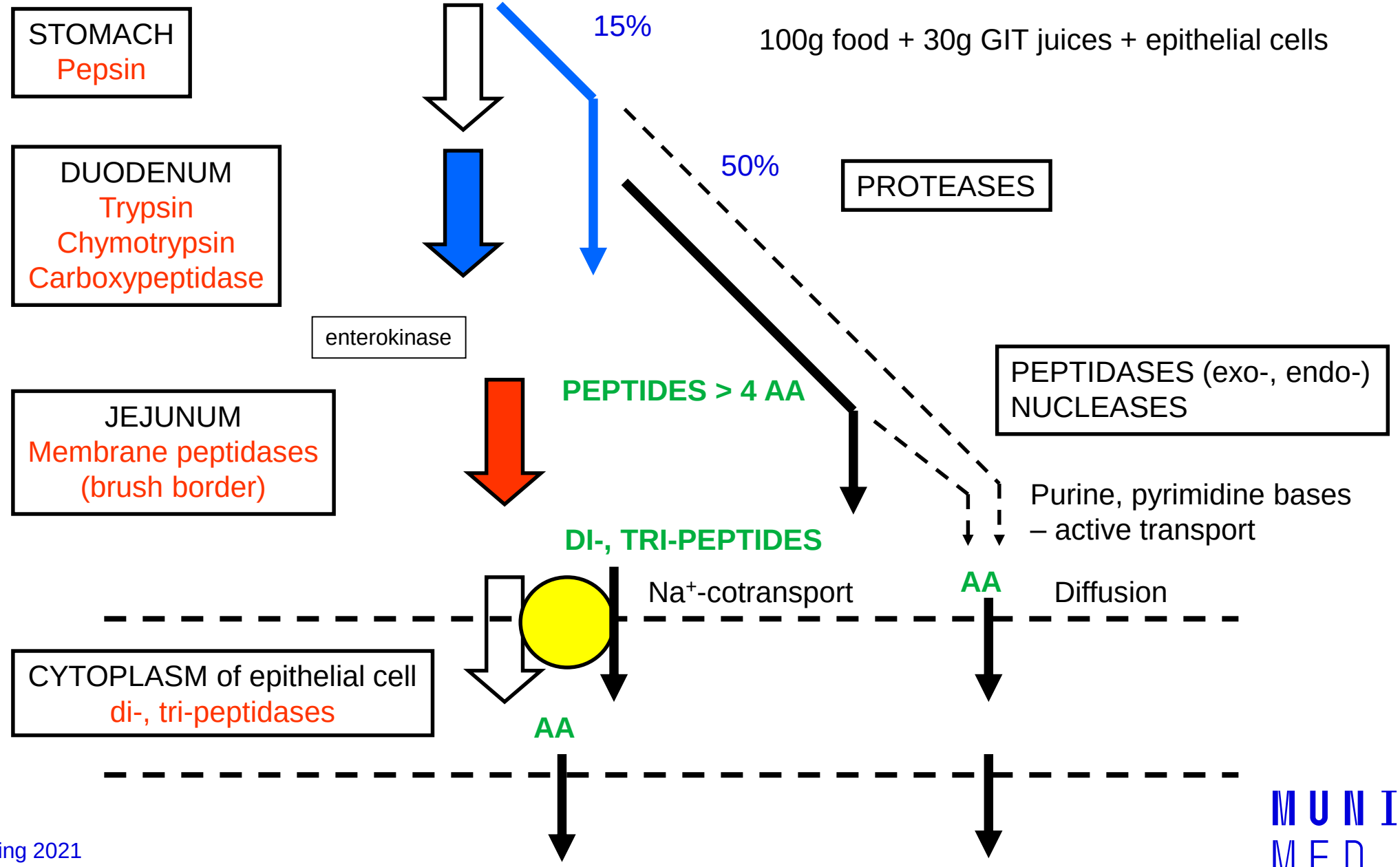
DIGESTION AND ABSORPTION OF SACCHARIDES



- Lactase intolerance
- Diarrhoea

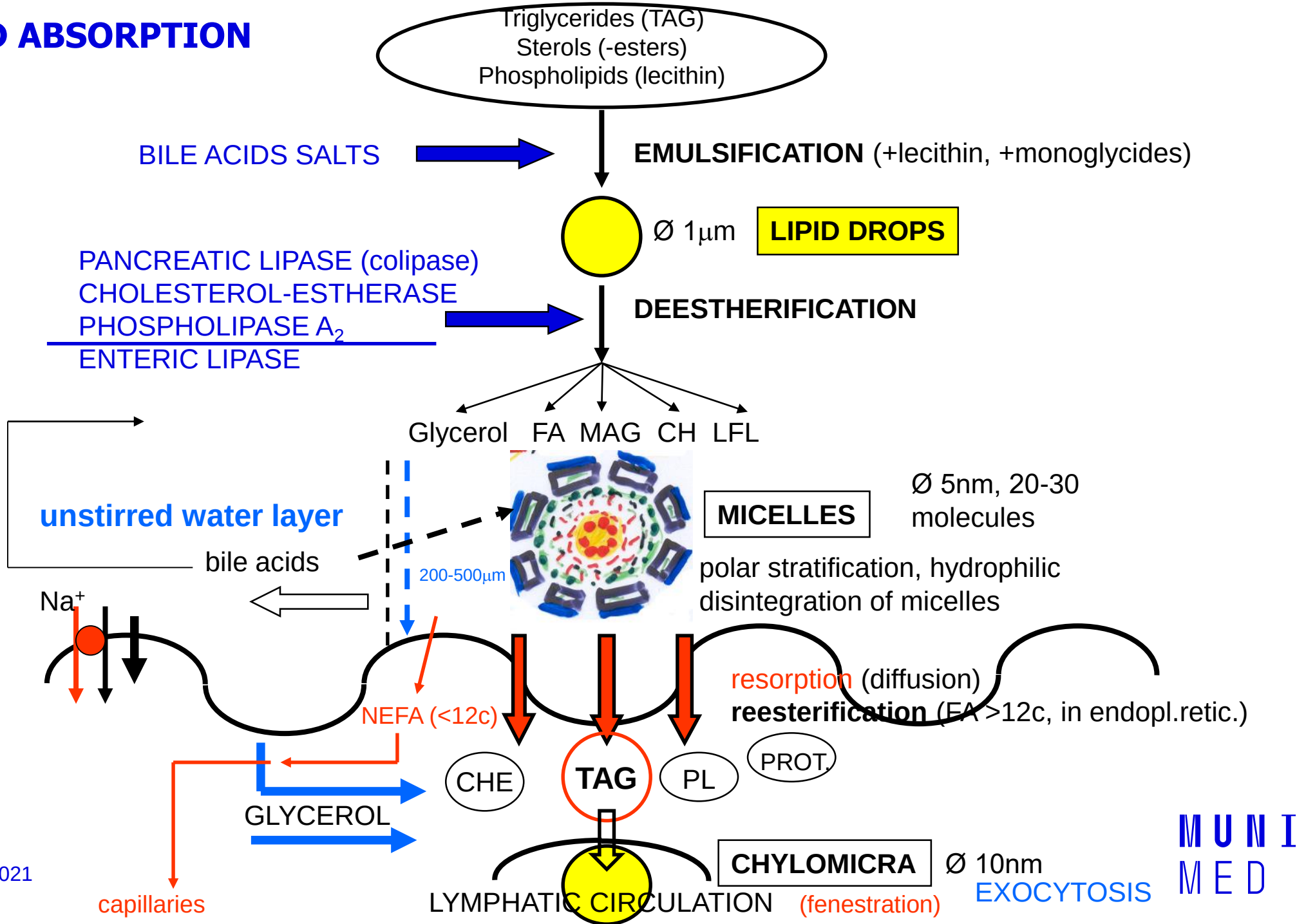
MUNI MED

DIGESTION AND ABSORPTION OF PROTEINS



MUNI MED

DIGESTION AND ABSORPTION OF LIPIDS



MUNI MED

ABSORPTION IN COLON

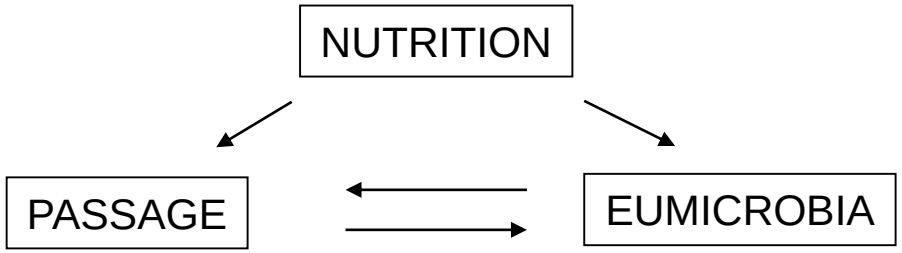
- Na^+ (active transport, aldosteron) H_2O (90% water in colon)
- Cl^-

