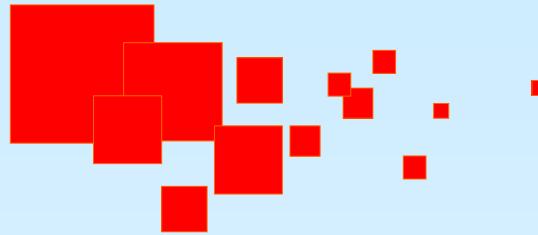


Serotonin, agonists and antagonists, Therapy of migraine, Histamine, antihistamines

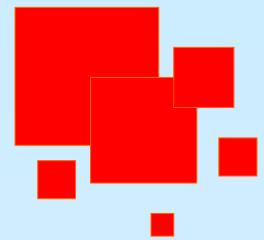
Balázs Varga Pharm.D., PhD

Department of Pharmacology and Pharmacotherapy

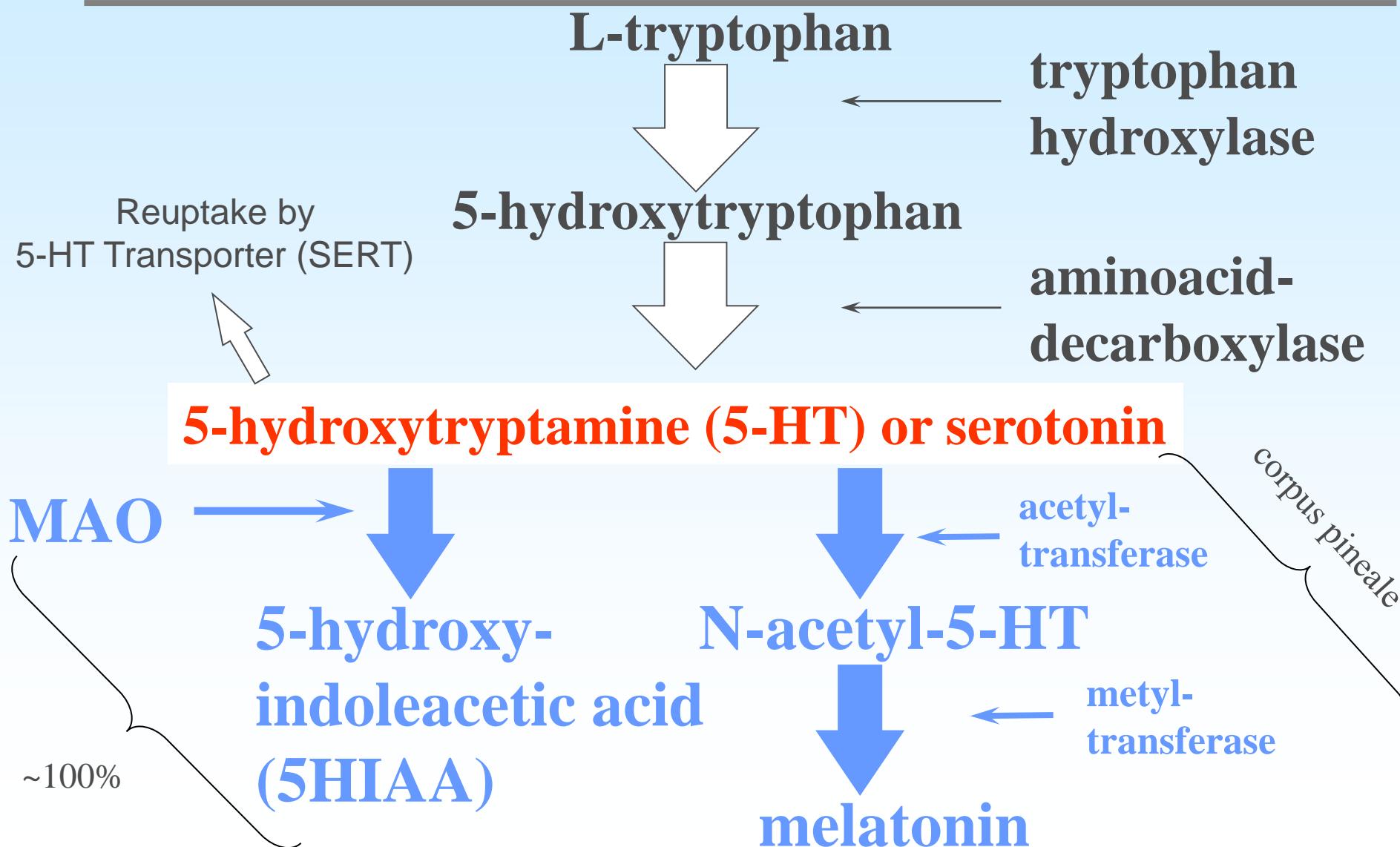
University of Debrecen

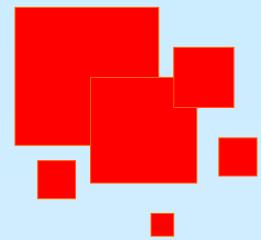


Serotonin agonists, antagonists

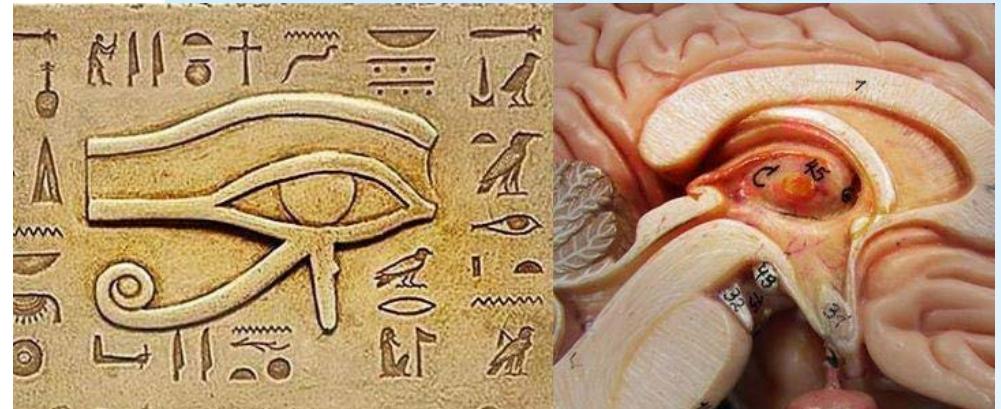
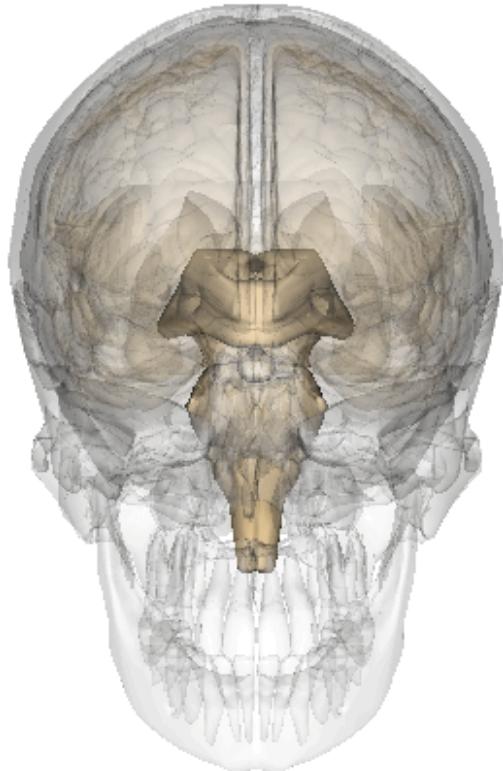


Synthesis and breakdown of serotonin

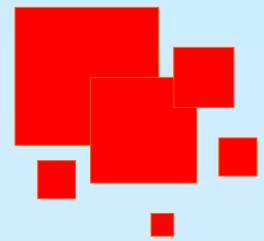




Corpus pineale - melatonin

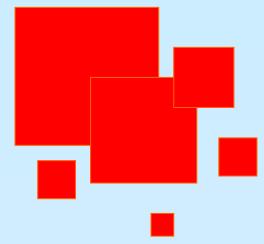


- Remember the Eye of Horus and the circadian rhythm? (see Seminar 1)



