HISTAMINE & PHARMACOLOGICAL TREATMENT OF ALLERGY

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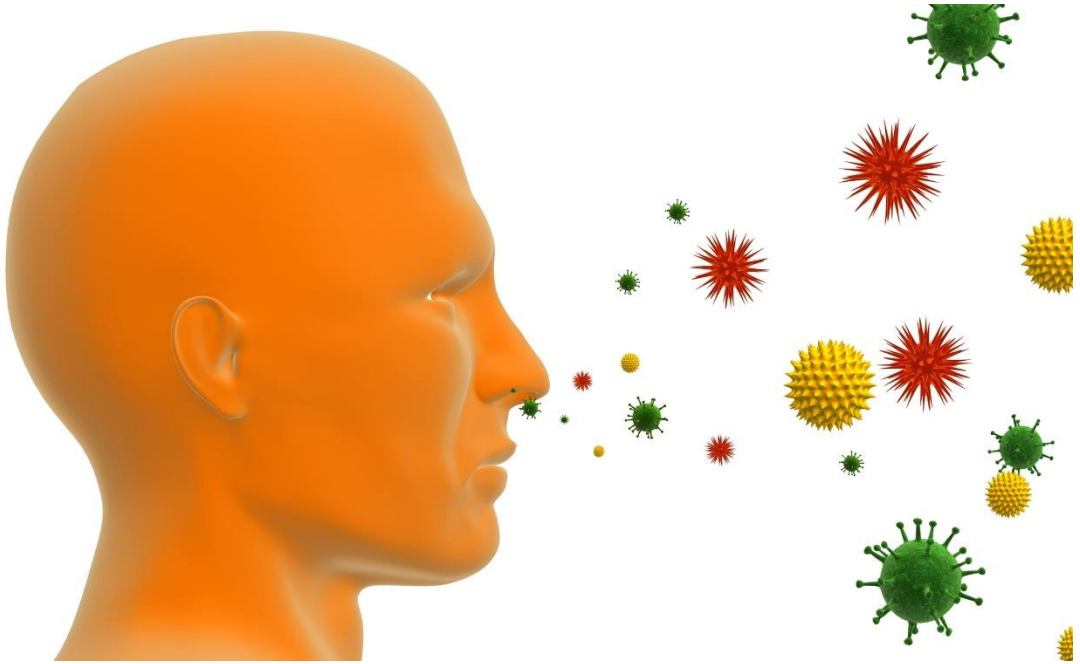
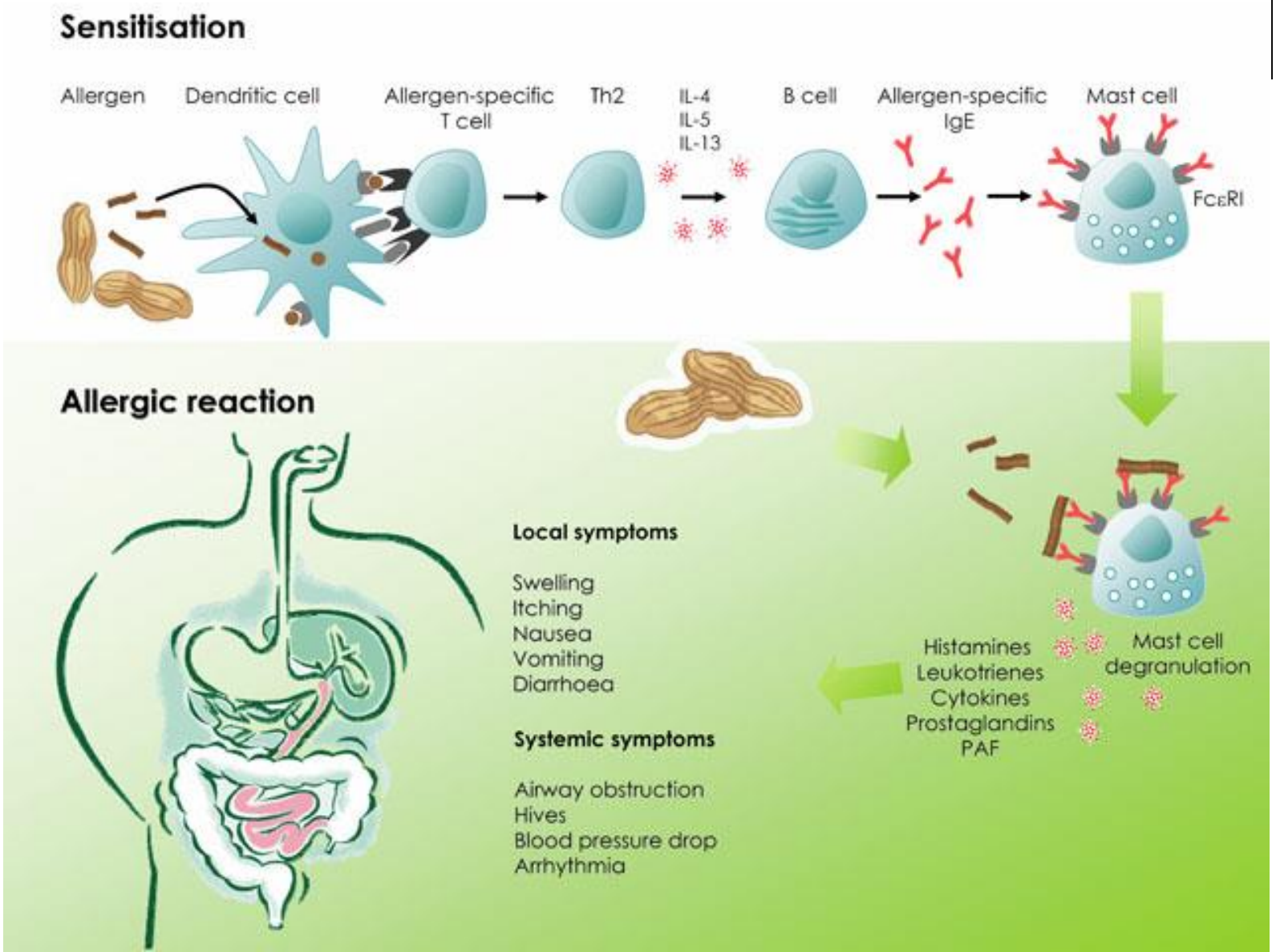
Allergy

- an inappropriate response of the body's immune system to **normally harmless** substances

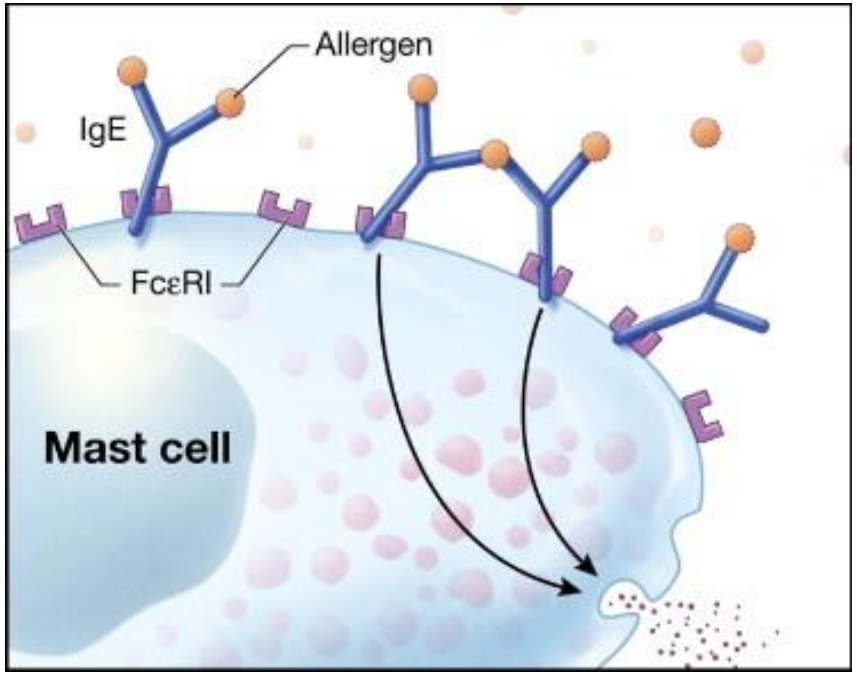
(pollens, foods, house dust mite, pets, insect poisons, drugs...)