REST OF CHYME

1. Cellulose, collagen
2. Bile acids, epithelia, mucin, leucocytes

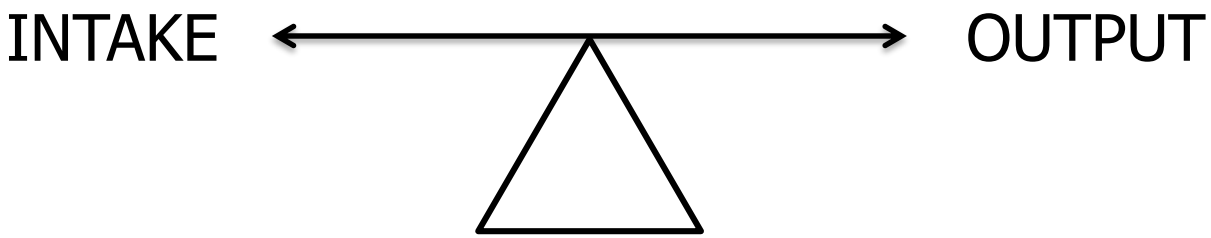
- Bacteria **fermenting**: fibre (pectin, cellulose) – lactate, alcohol, acetate, CO_2, methane
- Bacteria **putrescent**: residues of AA – NH_3, SH_2, phenol, indole, solatol (carcinogenic)

