PharmPill team

1429 -1428
2008-2007

اللهم طهر قلبي من النفاق وعملي من الرياء ولساني من الكذب وعيني من الخيانة فأنت تعلم خائنة الأعين وما تخفي الصدور

اللهم اهدني لأحسن الأعمال والأخلاق ..

اخواني الطلاب .. اخواتي الطالبات دفعة 426

نحن فارم بل تيم قمنا بجمع مذكرات البنات مع الأولاد في هذه المذكرة

مع إضافة نوتات هذا العام

نسأل الله أن تنفعنا واياكم ... وتعود بالنفع لغيرنا

ان اصبنا فمن الله وان اخطانا فمنا ومن الشيطان

"اوجة شكر خالص الى الاخت دعاء البلوي دفعة 424 "

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AUTOCOIDS
-LOCAL HORMONES-

- Endogenous substance with biological activity.
- Local hormones
- Not stored nor released by glands
- Formed locally at the site of action
- Not circulated in blood

Classification:

1. Biological active amines. e.g: Histamine, Serotonin
2. Lipid derived autocoids. e.g: Eicosanoids (PGs: Thromboxane , Leukotriens) & PAF
3. Polypeptides. e.g: Kinins
4. Endothelium derived autocoids. e.g: EDRF

Histamine:

- mediators of allergic and inflammatory reactions; involved in Gastric Acid Secretions , and as Neurotransmitter & Neuromodulator.

Synthesis :

L-Histidine —Histidin decarboxylase→ Histamine

Occurrence:

- Tissues exposed external environment (GIT, Lung, Skin, Brain)
- Stored in: mast cells and basophiles. [bound with heparin]
- Enterochromaffin cell (ECL), cells of the fundus of the stomach

Metabolism:

- Monoamine oxidase (MAO).
- Diamine oxidase or histaminase.
- Imidazole N-methyl transferase.

Histamine should be released from the cell to work

Release:

A. Immunological release:

✓ Mast cells sensitized by IgE attached to their surface membrane.