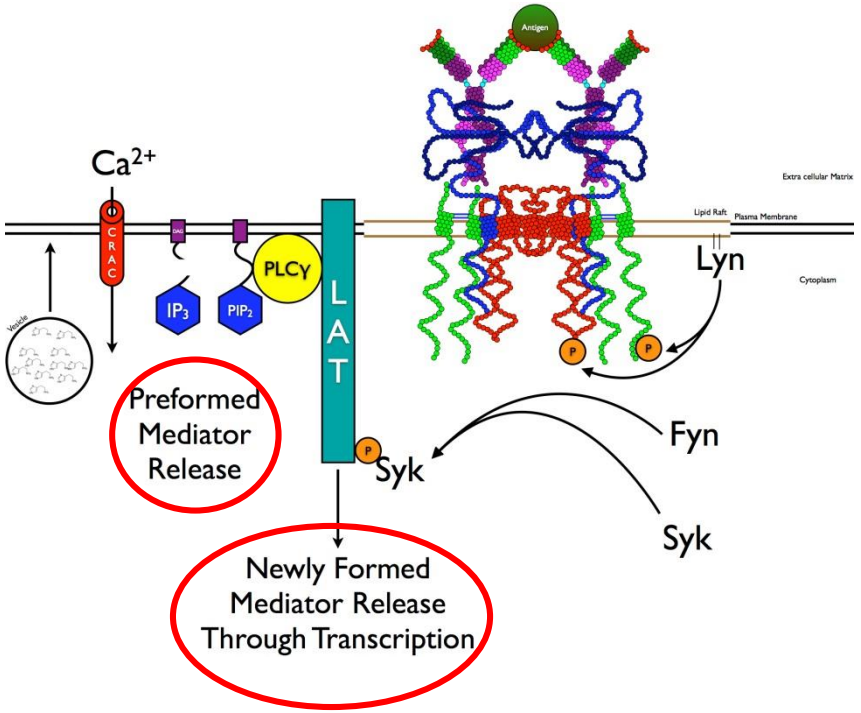


Sensitisation & allergic reaction



Crosslinking of the FcεRI via IgE-antigen complexes - degranulation



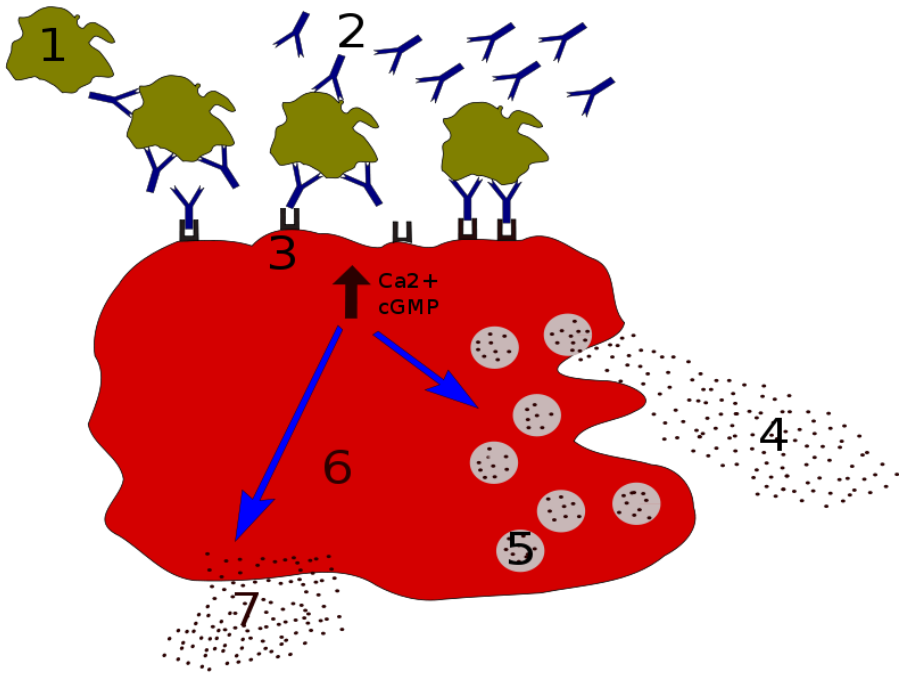


http://en.wikipedia.org/wiki/File:IgE_Fc%CE%B5RI_Receptor_Signal_Cascade.jpg

http://www.sciencedirect.com/science/article/pii/S0002934308000685

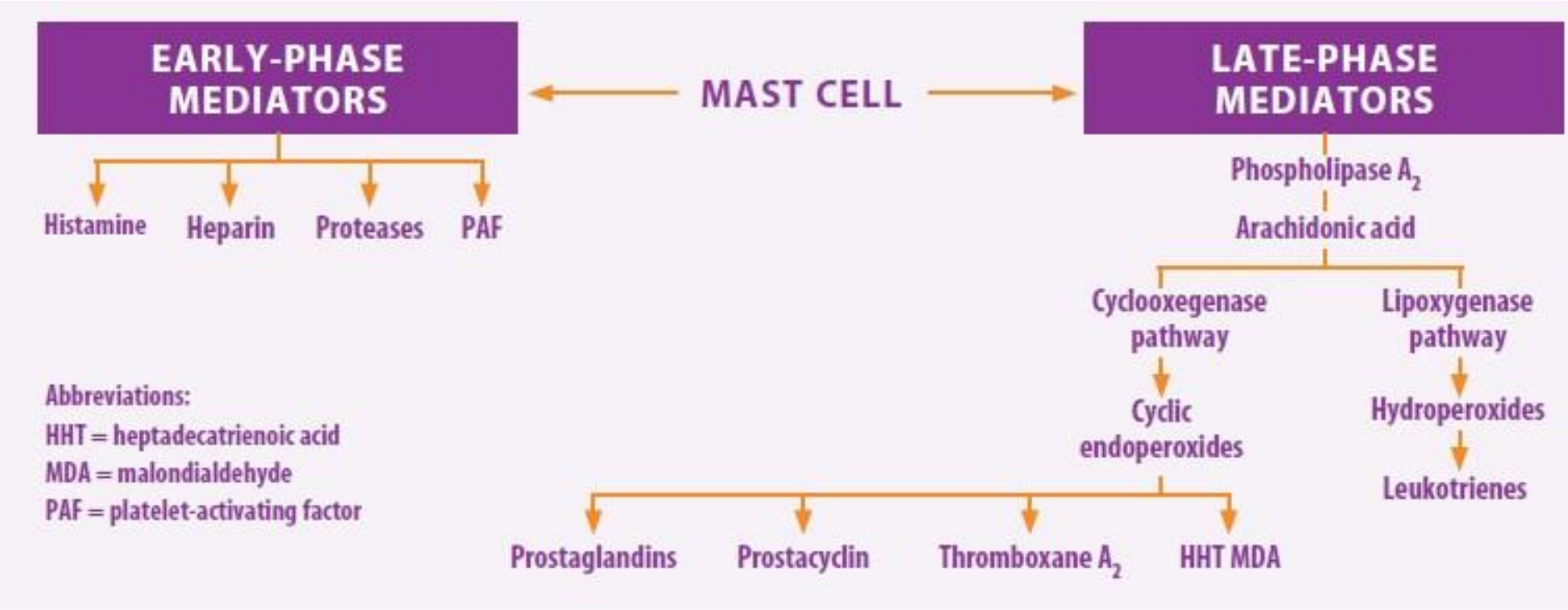
Allergic reaction

Degranulation processes



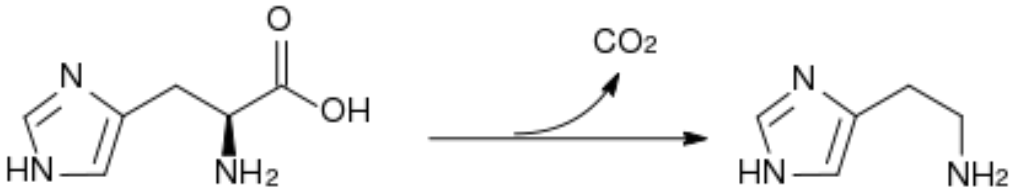
1. antigen
2. IgE antibody
3. **FcεRI receptor** (high-affinity IgE receptor)
4. preformed mediators (early-phase mediators)
5. granules
6. mast cell
7. newly formed mediators (late-phase mediators)

Types of allergy mediators



HISTAMINE

- **hydrophilic vasoactive amine**
- it is involved in:
- **local immune responses**
- **regulation of physiological function in the gut**
- **acting as a neurotransmitter**
- **it also triggers the inflammatory response**



- it is derived from the amino acid *histidine* by decarboxylation (L-histidine decarboxylase)
- it is broken down by histamine-N-methyltransferase & diamine oxidase

History of histamine

- ***Adolf Windaus***
- **Nobel prize in chemistry 1928**
- discovered 7-dehydrocholesterol, precursor of vitamin D, & he showed that it is a steroid
- discovered that it is converted into the vitamin by the action of sunlight
- **discovered histamine**

1876-1959

Histamine localization & release

- Localization:
- **mastocyte & bazophile (granules) – bound to** heparan sulfate & acidic protein
- Mastocyte & bazophile - in various tissues - preferentialy in:
- **respiratory system**
- **GIT**
- **skin**

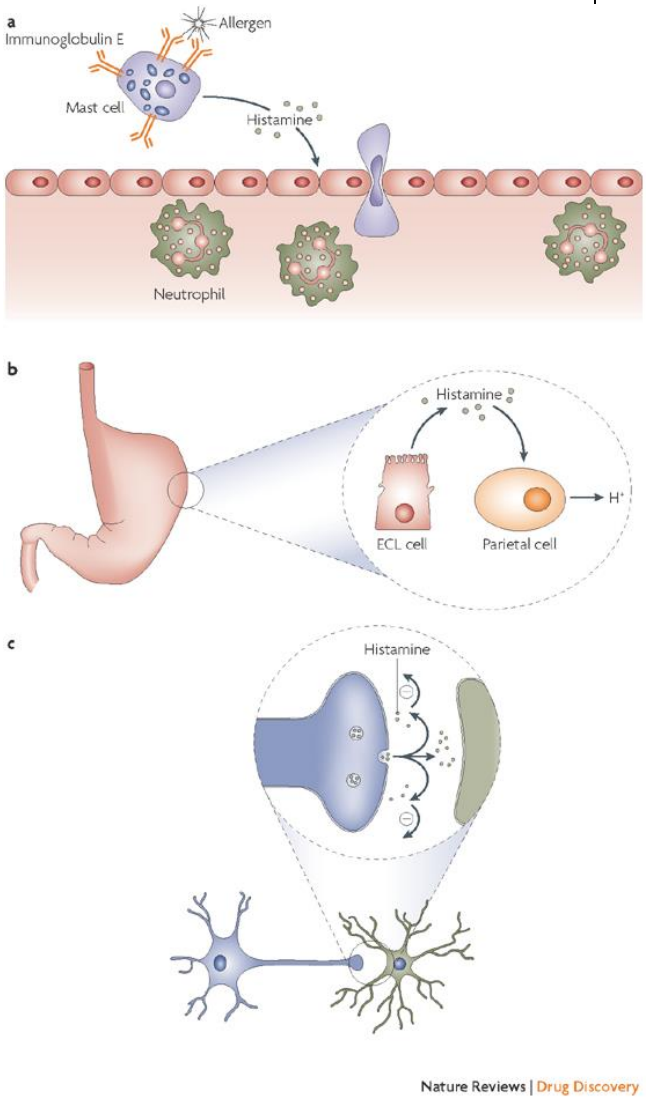
- Triggering factors for histamine release:
- **UV, allergenes (IgE) – type I.**
- **drugs: *morphine, codeine, tubocurarine***
- **inflammatory reaction**

Histamine receptors

Distribution

- **H_1-receptors:**
  - **endothelium**
  - **smooth muscles**

  (blood vessels, bronchial system, uterus, GIT)
- **H_2-receptors:**
  - **gastric mucosa**
  - **heart**
  - **immune system**
- **H_3-receptors:**
  - **CNS**
- H_4-receptors:
  - immune cells



Histamine receptors
Function

H_1	H_2	H_3
Smooth muscle: • ⇑ tone → contraction (bronchi, intestine, uterus) **Blood vessels:** • endothelium NO release → vasodilatation • endothelial cell slots opening → ⇑ vascular pemeability **Sensitive nerve endings:** • itching **CNS:** • ⇑ vigilance	**Stomach:** • ⇑ HCl secretion **Blood vessels:** • direct vasodilatation **Heart:** • ⇑ contraction force • ⇑ frequency • arytmogenity	**CNS:** • ⇓ of histamine release & other NTs

Effects of histamine in CVS

- **H_1-receptors stimulation :**
  - vasodilation small arterioles & capillaries
  - blood vessel wall permeability increase
  - ⇓ BP, reflex tachycardia, edema
  - **Lewis reaction (intradermal histamine injection):** → localized red macula (capillary dilation) → spreading of macula (arteriolar dilation - axonal reflex) → papular induction (localized edema)

- **H_2-receptor stimulation in the heart:**
  - ⇑ contractility
  - ⇑ pacemaker activity

Effect of histamine in smooth muscles & mucose

- **Bronchial smooth muscle**
  - **H_1-receptor stimulation** ⇨ bronchoconstriction

- **GIT smooth muscle**
  - **H_1-receptor stimulation** ⇨ intestinal contraction; diarrhea in higher concentrations

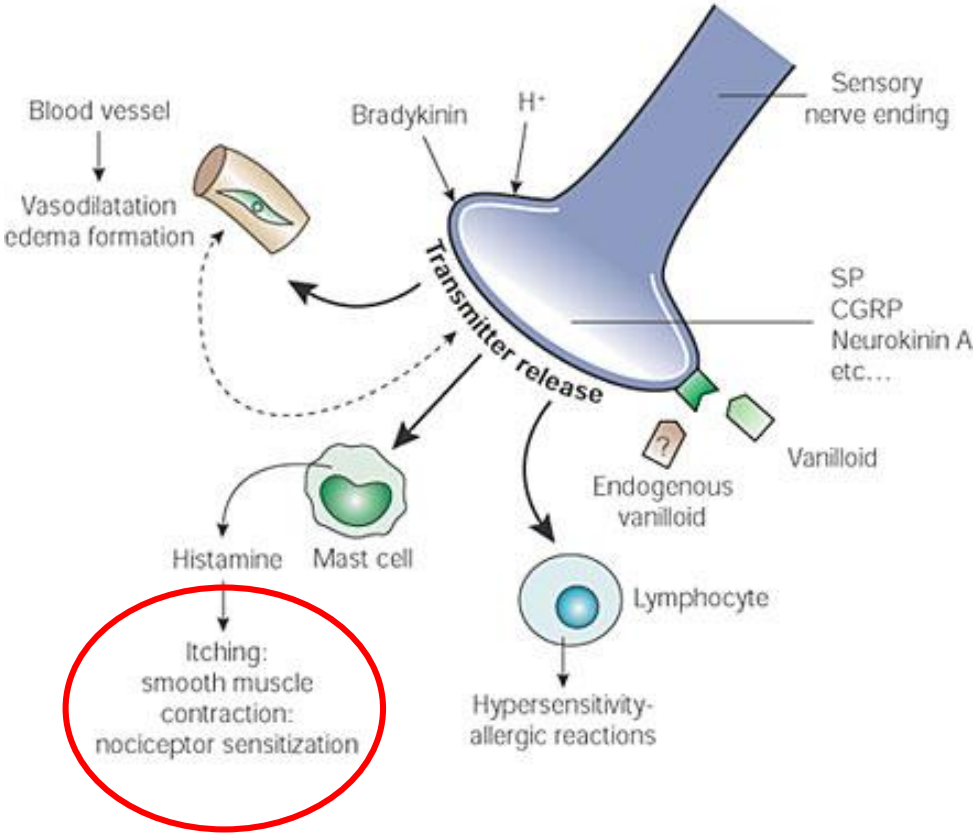
- **Gastric mucosa**
  - **parietal cell H_2-receptor stimulation** ⇨ gastric acid secretion & pepsin activation

