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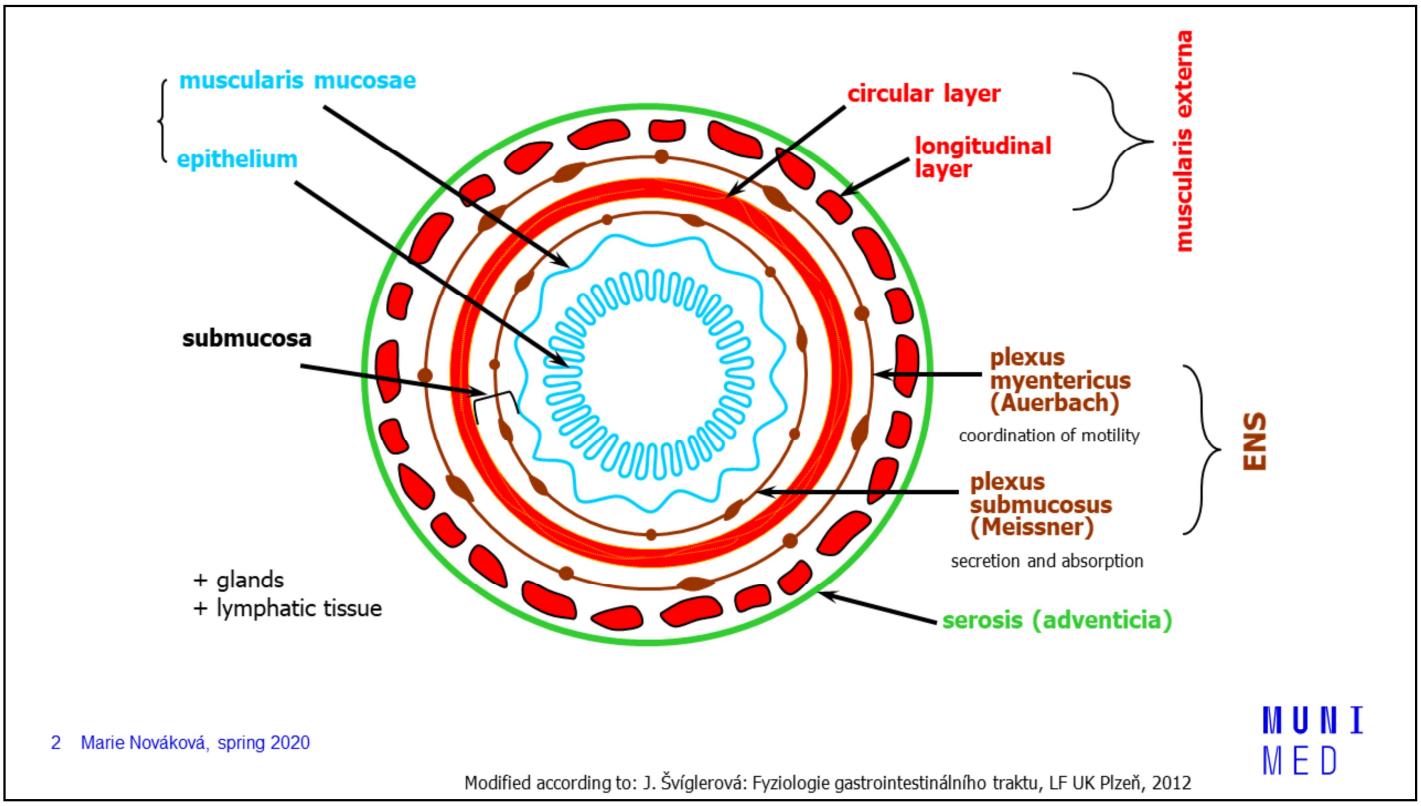
GASTROINTESTINAL TRACT

1 Marie Nováková, spring 2020

- The GIT is a tube, specialized along its length for the sequential processing of food
- Assimilation of substrates from food requires both digestion and absorption
- Digestion requires enzymes, which are secreted in various parts of GIT
- GIT stores certain substrates, ions and vitamins
- Food ingestion triggers complex whole-body responses (endocrine, neural, paracrine)
- GIT plays an important role also in homeostasis (absorption *vs.* excretion, isovolemia, isoionia, etc.) and immunity
- As well as in other systems, there is very important time aspect – all GIT processes are interrelated and coordinated



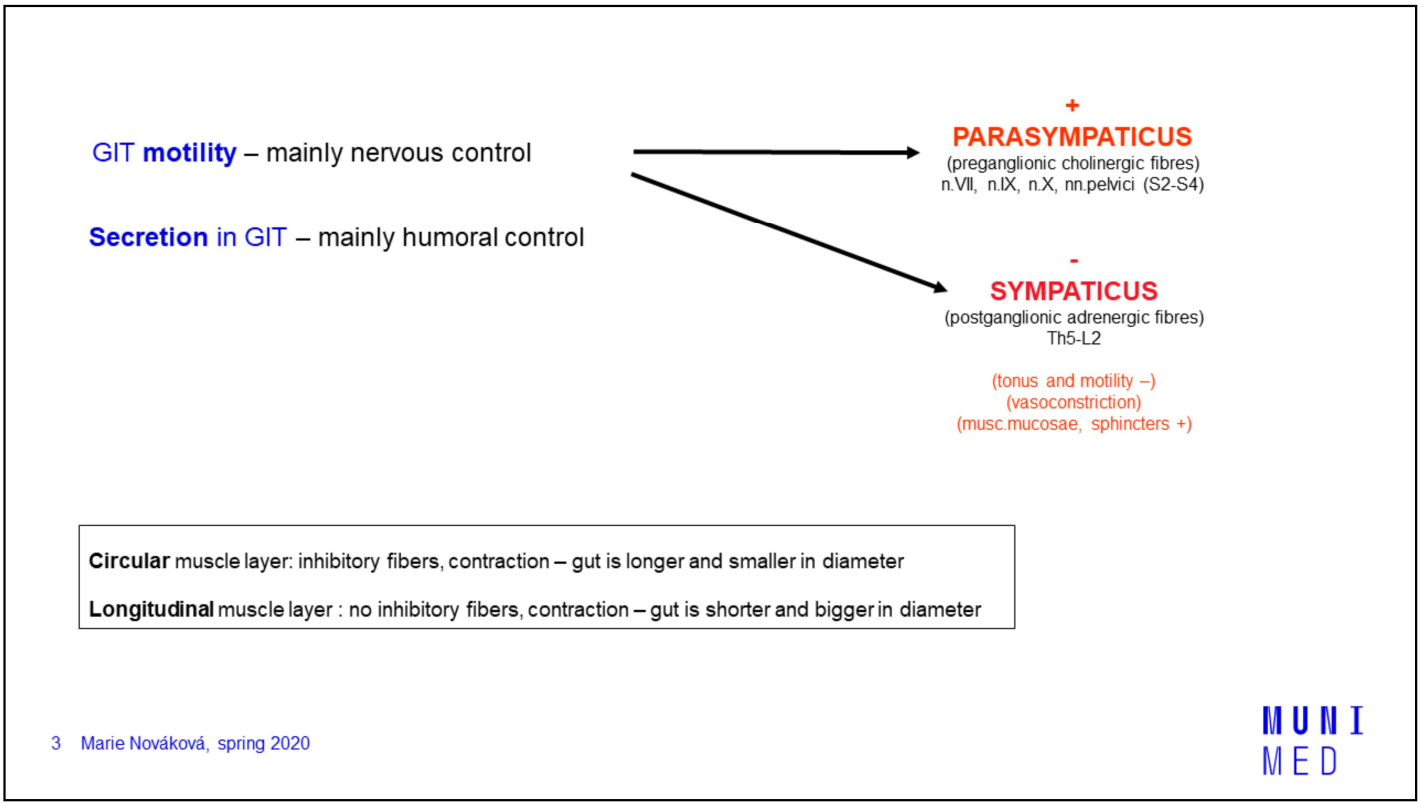
The gastrointestinal tract is formed by a tube composed of the oral cavity, pharynx, esophagus, stomach, the small and large intestines, and rectum. The exocrine glands - the salivary glands, the pancreas and the liver - secrete their products into the tube.

The individual parts of the digestive tract have their own specific functions, but essentially the **structure of the wall of the digestive tube** does not differ in any significant way throughout its whole course from the oesophagus to the rectum. It is formed by the mucous membrane, the submucosal fibrous tissue, a muscular layer, and an external surface layer.

The tonus and motility of the digestive tube are ensured by muscular fibres. The muscular layer (tunica muscularis) in the oral cavity, pharynx, the upper part of oesophagus, as well as in the area of the anus is formed by striated muscle fibres. In the other parts of the digestive tube there are smooth muscle fibres, mostly made up of an inner circular and an outer longitudinal layer. Contractions of the circular muscle fibres cause a lengthening and narrowing of the intestine, contractions of the longitudinal layer result in a shortening and widening of the intestine. In certain places of the digestive tube the circular muscle fibres are characteristically thickened and form so-called a sphincter. The sphincters separate individual parts of the gastrointestinal tract; they regulate the shifting of the chyme to the distal levels and at the same time prevent reflux of the chyme back to the higher levels of the digestive tract.

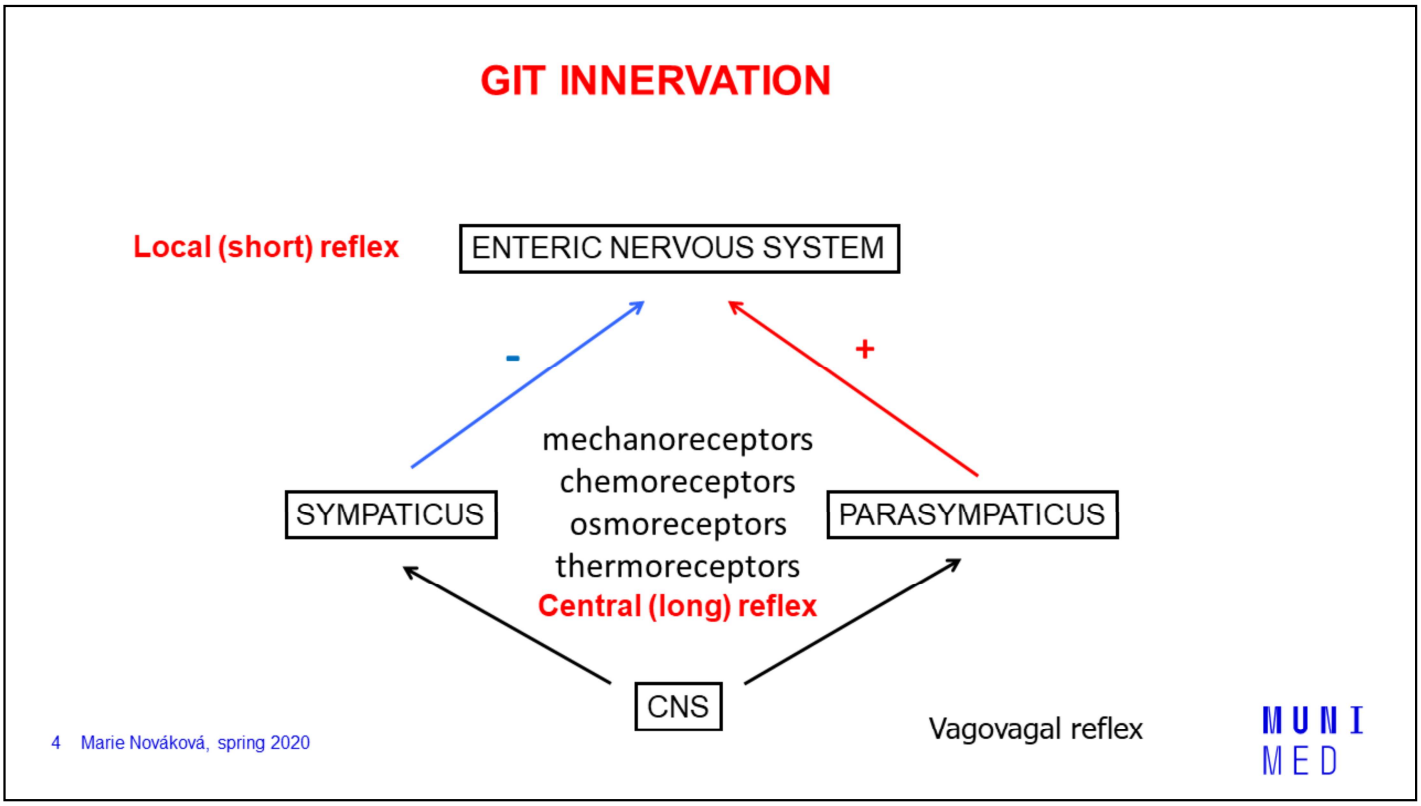
The wall of the digestive tube contains two neural plexuses, linked both morphologically and functionally: the inner **submucosal plexus (plexus submucosus Meissneri**),

located in the submucosal fibrous tissue, affects primarily actions associated with secretion and absorption; the outer **myenteric plexus (plexus myentericus Auerbachi**) is located between the circular and the longitudinal smooth muscle fibres, and thus logically participates in co-ordinating the motility of the digestive tract.



As has been said before, there are four processes which take place in the digestive tube: **digestion** (mechanical and chemical), **absorption** (the passage of nutrients through the intestinal mucosa into the blood or lymph circulation), **storage** (substances such as glycogen, vitamins, and ions), and **excretion** (removal of the unresorbed rests of food and toxic or heterogeneous substances). All these processes are controlled both neurally and humourally, both in the endocrine and paracrine ways.

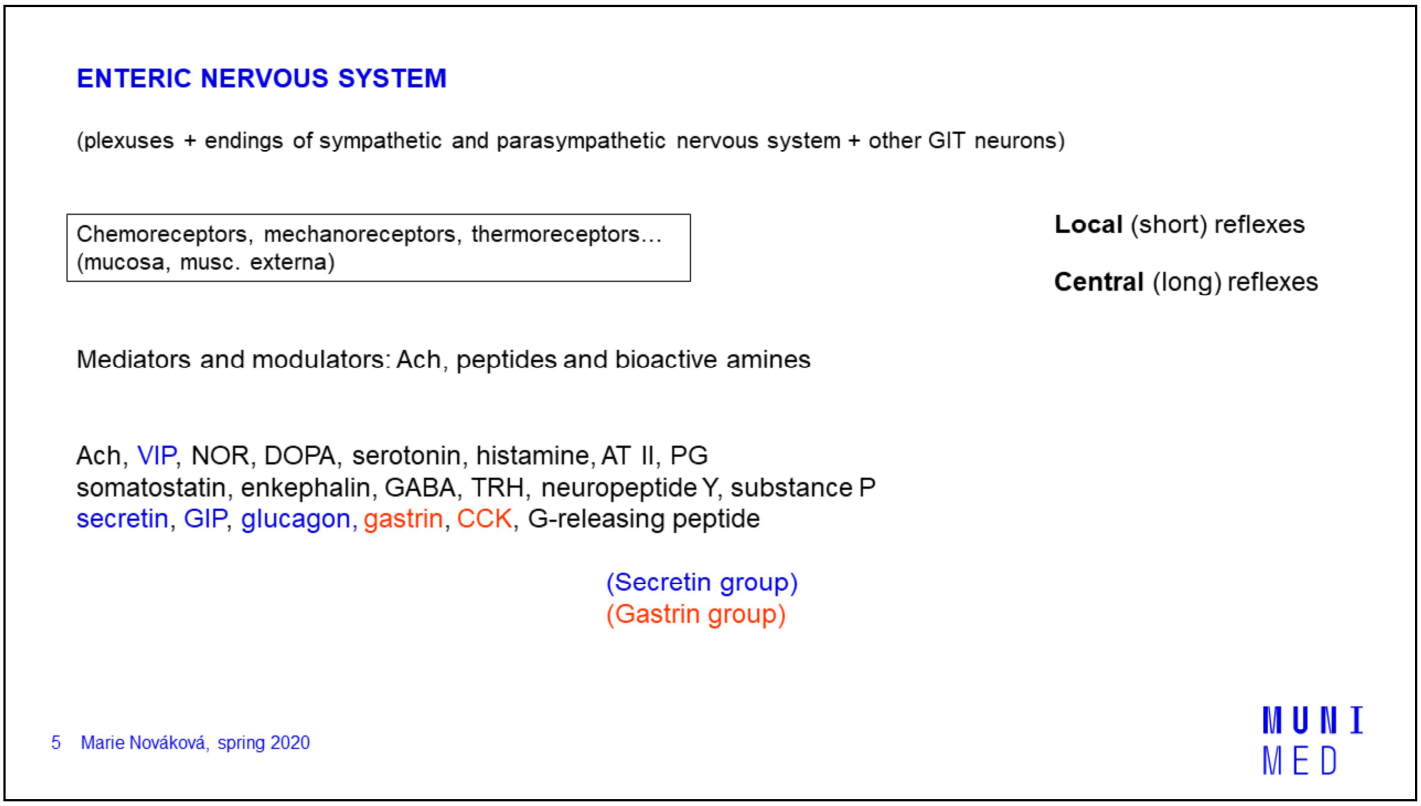
Various types of motility and secretory activity can be observed in GIT. Both these processes are regulated by nervous and humoral pathways at various levels. Key role plays autonomous nervous system. Parasympathetic system – sometimes called trophotropic system – exerts stimulatory effects, increases motility (tonus of the gut and frequency and amplitude of various types of movements, BUT decreases tonus of sphincters). Sympathetic system exerts opposite effects, moreover – due to its vasoconstrictive effect – decreases production of various secretions in GIT (ability of exocrine gland to produce secretion is directly proportional to its perfusion with blood). Next to abovementioned, the sympathetic system increases tonus of muscularis mucosae, which changes the absorption area and thus positively affects absorption.



Both abovementioned plexuses - **plexus submucosus Meissneri** and **plexus myentericus Auerbachi** - form what is called **enteric nervous system**, which is part of the autonomic nervous system (together with the sympathetic and parasympathetic nervous systems). It consists of roughly one hundred million mutually interconnected neurons - afferent, efferent, and interneurons, both inhibitory and excitatory.

In the wall of the digestive tube there are receptors which detect temperature, mechanic, chemical, and osmotic changes. After the processing on interneurons, efferent neurons subsequently affect the activity of the target tissues (smooth muscle fibres, secretory and endocrine cells, immune tissue). The enteric nervous system can operate totally independently of the central nervous system. Due to its marked autonomy and the large number of neurons it is sometimes also called the "**minibrain**" of the gastrointestinal tract.

It is necessary to emphasise again, that the enteric nervous system is under a permanent influence of the autonomic nervous system. The parasympathetic nervous system has generally a stimulatory influence on secretion and motility, the sympathetic nervous system has opposite effects.