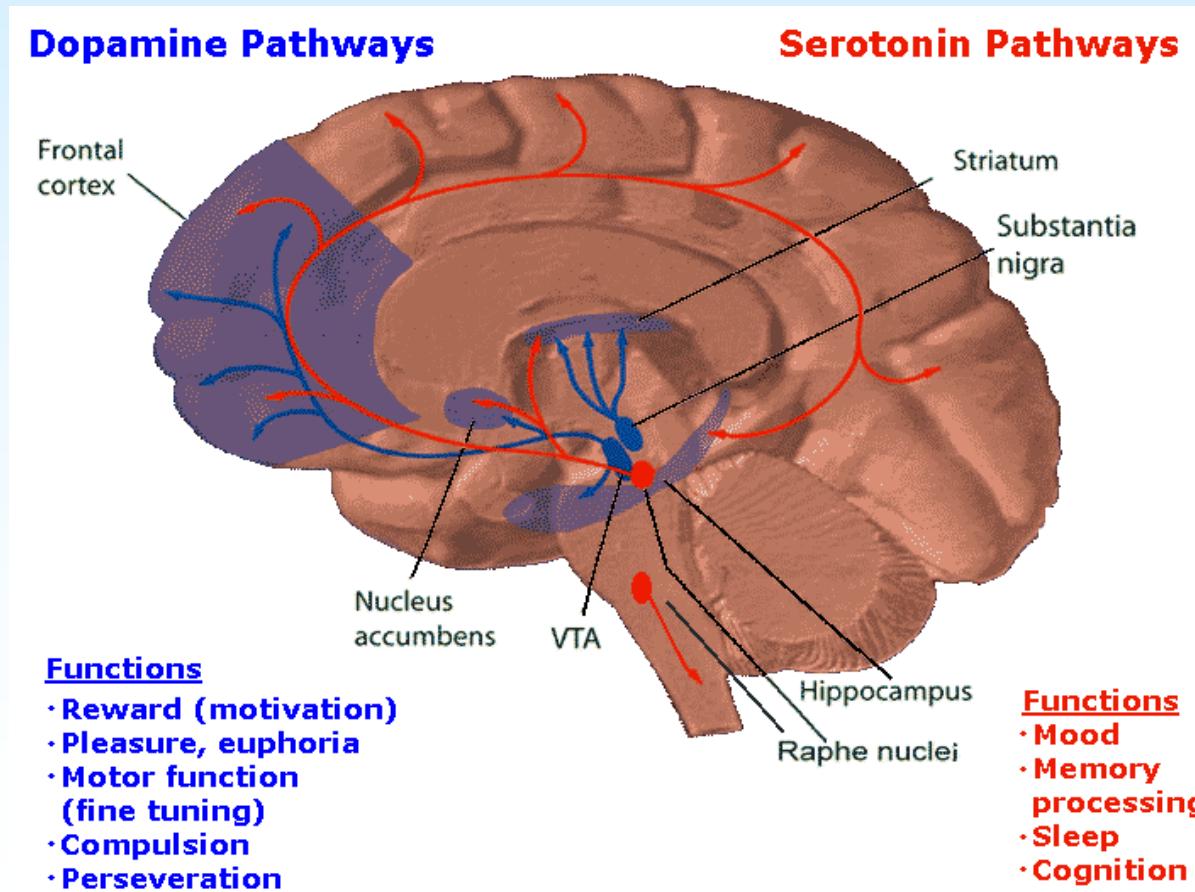
Serotonin

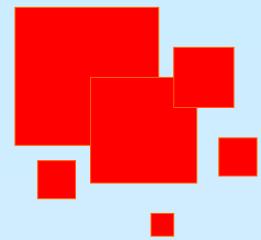
- Serotonin is a biogenic amine formed from tryptophan.
- Localisation of Serotonin in the body:
 - almost 90% is in the enterochromaffin cells of the intestines
 - These locally regulate the functions of the GI-tract (vagus stimulation / physical extension = serotonin excretion → through at least 6 types of receptors – causes motility to increase = smooth muscles to contract/relax)
 - The remaining is in the granules of the thrombocytes.
 - The serotonin participate in the mechanism of the coagulation (released from thrombocytes serotonin act back on them)
 - Some is localised in the raphe nuclei of the mesencephalon



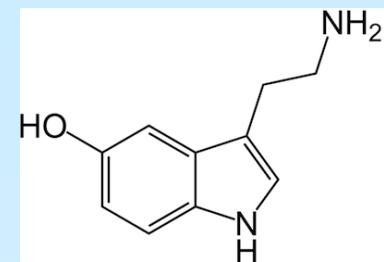
Serotonin

- From the raphe nuclei of the mesencephalon:

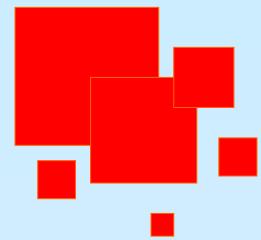




Serotonin-receptors

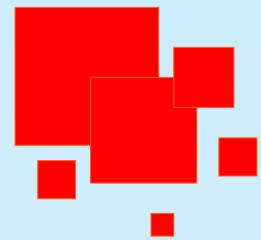


Type	Signal transduction	Localisation, effects:
5-HT ₁	G _i	A,B,D,E,F 5-HT _{1A} - CNS : neuronal inhibition, behavioural effects (sleep, food intake, thermoregulation, aggression, nervosity) 5-HT _{1B} - CNS : presynaptic inhibition, behavioural effects vascular effects: pulmonar vasoconstriction
5-HT ₂	G _q	A,B,C 5-HT _{1D} - CNS : locomotion,nervosity; vascular effect: cerebral vasoconstriction 5-HT _{2A} - CNS : neuronal excitation, behavioural effects , learning, nervosity; on smooth muscles : contraction, vascular effect: vasoconstriction / vasodilation; on platelets : aggregation 5-HT _{2B} – stomach : contraction 5-HT _{2C} – CNS : nervosity; liquor secretion
5-HT ₃	Na ⁺ and K ⁺ channel	5-HT ₃ – CNS, PNS : neuronal excitation, nervosity, vomiting
5-HT ₄	G _s	5-HT ₄ – GI : gastrointestinal motility CNS : neuronal excitation, learning, memory
5-HT _{5A}	G _i	5-HT _{5A} – CNS (cortex, hippocampus, cerebellum): unknown effect
5-HT ₆	G _s	5-HT ₆ – CNS : it regulates the release of glutamate and acetylcholine
5-HT ₇	G _s	5-HT ₇ – CNS, GI, vessels : unknown effect



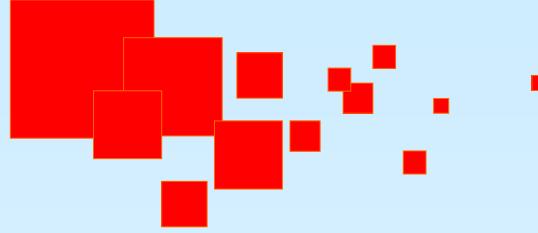
Primary effects of serotonin

- Blood vessels – decrease in blood pressure in 3 phases
 - blood pressure decreases, due to the excitation of the serotonin-receptors of the chemosensitive trigger area
 - blood pressure rises, due to the developing vasoconstriction
 - blood pressure decreases, due to the dilatation of the skeletal muscular blood vessels
- Constricts the smooth muscles of the bronchioli
- Constricts the smooth muscles of the gut (increasing motility)
- Triggers the aggregation of the thrombocytes
- Emesis (5-HT_3 stimuli may arise from the chemosensitive trigger area and the visceral afferent nerves)
- CNS effects
 - Regulation of sleep/awakeness (5-HT deficiency = insomnia)
 - Regulation of behaviour (serotonin acts as anxiolytic, antidepressive, antipsychotic, and sedative) (also 5-HT deficiency = aggression)
 - Plays a role in anti-nociception (inhibition of feeling of pain)
 - In the center of satiety (serotonin = satiety)
 - Also takes part in the regulation of bodytemperature (increases, but overstimulation decreases)
 - Sexual activity

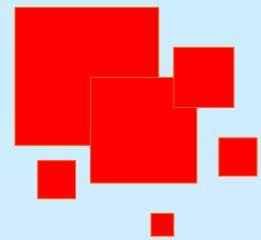


Serotoninerg drugs

- 5-HT₁-agonists
 - Antimigraine effect
 - Anxiolytic, sedative effect
- 5-HT₂-antagonists
 - Antimigraine effect
 - Anxiolytic, antidepressive, antipsychotic effect
- 5-HT₃-antagonists → Antiemetic effect
- 5-HT₄-agonists → Prokinetic effect



5-HT₁ agonists



5-HT₁-agonists

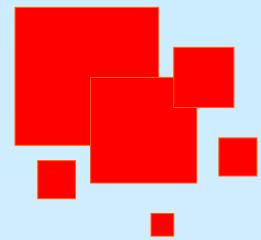


■ Antimigraine drugs

- Triptans (Almotriptan, Eletriptan, Frovatriptan, Naratriptan, Rizatriptan, Sumatriptan, Zolmitriptan)
 - Mechanism of effect:
they are agonists of 5-HT_{1B} and 5-HT_{1D} -receptors
 - on cerebral blood vessels (vasoconstriction) and
 - on cerebral nerve endings (they inhibit the release of inflammatory substances as CGRP and substance P)
 - Application: migraine paroxysmal-therapy
- Ergot alkaloids (Dihydroergotamine, Ergotamine, Methysergide) (see next slide)

■ Anxiolytics

- 5-HT_{1A}-receptor agonists (Binospirone, **Buspirone**, Gepirone, Ipsapirone, Tandospirone)



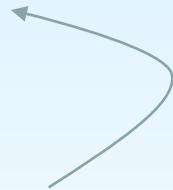
Ergot alkaloids



- Mechanism of effect: agonists or antagonists on adreno-, dopamine- and serotonin-receptors: they have very complex effects;

antimigraine effect-mechanism:

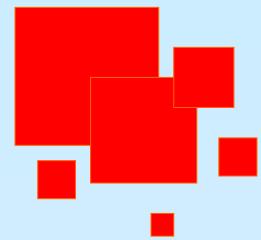
- ergotamine, dihydroergotamine are 5-HT_{1B} and 5-HT_{1D}-receptor agonists,
- at the same time the methysergide is 5-HT_{2A/C} antagonist!



- Application:

- Methysergide migraine in interval-therapy (as prophylaxis)
- Ergotamine, Dihydroergotamine in migraine paroxysmal-therapy, and also...
- ...beside Ergonovine/Ergometrine and Methergine/Methylergometrine, due to strong vasoconstrictor (*α-agonist*) effect in postpartum/postabortus haemorrhage to arrest bleeding
- Bromocriptine, Cabergoline, Dihydroergocryptine, Lisuride, Pergolide, as antiParkinson drugs due to their *dopamine-agonist* effect
- LSD - Psychedelic narcotic (5-HT_{1A} agonist, partial agonist on 5-HT_{2A} and 5-HT_{2C} receptors)

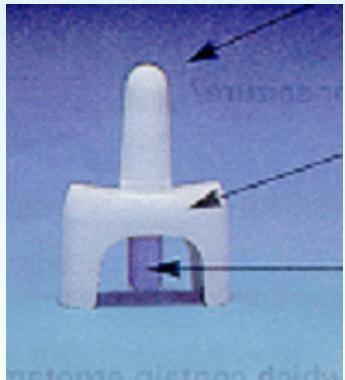




Imigran nasal spray

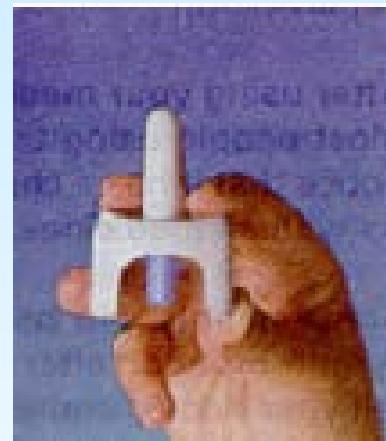
Parts of the nasal spray

Mouth piece

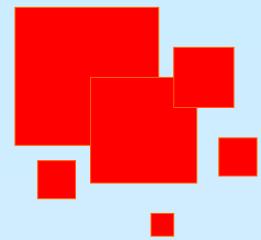


Shoulder part

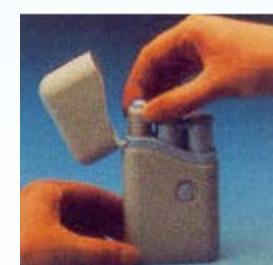
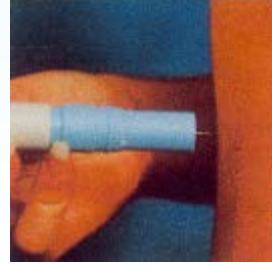
Blue pump



Patient have to breath in through the nose and simultaneously press the pump.
After this breathing should be: through the nose in, through the mouth out.