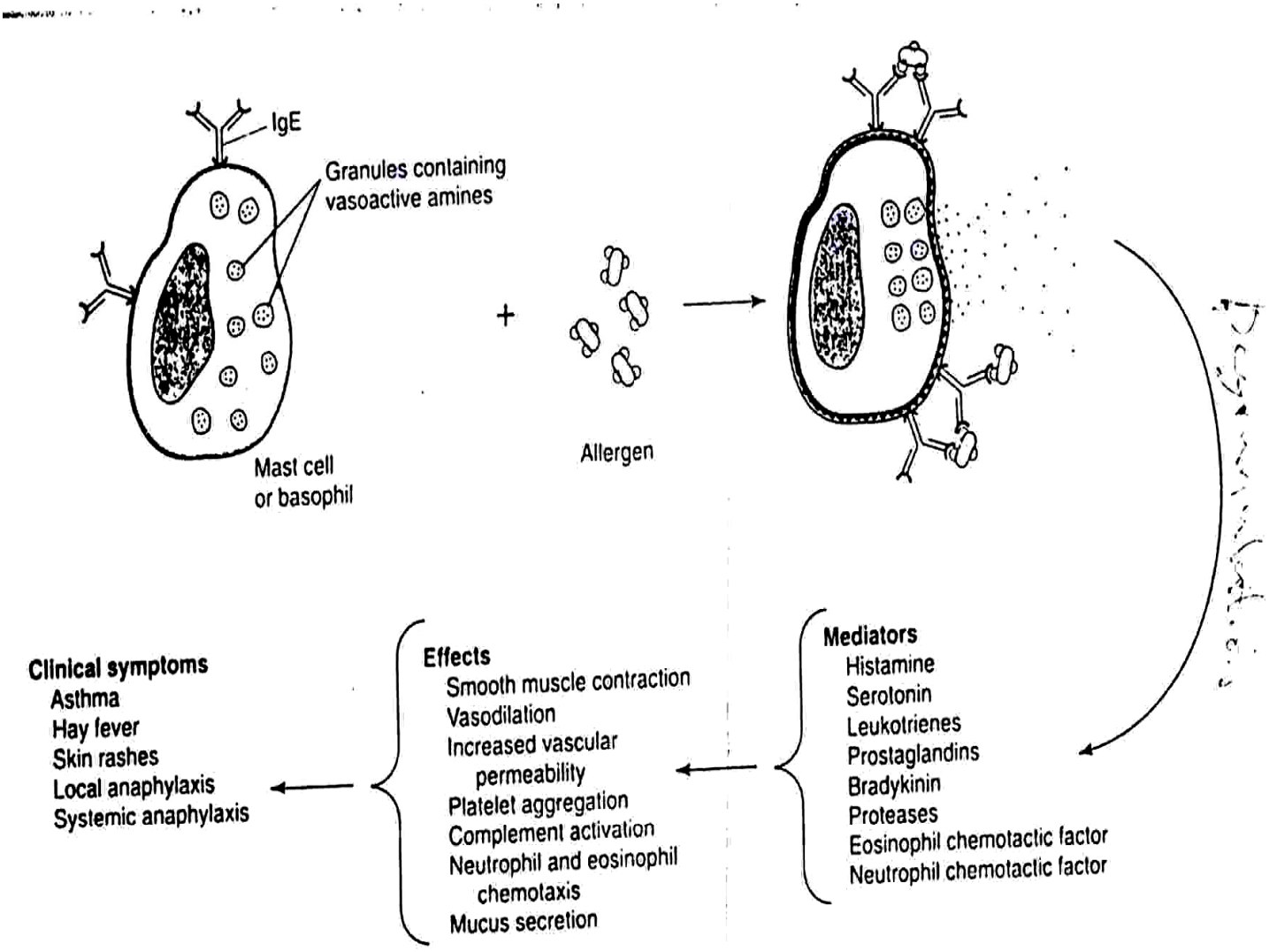


Figure 56–5. Mechanism of type I hypersensitivity. Initial exposure to allergen leads to production of IgE by plasma cells differentiated from allergen-specific B cells (not shown). The secreted IgE binds cognate IgE-specific receptors on blood basophils and tissue mast cells. Re-exposure to allergen leads to cross-linking of membrane-bound IgE. This union causes degranulation of cytoplasmic granules and release of mediators that induce vasodilation, smooth muscle contraction, and increased vascular permeability. These effects lead to the clinical symptoms characteristic of type I hypersensitivity.

B. Non Immunological release (drug induced)

- Morphine – Apomorphine – Curare.
- Chemical and physical injury of mast cells.

So, Tissue injury ➔ Mast cell ➔ degranulation

(Chemical and Physical Agents that Release Histamine)

☺ما وضع تحته خط هو ما ركز عليه الدكتور ،،

Chemical Agents	Physical Agents
Antihistamine (H1–type), Chymotrypsin, Compound 48/80, Detergents, Dextran, DMSO (dimethyl- sulfoxide), Morphine and other Opiods, Pentamidine , Polymyxin B, Polyvinyl pyrrolidine, Propamidine, eserpine, Surface active agents, Stilbamidine, Toxins, **Tubocurarine**, **venoms**, X-ray contrast media: Bradykinin, SP	Mechanical trauma, Radiant energy, Thermal energy

Mechanism of action:

H_1 receptor:

- **There receptor are coupled to phospholipase C (type II receptor-G protein receptoer) and increase intracellular Ca (so contraction of smooth muscle).**
- **Smooth muscle (contraction of bronchi, GIT (increase motility), uterus except BV → VD will occur) and nerve ending [itching due to stimulation of H1 in nerve ending]**

H_2 receptor:

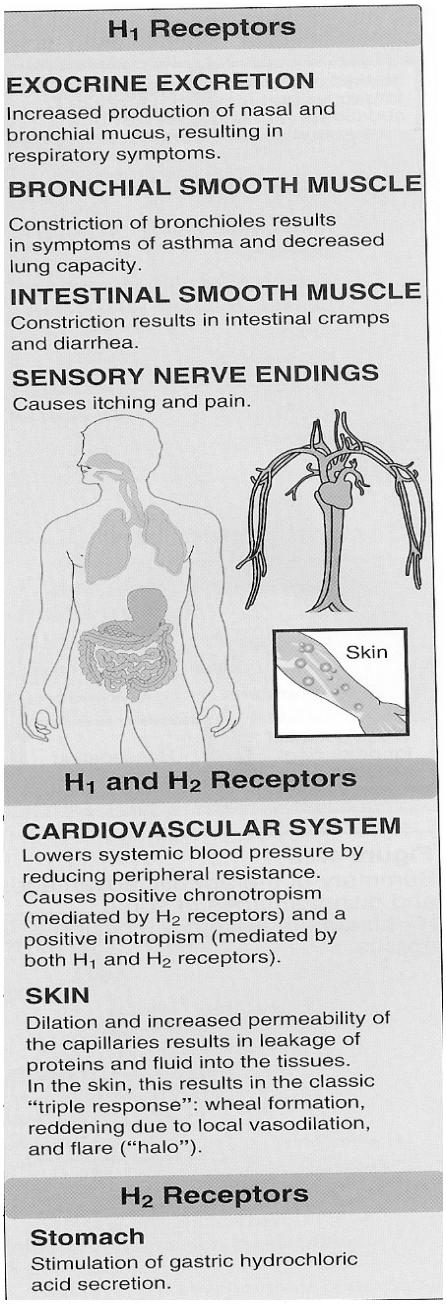
- **These receptor stimulate adenylel cyclase enzyme and increase intracellular cAMP (cAMP is the 2nd messenger).**
- **Heart (+ve inotropic [contraction] & chronotropic effects [H.R])**
- **Stomach (↑ acid secretion)**

H_3 receptor:

- **Mainly at presynaptic site (MCQ)(IMP)**
- **in CNS & control histamine release and other neurotransmitter.[if we block H3 histamine wont released]**
- **Are probably inhibitory to adenylel cyclase enzyme.[↓cAMP → ↓Ca]**
- **They are G-protein coupled receptors**

H_4 receptor:

- **On the blood cell mainly basophils and neutrophils**



Receptor Subtype	Distribution	Postreceptor Mechanism
H_1	Smooth muscle, endothelium, brain	↑ IP_3, DAG (G_q)
H_2	Gastric mucosa, cardiac muscle, mast cells, brain	↑ cAMP (G_s)
H_3	Presynaptic: brain, myenteric plexus, other neurons	↓ cAMP, Ca_i^{2+} (G_i)
H_4	Eosinophils, neutrophils, CD4 T cells	↓ cAMP, Ca_i^{2+} (G_i)

هذا الجدول هام جدا يشرح لك بشكل عام أرجو التركيز عليه(MCQ)

Receptor sub type	Distribution	Post receptor Mechanism	Partially Selecetive Agonists	Partially selective Antagonists
H1	Smooth muscle , endothelium , brain	↑IP3 , DAG	2-(m-fluorophenyl)-histamine	Mepyramine , triprolidine
H2	Gastric mucosa , Cardiac muscle , mast cells , brain.	↑cAMP	Dimaprit, impromidine , amthamine	Ranitidine , tiotidine
H3	Presynaptic: brain, myentric plexus, other neurons	G protein – coupled (decrease Ca+2)	R- α-Methylhistamine, imetit , immepip	Thioperamide, iodophenpropit ,. Clobenpropit

Pharmacological action:

- Contraction of **smooth muscle** (bronchi, uterus [induction of abortion] and GIT)not BV.