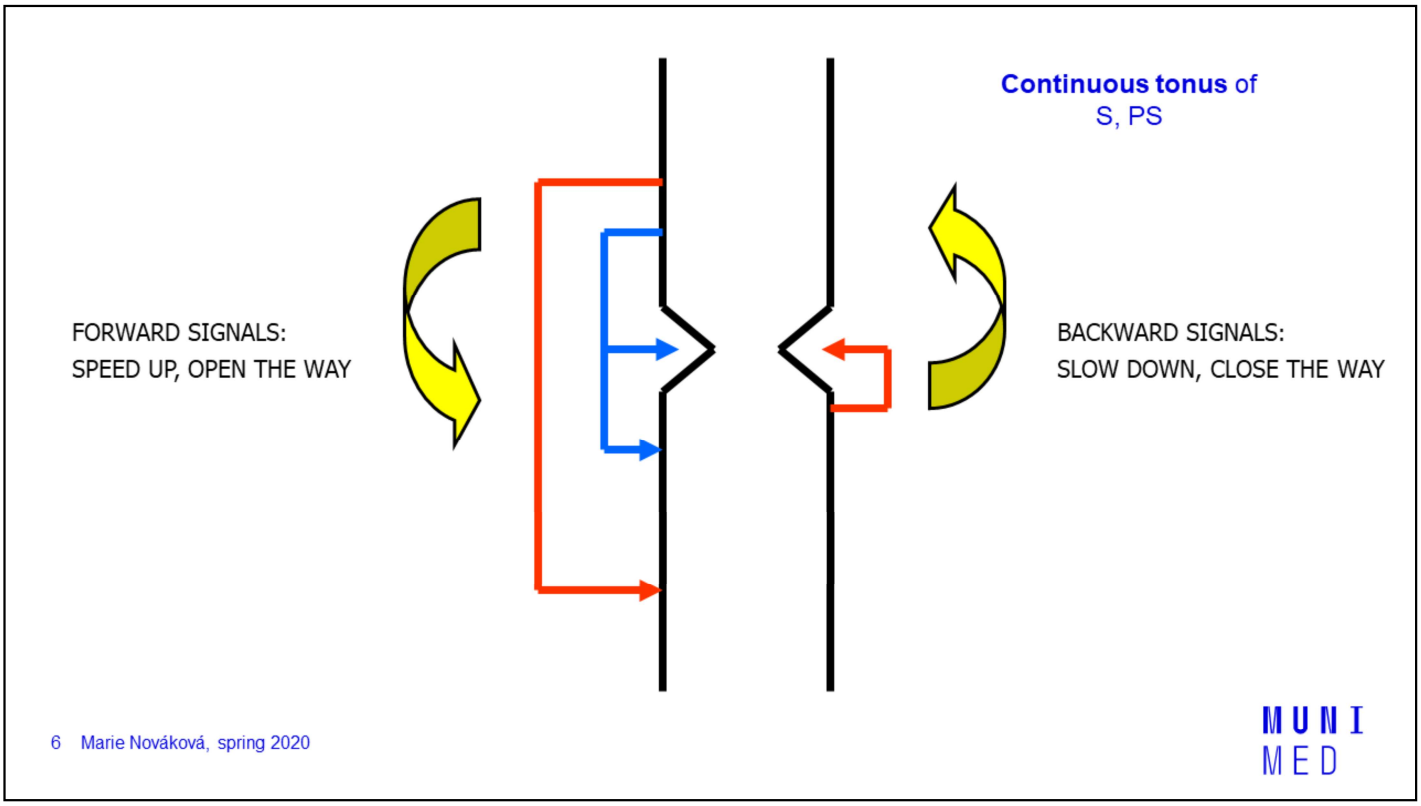


The reflexes that affect the activity of the gastrointestinal system can be divided, according to the arrangement of the reflex arc, into short and long ones:

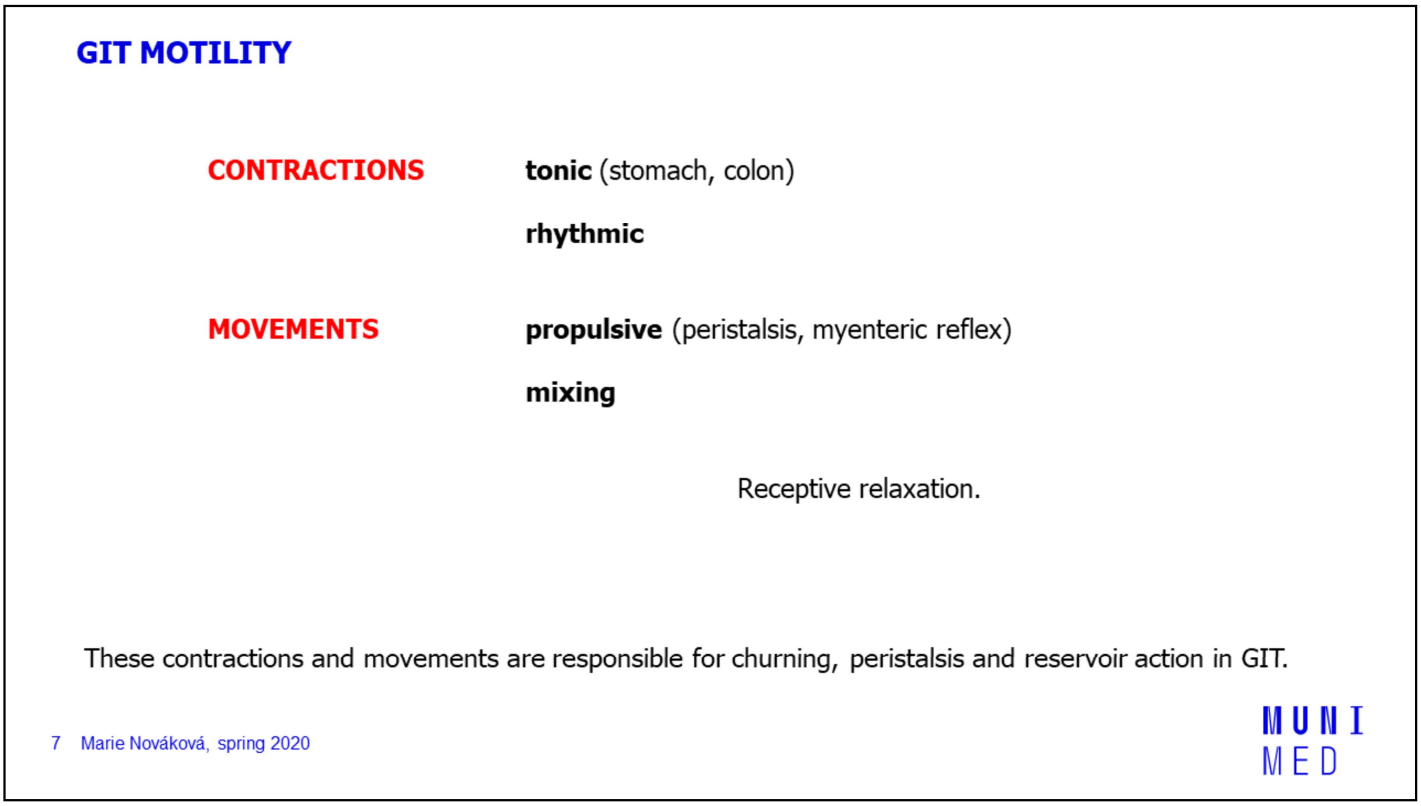
In case of a **local reflex** (also called **short** reflex), the response is exclusively mediated through the enteric nervous system.

In case of a **long reflex (central)**, the information from the receptors is processed by the central nervous system (either in the spinal cord or in the brain stem) and the efferent sympathetic and parasympathetic fibers then modulate the activity of the efferent part of the enteric nervous system.

This system employs the whole range of neurotransmitters which can be divided according to their chemical structure or according to their effect into several groups. It is interesting that many of these substances exert also paracrine effects and some of them are also „classical“ hormones (gastrin). Many of these substances are neuromodulators in various receptor systems in CNS. Their presence in GIT may explain the whole range of physiological reactions during stress reaction, pain management, food intake regulation, etc. (enkephalin, neuropeptide Y, substance P, etc.)



The enteric nervous system, and thus the digestive tract, are under a permanent influence of the autonomic nervous system. The so-called **forward** (progressive) **signals** (in case of increased stimulation by the parasympathetic system) thus include an increase of the tone and motility on the one hand, and relaxation of the sphincters before the progressing food on the other; the **backward** (retrogressive) **signals** mean a decreased tone, a slowing down of the bowel movements and closing of the sphincters.



The motility of the digestive tube is necessary for the mixing of the chyme with the digestive juices, shifting of the chyme from the oral cavity toward the rectum (aboral direction), and storing of the chyme (particularly in the stomach and subsequently in the large intestine).

There are two basic types of CONTRACTION in the gastrointestinal system:

Tonic contractions take longer, minutes to hours. They are particularly typical of those organs where the chyme is stored, which is stomach and large intestine. They hinder excessive extension of the digestive tube and prevent the chyme from moving too fast in aboral direction.

Rhythmic contractions are shorter and serve for pushing food in the aboral direction and for its mixing with gastrointestinal juices.

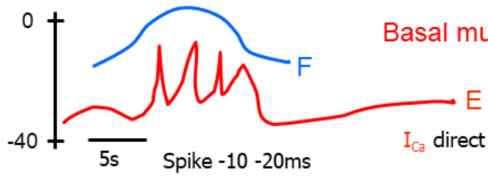
The MOVEMENTS in the digestive tract are divided into propulsive and mixing movements.

The prototype of **propulsive** movements is represented by **peristaltic movement**. It is present along the whole length of the digestive tube except for the oral cavity, with its highest frequency in proximal parts of the gastrointestinal system. It is a transverse, aborally propagating contraction, triggered as a reflex from the mechanoreceptors or chemoreceptors of the intestinal wall. A peristaltic wave pushes the chyme forward by several centimetres; there the chyme stimulates further receptors, and the entire process repeats itself. Peristaltic movement is co-ordinated by the myenteric neural plexus and cannot be effected without its presence. Therefore, it is also designated as the **myenteric reflex**. The autonomic nervous system and some of the hormones only modulate the course of the peristaltic reflex and are not indispensable for its triggering.

Mixing movements are local movements of individual organs of the gastrointestinal system and serve to mix the chyme with gastrointestinal juices. Here belong for example the pendular and segmentation movements of the small intestine, as well as

ELECTROPHYSIOLOGY OF GI SMOOTH MUSCLE

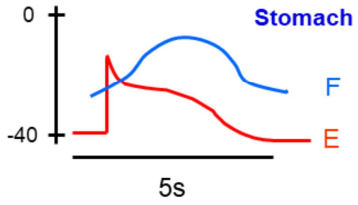
Resting potential:	from - 40 to - 80mV (↑gNa : ↓gK)
Lower activity of Na+/K+-ATPase	
Slow waves (oscillation of rest.MP)	3 (stomach) – 12(duodenum)/min – **basal electric rhythm**
Spike (AP)	low voltage, depolarisation – Na^+ and Ca^{2+}, 1-10/sec
Pacemaker cells in ENS	automacy
Variability	neurohumoural regulation
Innervations: nexus, innervations of circular muscle >> longitudinal muscle	
No motor endplate	Ach, ENS, exceptions



Basal muscle tonus, basal rhythm (time summation)

Modulation of slow waves – amplitude (less by frequency)

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



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

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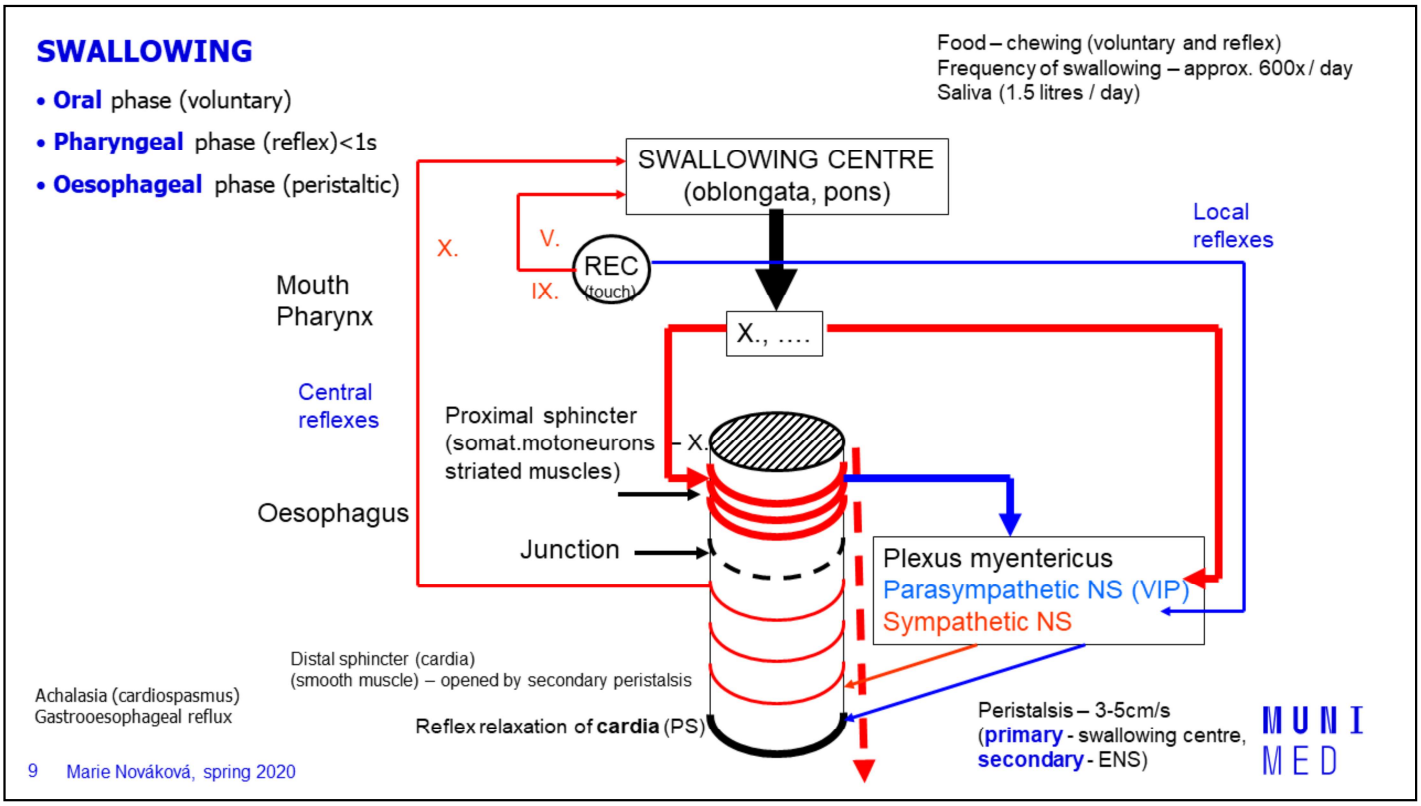
The smooth muscle fibres of the gastrointestinal system exhibit special electrical qualities: the **basal electrical rhythm, BER** (also called slow waves) generated by pacemaker cells, and the adjoining spikes. These spikes resemble action potentials of quickly depolarizing cells, such as neuron or striated muscle. However, the duration of GIT smooth muscle spikes is longer and the amplitude is smaller as compared to these excitable cells.

The frequency of the basal electrical rhythm is affected by the enteric nervous system and differs in various parts of GIT (very slow in stomach; in intestine, the fastest in duodenum and then progressively decreases). It is enhanced by the action of the parasympathetic nervous system, acetylcholine, stretching of smooth muscle cells, and stimulation of mechanoreceptors in the intestinal wall.

This phenomenon is caused by less stabile and less negative resting membrane potential of smooth muscle cells – see the slide.

This system is rather exceptional also in another feature – BER is modulated by amplitude (e.g. slow waves change their amplitude, in another words – in case of higher fluctuation, there is higher probability of reaching threshold membrane potential and triggering of spike. In case several spikes originate (burst) on the top of slow wave, the system behaves as frequency-modulated one (e.g. the higher number of AP, the stronger contraction will be triggered).

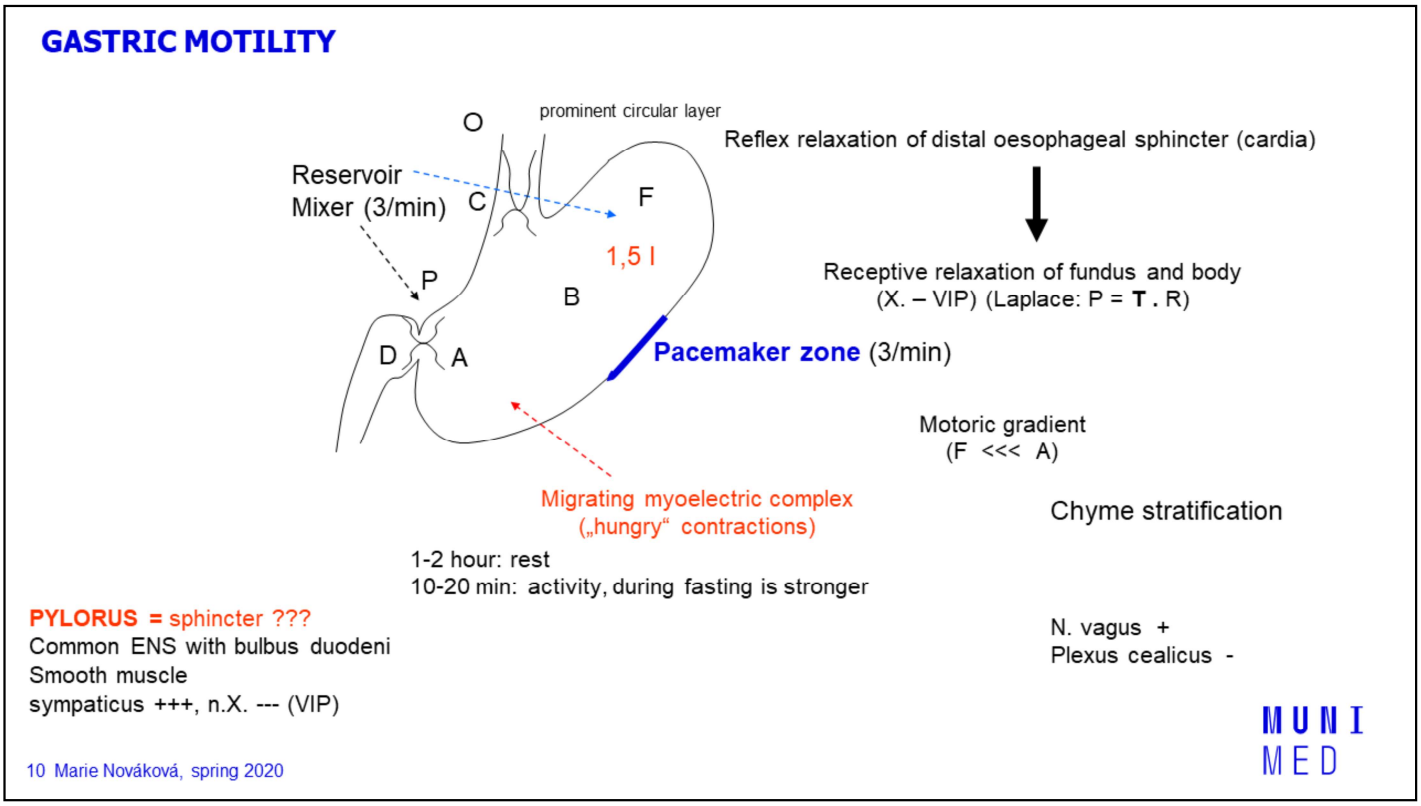
Stomach muscle can contract even without spike, based only on slow wave.