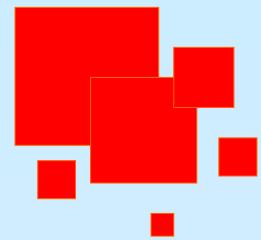
Imigran autoinjector



autoinjector

case

plunger



Serotonin reuptake inhibitors

Also have 5-HT₁ agonistic effect

- Antidepressants (see 3rd Seminar)

- Tricyclic antidepressants

- Desipramine, imipramine, amitriptylline, dibenzepine, doxepine, clomipramine

- SSRI drugs

- Citalopram, seropram, fluoxetine, paroxetine, fluvoxamine, sertraline

- NSRI drugs

- Venlafaxin, duloxetin

- SARI agents

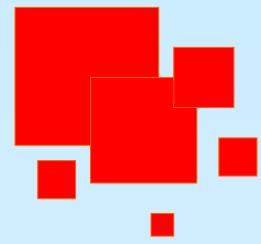
- Trazodone, Nefazodone

- Anorectics

- In the center of satiety (serotonin = satiety)

- Sibutramin (withdrawn from market of Hungary)

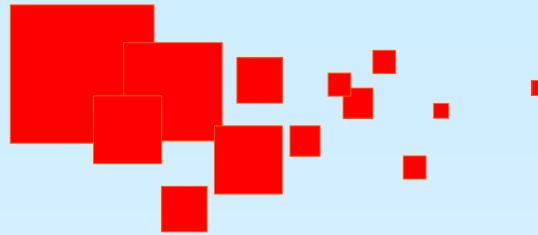




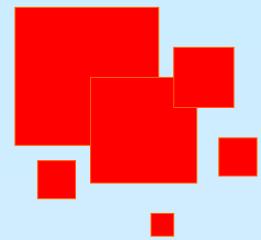
Other Serotonergic agents

Also have 5-HT₁ agonistic effect

- Antidepressants (see 3rd Seminar)
 - MAO-inhibitors
 - moclobemid



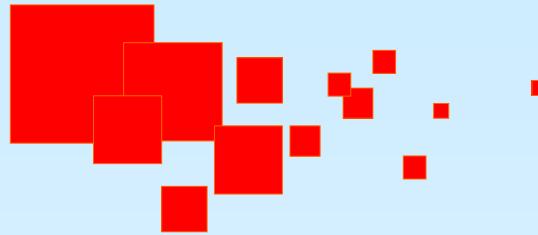
5-HT₂ antagonists



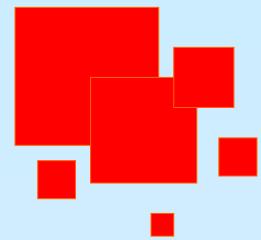
5-HT₂-antagonists

- This group contains drugs with mixed effects, that also have 5-HT₂-receptor antagonist effect
- Antimigraine-drugs
 - due to 5-HT_{2A,C} inhibitor effect they dilate the cerebral blood vessels, → in the migraine interval-therapy, as prophylaxis
 - Pizotifen, Iprazochrom, (methysergide)
- Anxiolytic, antidepressive effect
 - are α_2 -antagonists as well, and **presynaptic** inhibitors of 5-HT_{2A,C} (→ they help adrenaline/serotonin release → **agonist-like** effect (!) → anxiolytic, antidepressant)
 - Mianserin, Ritanserin; TCA; Trazodone, Nefazodone
- Antipsychotic effect (so called atypical antipsychotics)
 - 5-HT₂-rec. inhibition = decreased dopamine release; and usually also have dopamine-receptor antagonist effect → reduce dopamine = antipsychotic effect
 - Clozapin 5-HT₂ antagonist, 5-HT₁ agonist and D₄-antagonist as well
 - Olanzapin 5-HT_{2A} -antagonist and H₁R > D₄R > D₂R antagonist as well
 - Risperidon 5-HT_{2A,C} -antagonist and D₂-antagonist
 - Ziprasidone 5-HT_{2A} -antagonist and D₂-antagonist
 - Blonanserin 5-HT₂ -antagonist and D₂-antagonist
 - Fananserin 5-HT_{2A} -antagonist and D₄-antagonist





5-HT₃ antagonists

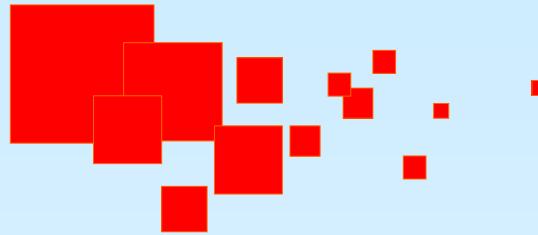


5-HT₃-antagonists

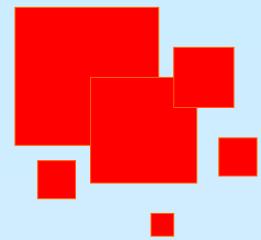
■ Antiemetics

- Alosetron, Azasetron, Bemesetron, Cilansetron, Dolasetron, **Granisetron**, Lerisetron, **Ondansetron**, Palonosetron, Ramosetron, **Tropisetron**, Zatosetron
- Mechanism of effect: they inhibit the 5-HT₃ stimuli coming to the emesis-center from the chemosensitive trigger area (from the blood and liquor) and from the visceral afferent nerves (nucleus tractus solitarii) (food, stimuli from inside the body), thus, they are antiemetics





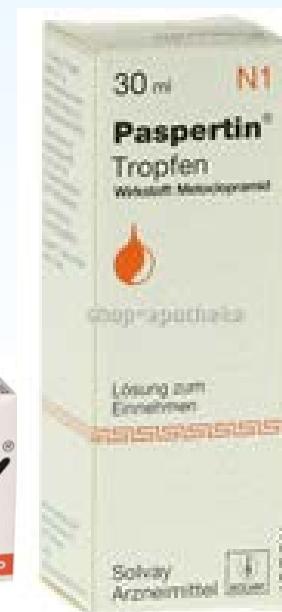
5-HT₄ agonists



5-HT₄-agonists



- **Metoclopramide, Cisapride, Mosapride, Prucalopride, Tegaserod, Zacropride**
- Mechanism of effect: they are agonists on 5-HT₄-receptors, thus, they increase the gastrointestinal motility, stimulate the peristalsis = they are called prokinetics
Metoclopramide is also D₂-receptor antagonist and 5-HT₃-receptor antagonist → used as antiemeticum
Zacopride is also 5-HT₃-receptor antagonist (antiemetic)
- Application:
 - Against ulcer („antiulcer” drugs)
 - Gastroesophageal reflux
 - Used to increase motility in gastroparesis, and constipation
 - In irritable bowel syndrome (spastic colon)





Therapy of Migraine



*Pictures were created by migraineous artists.

Forms of headache:

- cephalgia (short term, mild pain)
- cephalea (chronic, severe pain)
- heterocrania (one-side headache)

↑
e.g. migraine

Features of migraine:

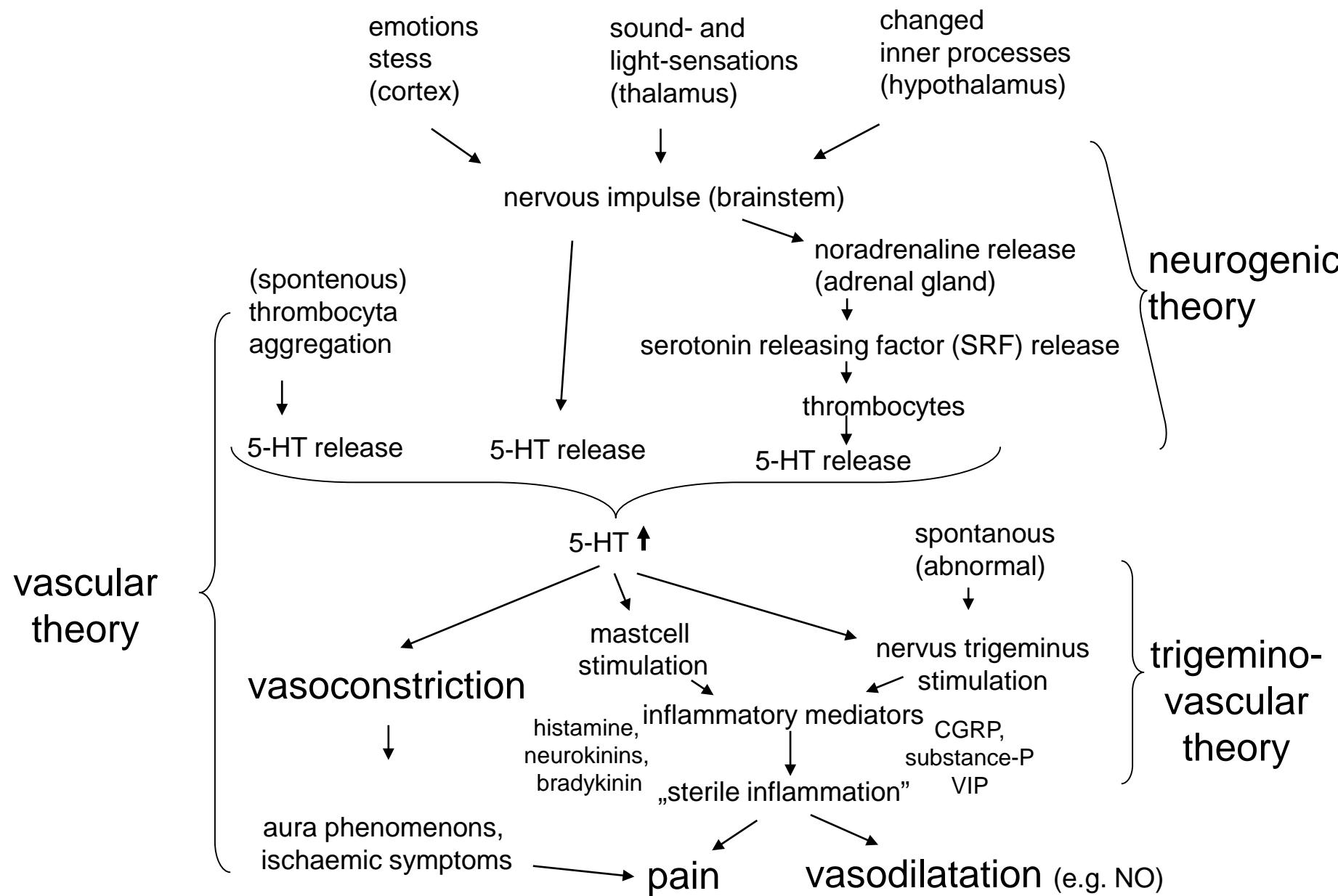
1. severe unilateral headache
2. recurring attacks
3. throbbing pain
4. increased by physical exercise
5. aura (the patient feels, that the attack is coming)
6. visual disturbances (scintillation, hemianopsia, etc.)
7. photo- and phonophobia
8. nausea/vomiting