Effect of histamine in other tissues

- **Uterus**
  - **H_1-receptor stimulation ⇨** contraction

- **Nerve endings**
  - **H_1-receptor stimulation ⇨** irritation

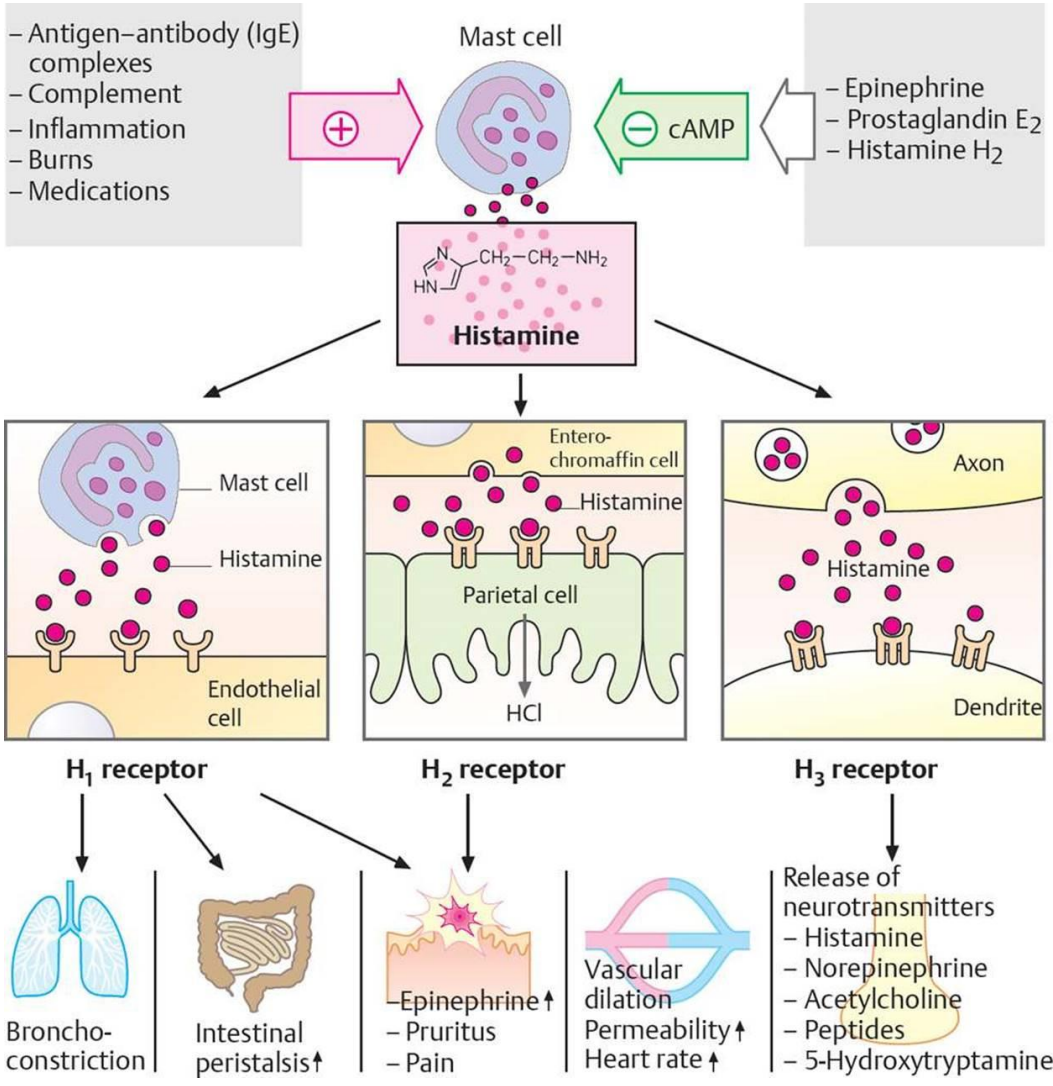
⇨ pain & itching (e.g. urtica in insect injury)



Histamine inhibition

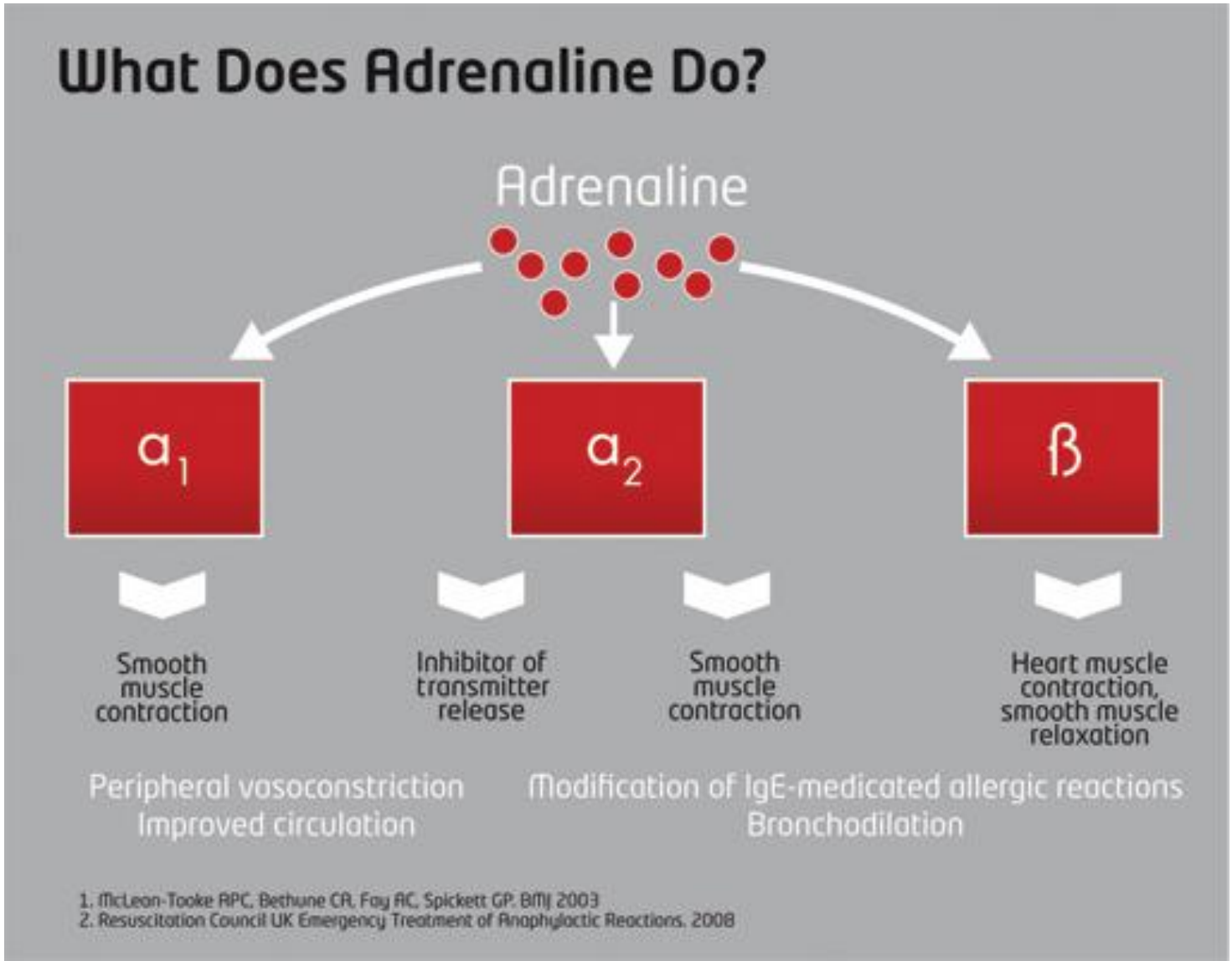
- **synthesis inhibition**
  - glucocorticoids
- **release inhibition**
  - cromoglycate (nedocromil sodium)
- **organ level inhibition**
  - ***adrenaline***

  (in anaphylaxis)
- **receptor level inhibition**
  - **antihistaminics**



Adrenaline

Mechanisms in anaphylaxis

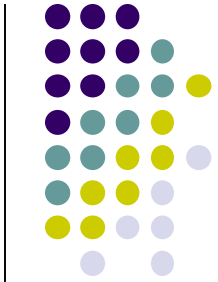


Adrenaline

Principal rules in anaphylaxis

- **Adrenaline is life saving & must be used promptly in anaphylaxis**
- Delaying the giving of adrenaline can result in deterioration & death
- using an adrenaline device is the **first line treatment for anaphylaxis**
- **IF IN DOUBT, GIVE ADRENALINE FIRST** & then call for help

H_1- ANTAGONISTS
I. generation

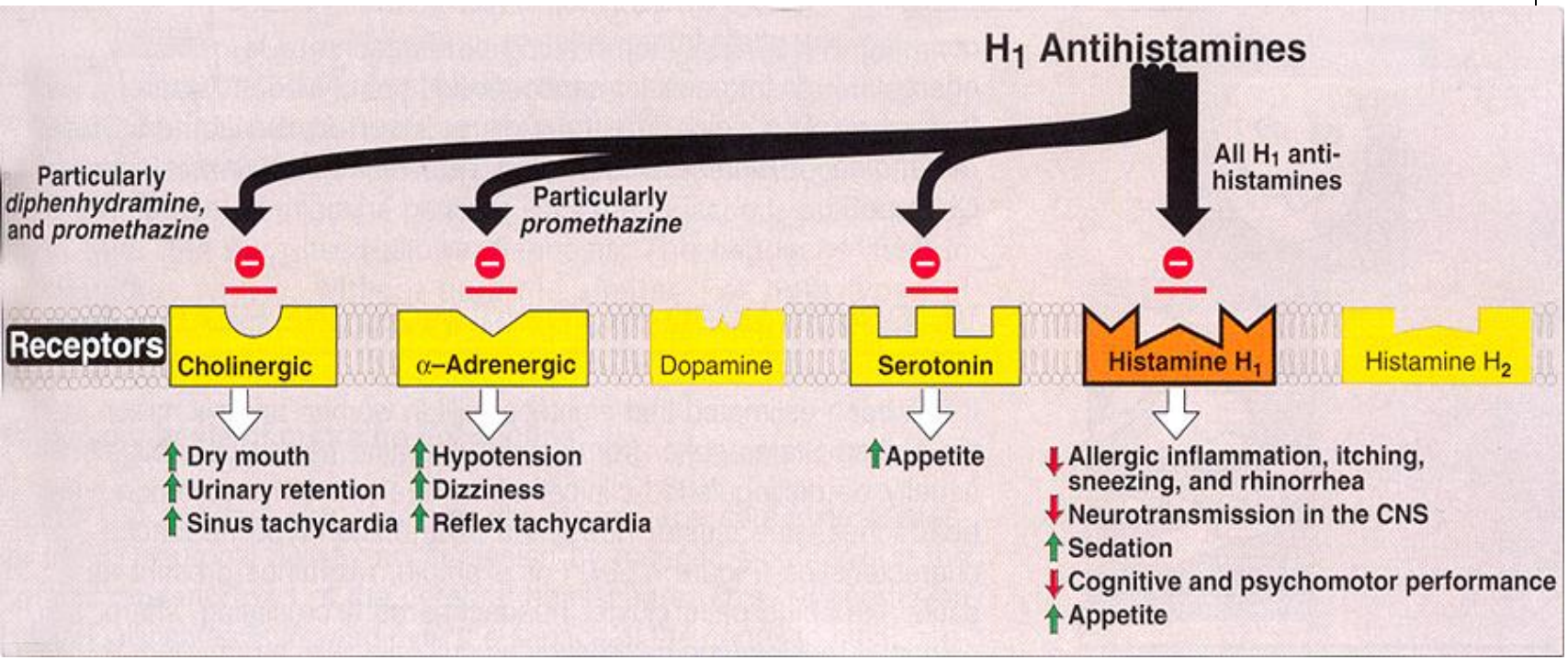


- **Competitive antagonists – H_1 receptors**
- blood vessel response inhibition including ⇑ **permeability** (edema)

! ! ! DO NOT AFFECT SHOCK SYMPTOMS ! ! !

- **inhibition of CNS → interactions** (can be oposite in children - stimulation, excitation, clinically as seizures)
- **antiemetic & antivertiginous effect** (vomiting & vertigo)
- **antimuscarinic effects – ⇓ mucosal secretion** (rhinitis treatment)

First generation H_1- antagonists



- **low specificity**
- some effects may be undesirable, others of therapeutic value (anticholinergic – drying of nasal mucosa; sedative effects - insomnia)

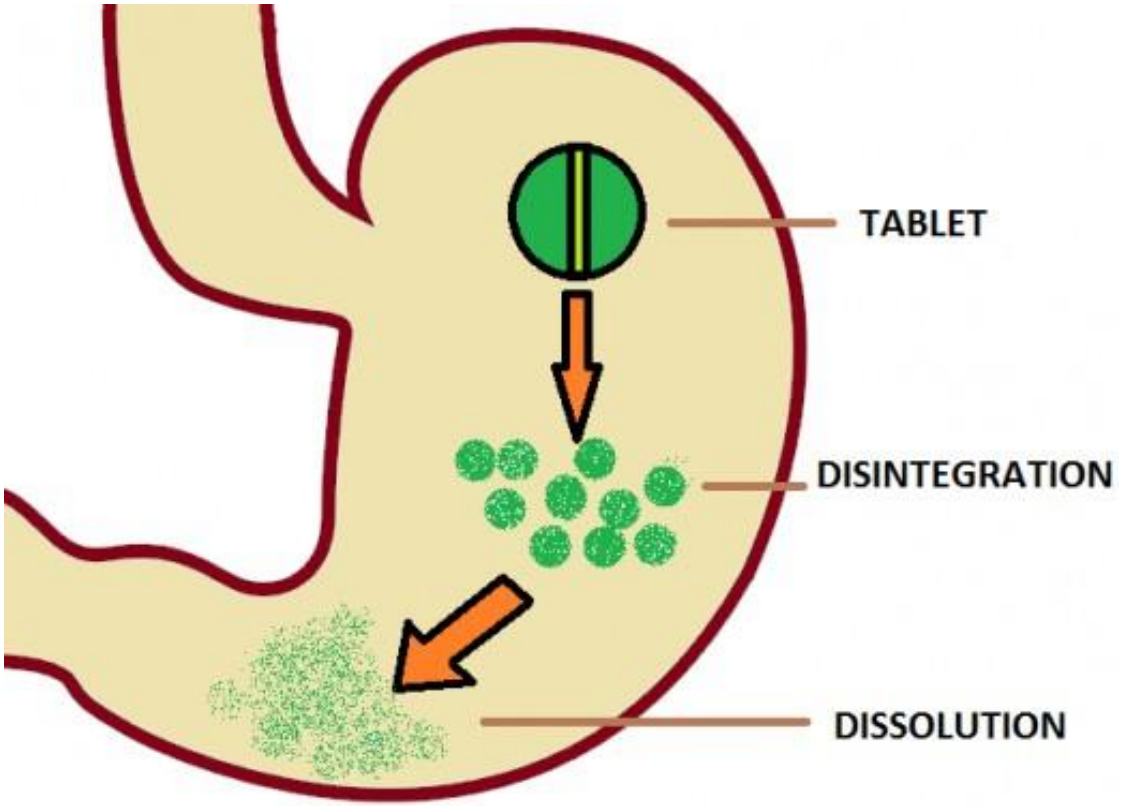
H_1- antagonists I. generation
Pharmacokinetics