First, repeat from anatomy the structure of organs which form gastrointestinal tract. Note that oesophagus is formed from both striated and smooth muscle (upper third – striated muscle, middle part is mixed and lower part is formed by smooth muscle).

Food intake starts as three-phases process of swallowing. First phase is voluntary (next to saliva, which we swallow without even thinking about it, food and liquids are swallowed voluntarily), second phase is a reflex one (triggered by stimulation of mainly tactile receptors on soft palate and in pharynx) and the third phase is a peristaltic one. Primary peristalsis is triggered from swallowing center in CNS, the secondary peristalsis is local (based on myenteric reflex from ENS of oesophagus). When the secondary peristaltic wave reaches lower oesophageal sphincter, it opens due to s.-c. reflex relaxation of cardia.

Movement of bite through upper part of GIT is quite fast. These structures serve for intake and fast transport of food into the stomach. Next to significant mechanical events we can observe also significant secretory activity – production of saliva in mouth – and basic secretion in pharynx and oesophagus, which protects these structures from chemical and mechanical irritation.

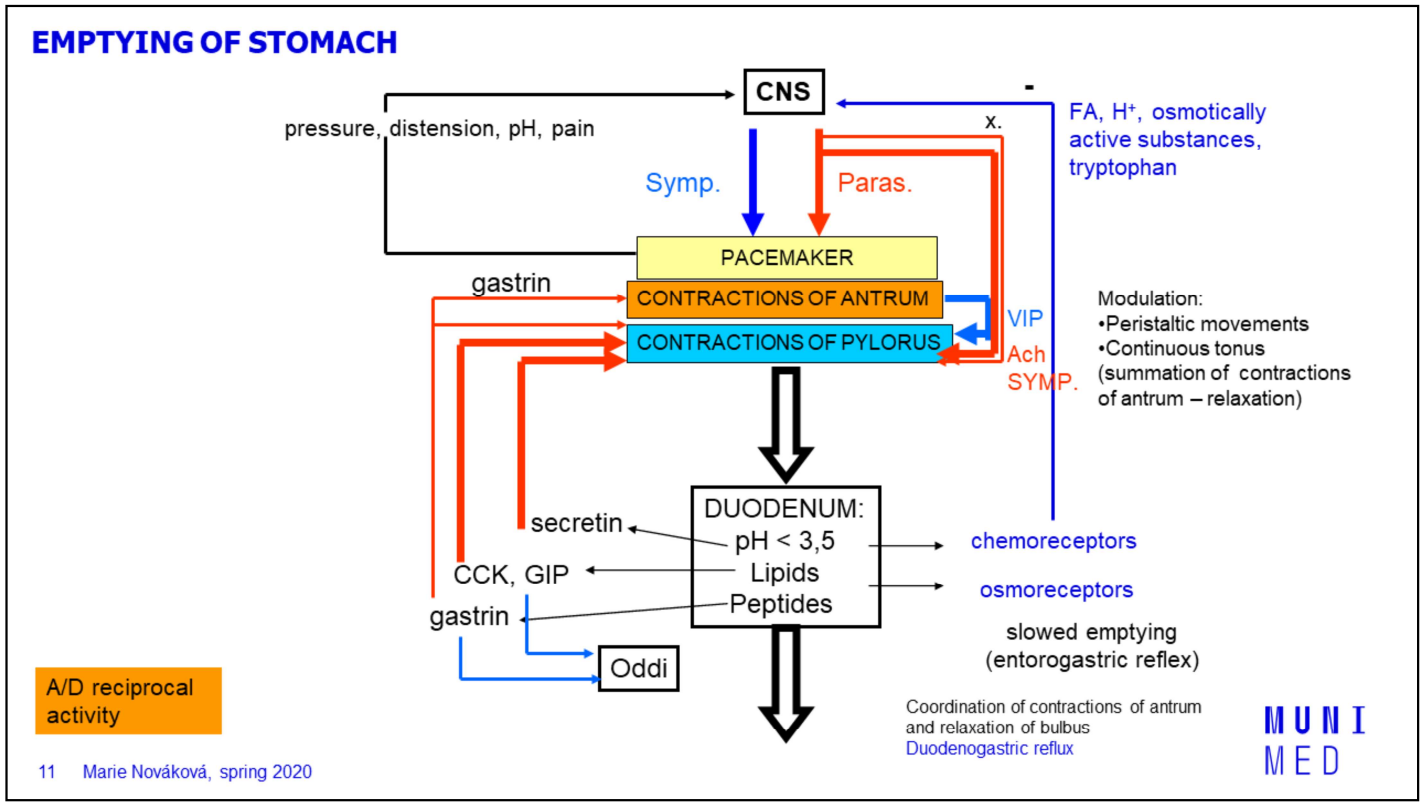


Stomach has several important functions: its mechanical and chemical activity ensures grinding of food and first digestion (pepsins, gastric lipase); next to this, very low pH of gastric juice protects the organisms against most of pathogens (bactericide effect).

Food entering the stomach increases its volume, however the pressure inside doesn't change markedly. Smooth muscle cells are stretched due to increasing volume and their tonus temporarily increases. After several minutes, their tonus decreases back, although the stomach is filled – this is a typical feature of visceral smooth muscle, called **plasticity**. See the slide – application of Laplace law.

Key function is played by the stomach in coordination of GIT functions. After food intake, chyme stratification is observed (solid parts are stratified, high-lipid-content on the top, liquids pass around, on the stomach walls) and then so-called **peristole** starts (period of relative motionlessness, approximately 60 minutes, characterized by tonic contraction). This delay enables distal parts of GIT to finish processes of digestion and absorption of chyme which is located there from previous food intake. Then the stomach starts to evacuate and the information about its increased activity is sent „forward“ as gastroileal reflex and gastrocolic reflex. As a result, these distal parts of GIT also increase their motility and evacuate the chyme and faeces.

O – oesophagus, C – cardia, F – fundus, B – body, A – antrum, P – pylorus, D - duodenum



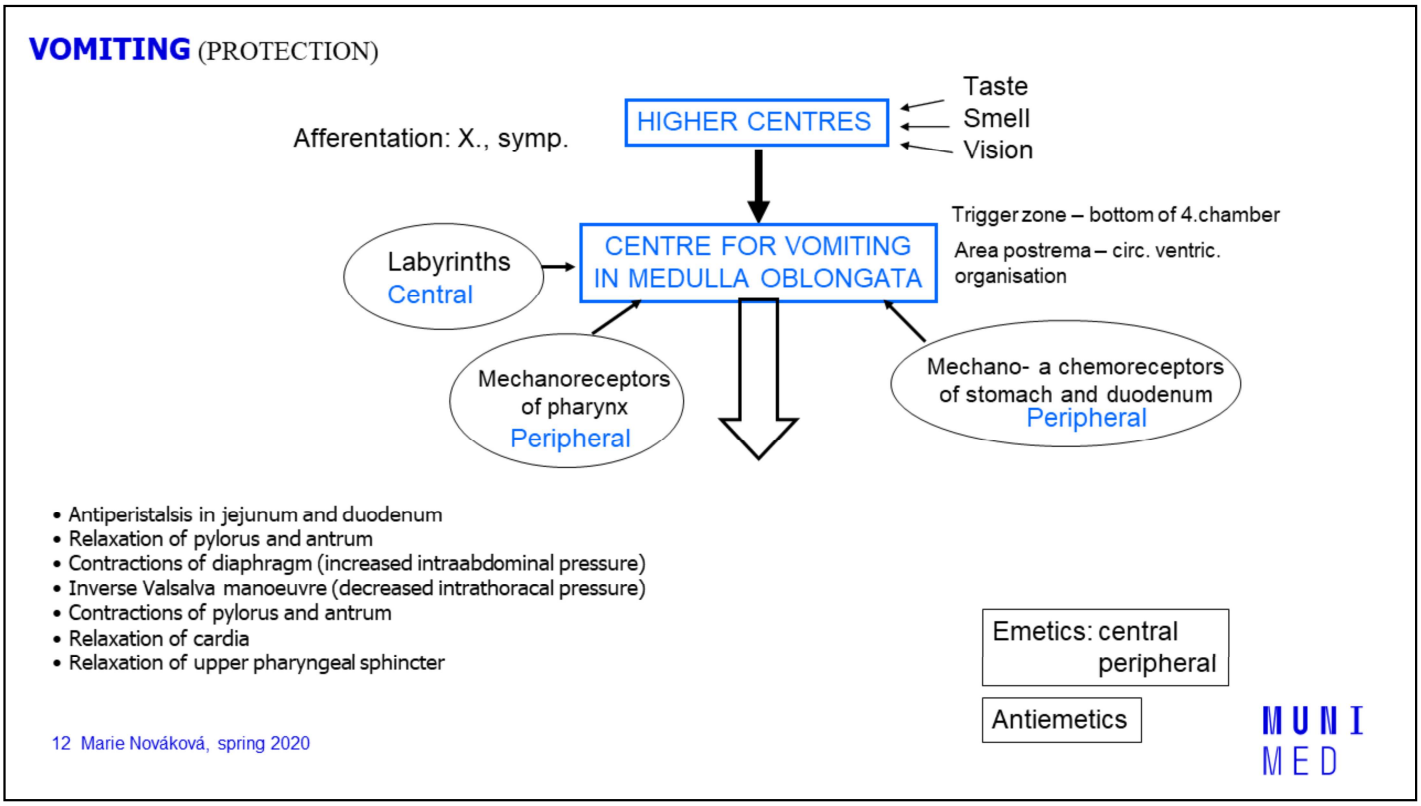
Evacuation of stomach content is stimulated by its peristaltic movements. High tonus of pyloric sphincter slows down stomach evacuation.

During mixing movements of stomach, the pyloric sphincter is tightly closed and chyme returns from pyloric channel back to the lumen of stomach (**propulsion**, **retropulsion**). The stomach body still keeps tonic contraction and chyme slowly moves from this area down to suprapyloric area (antrum).

When the peristaltic wave reaches sufficient intensity in pyloric area (and when the chyme is sufficiently grinded), tonus of pyloric sphincter decreases for a while and several ml of the chyme is squirted into duodenum. This repeating process is called **pyloric pump**.

Chyme spends approximately 1 - 6 hours in the stomach. Emptying of the stomach is faster in case of runny stomach content. First, high-saccharide content leaves the stomach, last – chyme with high content of lipids.

Reciprocal coordination of stomach pacemaker, mechanical activity of antrum and pyloric sphincter tonus – modulated by both nervous and humoral inputs (autonomous nervous system, gastrin) – decides about the speed of stomach emptying. This process is crucial for other processes in GIT – digestion and absorption (too fast stomach evacuation would be contra productive!!!). Bulbus duodeni detects chyme composition and indirectly also its amount (based on detection of pH) and eventually slows down further stomach evacuation. This mutual coordination of duodenum and stomach is called duodenogastric reflex (ATTENTION – don't mix up with reflux – „non-sealed" pylorus and chyme regurgitation into the stomach !!!).

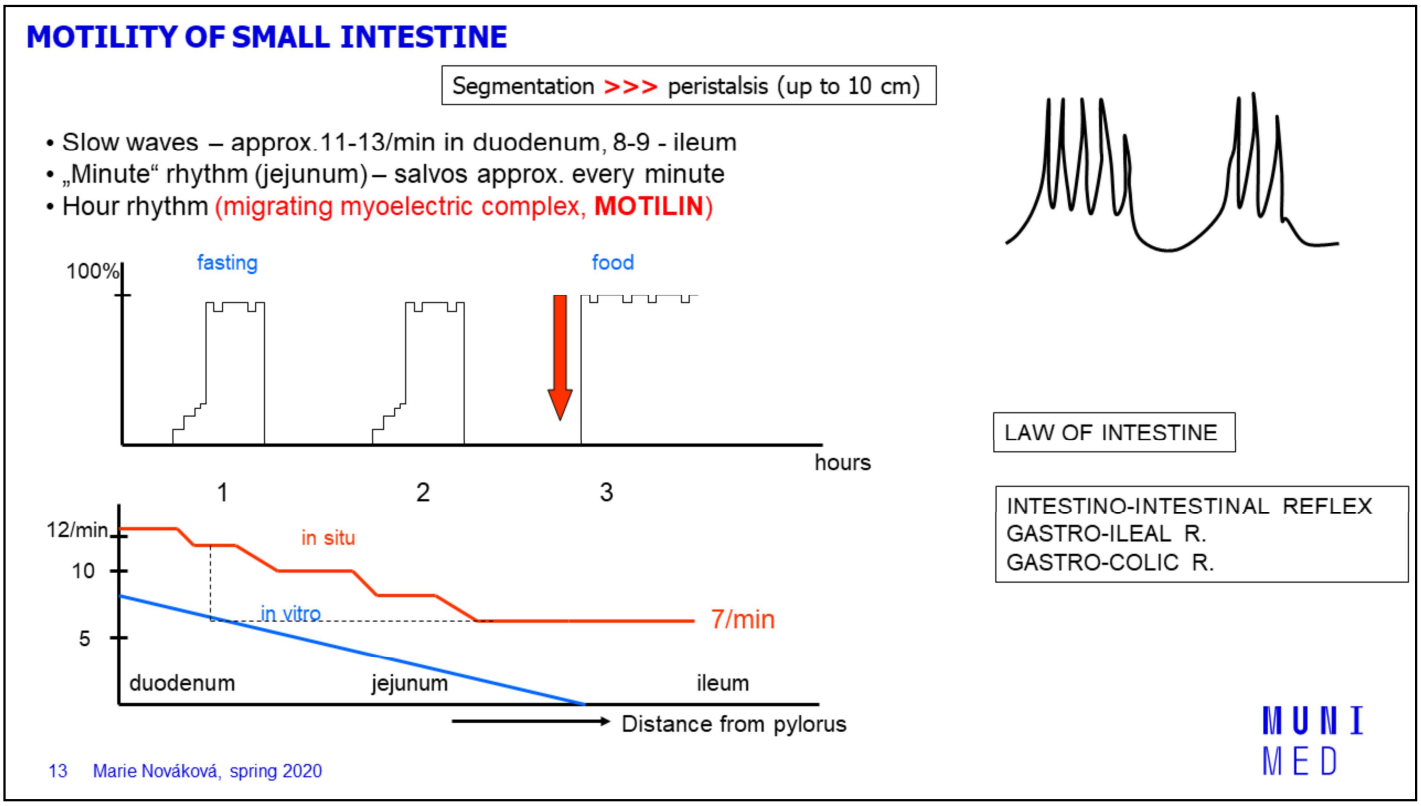


Vomiting represents protective mechanism, protecting GIT from chemical irritation or from damage caused by extreme distension.

It can be triggered from periphery, by stimulation of various GIT receptors (via vagal nerve), or centrally – either by labyrinths irritation or from CNS (various stimuli, see

slide, it can be even imagination of something unpleasant, negative emotion, negative experience).

Process of chyme evacuation from GIT is reverse sequence of physiological processes.



Small intestine movements ensure mixing of chyme with GIT juices and its movement aborally. In the small intestine, two types of movements are observed:

Mixing movements serve to mixing of intestinal chyme with bile, pancreatic and intestinal juices. They also help to mix the chyme which is in contact with intestinal wall and the chyme which is in the lumen of intestine. Mixing movements are either **swinging movements** (repeating stretching and shortening of longitudinal muscle layer in particular intestinal parts) and **segmentation movements** (alternating contractions and relaxations of circular muscle layer). Individual contractions are several centimetres apart, the muscle between them is relaxed, after a while the contraction fades out and a new one appears, in the place of previous relaxation.

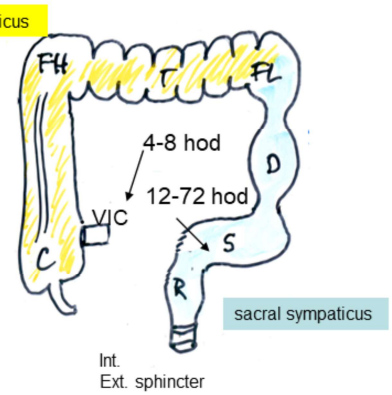
Propulsive movement is represented by peristaltic movement of small intestine. It moves the chyme aborally. It arises in the whole length of intestine, spreads aborally and fades out after several centimetres. The principle of peristaltic movement is myenteric reflex. Peristaltic activity of the intestine increases after food intake based on gastroenteral reflex, which is mediated by ENS. The impuls for triggering this reflex is filling of stomach.

Under physiological conditions the chyme passes through the whole small intestine during 5 – 8 hours.

At the bottom of the slide, frequency of movements in various parts of small intestine is drawn. Note how ENS affects the frequency – frequency decreases in the aboral direction, however on isolated intestine (without the effect of ENS) is the frequency always lower than on the same intestinal part *in situ*, e.g. under neurohumoral modulation.