Types of migraine:

- „classic” migraine (preceded by aura)
- „common” migraine (without aura)



Development of migraine



Diagnostic criteria for migraine according to International Headache Society (2004):

- A. At least five attacks fulfilling criteria B-D
- B. Headache attacks lasting 4-72 hours [when untreated in adults]
- C. Headache has at least two of the following characteristics:
 - unilateral location
 - pulsating quality
 - moderate or severe pain intensity
 - aggravation by or causing avoidance of routine physical activity
- D. During the headache, at least one of the following [is present]:
 - Nausea and/or vomiting
 - Photophobia and phonophobia
- E. Not attributable to another disorder



1. Migraine without aura („common migraine”)
2. Migraine with aura (15-30%) („classic migraine”)
 1. Typical aura with migraineous headache
 2. Typical aura with non-migraineous headache
 3. Typical aura without headache
 4. Familial hemiplegic migraine
 5. Sporadic hemiplegic migraine
 6. Migraine with brainstem aura
3. Childhood periodic syndromes that are commonly precursors of migraine:
 1. Cyclical vomiting syndrome
 2. Abdominal migraine
 3. Benign paroxysmal childhood vertigo
4. Retinal migraine
5. Complications of migraine
 1. Chronic migraine
 2. Status migrainosus (<72h)
 3. Persistent aura without infarction
 4. Migrainous infarction
 5. Migrainous stroke

Migraine subclasses according to IHS 2004 classification:

6. Probable migraine
 1. Probable migraine without aura
 2. Probable migraine with aura
 3. Probable chronic migraine



Phases of migraine



- Prodrome
 - Greek word *prodromos*, meaning "precursor,"
 - early symptom(s) that might indicate the start of migraine
 - From 2 hours to 2 Days before migraine (before aura)
 - altered mood, irritability, depression or euphoria, fatigue etc.
- Aura
 - transient focal neurological phenomenon that occurs before or during the headache: perceptual disturbance (usually visual)
 - Develops in minutes, generally lasts less than 60 mins
- Pain
- Postdrome
 - impaired thinking for a few days after the headache has passed
 - gastrointestinal symptoms, mood changes, and weakness, etc.

Some aura types



scintillating



scotoma



Blurred vision



hemianopsia

Nonpharmacologic Treatment

- avoidance of factors provoking migraine attacks:
 - chocolate
 - milk
 - dairy products
 - especially: fermented cheeses (brie, camembert, ementale, rockfort, blue etc.)
 - alcoholic beverages (espec. red wine)
 - american peanut
 - some chineese food
 - smoked meat
 - coffee in high amounts
- Preventive foods:
 - vegetables and fruits,
 - cabages,
 - broccoli,
 - cauliflower,
 - Brussel sprouts,
 - asparagus,
 - celery,
 - salad,
 - legumes,
 - spinach
 - avocado
 - apple
 - fish rich in omega-3-fatty acids as tuna and salmon
 - salt-restricted diet
- Herbal teas
 - clove and coriander tea (Peru)
 - strong chili tea (south-america)
 - ginger tea (Asia)
 - cinnamon tea
 - feverfew
 - chamomile,
 - ginkgo,
 - peppermint,
 - lemongrass
 - bay
- Acupuncture
- Consistent sleep patterns
(Not too much / too little)
- relaxation techniques



Pharmacologic treatment – Acute therapy

1. Acute therapy

According to the severity of attack:

- mild attack → analgeticum, may be combined with antiemeticum
- more severe headache: analgeticum + caffeine + antiemeticum; specific acute antimigraine agents as needed.
- Severe migraine: specific acute antimigraine agents



1.1. Analgetics:

Agent	Dózis	level of recommendation	Notes
Acetylsalicyl-sav (ASA)	1000 mg (orally) 1000 mg (iv.)	A	gastrointestinal side effects and rarely blood forming disorders
Ibuprofen	200-800 mg	A	gastrointestinal side effects and rarely blood forming disorders
Naproxen	500-1000 mg (orally)	A	gastrointestinal side effects and rarely blood forming disorders
Diclofenac	50-100 mg	A	
Paracetalmol	1000 mg (orally) 1000 mg (kúp)	A	caution if liver- or renal insufficiency
ASA + paracetamol + caffeine	250 mg + 200- 250 mg + 50 mg (orally)	A	same as with ASA and paracetamol
Metamizol	1000 mg (orally) 1000 mg (iv.)	B	agranulocytosis and hypotension
Phenazon	1000 mg (orally)	B	same as with paracetamol
Tolfenamat	200 mg (orally)	B	same as with ASA

A: first line drug; B: second line drug
C: third line drug (in later tables)

Pharmacologic treatment – Acute therapy

1.2. Antiemetics/prokinetics:

metoclopramide and domperidone

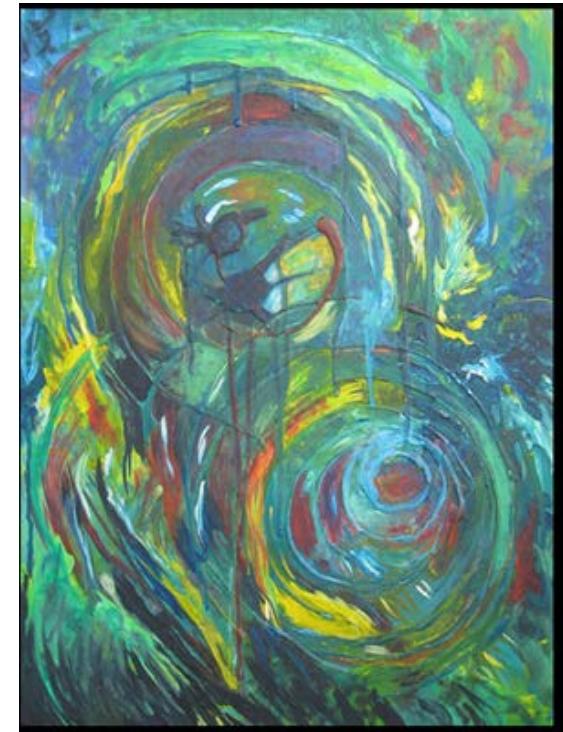
mechanism of effect: **D2-antagonists;**

(metoclopramide also 5-HT3 antagonist
and 5-HT₄ agonist)

→ increase gastro-intestinal peristaltics

→ antiemeticums

Metoclopramid is advised for adults and adolescents in 20mg dose, for children 10 mg domperidone is advised, as metoclopramid may cause extrapyramidal symptoms.



Agents	Dose	Level of recommendation	Notes
Metoclopramid	10-20 mg (orally)	B	side effects: dyskinesia, contraindicated in childhood and pregnancy
	20 mg (rectally)		
	10 mg (im., iv., sc.)		
Domperidone	20-30 mg (orally)	B	side effects are less severe as with metoclopramid, thus adviseable for children

Pharmacologic treatment – Acute therapy

1.3. Specific acute antimigraine agents:

1.3.1. Ergot alkaloids: (ergotamin-tartarate)

- Advantages (in some patients): longer half life and less recurrence-rate
- Mechanism of action:
 - inhibition of neurogenic sterile inflammation and
 - inhibition of neurotransmission of trigeminal system
 - 5-HT_{1B}, D and F partial receptor-agonists
- Adverse effects:
 - nausea,
 - vomiting,
 - paresthesia
 - ergotism (=ergot toxicity)
- Contraindicated:
 - cardiovascular and
 - cerebrovascular disorder,
 - Raynaud-syndrome,
 - arterial hypertension,
 - renal insufficiency,
 - pregnancy and lactation.



Pharmacologic treatment – Acute therapy

Specific acute antimigraine agents: (cont.)

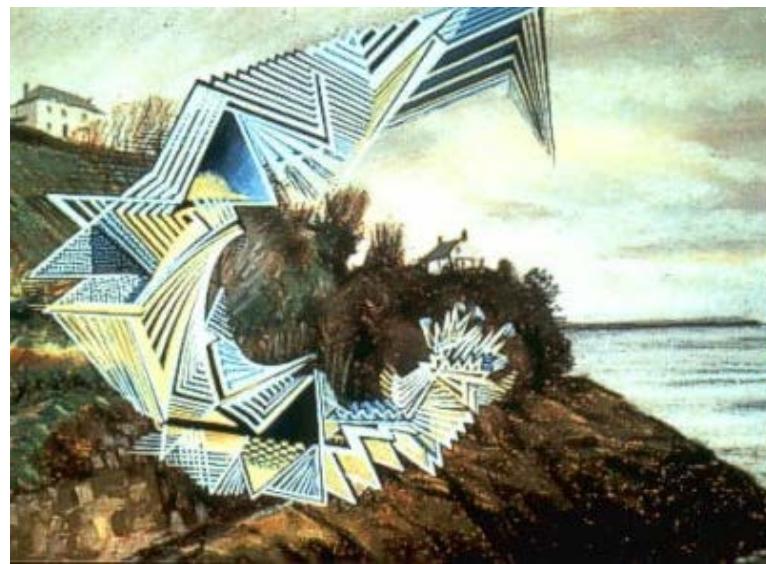
1.3.2.Triptane-s:

- Mechanism of action:
 - 5-HT_{1B/1D} agonists.
 - constrict cerebral vessels
 - inhibit neurotransmitter release (by inhibiting n. trigeminus sensory nerve-ending depolarisation),
 - inhibit neurotransmission in trigeminal system
- Adverse effects:
 - myocardial infarct
 - arrhythmia
 - stroke
 - gastric stasis
 - returning headache 24 hours after successfull analgesia during attack (more longer half-life → lower recurrence rates)

} very rare (1:1 000 000)

- Contraindicated:
 - arterial hypertension,
 - coronary disturbances,
 - Raynaud-syndrome,
 - ischaemic stroke,
 - pregnancy,
 - lactation
 - severe liver- or renal failure.

triptanes are considered to be the best acute antimigraine agents, although they are not very effective in migraine with aura



Agent	Dose	Level of recomm endance	Notes
Sumatriptan	25, 50 and 100 mg (orally); 25 mg (rectally); 10 and 20 mg (nasal spray); 6 mg (sc.)	A	100 mg sumatriptan instead of the others
Zolmitriptan	2,5 and 5 mg (orally) 2,5 and 5 mg (nasal)	A	
Naratriptan	2,5 mg (orally)	A	less but longer effect than sumatriptan.
Rizatriptan	10 mg (orally)	A	dose 5 mg, if given with propranolol.
Almotriptan	12,5 mg (orally)	A	less probable side effect than sumatriptan.
Eletriptan	20 and 40 mg (orally)	A	up to 80 mg if no effect
Frovatriptan	2,5 mg (orally)	A	less but longer effect than sumatriptan.