- **rapid GIT absorption**

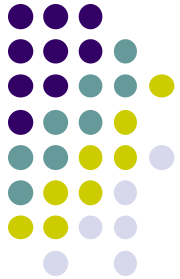
  (effect in 1/2 h)
- liver metabolism
- renal excretion

- **newer I. generation drugs – longer $t_{1/2}$**

  (12-24 h)
- prophylaxis



H_1- antagonists I. generation
Indications



- **symptomatic therapy of allergies -** allergic rhinitis (hay), urtica, Quincke edema, drug & food allergies
- **adjuvans in anaphylactic reactions therapy**
- **prophylaxis in desensitisation therapy**
- **pruritus of different origin -** allergic & nonallergic dermatoses, pruritus in infective diseases – (scarlatina, measles)
- **insect injuries**
- **kinetoses -** vertigo, tinnitus, morbus Meniere, migraine
- **nausea & vomiting of different ethiology** (except organic GIT disturbances)
- **insomnia**

H_1- antagonists I. generation

Side effects

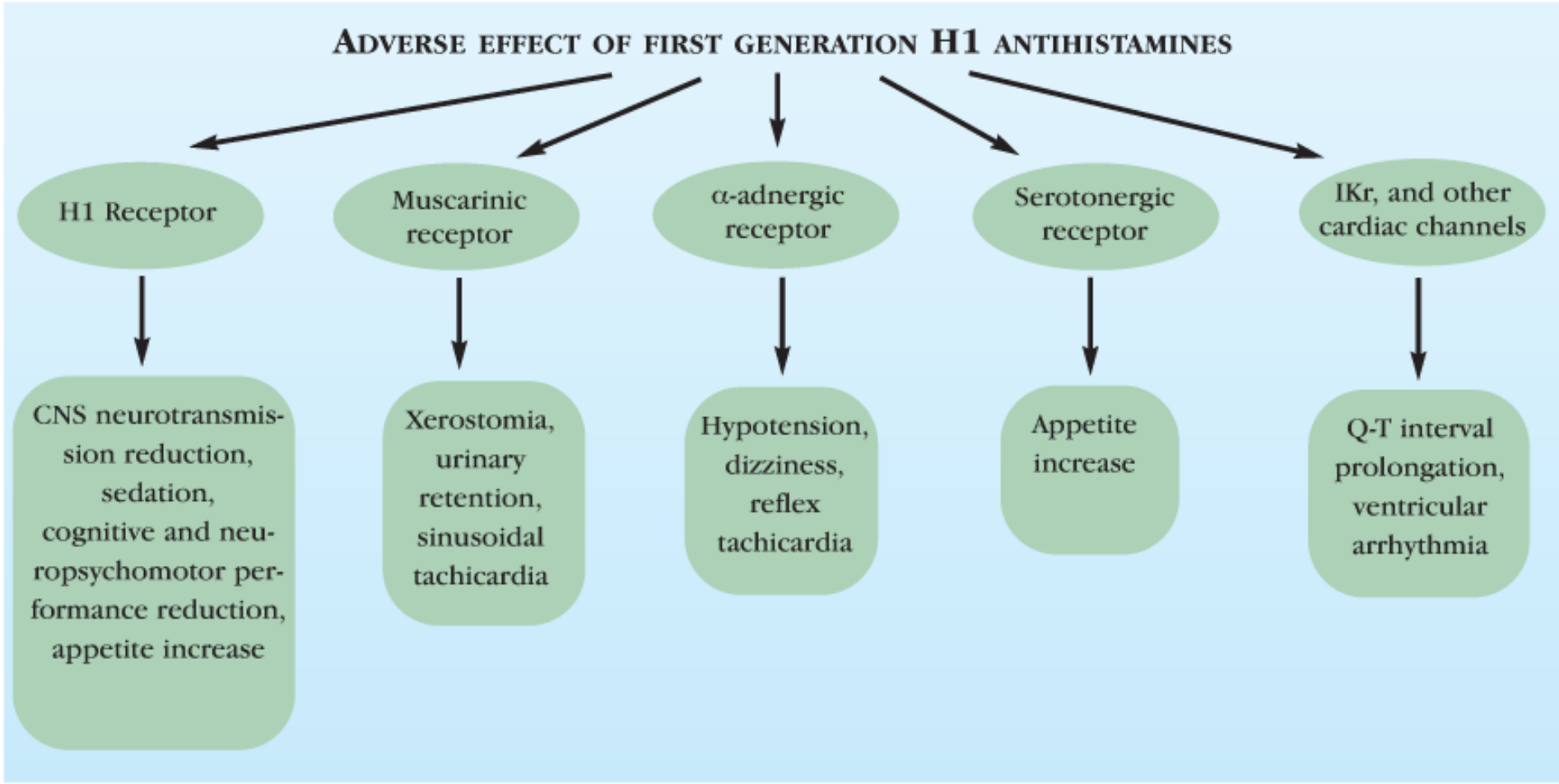
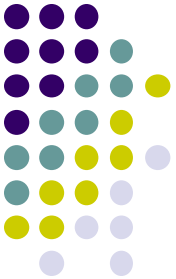


FIGURE 5: Symptoms and signs of the adverse effects of first-generation H1 antihistamines

H_1- antagonists I. generation
Representatives

Generic name	Trade name	Duration (h)	Sedation	Dose (mg)
diphenhydramine	-	**6**	±	**50**
promethazine	PROMETHAZINE PROTHAZINE	**20**	**+++**	**10-20**
bisulepine	DITHIADEN	**7**	**+**	**2**
dimetinden	FENISTIL	**7**	**+**	**1-2**
clemastine	TAVEGYL	**12**	±	**1**
moxastine	THEADRYL KINEDRYL	**2**	**+**	**25**

H_1- ANTAGONISTS
II. generation

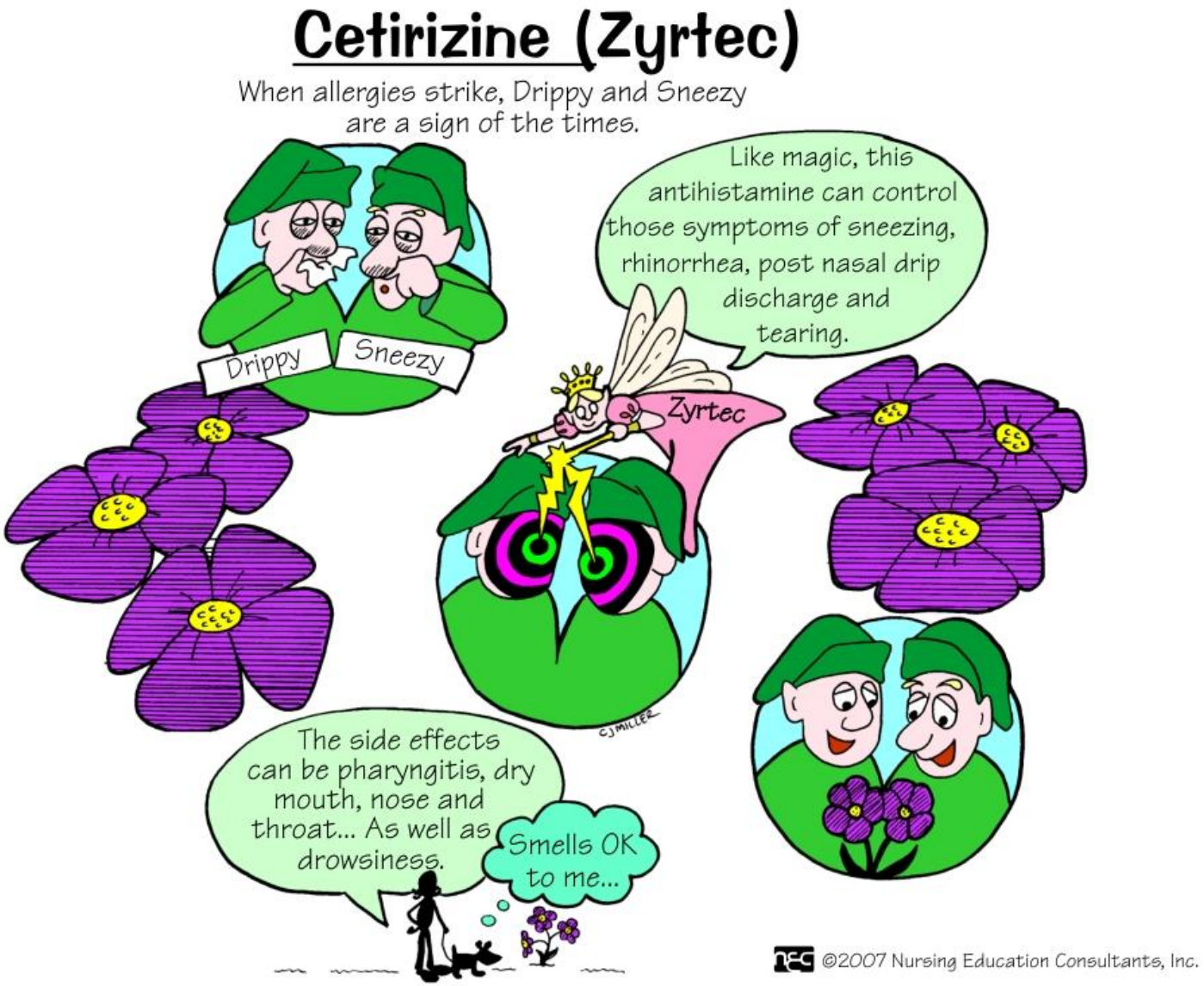


- **minimal sedative effects**
- prolonged H_1 - antagonist effects

Generic name	Trade name	Duration (h)	Sedation	Dose (mg)
astemisol	HISMANAL	**24**	**0**	**10**
cetirizine	ZYRTEC	**24**	**0**	**10**
loratadine	CLARITIN	**24**	**0**	**10**
terfenadine	SELDANE	**12**	**0**	**60**