- **CVS:**
  - ✓ vasodilation of BV. [histamine cause Nitric oxide release which cuase VD]
  - ✓ increased capillary permeability (edema).
  - ✓ Tachycardia = cardiac stimulation (H_2)➔ ↓ systolic and diastolic blood pressure (Flushing and headache)
  - ✓ Dilation of cerebral vessels (headache ; i.e migrane histamine cephalgia)

- **Exocrine glands**; stimulate gastric secretion.

- Stimulation of sensory **nerve ending** (pain Itching , urticaria).

- **Skin**:
  - * Redness (vasodilation of capillaries).
  - * Wheal (edema).
  - * Flare (stimulation of sensory nerve endings).

- Release of CA (catecholamine) form adrenal medulla.

Toxicity and contraindications:

- How does it occur?

Exogenous or endogenous

- Manifestations:

Same as pharmacological action (revise it) ☺

- Treatment:

✓ Physiologically we give epinepherine .
✓ Or we give drug that are antagonist of histamine .
✓ Or we give corticosteroid .

Histamine agonist:

- Used For diagnosis of phaeochromocytoma. (MCQ)

Phaeochromocytoma :

It is a tumor of adrenal medulla causes increased secretion of catecholamine , so we expected the patient to have high BP.

- Used to test pulmonary function (bronchial hyperactivity)

We give the normal person histamine to diagnose hypotension

Histamine antagonism:

❖ Mast cell stabilizers e.g: cromoglycate (antiosmotic)

Inhibit the release of the histamine by inhibiting the degranulation . this used to treat people with asthma.

❖ Physiological antagonism by adrenaline.
❖ Receptors antagonism:
  ✓ H_1-receptor blocker (antihistamines, allergy)
  ✓ H_2- receptor blocker (peptic ulcer)

H_1-blocker (Antihistaminic)

Mechanism of action:

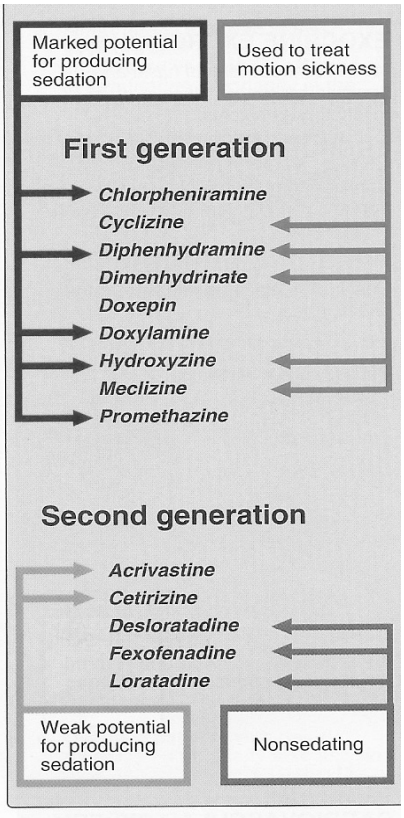
They are competitive antagonist for H1 receptor.

Pharmacological action:

- H_1 receptor blockade: they block histamine effect on smooth muscle and blood vessels.
- Atropine-like action: dry mouth ,urinary retention, tachycardia (side effect)
- α –blocking activity (postural hypotension)
- Block serotonin receptors as Cyproheptadine.

On CNS: -MCQ-

- Sedation and hypotonic effect : (MCQ)(IMP)
  - First generation produce sedation and hypnosis.
  - Second generation have little or no sedative action.
- Antimimetic action. (motion sickness) → so it prevents vomiting.
- Antiparkinsonian effects.
- Local anesthetic effect.
- Antiallergic and inflammatory action.

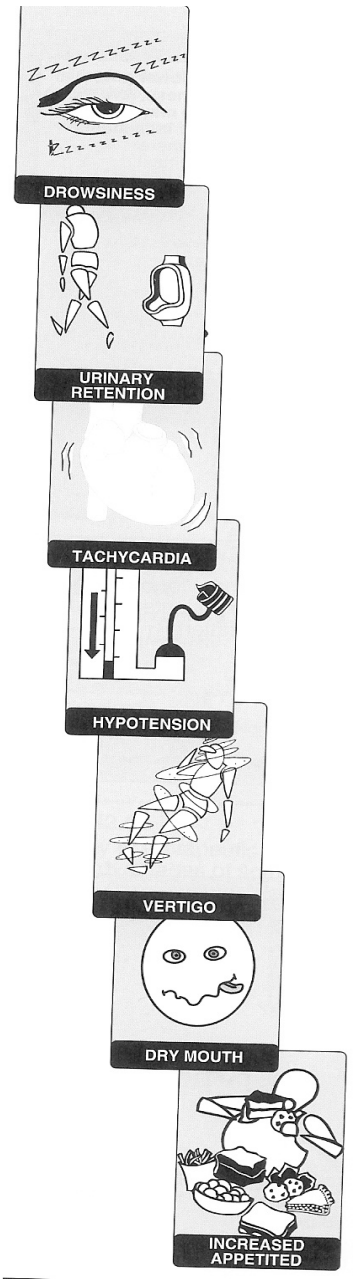


Histamine can be antagonized by the followings:

a) Physiological Antagonism by epinephrine

b) Mast cell release inhibitors (Sodium Chromoglycate)