Production of vitamin K and vitamins of B group – BUT NO ABSORPTION MECHANISMS



MUNI MED

REGULATION OF FOOD INTAKE AND NUTRITIONAL STATE

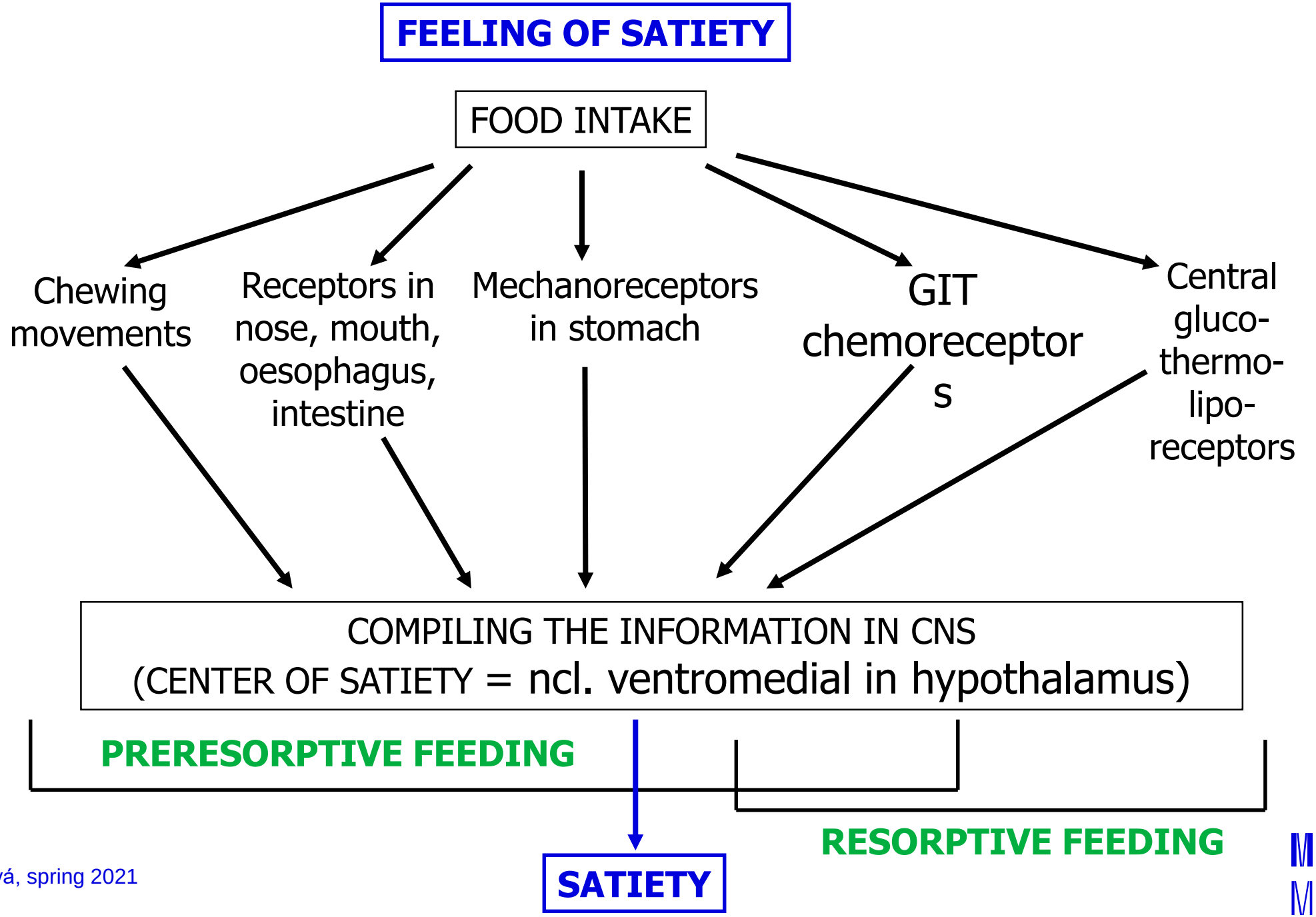


CENTER OF SATIETY **–** CENTER OF HUNGER
(permanently active)