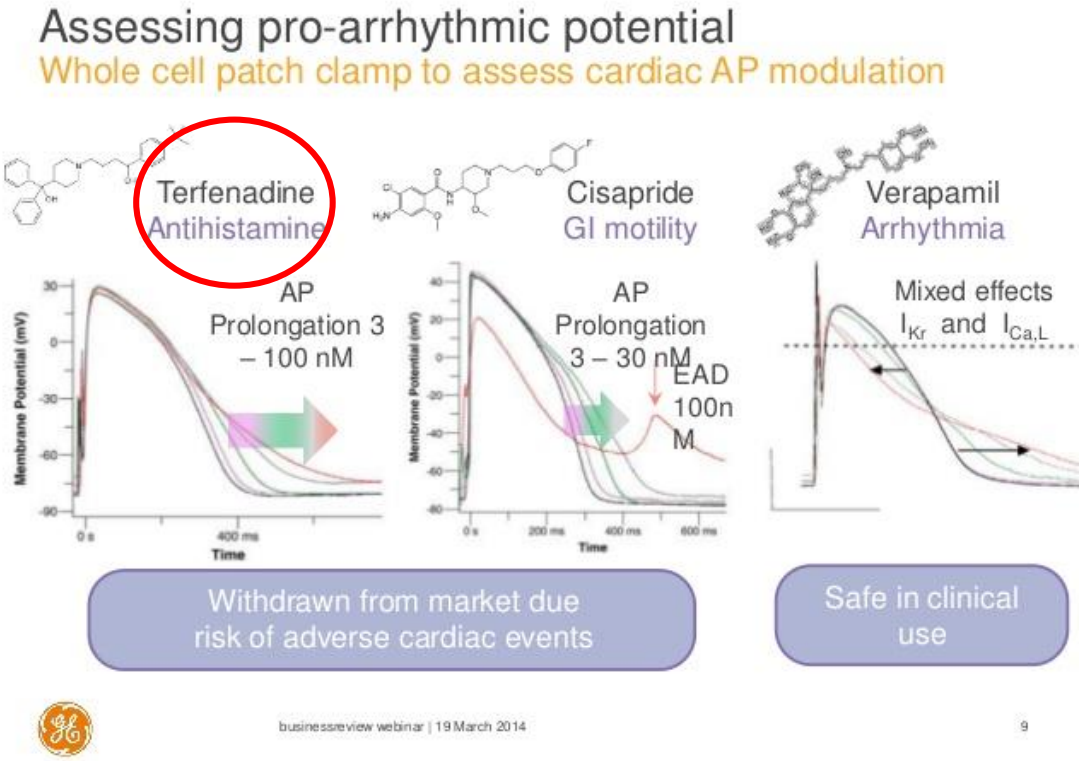
Cetirizine

Effects & side effects



H_1- antagonists
II. generation

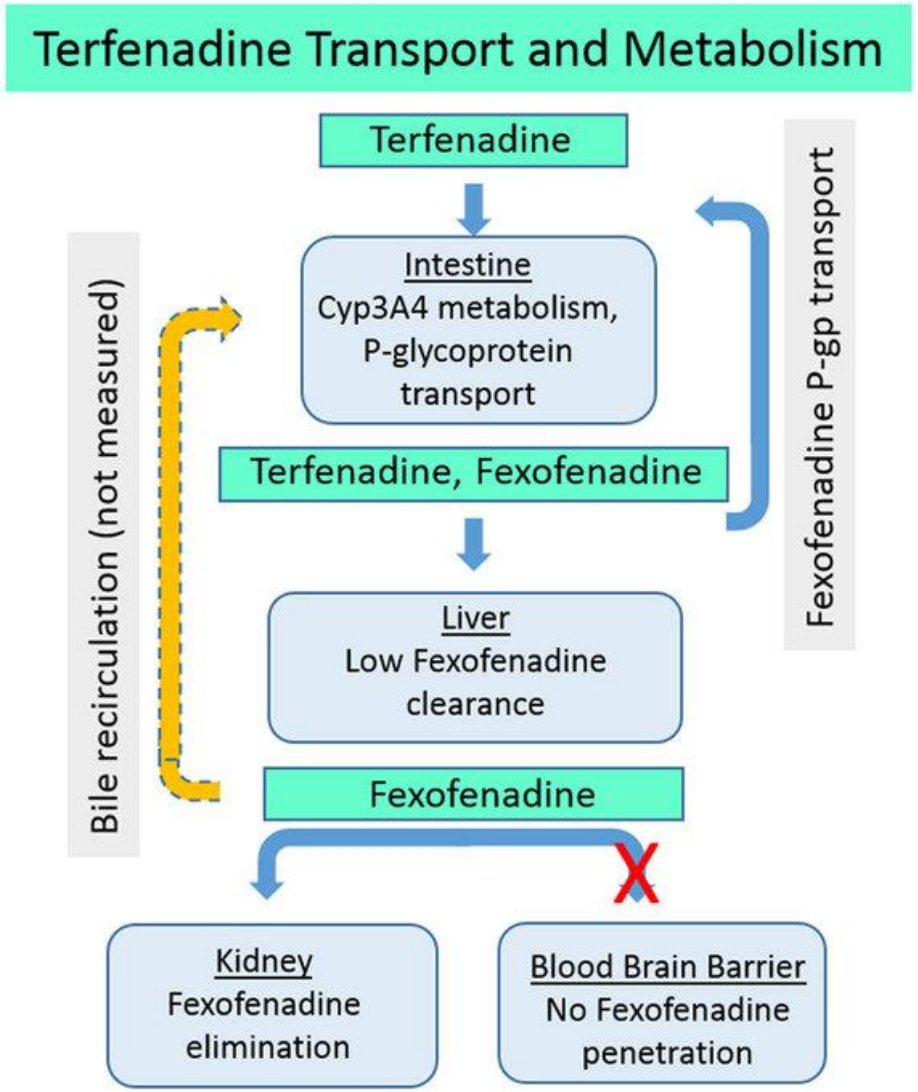
- *astemizole & terfenadine* were found to cause potentially **serious arrhythmias** (including death, cardiac arrest, torsades de pointes, & other ventricular arrhythmias), when plasma concentrations became elevated subsequent to:
  - impaired metabolism or
  - drug interaction (macrolides, antifungals)



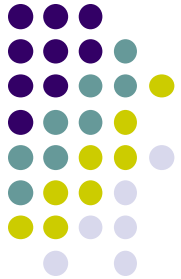
H_1- ANTAGONISTS
III. generation

- they are even an **active enantiomer** or **metabolite** of a II. generation drug designed to have:
  - ⇑ **efficacy** &
  - ⇓ **side effects**

- they are **devoid of cardiac toxicity**



H_1- antagonists
III. generation

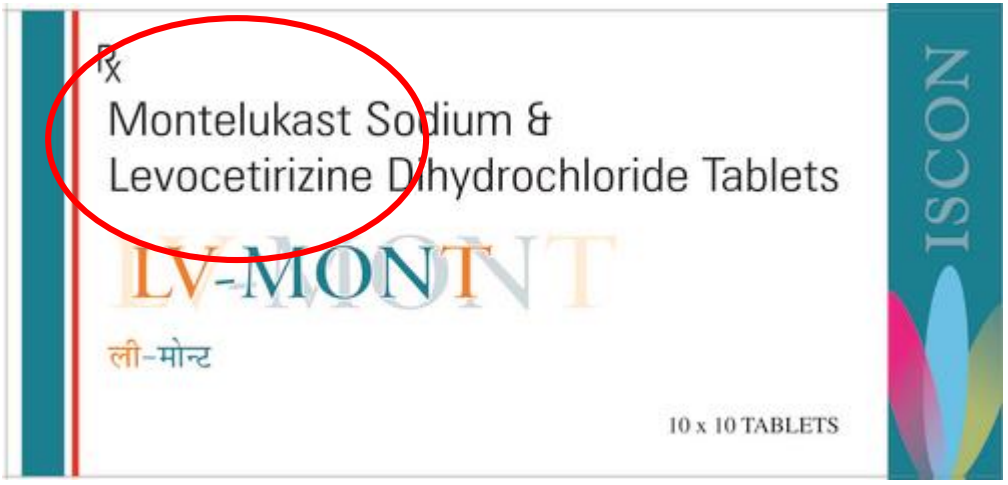


- minimal sedative effects
- prolonged H_1 - antagonist effects
- no cardiovascular side effects

Generic name	Trade name	Duration (h)	Sedation	Dose (mg)
levocetirizine	LEVOCETIRIZINE ACTAVIS	**24**	**0**	**5**
desloratadine	DESLORATADINE ACTAVIS	**24**	**0**	**5**
fexofenadine	FIXIT 120	**12**	**0**	**120**

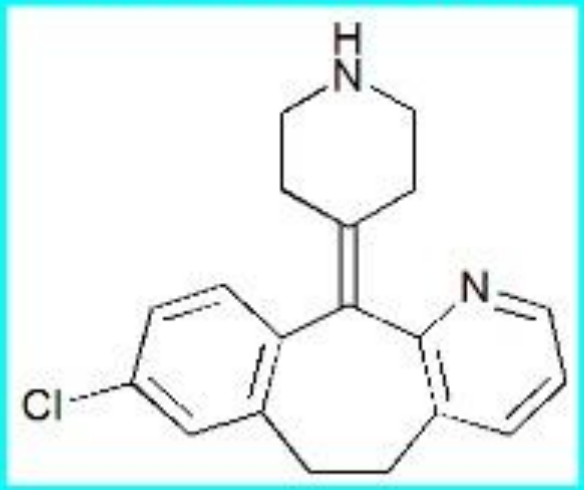
H_1- antagonists
III. generation

- ***Levocetirizine***
- an active enantiomer of *cetirizine* (more effective with fewer advers effects)
- not metabolized & is likely to be safer than other drugs (due to a lack of possible drug interactions)
- it does not cross BBB & does not cause significant drowsiness
- it has been shown to reduce asthma attacks by 70% in children
- can be combined with LT-receptor antagonist



Third generation H_1-receptor antagonists

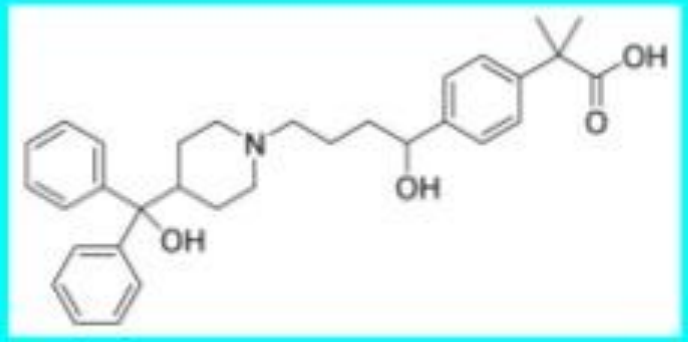
Deslortadine (Clarinex)



- It is the active metabolite of Lortadine
- Even though it is thought to be more effective, there is no concrete evidence to prove this

http://en.wikipedia.org/wiki/Image:Desloratadine.png

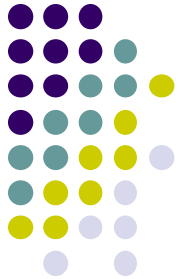
Fexofenadine (Allegra)



- It was developed as an alternative to Terfenadine
- Fexofenadine was proven to be more effective and safe

http://en.wikipedia.org/wiki/Image:Fexofenadine_Structure.png

H_3 – ANTAGONISTS
Pharmacodynamics



Betahistine

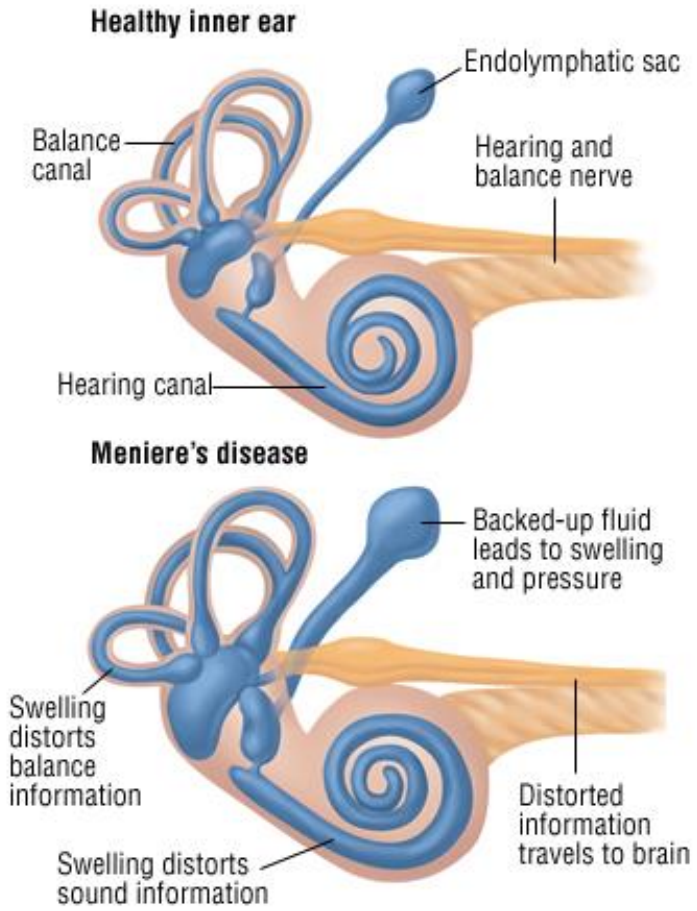
- **antagonist effects at H_3 - receptors** $\rightarrow \Uparrow$ the levels of neurotransmitters released from the nerve endings *(histamine, acetylcholine, norepinephrine, serotonin, & GABA)*

- **direct agonist effect on H_1 - receptors** (located on blood vessels in the inner ear) $\rightarrow$ dilates the blood vessels (within the inner ear) $\rightarrow$ can relieve pressure from excess fluid & act on the smooth muscle

Betahistine

Indications

- it is used to:
  - balance disorders or
  - to alleviate symptoms associated with Ménière's disease (defective absorption in endolymphatic sac,...):
    - vertigo
    - tinnitus
    - the loss of hearing
    - nausea & vomiting, reactions to food
    - mental disorientation
    - mood swings
    - photosensitivity
    - extreme fatigue
    - cold sweath, palpitations...