C) Histamine Receptors Antagonists (The Most Important Clin. Approach)



First generation antihistaminic: -MCQ-

Classifications:

- Ethanolamine : diphenhydramine, doxylamine (antiemetic, sedative used in treatment of insomnia)
- Piprazine : meclizine, cyclizine (antiemetic)
  Are less sedative (use as antimotion sickness)
- Phenothiazine : promethazine (antiemetic, sedative)
- Alkylamine : chlorpheniramine (1st choice for allergy)
- Miscellaneous : cyproheptadine.

Pharmacokinetics:

- Well absorbed orally.
- Duration 3-6 hours.
- Widely distributed.
- Penetrate BBB. (that why they are sedative)
- Metabolized in the liver.

Note : ↓ Bronchial and nasal secretion

- **And use as Local anesthetics**

Side effects: ⟶

- Sedation and drowsiness.
- Antimuscarinic effects.
- α –blocking adverse effects. (atropine like action → dry mouth)
- Excitation in high doses in children.

ما نضع عليه خط هو ما ركز عليه الدكتور أثناء المحاضرة ،،،،،

FIRST – GENERATION ANTIHISTAMINES		
DRUGS	**ANTICHOL ACTIVITY**	**COMMENTS**
ETHANOLAMINES Dimenhydrinate(salt of dihphenhydramine (**Dramamine**R) Diphenhydramine (**Benadryl**R, dramamine ,etc	+++	Marked sedation , anti-motion sickness activity
Doxylamine (Decapyrin)	Nd	Moderate sedation, component of OTC “sleep aids”
PIPERAZINE derivatives Hydroxyzine (**Atarax**R etc)	Nd	Marked sedation
Cyclizine(Marzine) Meclizine (Bonine etc)	-	Slight sedation ,anti motion sickness activity
ALKYLAMINE Brompheniramine (Dimetane) Chlorpheniramine (Chlortrimeton etc)	+	Slight sedation Slight sedation, common component of OTC “cold “medication
PHENOTHIAZINE derivatives Promethazine (PhenergaanR ,etc)ركز عليه	+++	Marked sedation ,antiemetic
Miscellaneous Cyproheptadine (PeriactinR etc Triprolidine (ActivedR)	+	Moderate sedation, also has antiserotonin activity Marked sedation

Second generation antihistaminic:

- Astemizole (cardiac arrhythmia)
- Terfeinadine.
- Loratidine.
- Cetrizine.
- Acrivastine.
- Fexofenadine.

* Note : Drugs that inhibit (Cyto.P450), will increase the cardiac toxicity of the piperidines derivatives.

So, Astemizole (cardiac arrhythmia), Terfeinadine these two drugs have cardiac toxicity especially with cytochrome p450.

Advantages:

- Can not cross BBB.
- No sedation. (MCQ)
- Less atropine like action.
- Longer duration of action (IMP), so I can take them once a day
- More expensive.

Uses:

* Allergic reaction:
  - Rhinitis, high fever, mild asthma, conjunctivitis, urticaria.
  - Chlorpheniramine 1st generation.
  -2nd generation (mostly used)

* Anti-emetic in motion sickness:
  - Dimenhydrinate : Cyclizine , Meclizine

  - Promethazine : cinnarizine .

* Nausea & Vomiting of Pregnancy (Doxylamine (BendectinR) with pyridoxine

◙ **Note : Antihistamines are not used for Asthma (MCQ)**
- cuz it is not very effective in asthma , instead we use to work on B2 Which has the most effect in asthma treatment .

Side effect :

- Anticholinergic actions
- Sedation and psychomotor decrease performance and incoordination
- Drug interaction
  - MAO inhibitors
  - CNS depressant
  - Liver microsomal Enzyme inhibitors increase the arrythmogenic action of piperridine second Gen (Astemazole and Terfenadine).
  - . Sedative actions of antihistamine increase if given with alcohol or any sedative drugs

كل أسماء هذه الادوية ركز عليها بالمحاضرة ،،(طبعا بجانب كل دواء اسمه التجاري لم يركز عليه الدكتور)

Drugs	Anti-chol. activity	Comments
PIPERIDINES derivates Astemizole (Hismanal)	_	Slow onset of action (withdrawn) (Arrhythmia)
Fexofenadine (Allegra)	_	Lower risk of arrhythmia
Terfenadine (Seldane)	_	Prompt onset of action (arrhythmia)
Miscellaneous Loratidine(**Claritin**^{R}) Cetrizine (Zyretic^{R})	_ _	Longer action (no arrhythmia)

H2- antagonists:

Cimetidine – Famotidine

Used for:

- Peptic ulcer (it inhibits gastric secretion)
- Cytochrome p450 inhibitor (only cimetidine)

هذا خلاصة ما درست سابقا ،، (revise it)

Table 16–2. Some H_1 antihistaminic drugs in past or current clinical use.