Pharmacologic treatment – Prophylaxis

prophylactic therapy:

Aims:

- to decrease frequency of attacks
- to decrease severity of attacks
- to decrease duration of attacks

indications:

- (1) if acute drugs are not effective enough
- (2) if acute drugs cause too severe adverse effects or are contraindicated
- (3) attacks occur too often (more than once per week);
- (4) if aura is too long or unpleasant;
- (5) in special cases (e.g. hemiplegic migraine);
- (6) or if patient requires it

Prophylactic therapy of migraine is successfull if frequency of attacks falls with 50% in three months.

For the evaluation of treatment patients should keep a migraine diary during treatment.



First choice agents

Agents	Dose	Level
Beta-blockers		A
Metoprolol	50-200 mg	
Propranolol	40-240 mg	
Ca-channel-blockers	5-10 mg	A
Flunarizin		
Antiepileptics		A
Valproic acid	500-1800 mg	
Topiramat	25-100 mg	

Second line treatment

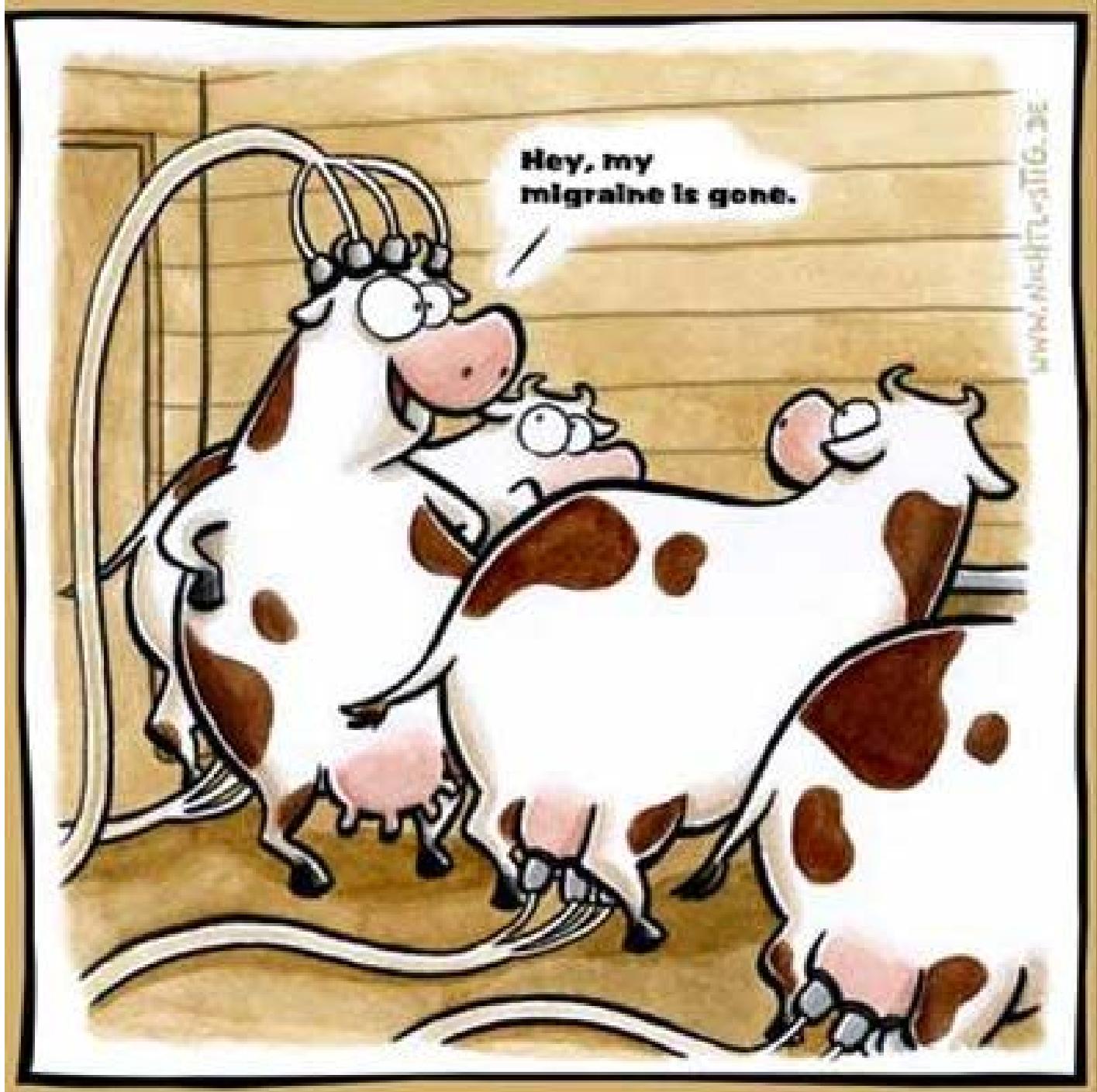
Agent	Dose	Level
Amitriptylin	50-150 mg	B
Naproxen	2 x 250-500 mg	B
Petasites	2 x 75 mg	B
Bisoprolol	5-10 mg	B

Pharmacologic treatment – Prophylaxis



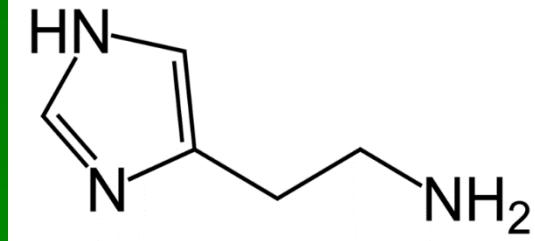
Third line treatment

Agent	Dose	Level
Acetylsalicylic acid	300 mg	C
Gabapentin	1200-1600 mg	C
Magnézium	24 mmol	C
Tanacetum parthenium	3 x 6,25 mg	C
Riboflavin	400 mg	C
Coenzim Q10	300 mg	C
Candesartan	16 mg	C
Lisinopril	20 mg	C
Methysergide	4-12 mg	C



Antihistamines

Histamine



- Hydrophilic molecule with an imidazole ring, a biogenic amine.
- Synthesis: Histamine is derived from the decarboxylation of the amino acid **histidine**, a reaction catalyzed by the enzyme **L-histidine decarboxylase**.
- Occurrence: everywhere;
large amounts in:
 - mast cells,
 - basophil granulocytes,
 - in lungs,
 - on the mucous membrane of the nose,
 - in skin,
 - in stomach (ECL cells),
 - in duodenum
- From mast cells and basophils histamine can be released mediated by IgE or by some drugs. (e.g. morphin, curare alkaloids).

Histamine-receptors

Type	Location	Signaling	Role
H ₁ -rec.	On smooth muscles, endothelium, CNS	G _q	Causes vasodilation, bronchoconstriction, bronchial smooth muscle contraction, increase of vascular permeability, and also pain and itching. This subtype is involved in allergic rhinitis and in seasickness
H ₂ -rec.	On parietal cells of the stomach	G _s	Triggers hydrochloric acid production
H ₃ -rec.	Presinaptically CNS (autoreceptor)	G _i	Causes decreased release of neurotransmitters: histamine, acetylcholine, norepinephrine, serotonin, dopamine, GABA.
H ₄ -rec.	Mainly on basophils and bone marrow; also on thymus, spleen, intestines	G _i	Probably causes the chemotaxis of mast cells.

Major effects of Histamine

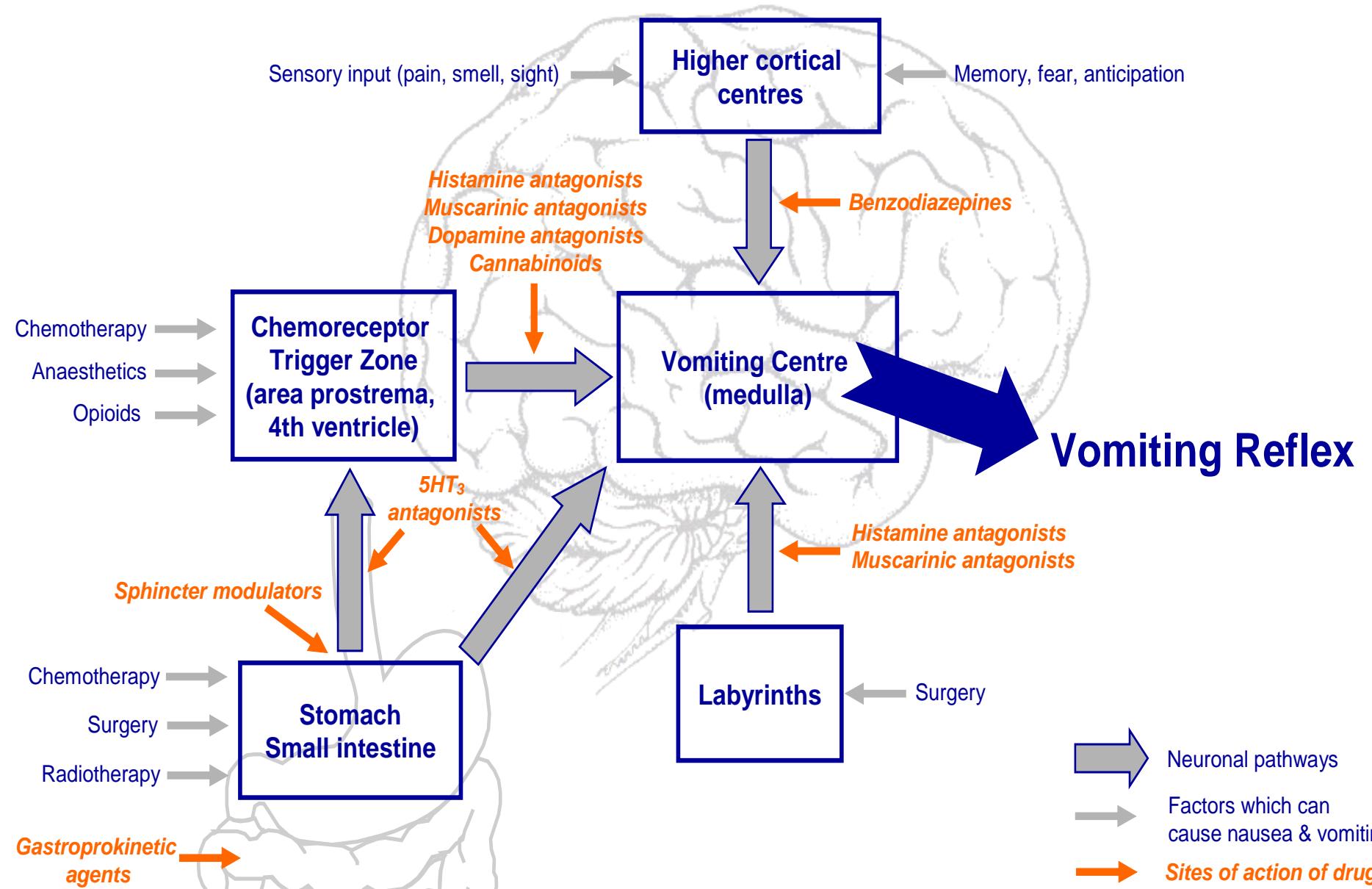
- Peripheral effects
 - Vasodilation, and increase of permeability,
 - Pain, itching
 - Mediates bronchoconstriction
 - Positive inotrop and chronotrop effect on heart
 - Enhances the production of gastric acid
- CNS effects
 - Increases wakefulness
 - Causes fear and distress/anxiety
 - Decreases hunger
 - Has emetic effect
 - Increases the respiratory frequency

Antihistamines

- H₁-receptor inhibitors (antiemetics)
- H₁-receptor inhibitors (antiallergic drugs)
- Inhibitors of Histamine-release
(antiallergic drugs)
- H₂-receptor inhibitors (anti-ulcer drugs)

Antiemetics

Vomiting :The act of vomiting and the sensation of nausea that accompanies it are protective reflexes that serve to rid the stomach and intestine of toxic substances and prevent their further ingestion



Causes that can lead to

Allergy

- The allergy is the pathological hyperfunctioning of the immune system.
- The main point of the disease that the immune system reacts to normally harmless environmental substances.