Antiemetics
Antiserotonic drugs

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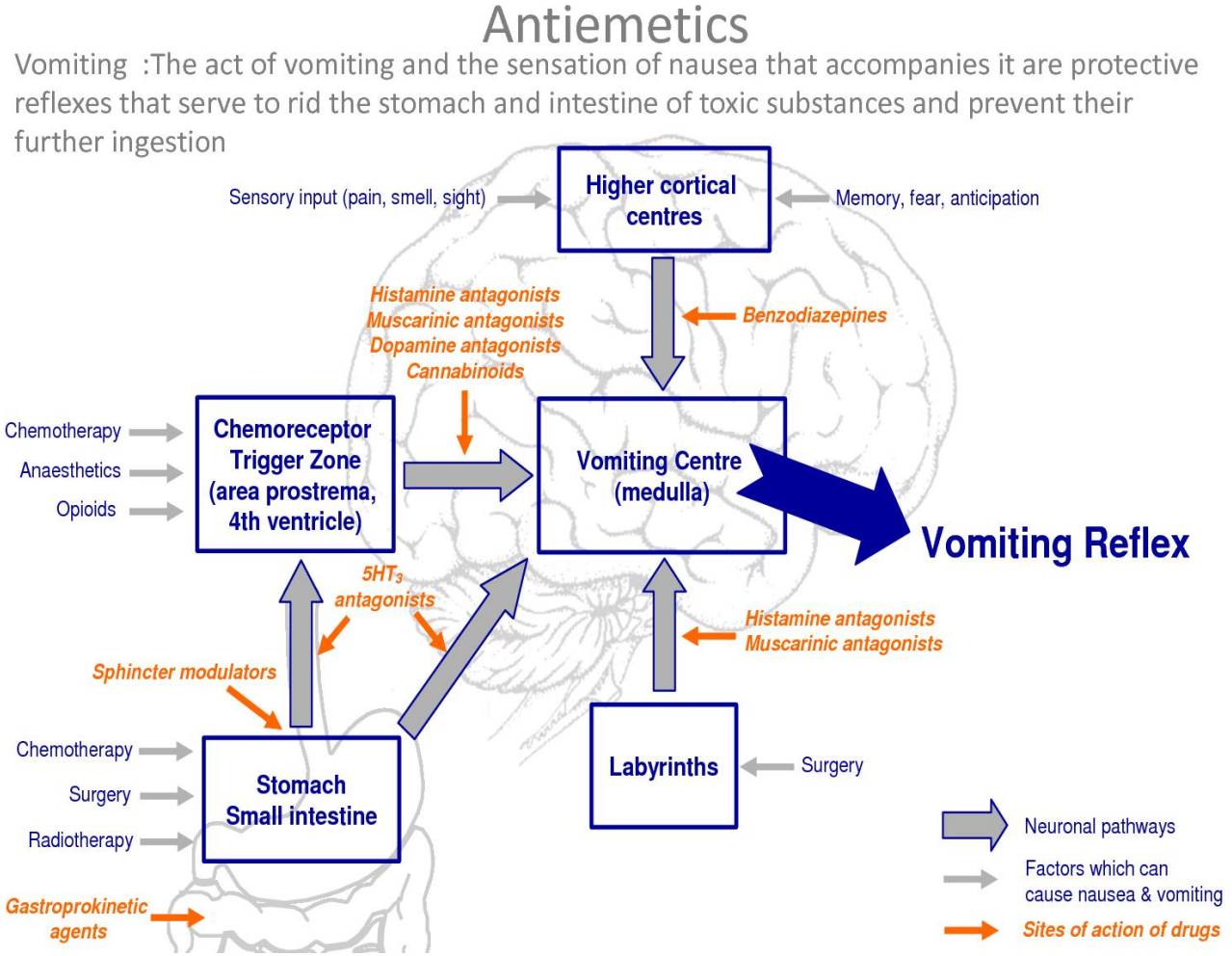
Nausea: Simona D'Auria 2005-2006

Nausea & vomiting

- **nerve ending stimulation –** stomach & duodenum
- **vagus nerve stimulation** in pharynx
- **drugs** (antineoplastics), **endogenous emetogenic substances** (radiation damage), **infections**
- **visceral senzory nerves stimuly** (testes or uterus damage)
- ⇑ **intracranial pressure**
- **emotional & psychological factors, odours**
- **endocrine factors** (pregnancy) ⇨ increased estrogene concentration in chemoreceptive zone
- **migraine**

Neurotransmiters involved in nausea & vomiting

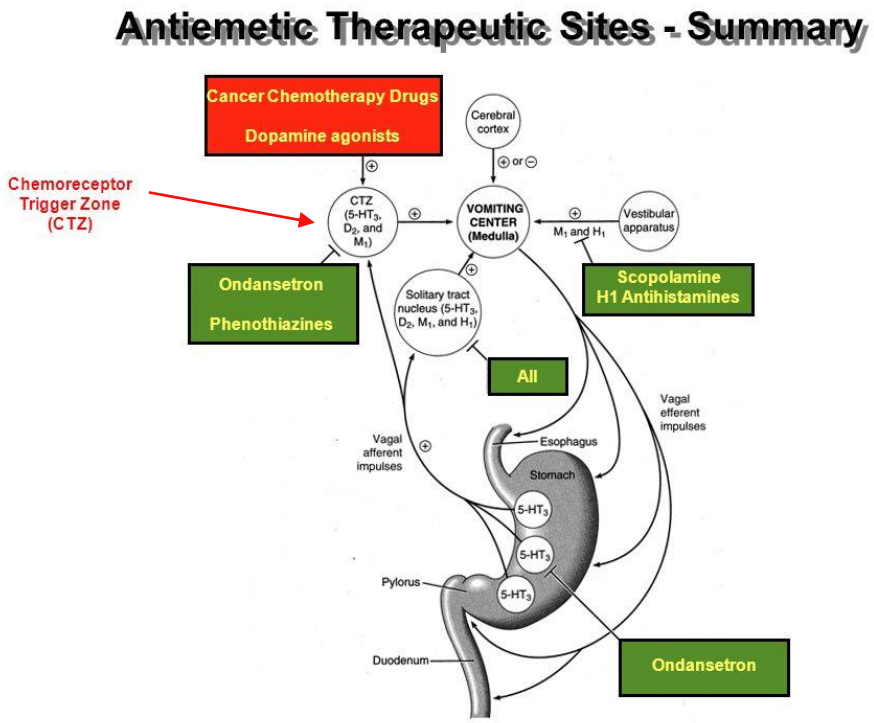
- *acetylcholine*
- *norepinephrine*
- *dopamine*
- *serotonin*
- *histamine*
- *glutamate*
- *GABA*
- *ATP*
- *substance P*
- *endorphines*



Antiemetic drugs
Based on receptor antagonism

H_1	M_1, M_3	D_2	5-HT_3	NK1
promethazine	*scopolamine*	*phenothiazines* *metoclopramide* *domperidone*	*setrons*	*aprepitant* *fosaprepitant*

- drugs which assist to **suppress emesis**
- successful therapy involves **blocking one or more receptors** for neurotransmitters involved in emesis regulation



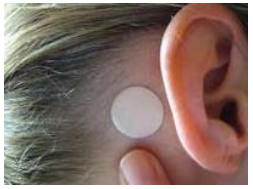
H_1- receptor antagonists as antiemetics

- ***promethazine, diphenhydramine*** **– Meniere´s disease**
- ***diphenhydramine, moxastine*** **– kinetosis**

- prevention
- maximal antiemetic effect **- 4 h after application** (duration 24 h)

M_1 - receptor antagonists as antiemetics

- ***scopolamine***
- **antagonist of M_1-receptors** in **cortex & pons**
- antagonist of H_1-receptors in **hypothalamus & vomiting center**
- suppresses also NA-system (improved adaptation to vestibular stimulation)
- transdermal application (patch)



- kinetosis, postoperative nausea & vomiting (PONV)
- 4 h onset of action (should be placed the night before in patients with ⇑ risk of PONV)

D - receptor antagonists as antiemetics

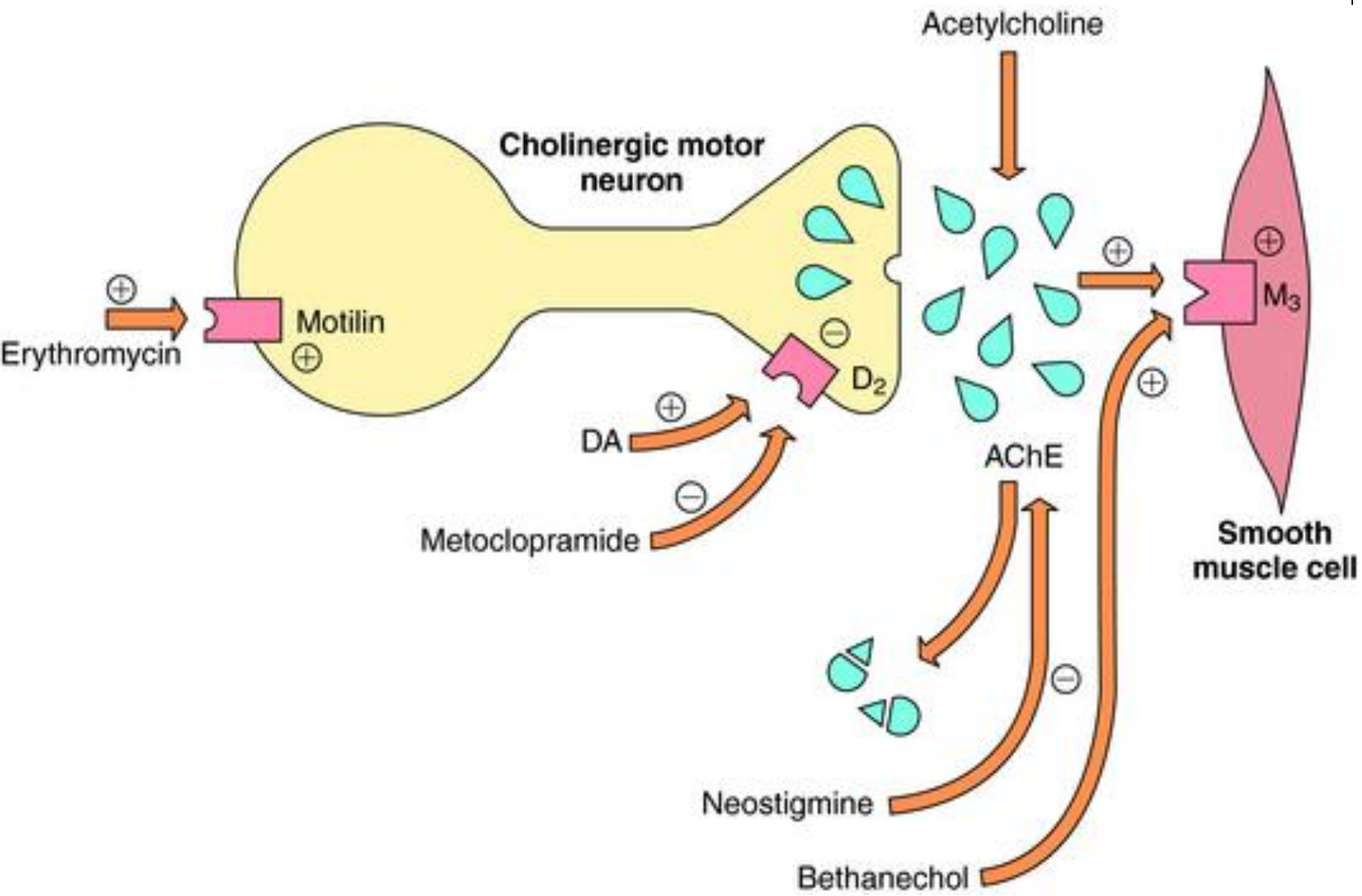
- **phenothiazines** *(chlorpromazine, prochlorperazine)*
  - ***thiethylperazine*** **– only as antiemetic**

(in chemoreceptive zone)

- nausea & vomiting also in:
  - uremia
  - radiation
  - kinetosis
  - acute viral gastroenteritis
  - PONV
  - antineoplastic chemotherapy
  - hyperemesis gravidarum

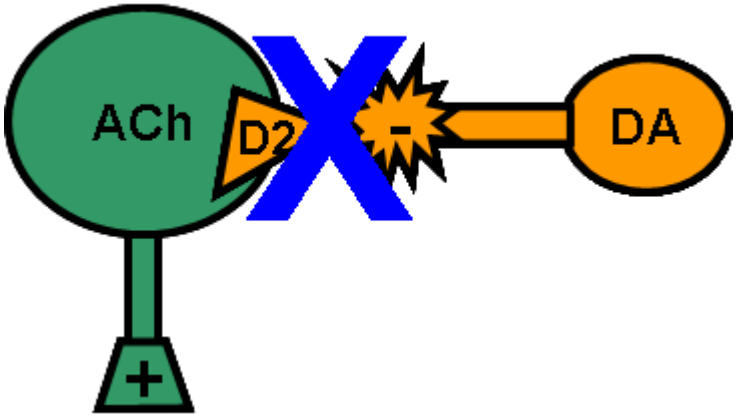
(tiethylperazine)

D - receptor antagonists as antiemetics



Metoclopramide
Mechanism of action

- ⇓ gastric smooth muscle relaxation produced by ***dopamine*** → therefore ⇑ cholinergic response of the GI smooth muscle



- it accelerates intestinal transit & gastric emptying

(by preventing relaxation of gastric body & increasing the phasic activity of antrum)

- this is accompanied by relaxation of the upper small intestine

(resulting in an improved coordination between the body & antrum of the stomach & the upper small intestine)

Metoclopramide
Additional actions

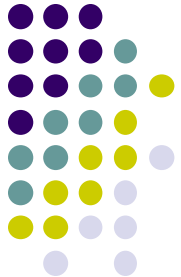
- it also ⇓ reflux into the esophagus

  (by ⇑ the resting pressure of the lower esophageal sphincter)

- dopamine antagonist action raises the threshold of activity in the chemoreceptor trigger zone &

  ⇓ the input from afferent visceral nerves

Metoclopramide
Indications



Adults:

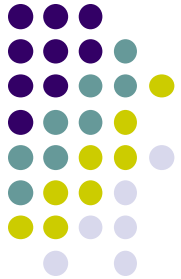
- short time (max. 5 days): **prevention & therapy of nausea & vomitting**

- migraine
- uremia
- radiation
- chemotherapy
- acute viral gastroenteritis

Children:

- therapy of **post-operative nausea & vomitting** (i.v. only)
- prevention of **delayed nausea & vomitting** after **chemotherapy** (oral or i.v.)