Drugs	Usual Adult Dose	Anti-cholinergic Activity	Comments
FIRST-GENERATION ANTIHISTAMINES			
Ethanolamines			
Carbinoxamine (Clistin)	4–8 mg	+++	Slight to moderate sedation
Dimenhydrinate (salt of diphenhydramine) (Dramamine)	50 mg	+++	Marked sedation; anti-motion sickness activity
Diphenhydramine (Benadryl, etc)	25–50 mg	+++	Marked sedation; anti-motion sickness activity
Doxylamine	1.25–25 mg	nd	Marked sedation; now available only in OTC "sleep aids"
Ethylaminediamines			
Pyrilamine (Neo-Antergan)	25–50 mg	+	Moderate sedation; component of OTC "sleep aids"
Tripelennamine (PBZ, etc)	25–50 mg	+	Moderate sedation
Piperazine derivatives			
Hydroxyzine (Atarax, etc)	15–100 mg	nd	Marked sedation
Cyclizine (Marezine)	25–50 mg	–	Slight sedation; anti-motion sickness activity
Meclizine (Bonine, etc)	25–50 mg	–	Slight sedation; anti-motion sickness activity
Alkylamines			
Brompheniramine (Dimetane, etc)	4–8 mg	+	Slight sedation
Chlorpheniramine (Chlor-Trimeton, etc)	4–8 mg	+	Slight sedation; common component of OTC "cold" medication
Phenothiazine derivatives			
Promethazine (Phenergan, etc)	10–25 mg	+++	Marked sedation; antiemetic
Miscellaneous			
Cyproheptadine (Periactin, etc)	4 mg	+	Moderate sedation; also has antiserotonin activity
SECOND-GENERATION ANTIHISTAMINES			
Piperidines			
Fexofenadine (Allegra)	60 mg	–	Lower risk of arrhythmia
Miscellaneous			
Loratadine (Claritin)	10 mg	–	Longer action
Cetirizine (Zyrtec)	5–10 mg	–	

Nd, no data found.

Serotonin (5-hydroxytryptamine, 5HT)

Synthesis:

- L-tryptophan by hydroxylation to give 5-hydroxytryptophane → decarboxylared again to 5-HT.

Present in:

- GIT (enterochromaffin cells) (90%)
- Platelets (stored but not formed there)
- Brain (raphe nuclei of brain stem)
- In pineal gland, it acts as precursor to melatonin.

Metabolism:

- MAO into 5-hydroxyindole acetic acid (5-HIAA) which is excreted in urine.
- Urinary 5-HIAA is increased by carcinoid tumor. (used in diagnosis in carcinoid tumor, which is cancer in cells that produce serotonin)

Carcinoid tumor :

Malignant tumor in enterchromaffin cells of GIT

Features:

- Bronchospasm
- GIT : diarrhea, colics
- Flushing of the face

Diagnosis:

- High plasma level of serotonin
- High 5 HIAA in urine

Treatment :

- Cyprohepatedine,
- methysergide

***Mechanism of action:**

-Interacts with 12 receptor subtypes

◙ **Note : Why is 5-HT3 receptor differs from other 5-HT receptors?** •
Cuz 5-HT 3 is linked to membrane ion-channels (NOT G-protein)

- **$5HT_1$ receptors**:
  inhibit adenylate cyclase ↓ cAMP (in CNS)
  → involved in the behavior anxiety depression.

- **$5HT_2$ receptors**:
  are linked to phospholipase C raising IP3 & DAG level. (smooth muscles, platelets, CNS) linked with hypertension.

- **$5HT_3$ receptors**:
  are directly linked to membrane ion-channels. (enteric N.S peripherally, CNS sensory nerves) → induction of vomiting.

- **$5HT_4$ receptors** :
  ↑ cAMP (enteric N.S , CNS) → motility of GIT (Ca^{++} – cAMP) used as prokinetics drug.

- **$5HT_{6,7,8}$** unknown (CNS).

Table 16–4. Serotonin receptor subtypes.

Receptor Subtype	Distribution	Postreceptor Mechanism	Partially Selective Agonists	Partially Selective Antagonists
5-HT_{1A}	Raphe nuclei, hippocampus	↓ cAMP, K^+ channels	8-OH-DPAT	WAY100635
5-HT_{1B}	Substantia nigra, globus pallidus, basal ganglia	↓ cAMP	CP 93129	
5-$HT_{1Da,b}$	Brain	↓ cAMP	Sumatriptan	
5-HT_{1E}	Cortex, putamen	↓ cAMP		
5-HT_{1F}	Cortex, hippocampus	↓ cAMP		
5-HT_{2A}	Platelets, smooth muscle, cerebral cortex	↑ IP_3	α-Methyl-5-HT	Ketanserin
5-HT_{2B}	Stomach fundus	↑ IP_3	α-Methyl-5-HT	SB204741
5-HT_{2C}	Choroid, hippocampus, substantia nigra	↑ IP_3	α-Methyl-5-HT	Mesulergine
5-HT_3	Area postrema, sensory and enteric nerves	Receptor is a Na^+-K^+ ion channel	2-Methyl-5-HT, *m*-chlorophenyl-biguanide	Tropisetron, ondansetron, granisetron
5-HT_4	CNS and myenteric neurons, smooth muscle	↑ cAMP	5-Methoxytryptamine, renzapride, metoclopramide	See Bockaert, 1992, reference.
5-$HT_{5A,B}$	Brain	Unknown		
5-$HT_{6,7}$	Brain	↑ cAMP		Clozapine (5-HT_7)