CHEMICALS

forming of free radicals,
deficient enzyme functioning

ATOPY

(congenital susceptibility)

INAPPROPRIATE NUTRITION

trace element and vitamin-deficiency

INJURY OF THE INTESTINAL FLORA

(mucosal lesion,
dysbacteriosis,
disturbance of the immunologic maturation)

ALLERGY

PSYCHOVEGETATIVE PSYCHOSOMATIC PSYCHOSOCIAL DISTRESS

(disturbed parent-child, teacher-child relationship)

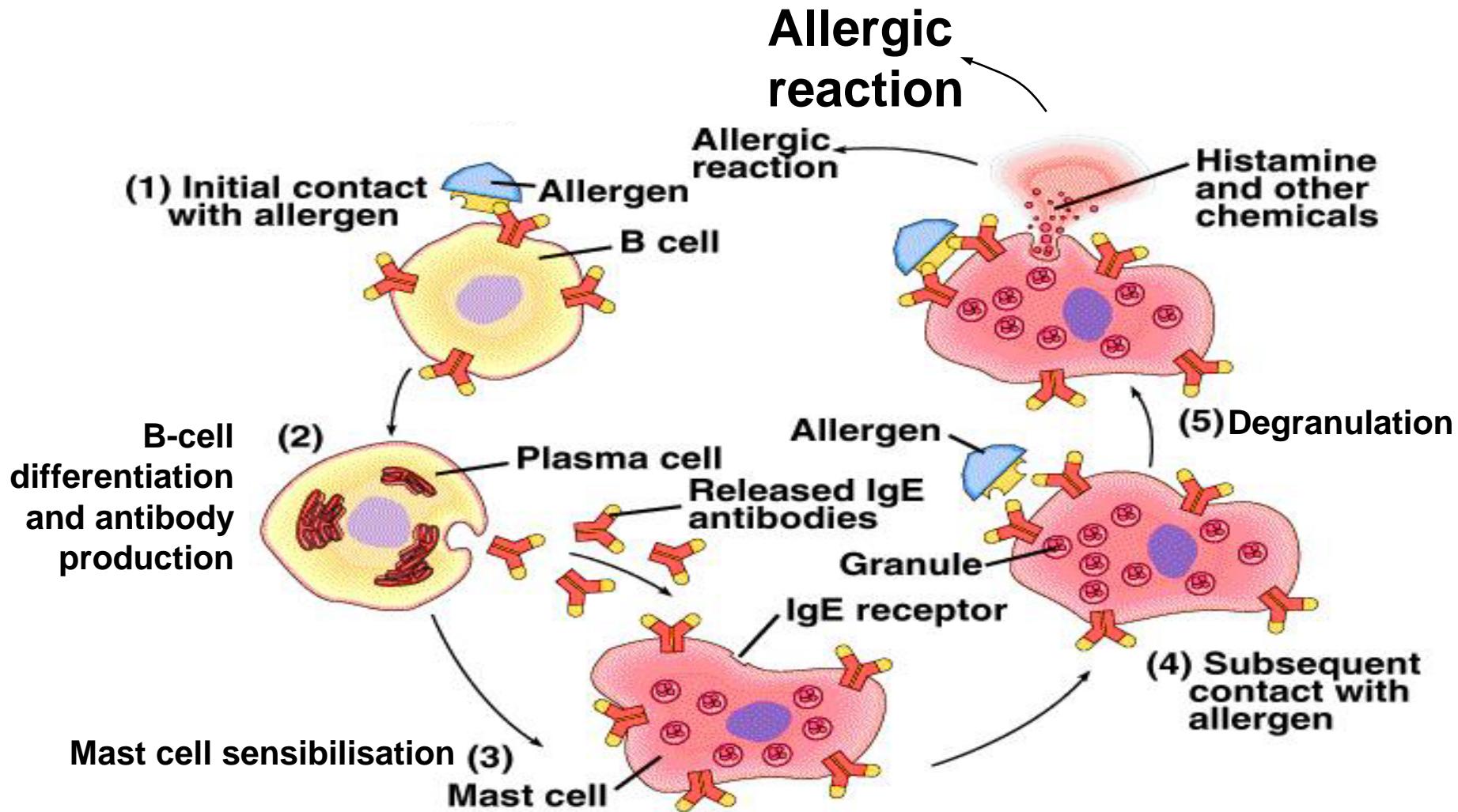
FOOD

WEAK IMMUNE SYSTEM

(infections)

AIR POLLUTION

Release of Histamine



H_1 -receptor inhibitors

- Generations:
 - I. generation drugs
 - Antiemetics, antiallergics
 - Sedative side-effect; elongated reflexes → car-driving, working with heavy machines, workers in dangerous places require attention!
 - Are not selective, many have m-acetylcholine-receptor antagonist effect; some act through α -rec., 5-HT-rec., D-rec. as well
(e.g. promethazine
 D_2 -rec inhibitor → antipsychotic, antiemetic
 H_1 -rec inhibitor → antiemetic, antiallergic)

H₁-receptor inhibitors

■ I. generation drugs (cont.)

■ Ethylene-diamine derivates

- Firstly discovered drugs
- **Chloropyramine**, Chlorothen, Histapyrrodine, Methafurylene, Mepyramine, Methapyrilene, Pyrilamine, Talastine, Thenyldiamine, Thonzylamine, Tripelennamine (Pyribenzamine)



■ Ethanol-amines

- Notable anticholinerg adverse effect, sedative side effect
- Bromazine/Bromodiphenhydramine, Carbinoxamine, Chlordiphenhydramine , Chlorphenoxamine, Clemastine, **Dimenhydrinate**, Diphenylpyraline, Diphenhydramine, Doxylamine, Embramine, Fluordiphenhydramine , Iododiphenhydramine , p-Methyldiphenhydramine, Moxastine, **Orphenadrine**, Phenyltoloxamine, Setastine



Chloropyramine

SUPRASTIN injekció EGISR06AC03

SUPRASTIN tabletta EGISR06AC03

Dimenhydrinate

ARLEVERT tabletta Hennig ArzneimittelN07CA52

DAEDALON tabletta Richter GedeonR06AA02

DAEDALON végbélkúp PharmamagistR06AA

DAEDALONETTA végbélkúp gyermeknek PharmamagistR06AA

Orphenadrine

NEODOLPASSE oldatos infúzió Fresenius Kabi AustriaM01AB55

H₁-receptor inhibitors

■ I. generation drugs (cont.)

■ Alkylamines



- Less sedative and GI side effect, instead → CNS stimulating adverse effect is common
- Bepotastine, Bamipine, Brompheniramine, Chlorpheniramine, Deschlorpheniramine , Dexbrompheniramine, Dexchlorpheniramine, **Dimetindene**, Fluorpheniramine, Iodopheniramine, Iproheptine, **Pheniramine**, Pyrrobutamine, Talastine, Thenalidine, Tolpropamine, Triprolidine



Dimetindene

FENISTIL belsőleges oldatos cseppek Novartis Hungária (Consumer Health részleg)R06AB03

FENISTIL gél Novartis Hungária (Consumer Health részleg)D04AA13

FENISTIL 24 retard kapszula Novartis Hungária (Consumer Health részleg)R06AB03

OTRIVIN Allergia adagoló oldatos orrspray Novartis Hungária (Consumer Health részleg)R01AB01

VIBROCIL oldatos orrcsepp Novartis Hungária (Consumer Health részleg)R01AB01

VIBROCIL oldatos orrspray Novartis Hungária (Consumer Health részleg)R01AB01

Pheniramine

FERVEX cukormentes granulátum oldathoz Bristol-Myers SquibbR06AK

FERVEX gyermek granulátum oldathoz Bristol-Myers SquibbR06AK

NEO CITRAN por felnőtteknek Novartis Hungária (Consumer Health részleg)N02BE51

NEO CITRAN por gyermeknek Novartis Hungária (Consumer Health részleg)N02BE51

H₁-receptor inhibitors

■ I. generation drugs (cont.)