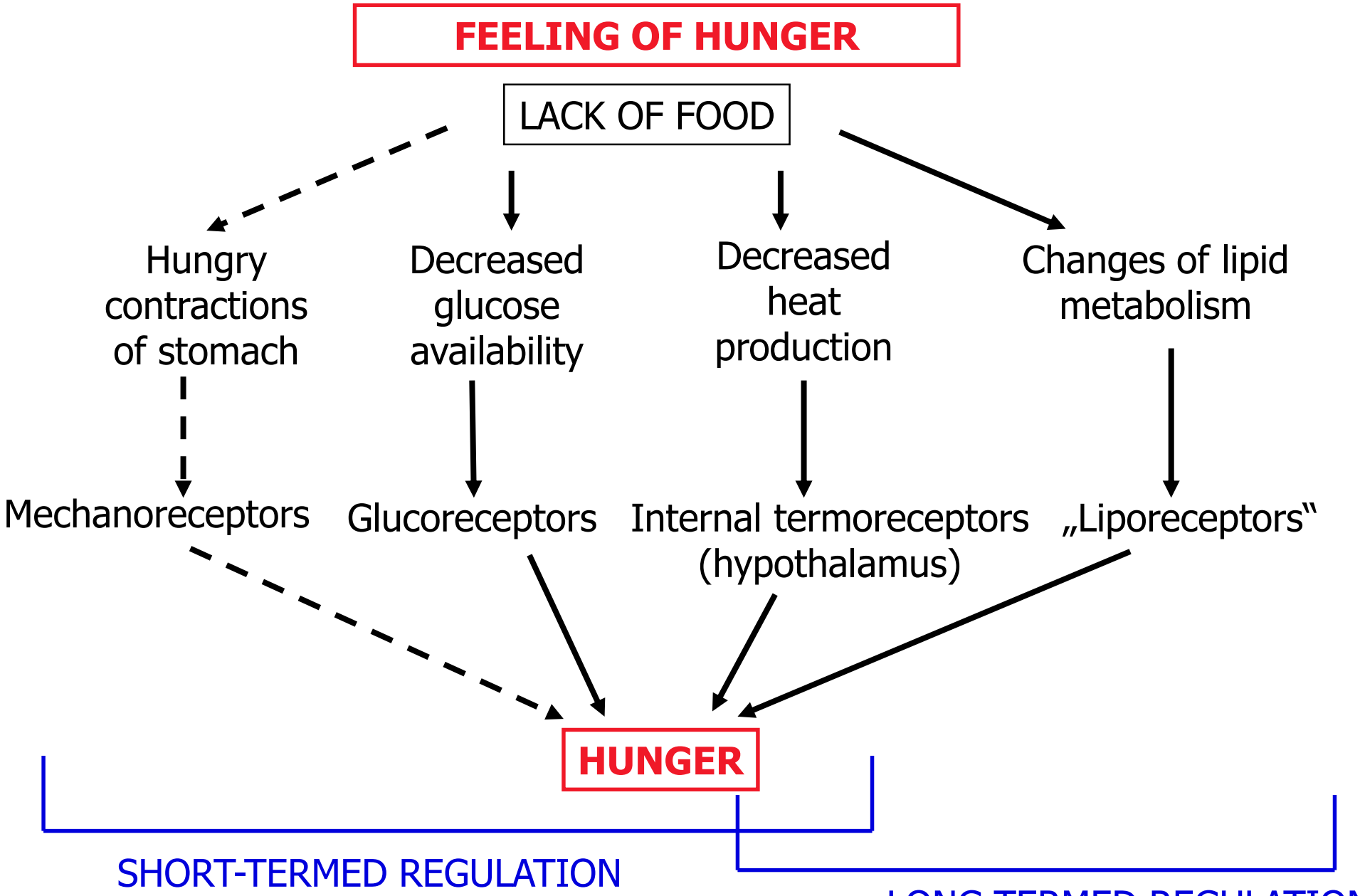
ncl. ventromedialis in hypothalamus

lateral hypothalamus
(nucleus under fasciculus telencephalicus medialis)

MUNI MED


FEELING OF SATIETY
FOOD INTAKE
Chewing movements
Receptors in nose, mouth, oesophagus, intestine
Mechanoreceptors in stomach
GIT chemoreceptors
Central gluco-thermo-lipo-receptors
COMPILING THE INFORMATION IN CNS
(CENTER OF SATIETY = ncl. ventromedial in hypothalamus)
PRERESORPTIVE FEEDING
RESORPTIVE FEEDING
SATIETY

MUNI MED


FEELING OF HUNGER
LACK OF FOOD
Hungry contractions of stomach
Decreased glucose availability
Decreased heat production
Changes of lipid metabolism
Mechanoreceptors
Glucoreceptors
Internal termoreceptors (hypothalamus)
„Liporeceptors"
HUNGER
SHORT-TERMED REGULATION
LONG-TERMED REGULATION
Compensation of dietary mistakes

REGULATION OF FOOD INTAKE

HYPOTHESIS:

1. Lipostatic
2. GIT peptides
3. Glucostatic
4. Thermostatic

OREXIGENIC FACTORS

- Neuropeptide Y
- Orexin A and B (hypocretin 1 and 2)
- ARP (agouti-related peptide)
- Ghrelin (lenomorelin) – s.-c. hormone of hunger (released from „empty“ stomach)
- Motilin
- Sugars (fructose)

ANOREXIGENIC FACTORS

- Leptin - – s.-c. hormone of satiety
- POMC – derivative MC4-R
- CRH (corticoliberin)
- CART (cocaine- and amphetamine-regulated transcript)
- Peptide YY (pankreatic peptide; L-cells in ileum and colon, suppresses gastric motility, increases absorption)
- CCK (cholecystokinin)
- glucagon

MEDICAMENTS !!!

LEPTIN (ob-protein)

Secreted by adipocytes into the blood
Binding proteins
Effect on CNS (regulation of body mass and stability of adipose tissue)

- Pulsatile and diurnal character of plasmatic levels
- Free and bound form (in serum)
- SLIM PEOPLE HAVE 2x MORE OF BOND FORM THAN OBESE PEOPLE
- LEPTIN REZISTANCE: often in obese patient with insulin resistance

RECEPTORS from cytokine family
- **Peripheral** (gonads)
- **Central** (hypothalamus, pituitary)

Modulates expression of genes for oestrogens.
Regulation of obesity by leptin mediated by NPY and MSH.

Leptin controls adipose tissue by coordination of food intake, metabolism, autonomous nervous system and energy balance.

ADIPOSE TISSUE

LEPTIN RESISTANCE

LOSS OF BODY MASS

↓

- LEPTIN

↓

HYPOTHALAMUS

↓

NPY

↓

NPY RECEPTOR (Y1, Y2, Y5)

↓

RESPONSE TO FASTING

+ Food intake
- Reproduction
- Temperature
- Energy expenditure

PARASYMPATHETIC ACTIVITY

INCREASE OF BODY MASS

↓

+LEPTIN

↓

HYPOTHALAMUS

↓

MSH

↓

MSH RECEPTOR

↓

POMC derivatives (MC4-R)

↓

RESPONSE TO OBESITY

- Food intake
+ Energy expenditure

SYMPATHETIC ACTIVITY

MUNI MED