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)
- Defecation: abdominal muscles +++, muscles of pelvic bottom –
- Reflex: colono-colonic, gastro-colic



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

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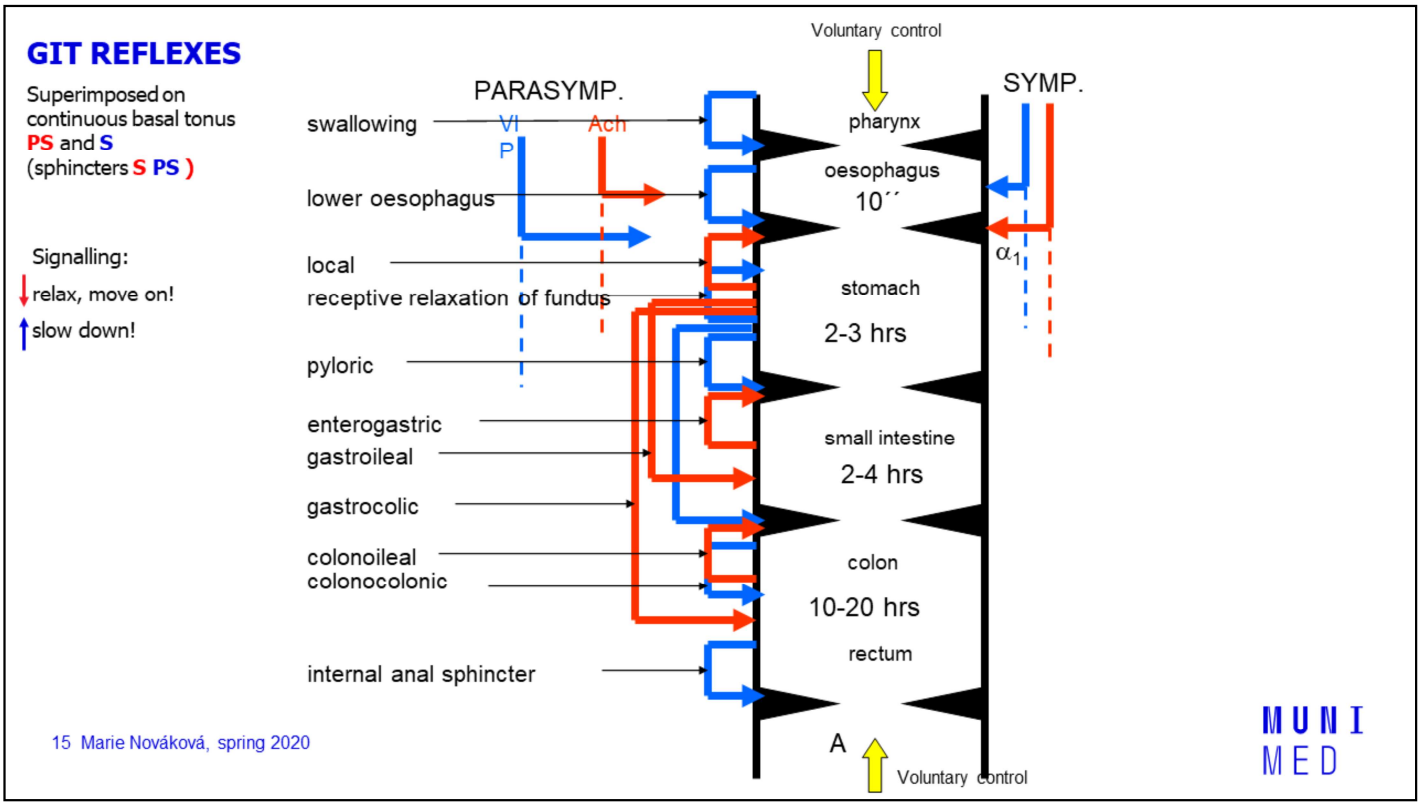
Proximal and distal part of large intestine differ both in movements and function. The main function of large intestine is finishing of absorption of water, ions and some vitamins (mainly in proximal part) and formation, storing and subsequent expulsion of faeces (in distal part). **There is no absorption of any substrates in large intestine!**

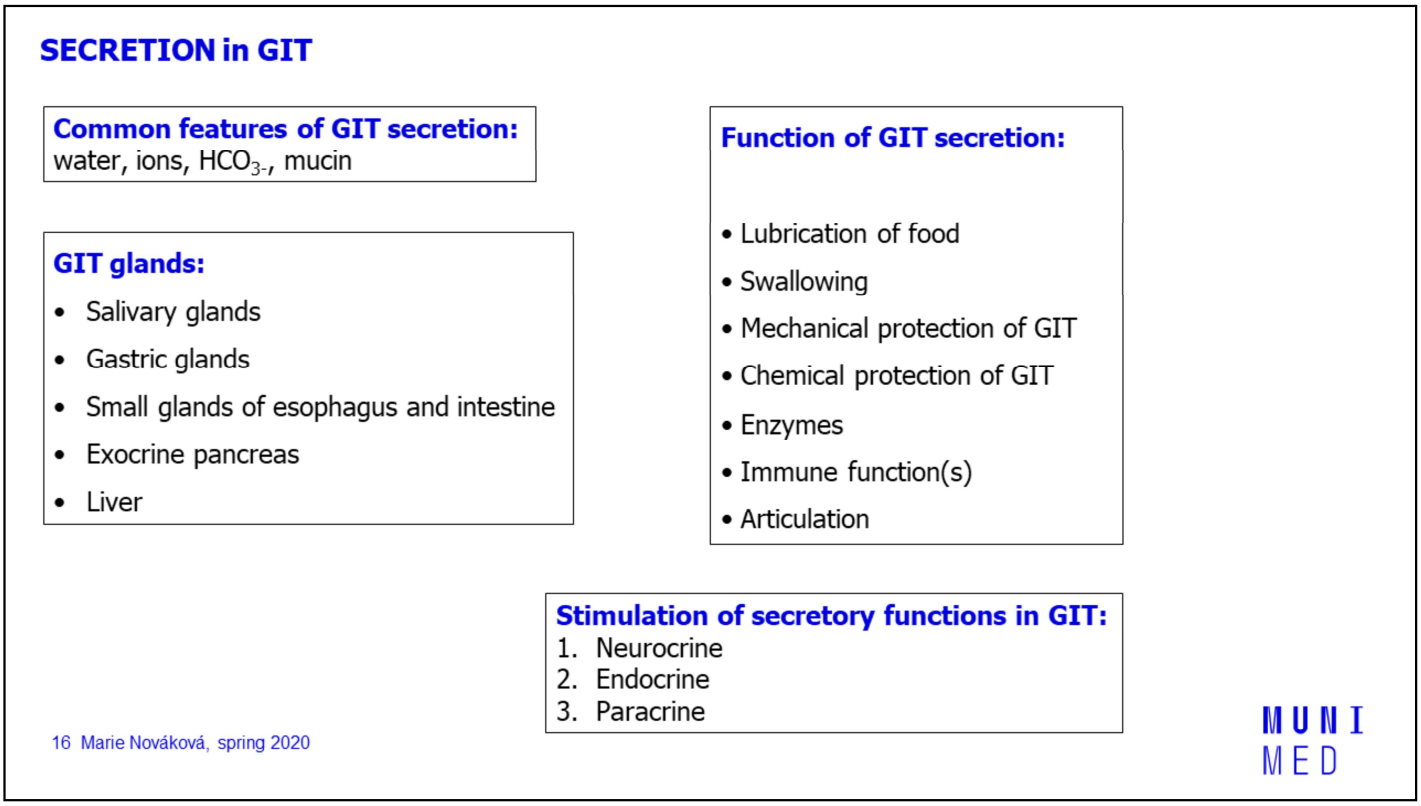
In proximal part, mainly mixing movements are present, which mix chyme with intestinal juice and move intestinal content aborally (similarly to segmentation movements in small intestine, repeated contractions of circular muscular layer and longitudinal taenies; they form characteristic concavities, so-called **haustra**).

In distal part of large intestine, propulsive movements are present (peristaltic, only several times per day – so-called **mass peristalsis**). They are formed by contraction of circular muscle layer in the area of transversal colon, spreading aborally, and move the content of the intestine towards the rectum. After several decimetres the contraction disappears and in the same place new contraction appears. These intensive contractions move the intestinal content on a big distance. In the area with mass peristalsis haustra disappear. These movements remove – together with rest of chyme – also certain amount of bacteria which grow there and thus keep balanced intestinal microbiome.



This is an overview of main reflexes which coordinate functions of various GIT parts, proper emptying of individual parts and help effective processing of chyme and maximal absorption. Note how long time the chyme spends in various part of GIT – both motility (e.g. types of movements) and secretion in particular part corresponds to it.

Motility is increased by parasympaticus, gastrin and cholecystokinin, and decreased by sympaticus and secretin.



Keep in mind that there are certain common parts of secretions in GIT – ALWAYS water, ions, mucin, hydrogen carbonate, just the proportions differ.

All exocrine glands located in GIT (see slide) have often very similar structure and process of secretion formation – first the primary secretion is formed (e.g. saliva or pancreatic juice) and then modified in the system of ducts (some parts of primary secretion are reabsorbed, others are actively secreted). The result may be isotonic to plasma or not.

Also the final secretion often quite significantly differs when the production during interdigestive period (basal production) and during stimulation is compared (of course there are difference among the glands, also it depends on the phase of food intake - cephalic, gastric, intestinal, e.g. different pH of gastric juice between the meals and after food intake). It is necessary to emphasise that the glands „never sleep“, they produce their secretion continuously, although in the interdigestive period the production is small in volume.

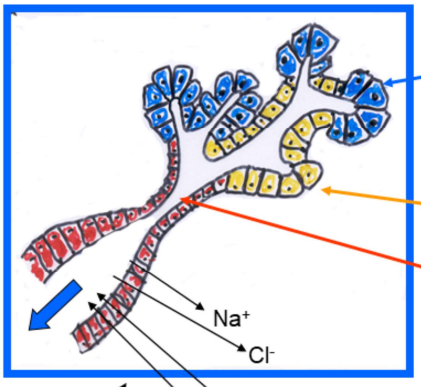
It is impossible strictly say when the gland is active and when not. Usually period of high secretory activity continues from one phase of food intake into the next one – for instance starts in cephalic phase, it is highest in the gastric phase and decreases in the intestinal phase, when inhibition of the production exceeds the stimulation of the gland (e.g. gastric juice production).

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



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

Resembles exocrine pancreas

SECONDARY SALIVA pH ~ 8
(hypotonic, after stimulation – increased tonus)

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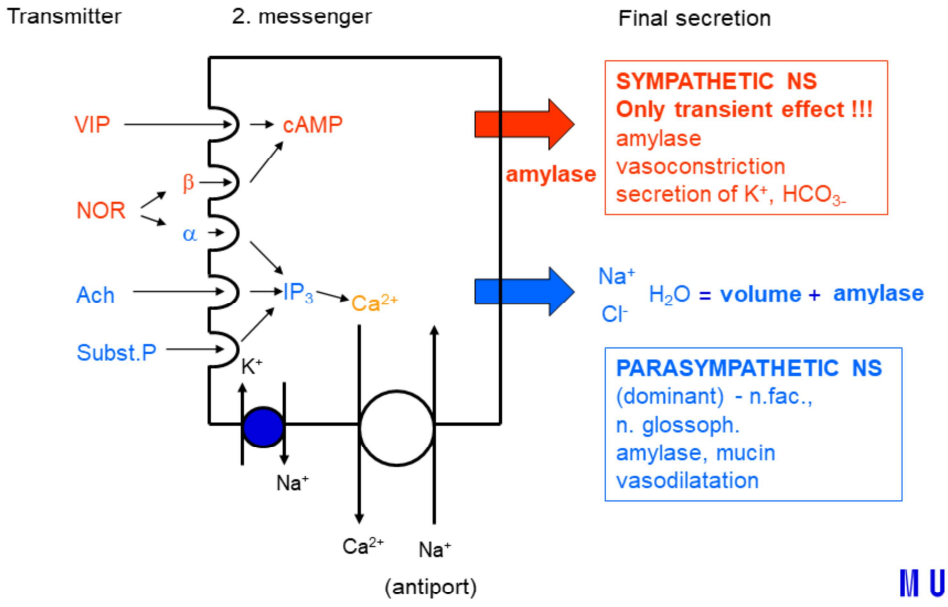
The ducts of salivary glands open into the oral cavity.

Big salivary glands - three paired tuboalveolar glands: **parotid** (glandula parotis), **sublingual** (glandula sublingualis) and submandibular (glandula submandibularis). Serous cells in acinus of these big salivary glands secrete water, ions and enzymes, mucinous cells produce water and mucin. Parotid gland is mostly serous gland, sublingual gland is a mixed gland and submandibular gland is also a mixed gland, with prevalence of mucous cells. Big glands produce saliva of smaller volume, however after the stimulation their production markedly increases. **Small salivary glands** – tubulose or tuboalveolar, scattered throughout all oral cavity (including tongue), contain both types of cells and continuously produce small volume of saliva.

Primary saliva is formed in acinus and it composition and osmolality resembles plasma. The first step in saliva formation is transport of chloride anions into the lumen of acini. Then, sodium cations follow (according to the electrical gradient). As a result, the lumen of acini becomes hyperosmolar, which leads to movements of water from interstitial space into the acini (according to the osmotic gradient). Next to ions and water, also enzymes or mucin are released into the lumen of acini (according to gland type).

Primary saliva composition is changing during its passage through the ducts, where Na+ and Cl- are absorbed and K+ and HCO3- are excreted. Absorption of Na+ and K+ excretion in the salivary ducts is stimulated by **aldosterone**. Ions are not followed by water (ductal wall is non-permeable for water). Primary saliva is changed in ducts into **secondary saliva** (definite) – it is always hypotonic as compared to plasma (less Na+ and Cl and more K+ and HCO3-).

REGULATION OF SALIVA PRODUCTION



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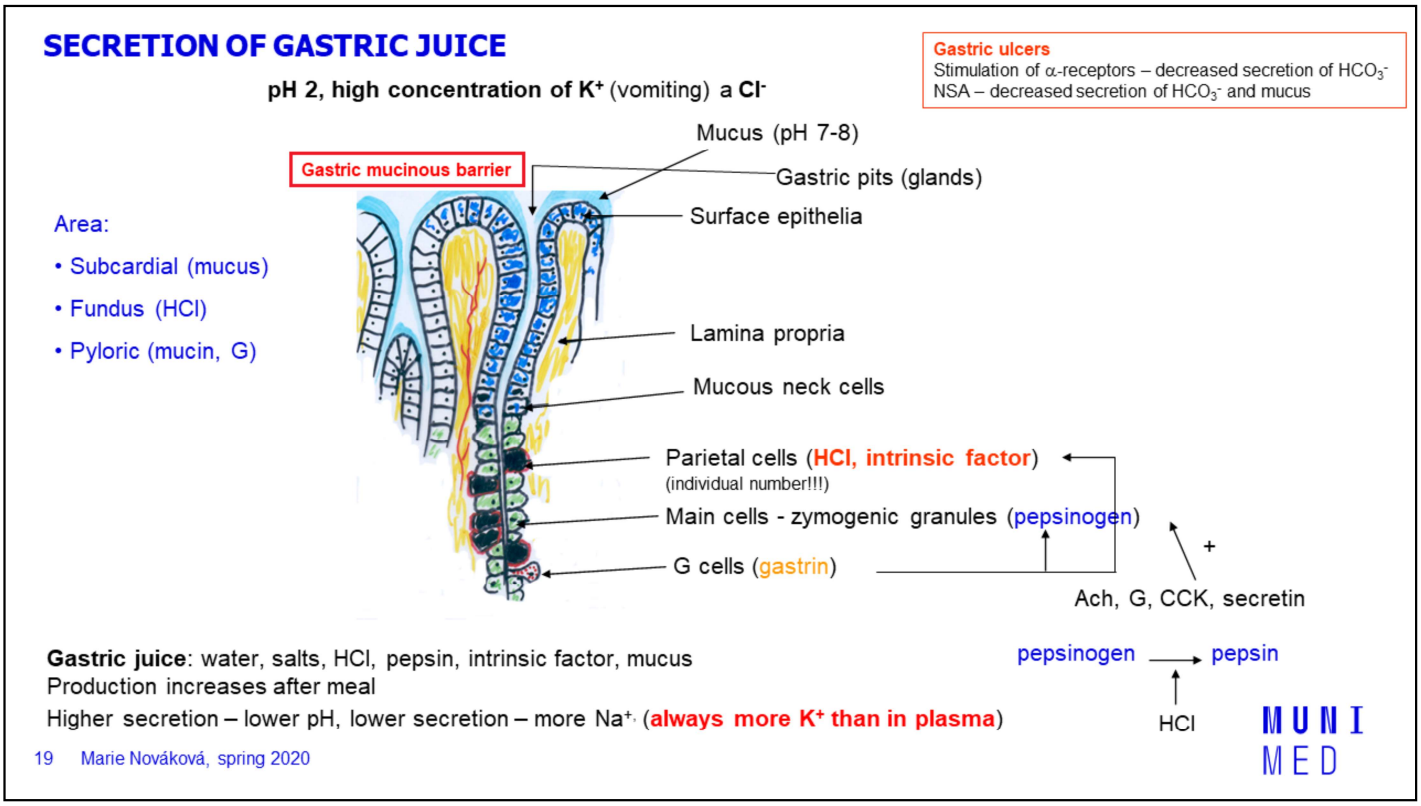
Activity of big salivary glands is controlled mainly by nervous system, based on non-conditioned and later also conditioned reflexes (remember famous experiments of I. P. Pavlov!).

It is necessary to emphasize that salivary gland are stimulated by BOTH parts of autonomous nervous system. The effect of sympathetic stimulation is however transient due to vasoconstriction of the blood vessels in the area.



Gastric juice is produced by gastric glands, which are part of gastric pits. They contain several types of cells with secretory activity (see the slide). Their mutual proportion differs according to location of the pit: for instance in subcardial area higher density of mucus producing cells is observed (it represents a sort of mechanical protection of gastric mucosa, since incoming bites are not properly processed yet, moreover this area is characterised by „storing“ function, the chyme spends here long time); pyloric are is typical with higher proportion of G cells producing gastrin (this area is really important for gastric emptying regulation, see above).

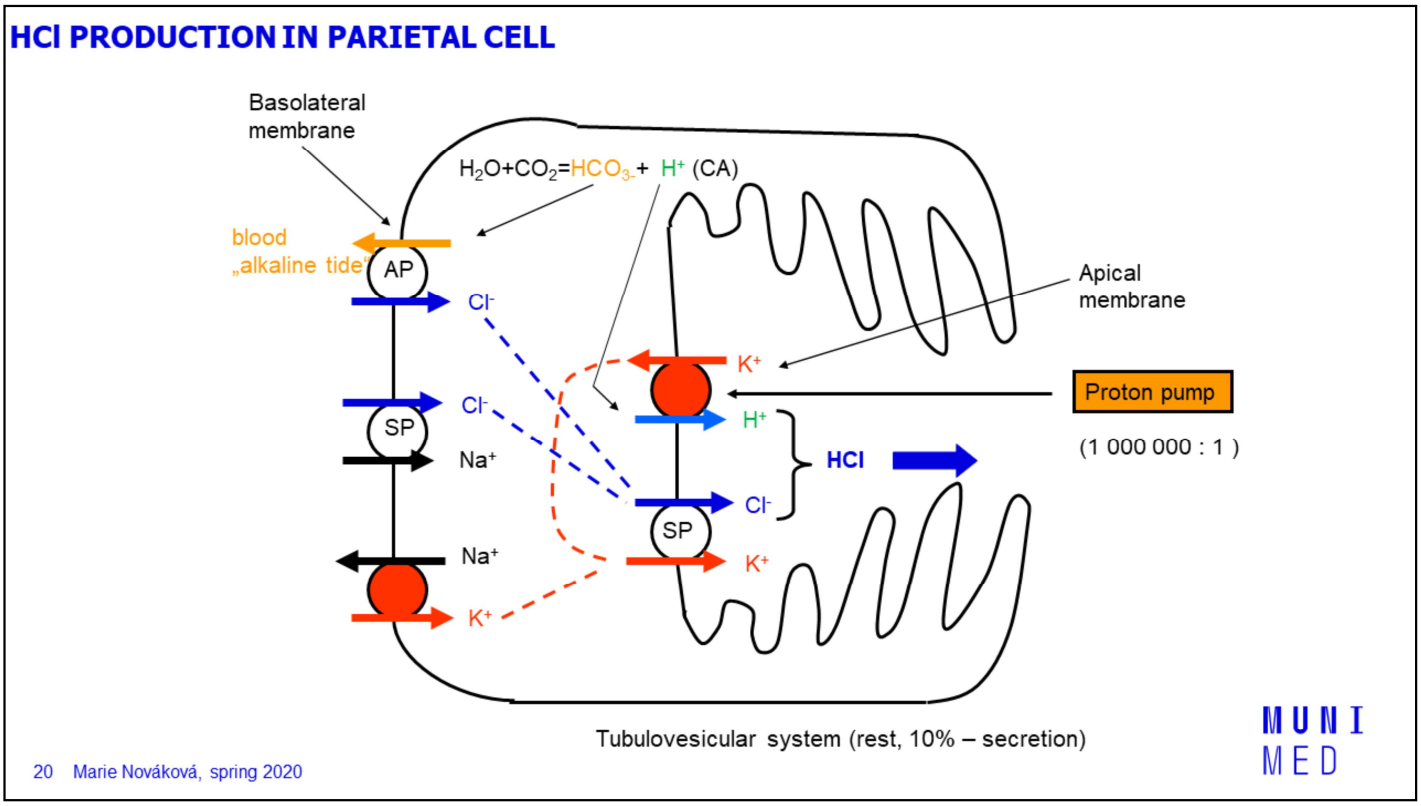
It is worth mentioning that number of parietal cells inter-individually differs which may explain differences in pH of gastric juice in healthy subjects in population,

pH of gastric juice varies from almost neutral during basal secretion up to values around 1 on the top of stimulation. Gastric juice always contains more potassium than blood plasma, which can cause hypokalaemia after repeated vomiting !!!