Key: 8-OH-DPAT = 8-Hydroxy-2-(di-*n*-propylamine)tetralin
CP93129 = 5-Hydroxy-3(4-1,2,5,6-tetrahydropyridyl)-4-azaindole
SB204741 = *N*-(1-methyl-5-indolyl)-*N'*-(3-methyl-5-isothiazolyl)urea
WAY100635 = *N-tert*-butyl 3-4-(2-methoxyphenyl)piperazin-1-yl-2-phenylpropanamide

Pharmacological actions:

Serotonin → increase in tone

* **CVS:**

- Vasoconstriction of blood vessels (renal , pulmonary , & cerebral vessels ($5HT_2$)) except those in the skeletal muscle and heart , it causes dilatation.
- Weak inotropic , chronotropic effects blunted by effects on the baroreceptors, chemoreceptors and vagal efferents that result in bradycardia (reflex bradycardia).
- Platelets aggregation mainly by receptor 2
- Hypotension – hypertension – hypotension

Hypotension – due to activation of chemoreceptor nerve ending → ↓ COP → reflex tachycardia
Hypertension – direct vasoconstriction
Hypotension – due to skeletal vasodilatation

- In other words , **:** 5- HT can give rise to triple action:
  - Decrease BP due to chemoreceptor response .
  - then increase BP due to Vasoconstriction (5-HT2),
  - then decrease B.P due to skeletal muscle V.D

* **Smooth muscles :**

- Contraction of smooth muscles (GIT , bronchial tree , & uterus)
- (via 5- HT_4 stimulated the release of ACH). (increase stomach epmptying) .

* **Respiration :**

- Weak Bronchoconstriction. (MCQ)
- Hyperventilation
- Stimulate sensory nerve endings (pain & itching sensation).

***CNS:**

- Control mood , Temp , sleep
- Inhibit appetite (anorexigenic effect), $5HT_1$
- Anxiety ,
- Induction of vomiting 5HT3.
- Disease migraine , carcinoid syndrome , anxiety , $5HT_3$
- Schizophrenia

Clinical Uses of Serotonergic Drugs:

- **Note1**: Unlike NE or DA, serotonin its self has no clinical uses, however, it agonists and antagonists have very important therapeutic applications.
- **Note 2**: Unlike histamine where only its antagonists are used, serotonin agonists and antagonists can be used.

Serotonin Agonists : -IMP.MCQ-(الاسم و الاستخدام)

Sumatriptan:

- 5HT $_{1d}$ agonist cranial vessels vasoconstriction.
- It has no CNS effects.
- Treatment migraine attacks (caused by vasodilatation) and is prophylactic.

Buspirone and Ipsapirone:

- partial 5HT$_{1A}$ agonists.
- Anxiolytics in anxiety disorder. Inhibition of anxiety, it is selective because of its short action

Dexfenfluramine: (Filifil)

- Acts by stim. Release and inhib. Reuptake of serotonin.
- As appetite suppressant (anorexigenic action)
- Stimulate 5HT release

Tegaserod :

- Partial 5HT$_4$ agonist.
- Use for IBS (irritable bowel syndrome) with constipation.

Metoclopromide:

* 5-HT$_4$ agonist as prokinetic agent (for Rx of gastroesophagial reflex).
* Use also via 5-HT3 antagonistic action

****5HT reuptake inhibitors :**

Fluxetine, Paoxetine → they are useful antidepressants

Serotonin antagonists: -IMP.MCQ-(الاسم و الاستخدام)

1. block of synthesis : parachlorophynlanin (PCPA)
2. block storage : resripine
3. block receptor

Cyproheptadine (periactin):

- $5HT_2$, histamine H_1 and muscarinic antagonists.
- used for **Rx carcinoid tumor** (significant increases in serotonin)
- **increase appetite**

Pizotifen (mosegor):

- It is similar Cyproheptadine
- appetite stimulation.

Methysergide(deseril):

- an ergot alkaloid acts as 5-HT1,2 antagonist used .
- Migraine prophylaxis, carcinoid tumor .

Ondansetron & Granisetron:

- $5HT_3$ antagonists.
- Block vomiting center and CTZ.(chemo-receptor trigor zone)
- Antiemetic very potent.(but not used in motion sickness)

Metochorpramide:

- Blocks $5HT_3$ receptor (Antiemetic action)
- Block dopamine receptor (Antiemetic action)
- Stimulate cholinergic system (prokinetic) [increase motility in GIT to push the food down with people having reflex esophagitis also it decreases acid secretion]

Ketanserin:

- Block $5HT_{1,2}$, H_1, α_1 receptor.
- (used as antihypertensive agent)

Lipid derived autocoids :

1- PAF (platelet activating factor)

2- Eicosanoids
- Leukotrienes
- Prostanoids (prostaglandins)

Platelet aggregation factors (PAF):

- Produced by platelets, macrophage and eosinophils.
- Platelet aggregation.
- Mediator of inflammation.
- Vasodilation.
- Increase capillary permeability (oedema)
- Chemotactic for leucocytes.
- Smooth muscle contraction (Bronchoconstriction)
- PAF antagonist : Alprazolam , Trizolam .