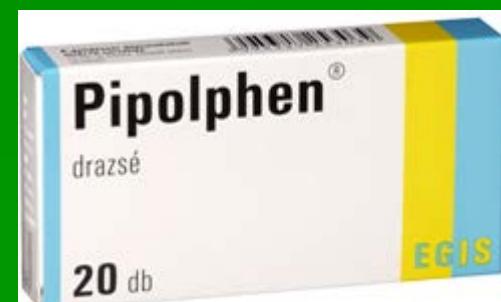
■ Piperazine-derivates

- Remarkable anticholinerg side effects
- Drugs from this group are often used in seasickness, vertigo, and vomiting as antiemetics
- Buclizine, **Chlorcyclizine**, Cinnarizine, Clozinazine, **Hydroxyzine**, Niaprazine, Oxatomide, Benzhydryl-compounds (**Cyclizine**, Meclizine)



■ Tricyclic-compounds

- They are similar to the Phenothiazine antipsychotics and the tricyclic antidepressants, this results in adverse effects
- Ahistan, Azatadine, Clobenzepam, **Cyproheptadine**, Deptropine, Etymemazine, Hydroxyethylpromethazine, Isopromethazine, Isothipendyl, Mequitazine, Methdilazine, Oxomemazine, **Promethazine**, Thiazzinamium



Hydroxyzine

Atarax filmtabellta UCBMedicaN05BB01

Cyproheptadine

PERITOL szirup EGISR06AX02

PERITOL tabletta EGISR06AX02

Promethazine

PIPOLPHEN dragsé EGISR06AD02

PIPOLPHEN injekció EGISR06AD02

H₁-receptor inhibitors

- II. generation drugs
 - More selective to the peripheral H₁-receptor
 - Thus, they have much less adverse effects, while the antiallergic effect remains the same
 - Acrivastine, ***Antazoline***, Astemizole, Azatadine, ***Azelastine***, Bampipine, ***Cetirizine***, Clemizole, Clobenztropine, Deptropine, Dimebon, Ebastine, ***Emedastine***, ***Epinastine***, ***Ketotifen***, Levocabastine, ***Loratadine***, Mebhydrolin, Mizolastine, ***Olopatadine***, Phenindamine, Pimethixene, Pyrrobutamine, Rupatadine, Terfenadine, Thenalidine, Tritoqualine

H₁-receptor inhibitors on the market of Hungary - II.generation

Antazoline

SPERSALLERG szemcsepp Novartis HungáriaS01GA52

Azelastine

ALLERGODIL orrspray Meda Pharma HungaryR01AC03

ALLERGODIL szemcsepp Meda Pharma HungariaS01GX07

Cetirizine

ALERID 10 mg filmtabлетта NeopharmaR06AE07

CETIGEN 10 mg filmtabлетта Merck GenericsR06AE07

CETIRIZIN 1a Pharma 10 mg filmtabлетта 1a PharmaR06AE07

CETIRIZIN HEXAL 10 mg/ml cseppek Sandoz HungáriaR06AE07

CETIRIZIN HEXAL 10 mg filmtabлетта Sandoz HungáriaR06AE07

CETIRIZIN-EP 10 mg filmtabлетта ExtractumPharmaR06AE07

CETIRIZIN-ratiopharm 10 mg filmtabлетта ratiopharm HungáriaR06AE07

CETRIN filmtabлетта TEVA MagyarországR06AE07

CETRIN AKUT filmtabлетта TEVA MagyarországR06AE07

MERZIN filmtabлетта Actavis HungaryR06AE07

PARLAZIN 10 mg/ml cseppek EGISR06AE07

PARLAZIN 10 mg filmtabлетта EGISR06AE07

REVICET 10 mg préselt szopogató tabletta Sager PharmaR06AE07

REVICET AKUT 10 mg préselt szopogató tabletta Sager PharmaR06AE07

ZYRTEC 1 mg/ml belsőleges oldat UCB MagyarországR06AE07

ZYRTEC 10 mg/ml belsőleges oldatos cseppek UCB MagyarországR06AE07

ZYRTEC 10 mg filmtabлетта UCB MagyarországR06AE07

ZYRTEC START 10 mg filmtabлетта UCB MagyarországR06AE07

ZYRTEC-D filmtabлетта UCB MagyarországR01BA52



H₁-receptor inhibitors market of Hungary - II.generation (cont.)

Emedastine

EMADINE 0,05% oldatos szemcsepp Alcon Laboratories (UK)S01GX06



Epinastine

RELESTAT 0,5 mg/ml oldatos szemcsepp Allergan Pharmaceuticals (Ireland)S01GX10

Ketotifen

ZADITEN 0,25 mg/ml szemcsepp Novartis HungáriaS01GX08

ZADITEN 0,25 mg/ml szemcsepp Novartis HungáriaS01GX08

Loratadine

CLARINASE tabletta SP EuropeR01BA52

CLARITINE 1 mg/ml szirup SP EuropeR06AX13

CLARITINE tabletta SP EuropeR06AX13

CLARITINE AKUT tabletta SP EuropeR06AX13

EROLIN szirup EGISR06AX13

EROLIN tabletta EGISR06AX13

FLONIDAN 5 mg/5 ml szuszpenzió TEVA MagyarországR06AX13

FLONIDAN 10 mg tabletta TEVA MagyarországR06AX13

LORANO 10 mg tabletta Sandoz HungáriaR06AX13

LORATADIN HEXAL 10 mg tabletta Sandoz HungáriaR06AX13

LORATADIN-ratiopharm 10 mg tabletta ratiopharm HungáriaR06AX13

ROLETTRA 10 mg tabletta Ozone LaboratoriesR06AX13

Olopatadine

OPATANOL 1 mg/ml oldatos szemcsepp Alcon Laboratories (UK)S01GX09



H₁-receptor inhibitors

III. generation drugs

- Practically these are the active derivates of the second generational drugs:
active enantiomer (**Levocetirizine**);
metabolite (**Desloratadine**, **Fexofenadine**)



Fexofenadine

- ALLEGRA 120 mg filmtabletta (10x buborékcsomagolásban pvc/pe/pvdc//al)
- EWOFEX 120 mg filmtabletta (10x)
- FEXGEN 120 mg filmtabletta (30x)
- FEXOFEP 120 mg filmtabletta (30x)
- TELFAST 120 mg filmtabletta (10x)

Levocetirizine

CETIZAL 5 mg filmtabletta (28x)

CEZERA 5 mg filmtabletta (30x)

HISTISYNT 5 mg filmtabletta (30x PVC/PVDC//Al buborékfóliában)

LERTAZIN 5 mg filmtabletta (30x (PVC/PVDC//Al buborékfóliában))

LEVOCEP 5 mg filmtabletta (30x PVC/PVDC//Al buborékcsomagolásban)

NOVOCETRIN 5 mg filmtabletta (10x)

PIXAL 5 mg filmtabletta (30x)

SEFALLER 5 mg filmtabletta (10x (pvc/pvdc//al buborékfóliában))

XYZAL 0,5 mg/ml belsőleges oldat (200 ml)

ZILOLA 5 mg filmtabletta (28x)

Desloratadine

AERIUS 0,5 mg/ml belsőleges oldat (150 ml (adagoló kanállal))

ALVOTADIN 5 mg filmtabletta (30x PVC/PCTFE (Aclar)//Aluminium
buborékcsomagolásban)

AZOMYR 5 mg filmtabletta (30x)

DESAERO 5 mg filmtabletta (30x)

DESLORATADIN TEVA 5 mg szájban diszpergálódó tabletta (30x)

DESLORATADINE ACTAVIS 5 mg filmtabletta (30x)

DESLORATADINE MYLAN 5 mg filmtabletta (30x)

DESLORATADINE RATIOPHARM 5 mg filmtabletta (30x
buborékcsomagolásban)

DESLOREP 5 mg filmtabletta (30x buborékcsomagolásban)

ESRADIN 5 mg filmtabletta (30x)

INALLER 0,5 mg/ml belsőleges oldat (1x150 ml (III-as típusú borostyánszínű
üvegpalack+mérőkanál))

LORDESTIN 5 mg filmtabletta (10x buborékcsomagolásban)

Histamine-release (degranulation) inhibitors

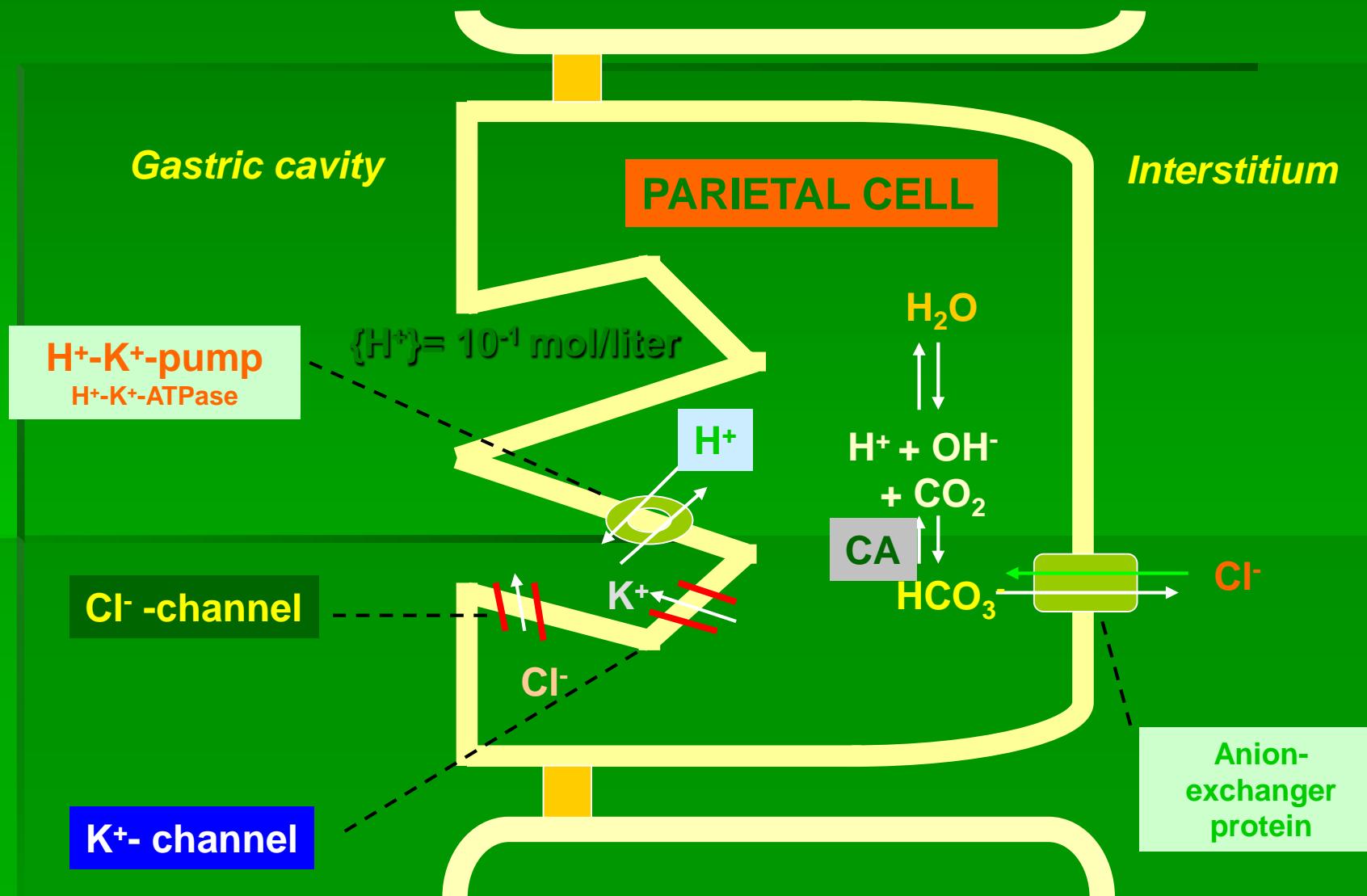
- They stabilise the membrane of the mast cells, thus, they have an antiallergic effect.
- Mechanism of action:
 - they inhibit the IgE-mediated Ca^{2+} -channels, thus, the Ca^{2+} -accumulation in the mast cells is also inhibited, so they inhibit the emptying of the histamine-containing vesicles
 - Some agents also inhibit the biosynthesis of the leukotrienes. (spaglumicum/isospaglumicum)
- Cromoglicate, Nedocromil, Spaglumicum, Isospaglumicum, Lodoxamine, Emedastine