Metoclopramide
Application



- **short-time treatment** in recommended doses & intervals to **minimize neurologic, cardiovascular & other side effects**

- i.v. bolus – slow (3 min) –same reasons

- **contraidicated in children up to 1 year – risk of:**
  - **neurologic reactions**
  - **methemoglobinemia**

Metoclopramide
Side effects

- **neurologic:**
  - extrapyramidal symptoms
  - irreversible tardive diskinesia

- **⇑ risk:**
  - high doses
  - long-term therapy
  - children

- **cardiovascular:**
  - hypotension
  - hypertension
  - tachycardia

- **⇑ risk:**
  - i.v.
  - elderly patients
  - arrhythmias

Domperidone
Indications

- in patients with Parkinson´s disease – prevention of vomiting in ***apomorphine*** treatment (unlike *metoclopramide*, it does not cross the BBB)
- gastroparesis (delayed gastric emptying)
- paediatric gastroaesophageal reflux

Do not confound with

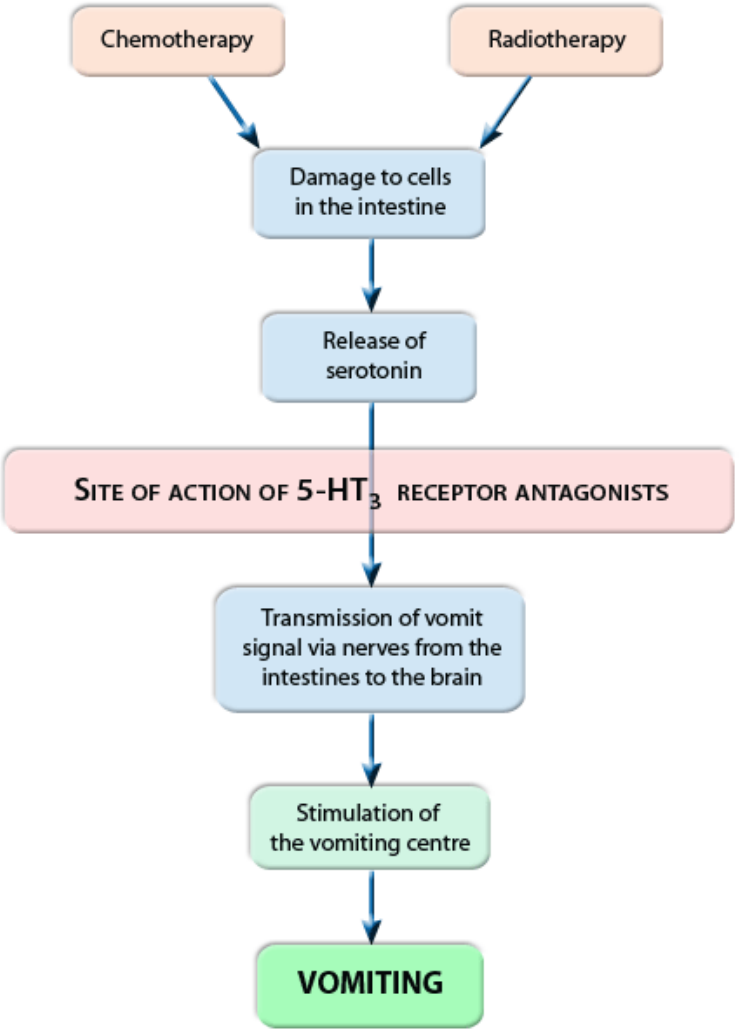
5-HT_3 receptors in vomiting

- *5-HT* is released by the enterochromaffin cells of the small intestine in **response to chemotherapeutic agents**
- 5-HT_3 receptors are present in several critical sites **involved in emesis** (vagal afferents, the solitary tract nucleus, the area postrema)
- the highest concentration of 5-HT_3 receptors in the CNS $\Rightarrow$
  - **solitary tract nucleus** &
  - **chemoreceptor trigger zone**
- 5-HT_3 antagonists may also suppress vomiting & nausea by acting at these sites

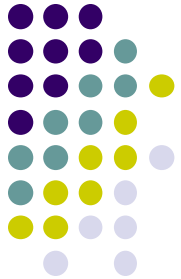
5-HT_3- receptor antagonists

Setrons

- ***ondansetron, granisetron, tropisetron, palonosetron***
- **nausea & vomiting ⇒ chemotherapy**
- they may be **given alone** or **with a:**
  - ***glucocorticoid*** *(dexamethasone)*
  - ***NK_1 receptor antagonist*** *(aprepitant)*
- the most common side effects: constipation or diarrhea, headache, dizziness



Neurokinin type 1 (NK1) receptors antagonist



aprepitant

- blocks substance P from binding to NK 1-receptor
- broader spectrum & activity in delayed emesis
- augments the antiemetic activity of **5-HT$_3$ receptor antagonists** & ***dexamethasone***
- inhibits both acute & delayed **chemotherapy-induced vomiting**
- good safety profile, high cost of the drug

Corticosteroids

Corticosteroids have antiemetic properties

Mechanism of action:

- possibly by suppressing peritumoral inflammation & prostaglandin production

Use:

- to **enhance efficacy of 5-HT_3-receptor antagonists** in the treatment of **chemotherapy-induced vomiting**

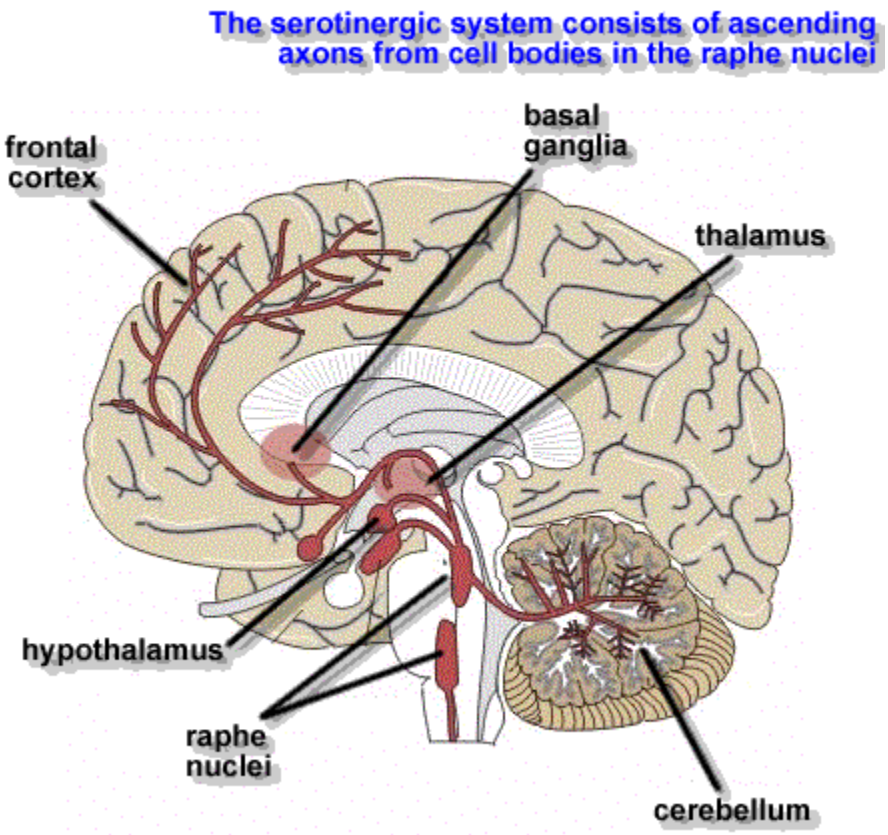
Benzodiazepines

Use:

- *benzodiazepines* such as ***diazepam*** are used prior to the initiation of chemotherapy to reduce anticipatory vomiting or vomiting caused by **anxiety**

SEROTONIN
(5-hydroxytryptamine, 5-HT)

- synthesized from **tryptophan**
- rapidly metabolised
- localization:
  - **GIT**
  - **thrombocytes**
  - **bronchial system**
  - **NS**



History of serotonin
5-HT

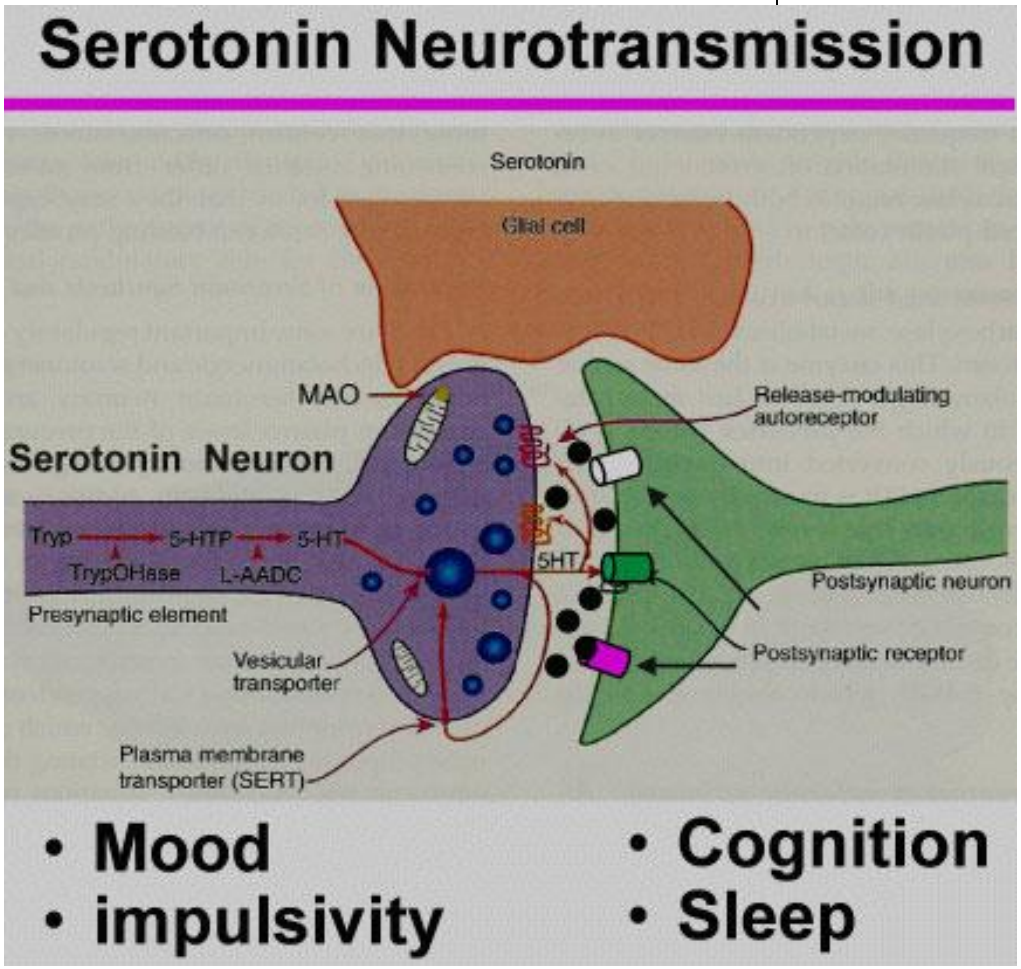
- *Dr. Erspamer* first detected serotonin in the GIT in the 1930's, and called it ***"enteramine„***
- it was isolated in 1948, when *Drs. Page, Green,* & *Rapport* called it ***"serotonin",*** identifying it as an agent that affected blood vessels
- it was identified in the brain in the 1950's
- serotonin system is widespread throughout the body
- it has far more implications than just effects of vasculature
- *"serotonin"* was the name that stuck, pharmacologists prefer ***5-hydroxytryptamine***

Irvine Page, M.D. (left)

Dr. Arta Green, team member, in front of machine used to isolate serotonin

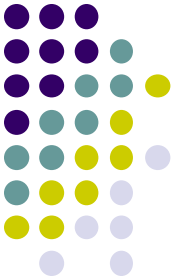
Effects of 5-HT
in CNS

- sleep influence
- thermoregulation
- mood
- aging
- anxiety
- circadian rhythms
- eating disorders
- bowel problems
- migraine
- nausea
- premature ejaculation
- pain
- drug abuse
- vasodilation/vasoconstriction (BP)
- memory