Don't forget that gastric juice contains also enzymes – chief cells release inactive precursor of protease pepsin - **pepsinogen**, and gastric juice also contains gastric lipase.

PATHOPHYSIOLOGICAL NOTE:

In case the gastric juice doesn't contain enough buffer (bicarbonate, e.g. long-lasting stimulation of alpha-adrenergic receptors during stress) or buffer and mucus (long-lasting use of non-steroidal anti-inflammatory drugs, such as ibuprofen), protective layer on the surface of gastric mucosa – **gastric mucosa barrier** - is weakened and it may lead to damage of mucosa (erosion) with subsequent development of gastric ulcer disease. This is a precancerous condition!



Step-by-step follow the transport mechanisms in the parietal cell and the reactions which bring ions for hydrochloric acid formation. Always start with the main, ubiquitous transporter – Na^+/K^+-ATP-ase.

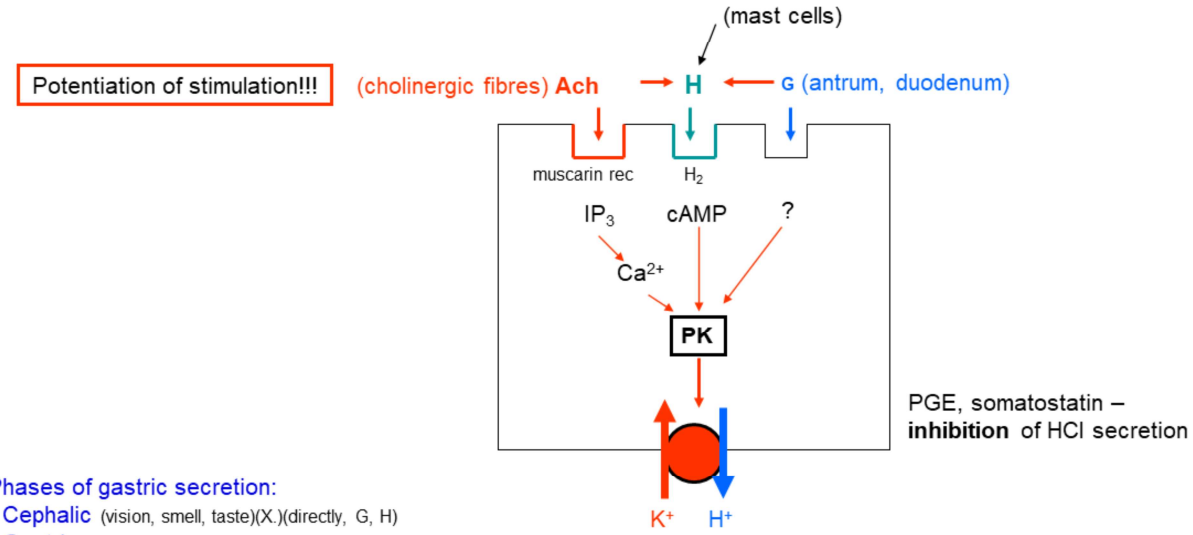
Note that the proton pump (rather problematic name for this transporter – it is an exchanger for H^+ and K^+) works against enormously high gradient, which means that the process is energetically very demanding.

When stimulated, parietal cells releases a lot of bicarbonate, which can be then found in venous blood from the stomach area – this phenomenon is called alkaline tide.

AP – antiport, SP – symport

Together with HCl parietal cell releases into the gastric juice also **intrinsic factor** (binding glycoprotein, necessary for vitamin B_{12} absorption.

CONTROL OF HCl PRODUCTION IN PARIETAL CELL



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)

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Inhibition of gastric secretion:
Low pH, FA, hypertonia v duodenum and jejunum; secretin, bulbogastron, GIP, CCK

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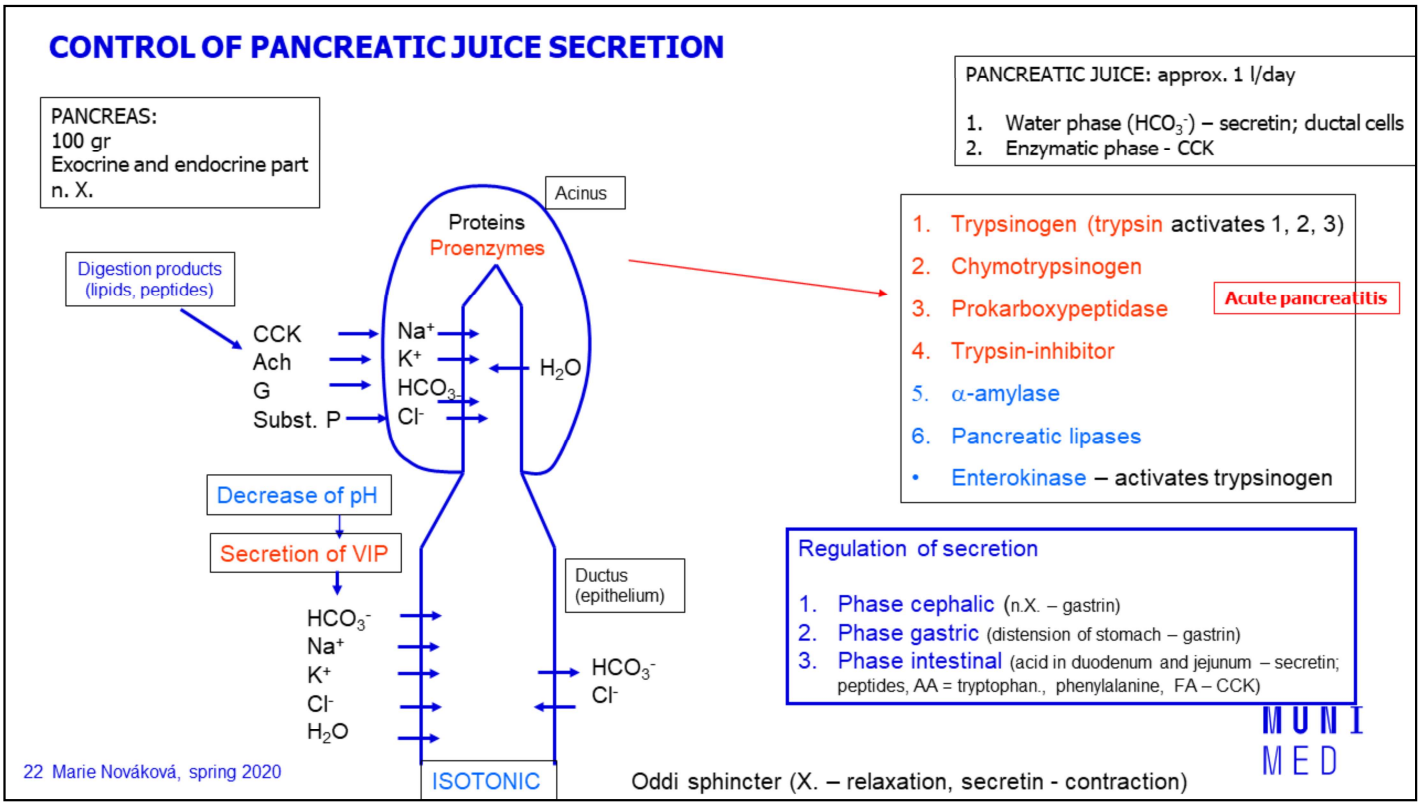
Gastric juice secretion can be traced in all three phases of food intake – in cephalic phase nervous regulation dominates, in gastric phase – neurohumoural (parasympaticus and gastrin); in intestinal phase the inhibition of further production prevails over the stimulation. Some stimulating foods – caffeine, alcohol – stimulate gastrin release and thus stimulate gastric juice secretion.

In the parietal cell, typical cooperation and mutual potentiation of stimulatory effects can be observed – the strongest stimulus is histamine release, which binds to H_2-receptors. Acetylcholine (vagal stimulation) is weaker and a gastrin is the weakest stimulus. Both affect the parietal cell directly, but at the same time also trigger release of histamine from mast cells in submucosa of the stomach.



Exocrine pancreas is a compound tuboalveolar gland, composed of acini formed by serous cells, which produce their secretion into the ducts. Smaller pancreatic ducts (intralobullar and interlobullar) get together into the main ductus (ductus pancreaticus), which opens into the duodenum on ampulla of Vater, either separately or together with bile duct. It is surrounded by smooth muscle which forms sphincter of Oddi, relaxed by parasympathetic system, its tonus increasing under the influence of secretin.

Pancreatic juice contains enzymes, necessary for chemical processing of food - digestion. Proteases are present in the inactive form and are activated by intestinal enterokinase. First, trypsinogen is activated to trypsin, which then activates other proteases. Activation of trypsinogen inside the pancreas is prevented by substance called **trypsin-inhibitor**. Premature activation, e.g. in exocrine pancreatic ducts, causes autodigestion and serious damage of pancreas and leads to **acute pancreatitis** (life-threatening situation).

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

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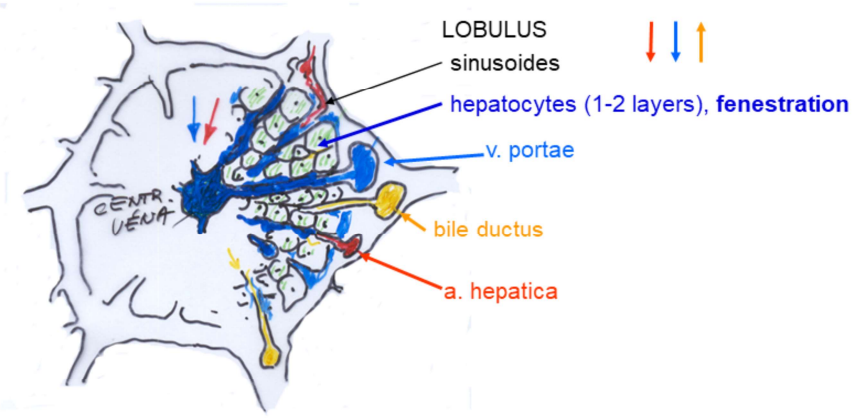
Liver is an exocrine gland producing bile. Next to the secretory function, liver play numerous roles in metabolic, storing, excretory and detoxication functions – see slide.

When you get question „Functions of liver“ during oral examination, you can use a lot of your knowledge from biochemistry ☺

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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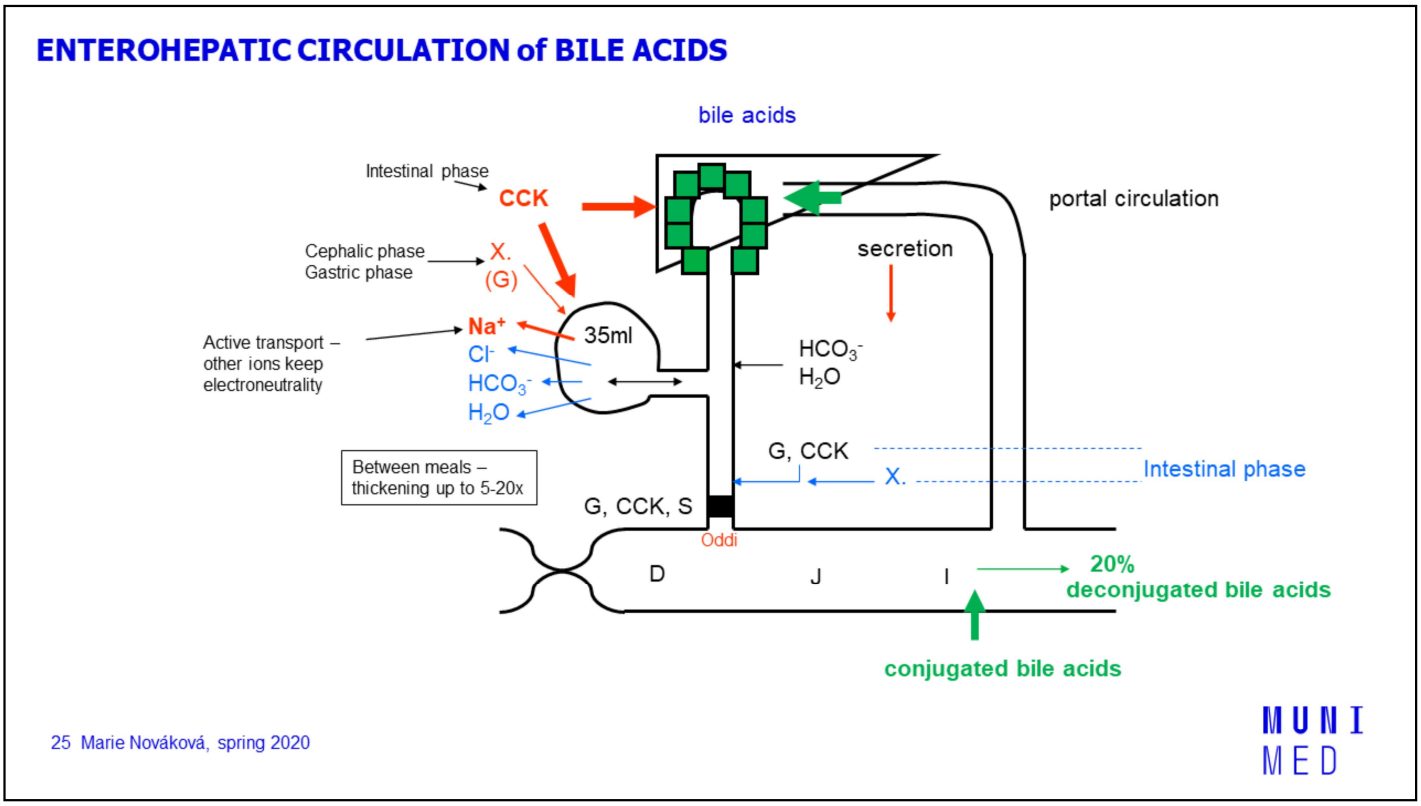
Repeat the structure of liver, namely the microscopic one – see slide. Don't forget on so-called **Kupffer cells**, macrophages localised among endothelial cells of liver sinusoids.

NOTE to bile composition: one half of dry (what is left if we evaporate all water from bile) represent bile acids, or exactly said their salts! It is enormous amount – see next slide.

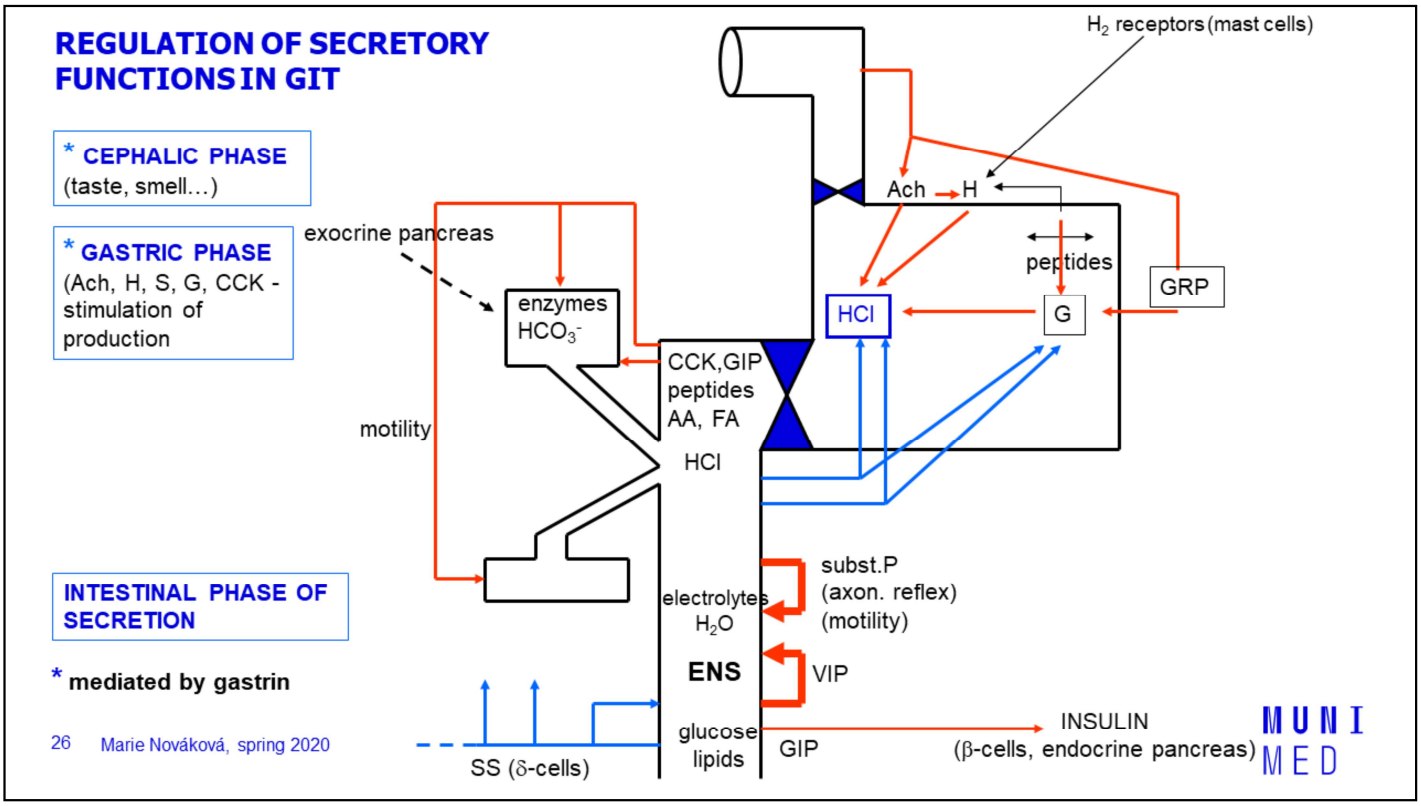
Note, that daily bile production is not high and varies markedly – it depends a lot on the frequency of meals and their composition!