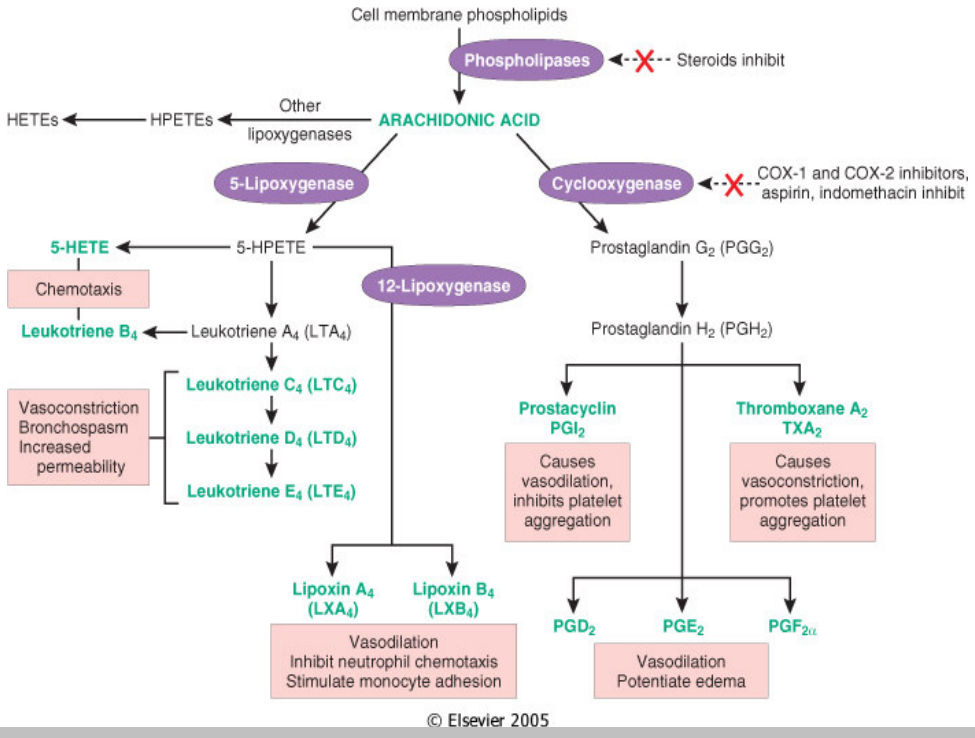
Eicosanoids:

Physiological and Pharmacological Actions of Eicosanoids :

Mechanisms and Receptors:
- Act on cell surface receptors

- All coupled to G-protein.

- PGI; PGE increases adenylate cyclase (decrease intracellular calcium) while TXA2 increases IP3 (increases intracellular calcium)



Leukotrienes:

- Mediators of inflammation and allergy in asthma.
- Vasodilatation.
- ↑ capillary permeability.
- Bronchoconstriction.
- Chemotactic agent.
- Intestinal contraction.

Type:

- LTA_4
- LTB_4 (Chemotaxic)
- LTC_4, LTD_4, LTE_4 (Bronchoconstriction)

Leukotrienes blockers: (IMP)

- Major use in treatment of **asthma**

- **Zileuton** (lipo-oxygenase inhibitors) → inhibit synthesis
- **Zafilurkast** - **; Montelukast** (leukotriene antagonist), only bronchoconstrictor not antinflammatory it blocks LTD4 receptor

- Anti-inflammatory and RA (NSAID
- Antiplatelet action (Aspirin)
- Dysmenorrhea

Prostaglandin:

Synthesis:

- By the action of phospholipase A_2 on phospholipids arachnoid acid and then by cyclooxygenase PGs.

Metabolism:

- PG dehydrogenase

PGI_2	TAX_2
- Inhibits platelets aggregation. - Vasodilation - Bronchodilation - Endothelium - Diuretic & natriuretic action - Increase GFR	- Stimulate platelets aggregation - Vasoconstriction - Bronchoconstriction - Platelets - No action
PGE_2 -MCQ-	**$PGE_{2\alpha}$**
- Vasodilation - Bronchodilation - GIT contraction - Contraction of pregnant uterus. - ↑ GFR - ↑ H_2O and Na excretion. - Mediate of fever. - Increase bicarbonate secretion	- Vasoconstriction - Bronchoconstriction - GIT contraction - Contraction of pregnant uterus. - No action

Note : - asprin inhibit PG, so when taken in excess it causes peptic ulcer
- PGF & PGE cause contraction of uterus .

Uses: **-MCQ-**

Note : PG are not given because it has very short duration of action .

Misoprostol (PGE_1) (MCQ)

- NSAID-induced gastritis (peptic ulcer)

Alprostadil (PGE_2):

- Because it causes VD, so it is used in impotence, placed in urethra (minisuppositories)
- maintain ductus arteriosus patent before surgery to infants.

Dinoprostone (PGE_2):(MCQ)(IMP)

- **Oxytocis agents**
- intravaginally, induce labour or abortion.

Carboprost tromethamine ($PGF_{2\alpha}$)

- induction of labour or abortion (intramniotic injection, IM, intravaginally)

Epoprostenol (PGI_2):

- Intravenous.
- Antithrombotic (inhibit platelets aggregation)
- Pulmonary hypertension.

- Note : **Glaucoma: Latanoprost PGF2**

Effect	PGE2	PGF2α	PGI_2	TXA_2	LTB_4	LTC_4	LTD_4
Vascular tone	↓	↑	↓↓	↑↑↑	?	↑,↓	↑,↓
Bronchial tone	↓↓	↑	↓	↑↑↑	?	↑↑↑↑	↑↑↑↑
Uterine tone	↑↑	↑↑↑	↓	?	?	?	?
Platelete aggration	↑ or ↓	?	↓↓↓	↑↑↑	?	?	?
Leukocyte chemotaxis	?	?	?	?	↑↑↑↑	?	?