...& the list goes on

Effects of 5-HT
in other tissues

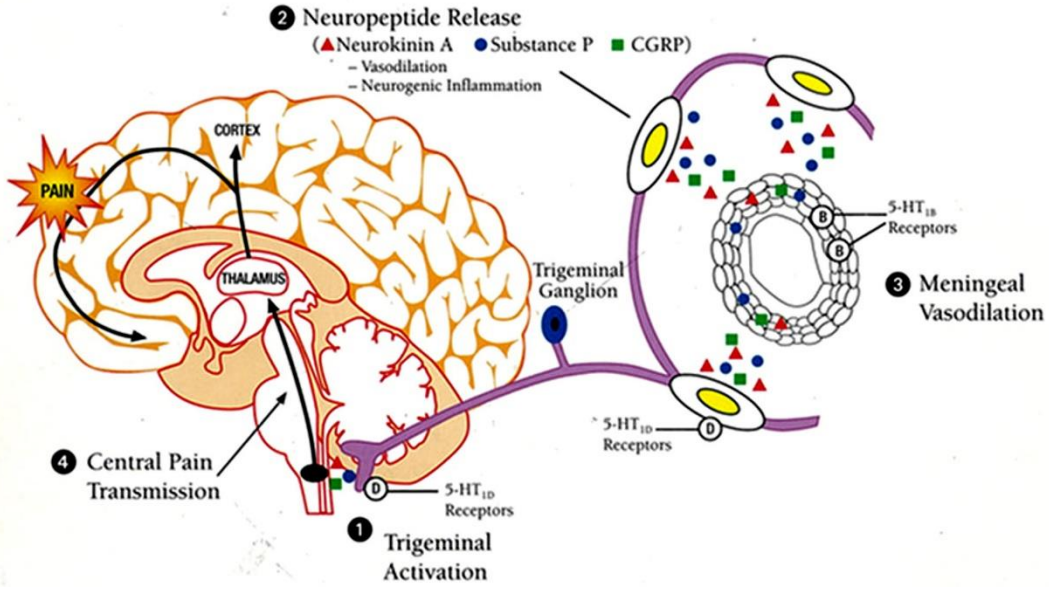


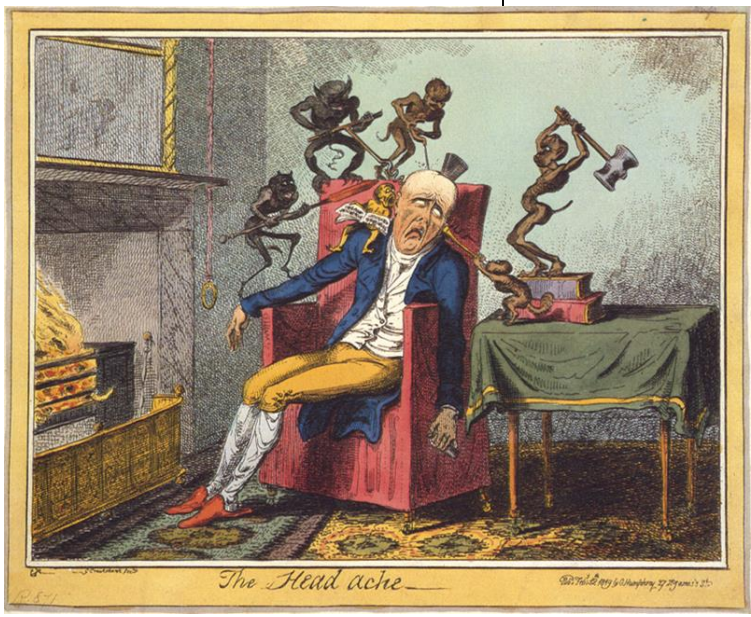
- **CVS**
- **vasoconstriction –** lungs, kidneys

  (direct effect in vessel wall)
- **vasodilation -** skeletal muscle, heart

  (NO-mediated)
- **GIT**
- **smooth muscle tone -** motility stimulation
- **Bronchi**
- **smooth muscle tone -** constriction

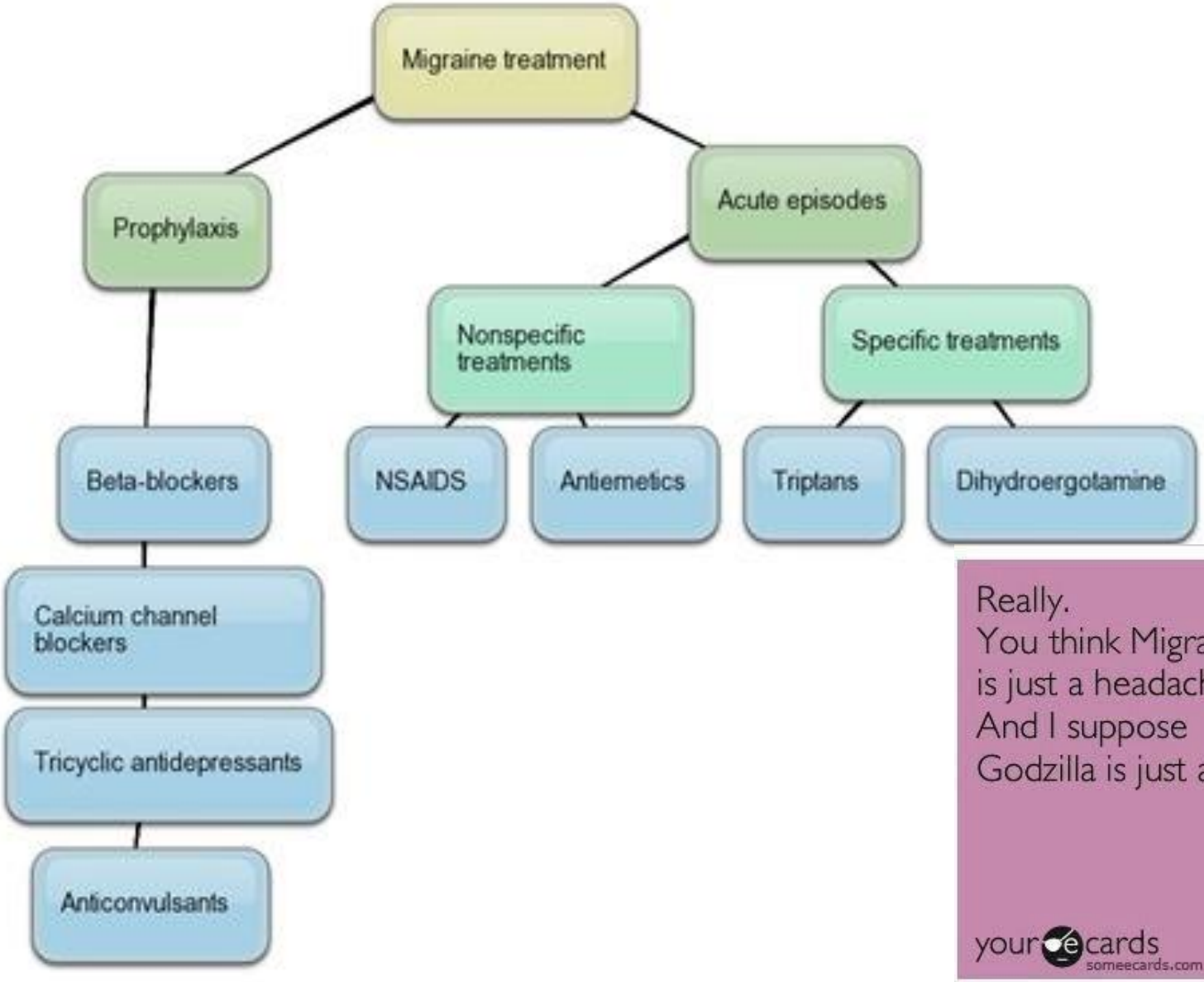
Migraine
Mechanisms & symptoms



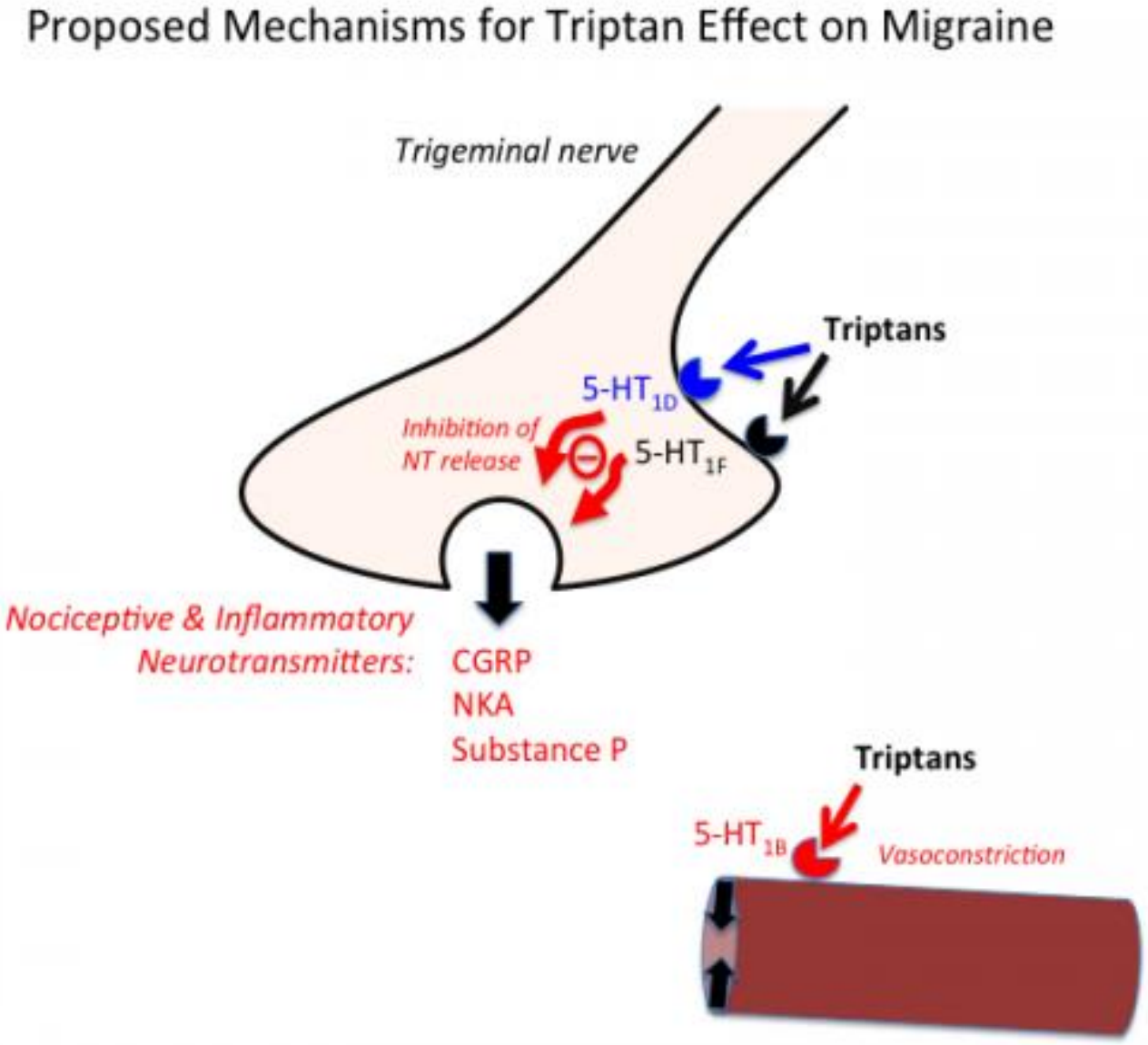


- inherited, episodic disorder involving **sensory sensitivity**
- patients complain of discomfort from normal lights & the unpleasantness of routine sounds

Migraine treatment



5-HT AGONISTS



Triptans

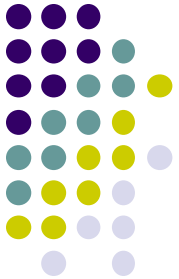
- ***sumatriptan***

- **5-HT_{1D} receptor agonist**
- **migraine therapy**
- ergotamine replacement

- side effects

Type	Common
CVS	**palpitations, syncope, changes in BP**
ENT	sinusitis, tinnitus; allergic rhinitis; upper respiratory inflammation; ENT hemorrhage
Neurological	phonophobia & photophobia
Endocrine	thirst
Muscular	myalgia
Urogenital	dysmenorrhea, ⇑ urination, intermenstrual bleeding
Eye	mydriasis, blindness & low vision, visual disturbances, eye edema & swelling, eye irritation & itching, accommodation disorders, external ocular muscle disorders

5-HT ANTAGONISTS



- ***cyproheptadine***
- 5-HT-, H-, M- antagonist
- allergy therapy (insects, food, drugs)
- **migraine prophylaxis**
- ⇓ GIT motility

- ***ketanserine***
- ⇓ in thrombocyte aggregation
- α-receptor inhibition (BP ⇓)
- amelioration of rheology – **ulcus cruris & decubitus therapy**

5-HT ANTAGONISTS

- ***ondansetron, granisetron, tropisetron***

  (antagonists of 5-HT_3-receptor subtype)

- **important antiemetics**
  (chemotherapy, radiotherapy)

- ***pizotifen, pipetiaden***

- **migraine prophylaxis**
- sedation
- ⇑ appetite

Vomiting girl

OKSENDAV TÜDRUK
1997