It would be very demanding for hepatocytes to produce new bile acids after every food intake. In fact, most of them are recirculated – in so-called **enterohepatic circulation** of bile acids. Minor portion (numbers differ among the textbooks ☺) is lost with faeces, major part gets back and can be used again.

As mentioned previously, bile is produces all the time – as all other secretions in GIT. In interdigestive period however is not entering the intestine, but is is diverted to gallbladder. By its contraction during food intake this „store“ of bile evacuates into the duodenum – for overview of stimulation of bile production in particular phases of food intake see slide.

According to composition we distinguish **liver bile** and **gallbladder bile** (the latter contains lower concentration of Na^+, Cl^- , bicarbonate and higher concentration of K^+, Ca^{2+}, bile acids, cholesterol, bilirubin and lecithin).



This is another „repeating“ slide – don't try to learn it by heart!

It should only help you to repeat and sort out your knowledge about regulation of secretory activities in GIT in the moment when you already know most of it and you start to repeat.

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**

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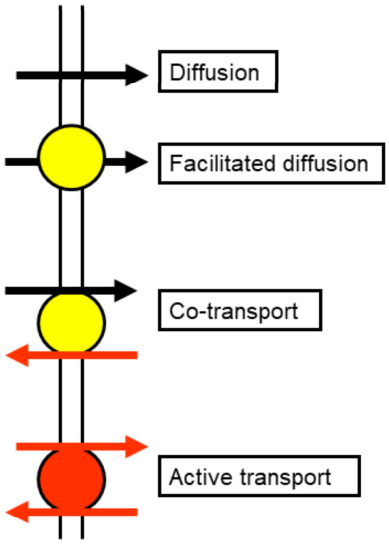
This doesn't need any comment ☺

It is a good idea to make such a list, overview after you finish reading of some chapter or studying of some organ system. Good suggestion – in Boron you find such „take-home messages" as sub-chapter titles. If you make a list of them, you summarize a key knowledge from the particular topic.

TRANSPORT MECHANISMS in GIT



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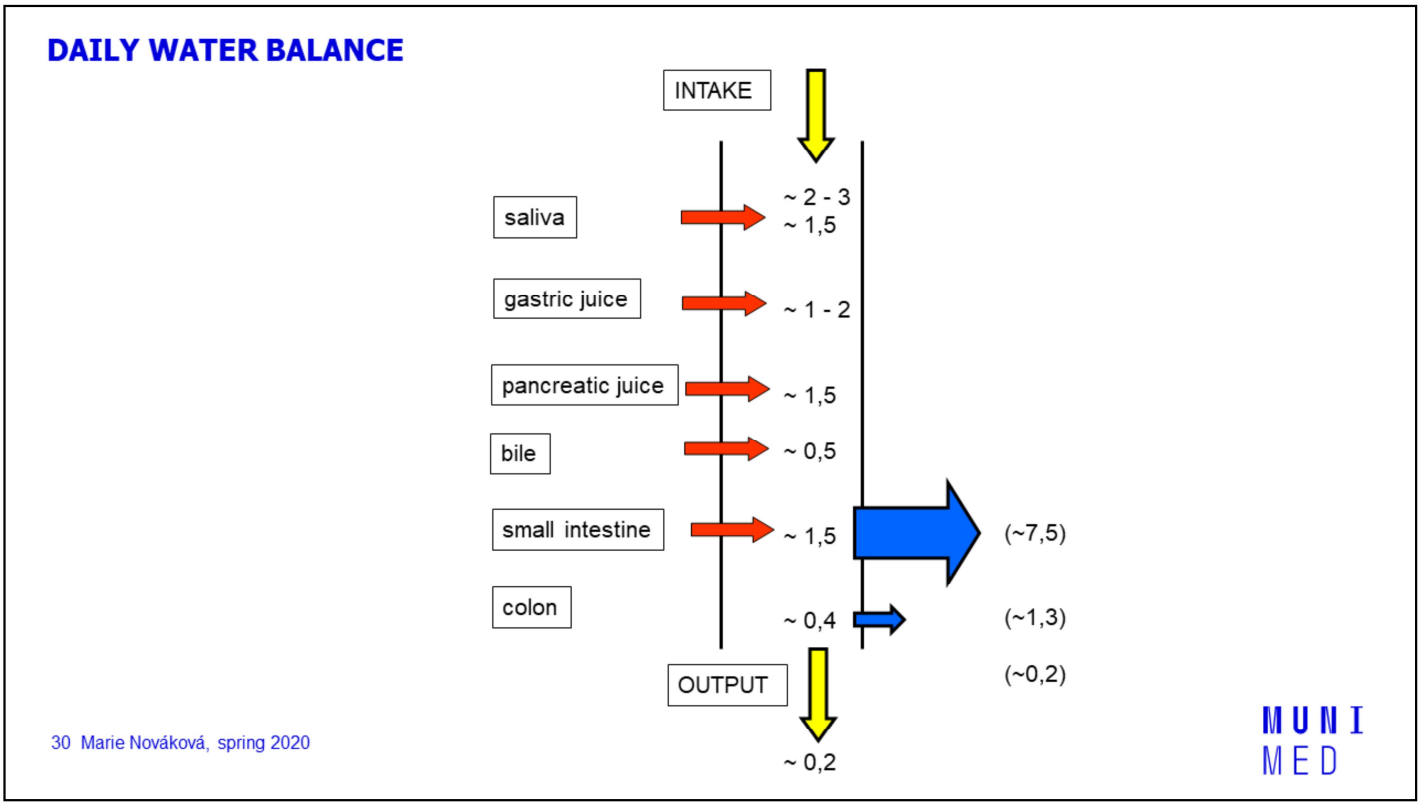
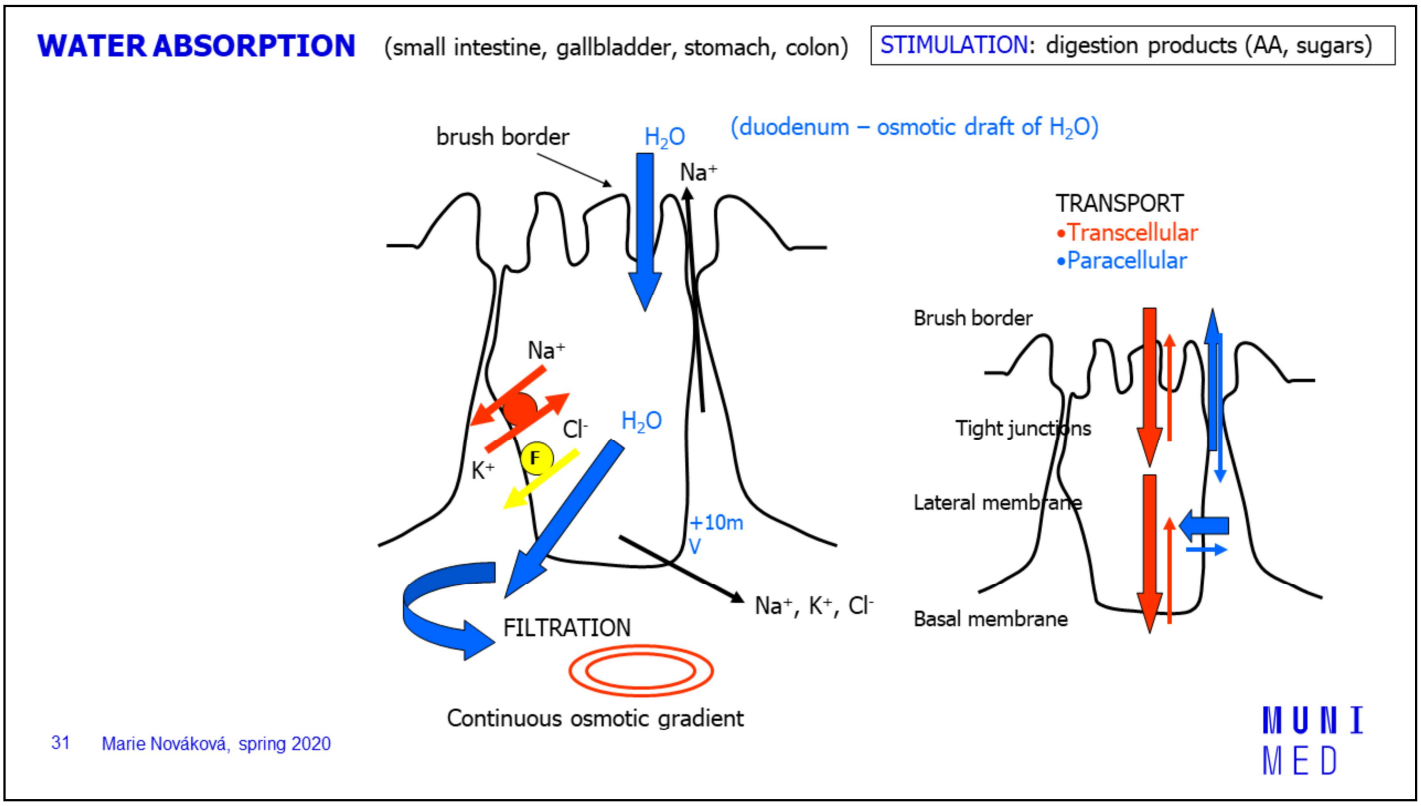
Repeat the principles of various transport mechanisms found in various parts of GIT (it was lectured in the very first lecture in semester Autumn 2019).



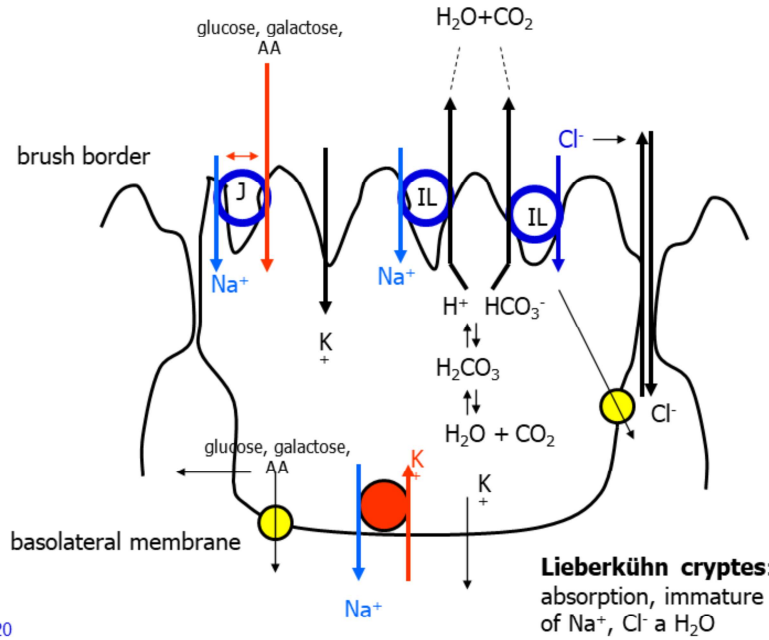
Review the approximate volumes of secretions released into the GIT lumen (number are in litres). Don't forget that amount of secretion varies according to frequency, amount and composition of food. The slide shows a model situation how it could be. However, if you eat fatty goose, the amount of secreted bile will be higher and at the same time due to high protein content also gastric juice and subsequently pancreatic juice will be produced in higher volumes… And I don't mention how much of saliva will be produces already in cephalic phase when the goose smells so well from the oven ☺



Digestion products which gradually originate and are absorbed in the small intestine „draw“ water into interstitium. In case of abrupt increase of osmotic pressure in duodenum (during evacuation of bigger amount of chyme from stomach, full of osmotically active substances), opposite movement of water may appear, e.g. from interstitium into the intestinal lumen – so-called **osmotic draft of water**.

TRANSPORT OF IONS

JEJUNUM
ILEUM



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

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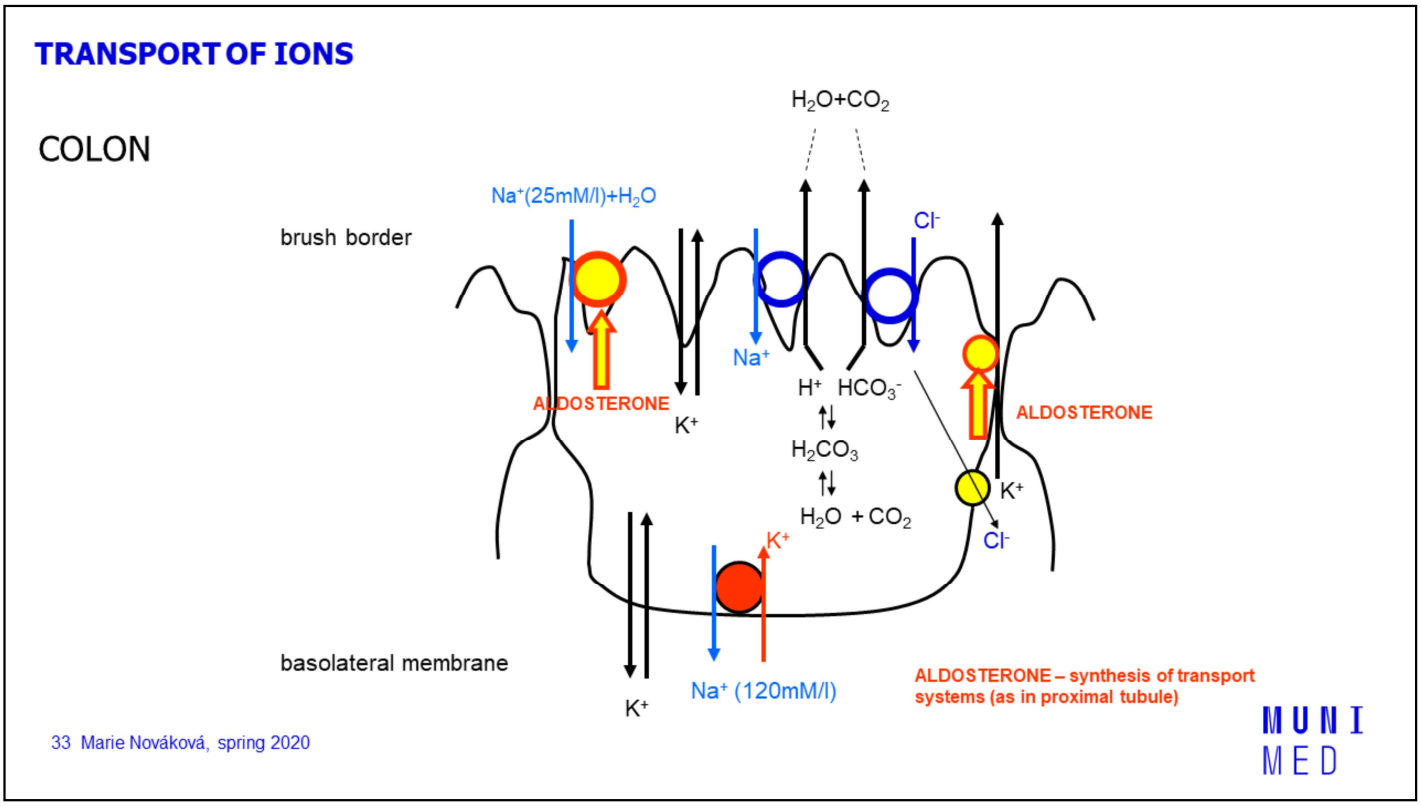
Some transports from this slide you can see again, at the end of this presentation, in the overview of absorption of the products of digestion of saccharides and proteins.

Don't forget that numerous transports depend on sodium gradient. And never forget to start with transports on the basolateral membrane of enterocyte which create the conditions for transport (Na^+/K^+-ATP-ase, potassium channels)!



It is important to remember that sodium concentration in chyme in distal parts of GIT is already low and thus its influx into enterocyte has to be supported. This job is done by aldosterone. By the way, aldosterone exerts the same effect also in salivary glands.

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)

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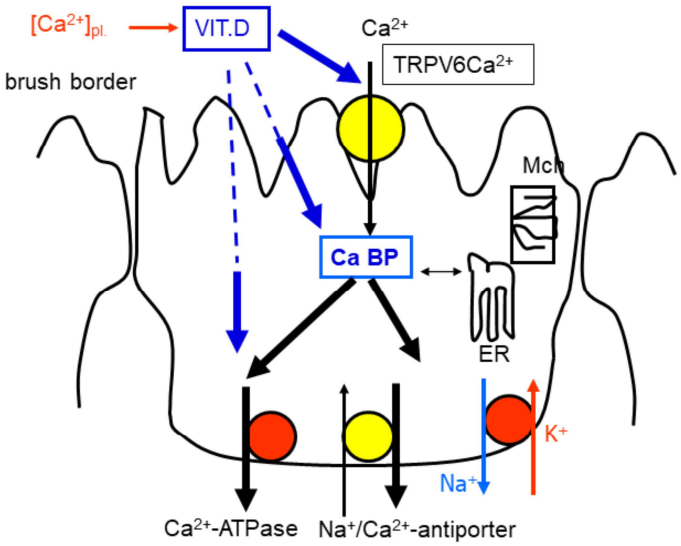
ABSORPTION OF Ca^{2+}

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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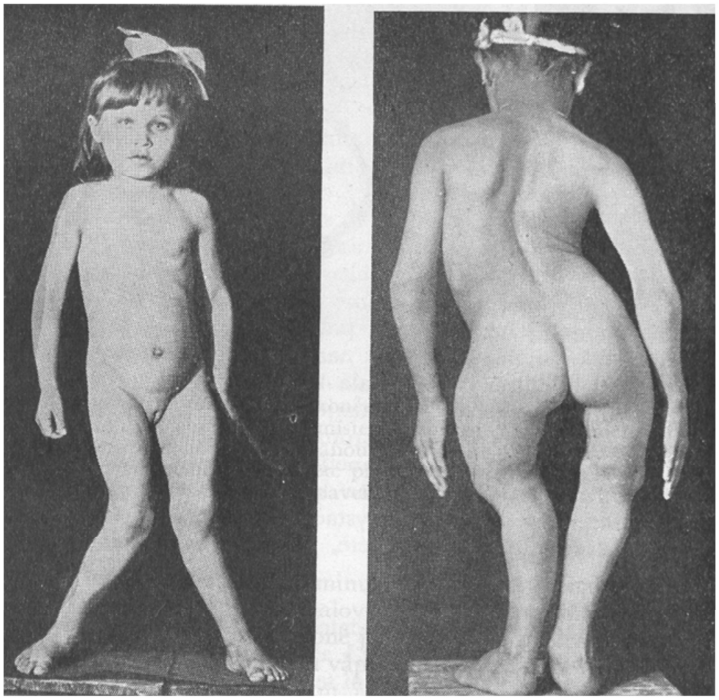
Calcium is cation with crucial role in numerous physiological processes (from excitable membranes to haemostasis). Its absorption is regulated by vitamin D, at several places. The transport of calcium via apical membrane of enterocyte happens via one of TRP (transient-receptor-potential) channels. Calcium in enterocyte – as well as in other cells in the body – is stored in endoplasmic reticulum and in mitochondria.