- A. Vasoconstrictors (angiotensin II ; vasopressin ; endothelins and neuropeptide Y).

- B. Vasodilators (Bradykinin and related Kinins; Natriuretic Pepties; Vasoactive Intestinal Peptide; substance P; Neurotensin)

Endothelin:

- Vasoconstriction
- Direct positive intropic and chronotropic effect
- Decrease GFR
- Constriction of bronchial smooth muscle
- Increase secretion of renin, aldosterone, ANP

Receptors :

- ET A : smooth muscle
- ET B : vascular endothelial cells

Bosetan :

- Endothelin receptor antagonist (A and B)
- Given orally and IV
- Used for treatment of pulmonary hypertension

The kallikrein-kinin system:

plasma kinins

- Present in plasma tissue as kidney, pancreas, intestine, sweat, and salivary gland
- **Kinins:** bradykinin , lysyl-bradykinin (kallidin)
- released from high molecular weigh protein precursors kallikrein.
- Degraded by kininase II , ACE

Action of kinins : -MCQ-

- Mediators of inflammation.
- Vasodilation of arterioles (10x histamine) direct and via EDRF
- Reflex increase HR, COP, contractility.
- increases the body capillary permeability
- Vasoconstriction of large arteries and veins.
- Smooth muscle contraction (intestine, bronchi and uterus)
- Pain sensation. (Intradermal injection of kinins elicited potent pain (Stimulate nociceptive nerve afferent fibers)
- Oedema.(due to vascular permeability)

Kallikrein inhibitors:

Aprotonin (trasylol):

Treat : Acute pancreatitis, carcinoid system.

Renin angiotensin aldosteron system:

Angiotensin : -MCQ-

Metabolism:

-Short duration of action.

-Metabolized by aminopeptidase into AngIII and angiotensinase into peptide fragments.

Action:

CVS:

- Blood pressure: hypertension

1. Vasoconstriction
2. Release of catecholamines.
3. +ve inotropic effect.
4. Increase sympathetic outflow.

Adrenal cortex:

- Aldosteron synthesis and secretion.

Renal blood vessels: Vasoconstriction.

CNS: increase secretion of ADH and ACTH.

Rennin angiotensin aldosterone blockers:

- Renin: B-blockers.
- ACE inhibitors: Captopril.
- AngII blockers: Iosartan.

Treatment of hypertension

** **ACE** : Angiotensin Converting Enzyme

* Natriuretic peptides:

Locations: Atrial (ANB) and Brain (BNP) (Found in ventricle as well)

- Clinical significant:

(increase in heart failure; renal failure; SISADH Actions: decrease the secretion of renin, aldosterone and vasopressin; decrease blood pressure and increase sodium excretion. Act via activation of guanalyl cyclase.

* Calcitonin:

- from thyroid and the most potent vasodilators in the body.

* Vasoactive-intestinal peptides:

Vasopressin (Antidiuretic hormone ADH)

Supstnace P: is an arteriolar vasodilator that is also pain-mediating neurotransmitter but causes venoconstriction and bronchoconstriction. Capsaisin (MCQ) releases substance P from nerve ending (used for arthritic joints and for postherpetic neuralgia).

Ergot alkaloids : -IMP.MCQ-

- Formed by fungus
- Several receptors (Dopamine, 5HT, α-receptors)

– **What is Ergot poisoning?**
- **MOA:** Act on several types of receptors either agonist, partial agonist, or antagonists . (simply act on a-adrenoceptors); Dopamine and 5-HT).

Pharmacological actions :

***CNS*:**
- Stimulate dopamine receptors and decrease prolactin and parkinsonism

✓ Stimulation of dopaminergic receptors especially in the pituitary decrease prolactin release and emoliorate the symptoms of parkinsonism (e.g: Bromocriptine)

- Stimulation of 5-HT2 receptors leads to hallucinogenic action (e.g.: by LSD)
- Stimulation of cerebral vessels (5HT2)

Smooth muscle:
- Contraction of uterus . (e.g.: Ergonovine)
- NVD (nausea, vomiting and diarrhea)

◙ **Why they are more effective in pregnancy?**
Answer : because in pregnancy the number of alpha 1 receptor increase
And ergonovine work on this receptor so , it becomes more effective.

CVS:
- Vasoconstriction via a-adrenoceptors and 5-HT2 receptors (Ergotamine via a1 and increase NE)

* **Ergotamine & Dihydroergotamine ($5HT_1$)** :- migraine treatment
* **Ergometrine ($5HT_1$) :**- Postpartum hemorrhage
* **Methysergide.** Migrane prophylaxis
* **Bromocriptin** (dopamine agonists):- Endocrine disorder – parkinsonism.
* Hyperprolactenemia **(Bromocriptine)**
* Post partum hemorrhage **(Ergonovine)** To induce vasoconstriction.
* Diagnosis of variant angina (**Ergonovine**)

Side effect (erogtism):

- VC => gangrine - Nausea & vomiting.
- GIT as diarrhea; N/V; Prolongs vasospasm (ergotamine and ergonovine) may progress to gangrene.

أنا مجهول .. رجاء لا تنسوا جدي – رحمه الله - من دعائكم ،،،

لكم منا في الفارما بيل كل الأمنيات بأن تنال الاعجاب ،،

ونأمل أن نكون قد وفقنا جميعا ،،،