Emedastine

EMADINE 0,05% oldatos szemcsepp Alcon Laboratories (UK)S01GX06

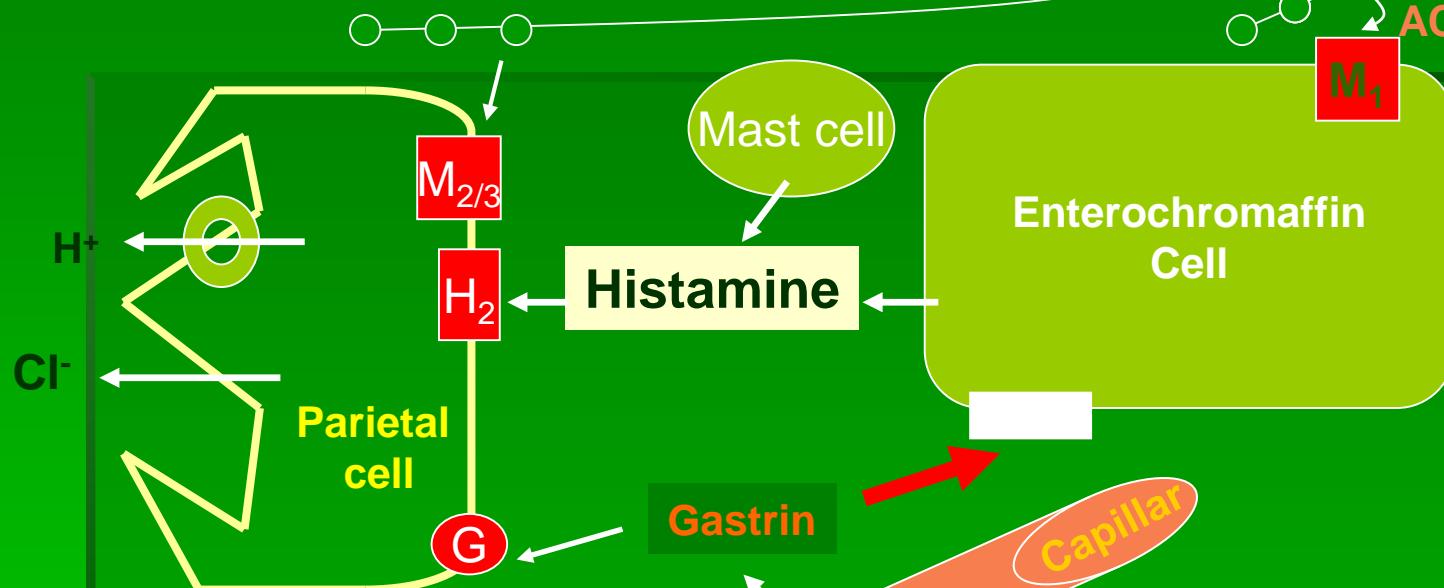


Production of gastric acid

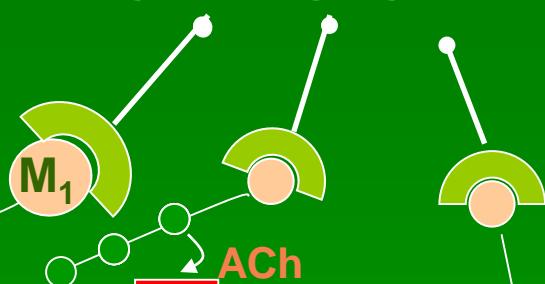


Factors affecting the production of gastric acid

CORPUS



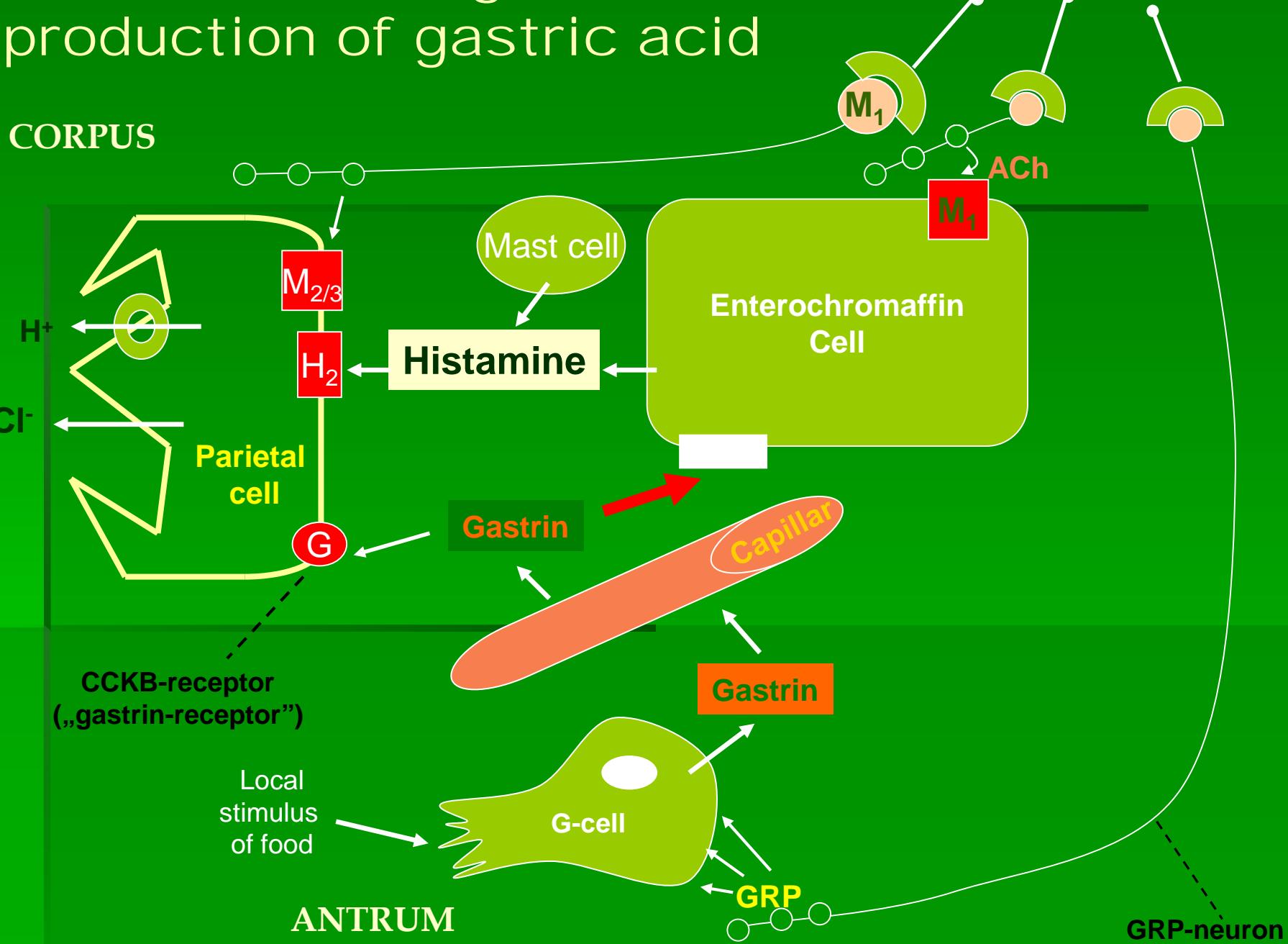
N. vagus praeganglionar axon



CCKB-receptor
„gastrin-receptor“)

Local
stimulus
of food

ANTRUM



GRP-neuron

H_2 -receptor inhibitors

- Mechanism of effect:
They inhibit the H_2 -histamine-receptors on the parietal cells of the stomach, thus decreasing the secretion of the gastric acid.
- Application: against ulcer
- In case of chronic application tolerance may develop. (except nizatidine)
- Upon discontinuation rebound effect may occur.
- Interactions may develop (most of these drugs are metabolised by the P450 enzyme-system)
(e.g.: cimetidine is an inhibitor of CYP2C19, CYP2D6, CYP3A4/5/7)
- **Cimetidine, Famotidine, Ranitidine, Roxatidine, Lafutidine, Niperotidine, Nizatidine**

H₂-receptor inhibitors on the market of Hungary

Famotidine

APO-FAMOTIDIN 20 mg filmtabletta [Toronto Pharma](#)A02BA03

APO-FAMOTIDIN 40 mg filmtabletta [Toronto Pharma](#)A02BA03

FAMOTIDIN HEXAL 20 mg filmtabletta [Sandoz Hungária](#)A02BA03

FAMOTIDIN HEXAL 40 mg filmtabletta [Sandoz Hungária](#)A02BA03

MOTIDIN 20 mq filmtabletta [Valeant Pharma Magyarország](#)A02BA03

MOTIDIN 40 mq filmtabletta [Valeant Pharma Magyarország](#)A02BA03

QUAMATEL 20 mq filmtabletta [Richter Gedeon](#)A02BA03

QUAMATEL 40 mq filmtabletta [Richter Gedeon](#)A02BA03

QUAMATEL 20 mq por és oldószer oldatos injekcióhoz [Richter Gedeon](#)A02BA03

QUAMATEL MINI 10 mq filmtabletta [Richter Gedeon](#)A02BA03

Ranitidine

RANITIC 150 filmtabletta [Hexal AGA](#)02BA02

RANITIC 300 filmtabletta [Hexal AGA](#)02BA02

RANITIDIN-B 150 mg tabletta [TEVA Gyógyszergyár, Debrecen](#)A02BA02

RANITIDIN-B 300 mg tabletta [TEVA Gyógyszergyár, Debrecen](#)A02BA02

ULCERAN 150 mq tabletta [TEVA Gyógyszergyár, Debrecen](#)A02BA02

ULCERAN 300 mq tabletta [Teva Gyógyszergyár, Debrecen](#)A02BA02

UMAREN 150 mq filmtabletta [EGISA](#)02BA02

UMAREN 300 mq filmtabletta [EGISA](#)02BA02

UMAREN injekció [EGISA](#)02BA02

ZANTAC 150 mg filmtabletta [GlaxoSmithKline](#)A02BA02

ZANTAC 300 mg filmtabletta [GlaxoSmithKline](#)A02BA02

ZANTAC injekció [GlaxoSmithKline](#)A02BA02