RACHITIS
(rickets)



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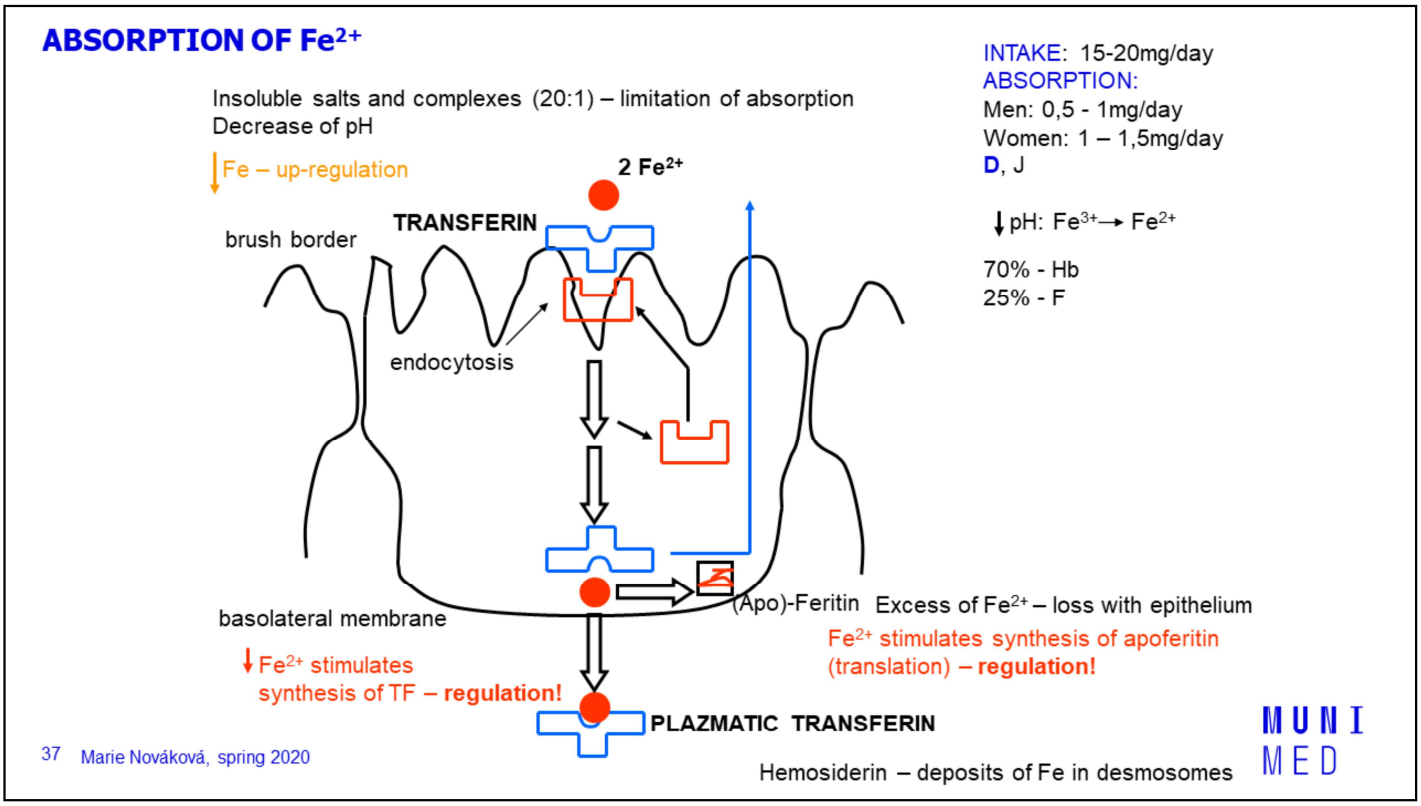
Deficiency of calcium in diet or its insufficient absorption (e.g. subject with low exposure to sunbeams) leads to disease characterised by deformations of long bones and backbone. It is very rare nowadays since all new-borns are supplemented with vitamin D during first several months of postnatal life.



TF – transferrin

Absorption of iron is interesting due to the fact that it is regulated in several places – see the slide.

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)

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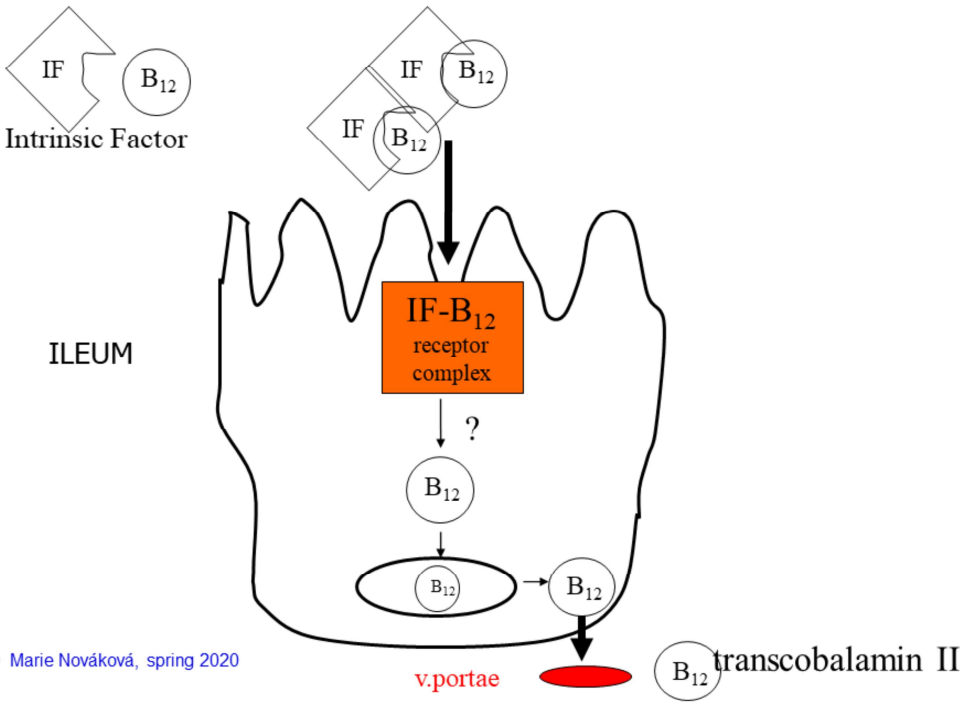
R-protein(s) are also known as **haptocorrin(s)**.

ABSORPTION OF B_{12} VITAMIN



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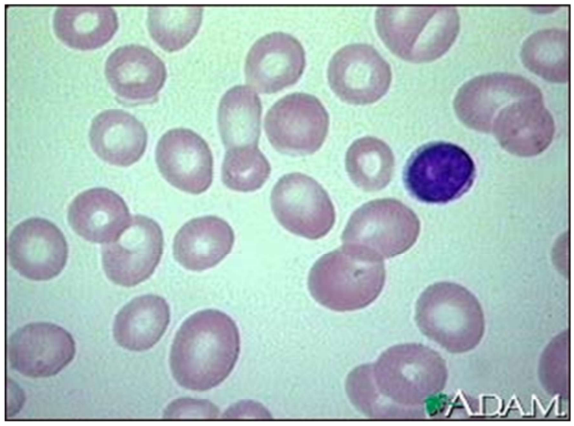
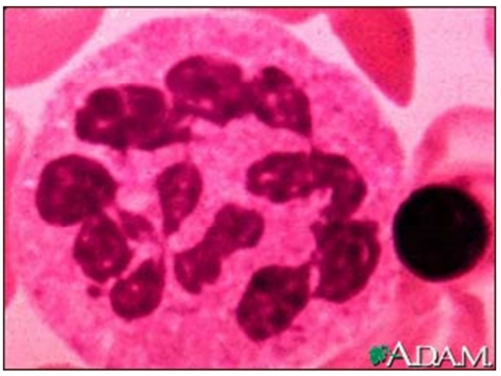


Pernicious anaemia
(megaloblastic)



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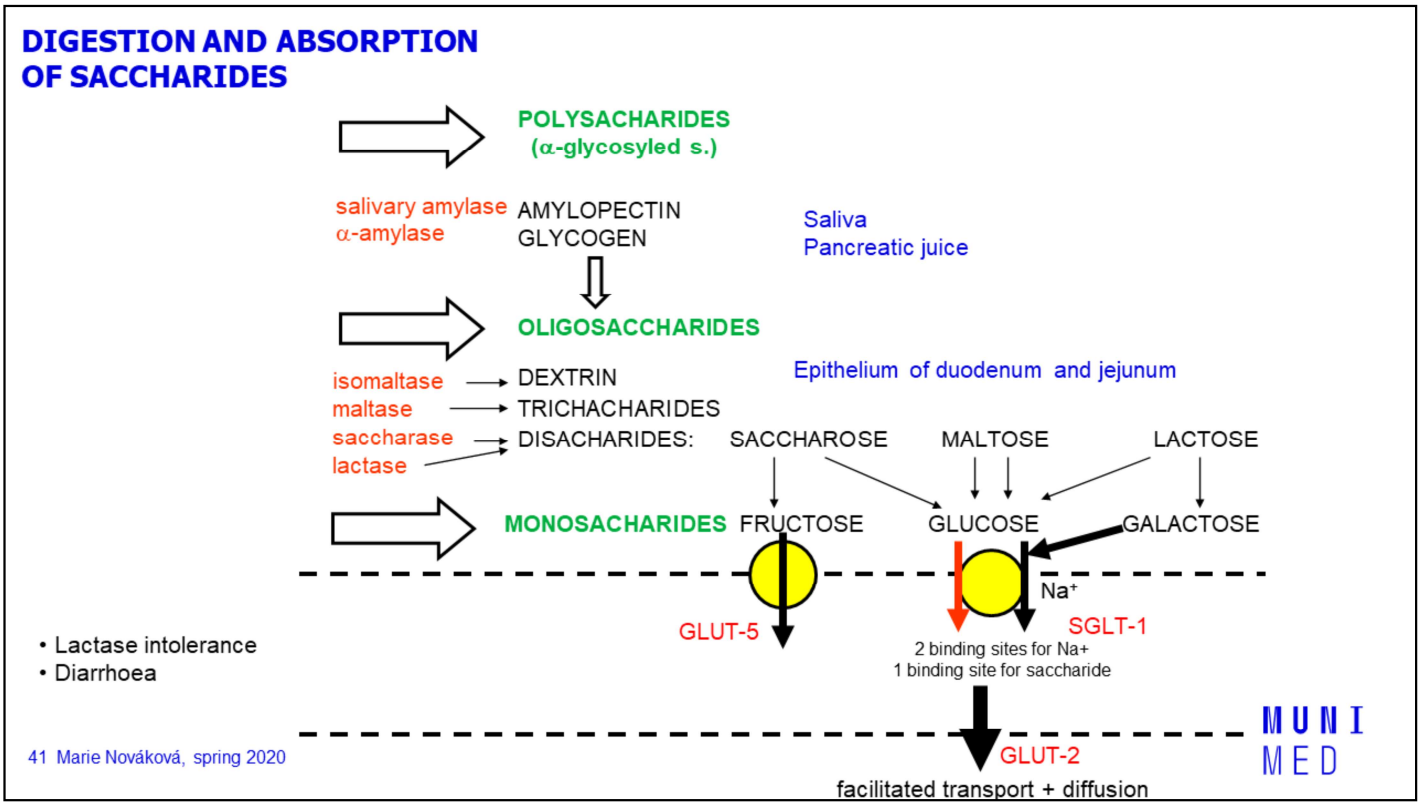
Function of vitamin B_{12}: synthesis of nucleic acids, cofactor during the conversion of ribonucleotides to deoxyribonucleotides, formation of metabolically active form of folic acid.

IT IS NEEDED FOR NORMAL DIVISION AND MATURATION OF RED BLOOD CELL LINE ELEMENTS.

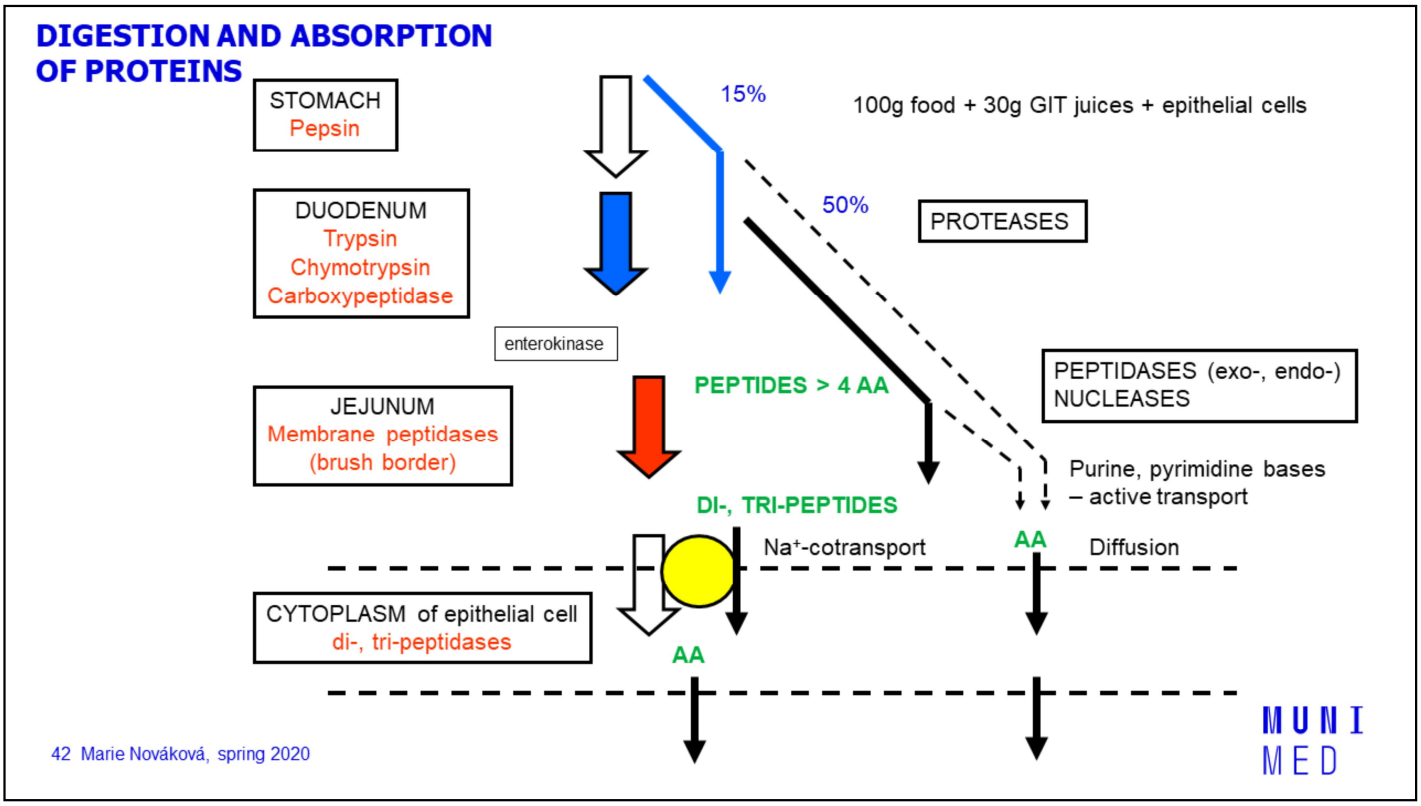
Hypovitaminosis B_{12} causes pernicious („malignant“) anaemia (megaloblastic anaemia).

Symptoms of this anaemia appear after years (see above – stores of B_{12} are mainly in liver, but also in pancreas, kidneys, brain, myocardium) !!!

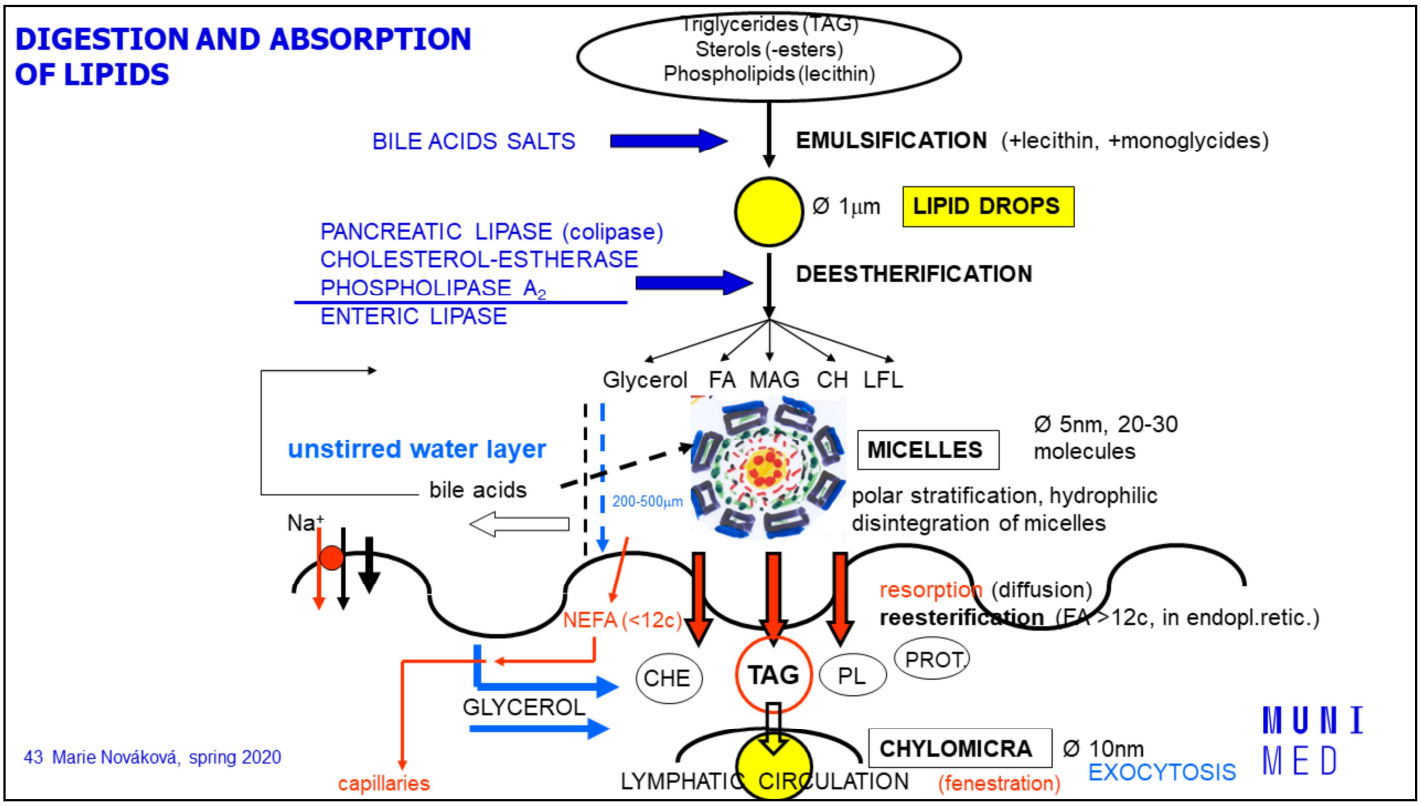


This and two following slides you can use for repeating, many things you know from biochemistry.

Remember that numerous transports of digestion products are sodium-dependent. Glucose and galactose compete on SGLT-1 transporter, fructose occupies GLUT-5 alone ☺



Total daily protein turnover in GIT is higher than simple dietary amount. Don't forget that GIT must process not only all dietary proteins, but also those proteins which are part of various GIT secretions and those from epithelial cells daily peeled off in the GIT.



It might seem that lipids can pass the membranes easily and there is no need of any specialized transport system. However, it is not so easy. There is unstirred water layer on the surface of brush border. Lipids cannot pass through it. Simply summarized – they must first be cleaved, organized into polar (water-soluble) structure and then again formed (in enterocyte).

Dietary fats must be first processed by lipases (of various origin – lingual, gastric, pancreatic, enteric). To be the effect of lipases effective, lipids must be first emulsified – this is ensured by bile, resp. salts of bile acids. (Bigger total surface of many small lipid drops opens wider space for the effect of lipases as compared to one big lipid drop with relatively small surface, which is the case in chyme before emulsification.)

After the lipases cleave the dietary lipids into glycerol, fatty acids, cholesterol, etc. (see the slide), these are organized into the micelles. Micelles are polar and therefore are able to pass through the unstirred water layer – lipid parts of the chyme are thus transported to proximity of apical membrane and they cross it by simple diffusion.

Inside the enterocyte they are re-esterified and travel further via lymphatic system.

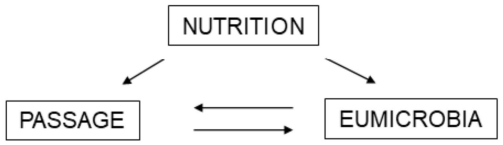
ABSORPTION IN COLON

- 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



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Absorption of sodium and water – see slide no. 33.

There is a significant microbial population in colon (in upper parts of GIT supressed by acidic gastric juice) – it is an important part of GIT, keeping of eumicrobial environment is crucial for the health of organism. It is important to keep balance between the food composition and speed of passage of chyme through GIT. Eumicrobial environment is also kept by mass peristalsis („sweeping movements“) in colon.

REGULATION OF FOOD INTAKE AND NUTRITIONAL STATE

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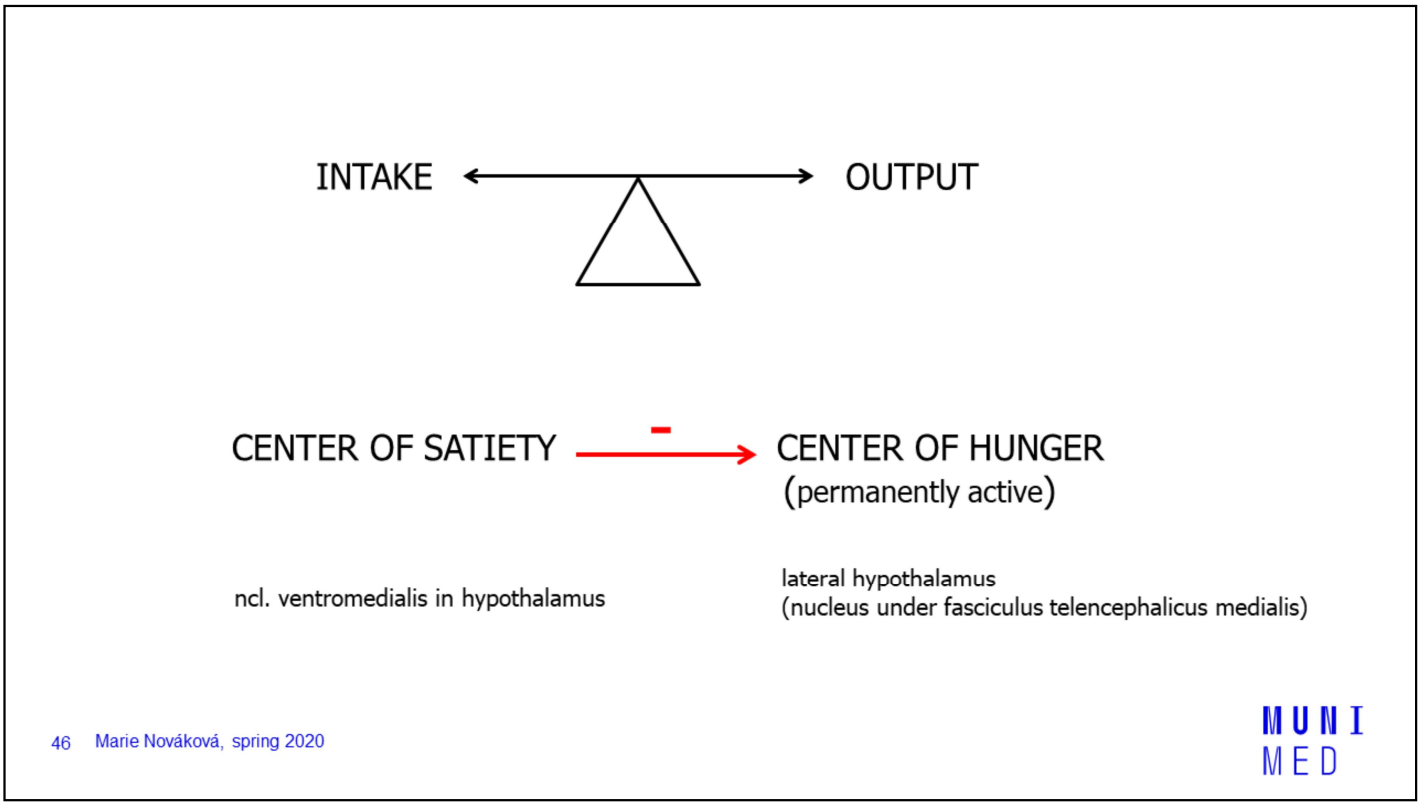
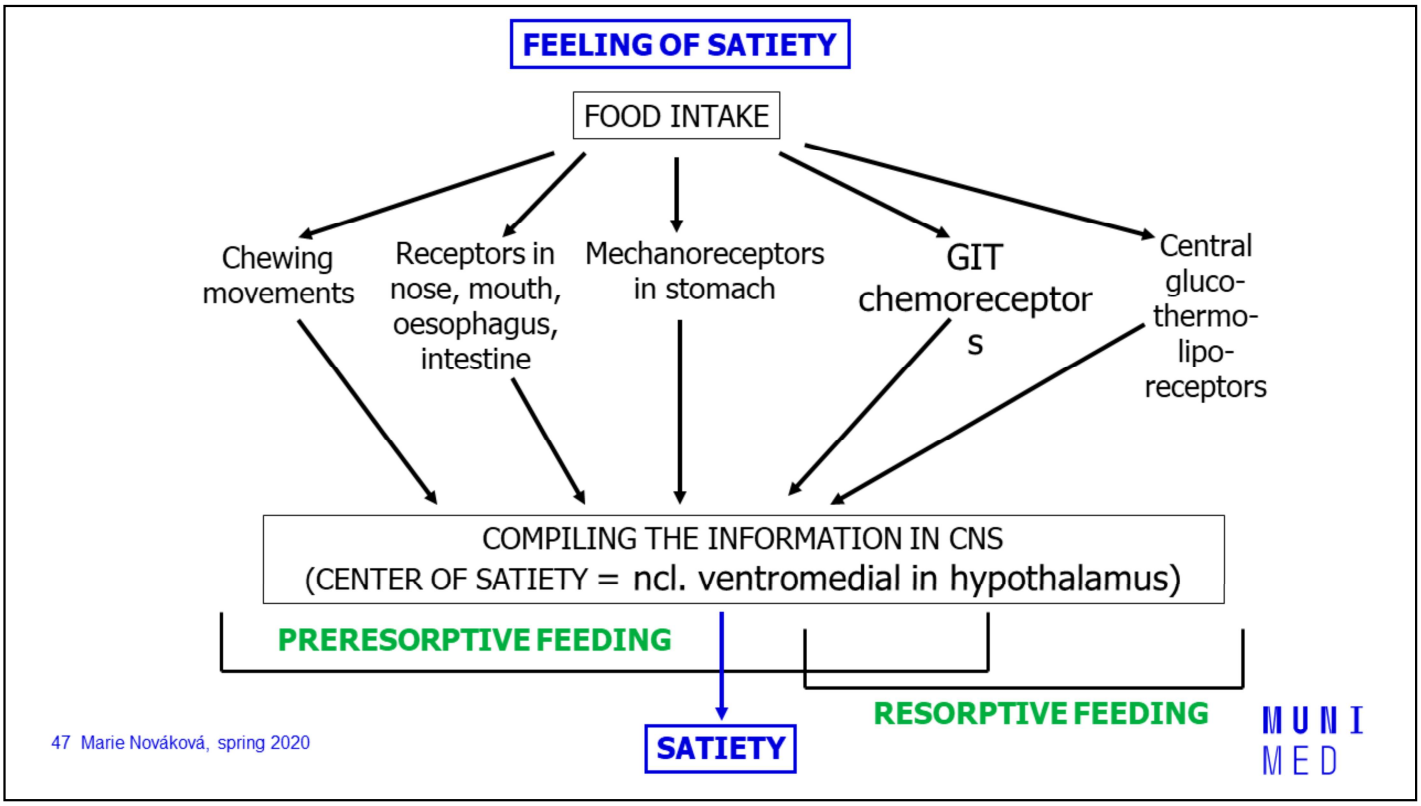
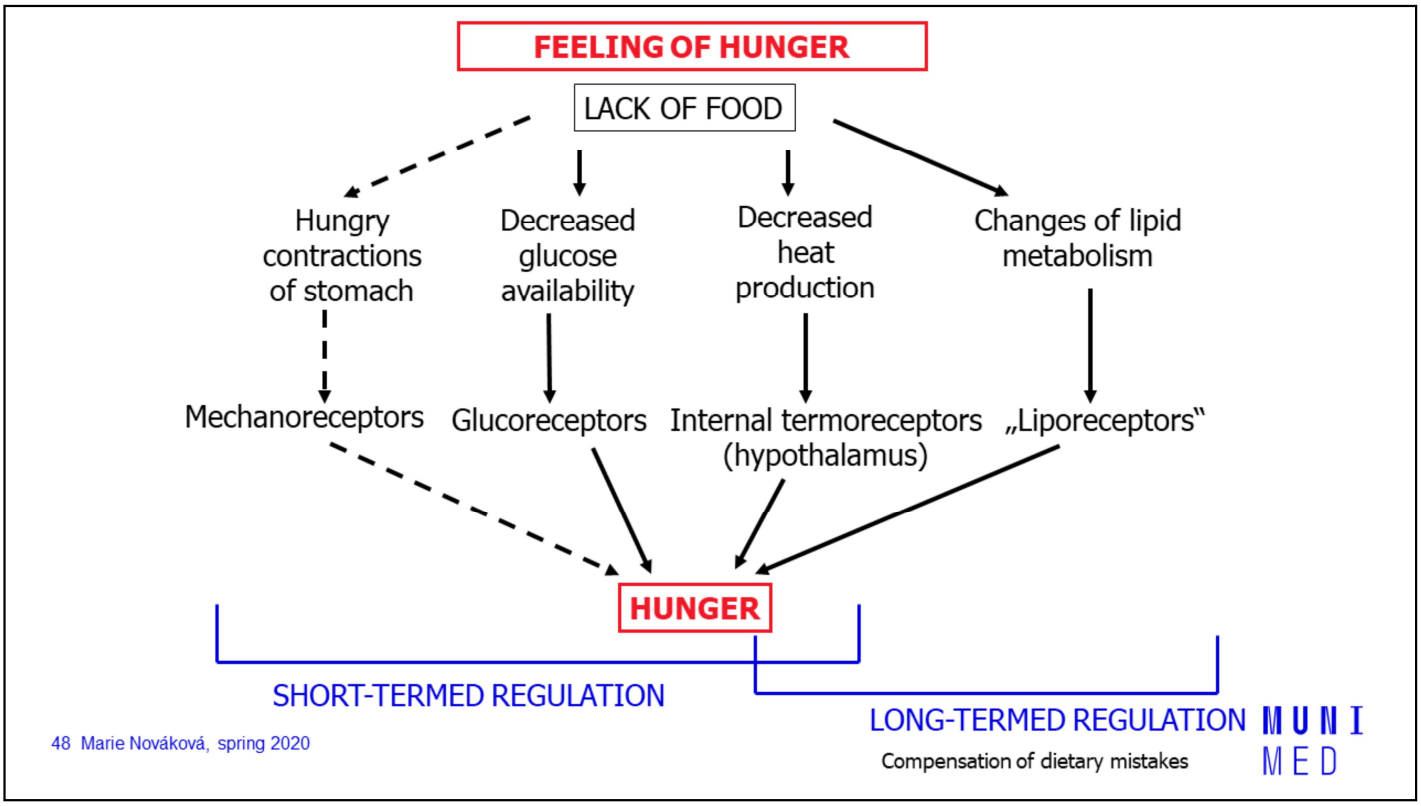


First, one bad new for those who want to loose weight ☺ Centre of hunger is permanently active and various stimuli can only less or more supress it.

It is necessary to keep balance between food (energy) intake and output (expenditure). Its keeping is crucial for optimisation of nutritional state (which is – of course - individual).



Note that feeling of satiety starts already during preresorptive feeding, e.g. during cephalic and gastric phases. It fully develops during absorption of digestion products, in intestinal phase.



Feeling of hunger is comprised from „chemical" factors, such as hypoglycaemia in short-termed regulation or lipid metabolism changes in long-termed regulation, but also other from other actions of GIT.

In short-termed regulation of feeling of hunger, also regular mechanical events in stomach participate – **hungry contractions**. This phenomenon is based on migrating motoric (myoelectric) complex - cyclic waves of electrical activity which originate mainly in the stomach (approx. 75 %), but also in the duodenum and proximal jejunum (25 %). MMC lasts approximately 80–120 minutes and consists of four phases. Hungry contractions disappear immediately after food intake starts.

Substrate thermogenesis also affects the regulation of feeling of hunger: during decreased food intake (and resulting decreased heat production) the decreased body temperature is detected and this information is another factor modulating hunger feeling – it affects both short-termed and long-termed regulation.

REGULATION OF FOOD INTAKE

HYPOTHESIS:

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

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There are several theories explaining food intake regulation. However, it seems that not a single one of them can completely explain the whole process and it seems that this complex process is regulated in a very complex way.

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 !!!

Orexigenic factors - appetite stimulating – and **anorexigenic factors** – appetite supressing – are humoral substances, modulating food intake. Note that they are often neuromodulators, many of them are involved in various functions of the hypothalamus.

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

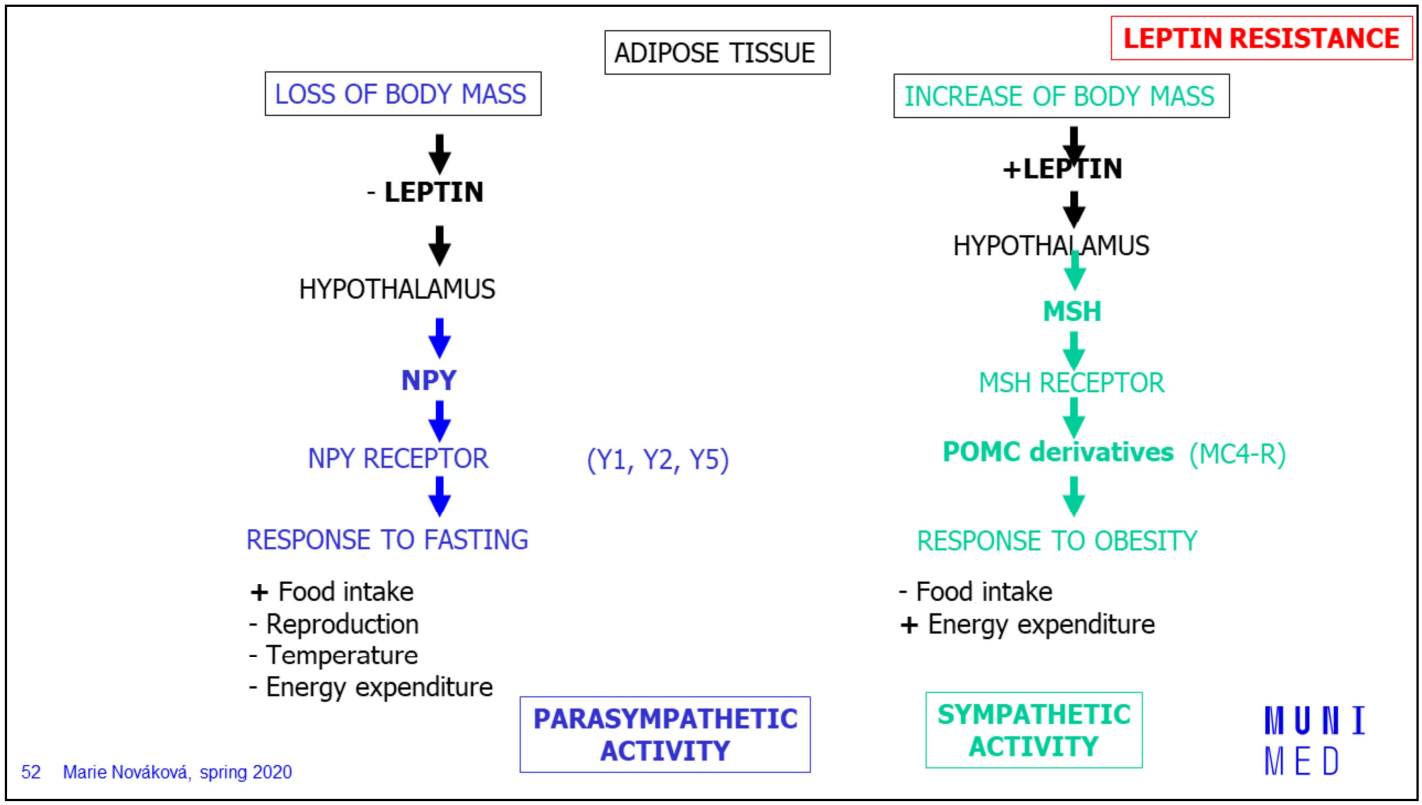
RECEPTORS from cytokine family
- **Peripheral** (gonads)
- **Central** (hypothalamus, pituitary)

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.

MUNI MED

You have met leptin in the lecture about reproduction system during semester Autumn 2019. This slide thus only adds to the information which you probably have from biochemistry or biology.



These pathways were originally studied in animal model. Later they were verified in humans. Don't forget to mention the role of autonomous nervous system – it is obvious that it plays its role not only in the processing of food in GIT, but also already during its intake.