**Autacoids**

**Autacoids** are locally acting hormones & they include: Serotonin, Histamine, Kinins, Angiotensine, Eicosanoids, Adenosine, substance P & others

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**SEROTONIN [5-HYDROXY TRYPTAMINE]**

**Synthesis:**

```
Tryptophan → 5-Hydroxytryptophan (Pass BBB)
```

```
5-Hydroxyindol acetic acid (5-HIAA) ← MAO → 5-Hydroxytryptamine (SEROTONON)
```

*Decarboxylase enz.*

(present in CNS & GIT but **not** in platelets)

---

**Physiology:**

1. **Biological Mono-amine**
2. **Site of [5H.T]**
   1. **C.N.S:** [Synthesis & storage]
      - Behavior control – Temperature Control – Migraine
   2. **G.I.T:** [Synthesis & storage] **90%**
      - Peristalsis control
   3. **Platelets:** [storage **only**]
      - ⤷ Platelet aggregation

---

**Kinetic:**

- Not absorbed orally
- Not pass B.B.B
- Metabolized by MAO → 5 HIAA
- 5 HIAA is excreted in urine
  - Carcinoid T. & Reserpine → ↑ 5 HIAA
  - MAO.I & α methylldopa → ↓ 5HIAA

---

**Mechanism of action:**

Through stimulation of 5 HT receptors, 7 types:

- $5HT_{1A,B,D,E,F} \rightarrow G_i$ ----------- present in CNS
- $5HT_{2A,B,C} \rightarrow G_q$ ----------- present in CNS, smooth m. & platelets
- $5HT_{3,4,5,6,7}$ ----------------------- present in CNS---& $5HT_4$ in smooth m

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**92**
Actions:

1) C.V.S
   - Heart ➔ stimulation
   - Bl. V ➔ V.C esp. veins ➔ V.D of coronary & sk.m.
   - Bl. Pr. ➔ I.V produces Triphasic effect
     - Initial Hypotension due to Bezold Jarish reflex.
     - Then hypertension due to ↑ Co & V.C
     - Then Hypotension due to Sk.m V.D

2) Platelets ➔ ↑ platelet aggregation

3) C.N.S: it’s a transmitter in C.N.S

4) Stimulation of sensory nerve ending ➔ pain

5) Stimulation of Ganglia

6) Smooth m. ➔ spasmogenic ➔[GIT – Bronchi - U.B – Uterus]

N.B: Selective Serotonin reuptake inhibitors [SSRIs]
e.g : Fluoxetine ➔ Antidepressant

N.B: Sertonin receptor agonists:
1- Buspiron ➔ 5HT_{1A} [anxiolyic]
2- Triptans as Sumatriptan ➔ 5 HT_{1D} [ttt of acute migraine]
3- Lysergic acid diethylamide (L.S.D) ➔ 5 HT_{2}
   Agonist in C.N.S but antagonist in periphery
4- Metoclopramide , Tegaserod (Obsolete) & Cisapride (Obsolete) ➔ 5HT_{4}

N.B: Sertonin receptor antagonists:
1- Cyproleptadine
   - Actions : Anti 5HT – antihistamine – antimuscarine - ↑ Appetite
   - Uses : 1. Allergy
     2. Appetite stimulant
     3. Prophylaxis of migraine
     4. Carcinoid tumor
   - Side effects : 1. Drowsiness
     2. Dry mouth

2- Pizotifen ➔ - Prophylaxis of migraine
   - ↑ Appetite

3- Methysergide ➔ -Prophylaxis of migraine
   -Retro peritoneal fibrosis

4- Ketanserin ➔ α_{1} blocker & dopamine blocker used in hypertension

5- Ondansetron, Granisetron & Topisetron ➔
   - Selective 5HT_{3} blocker
   - Central antiemetic

6- Others ➔ Ergotamine – Phenoxybenzamine – Tolazoline – Tricyclic antidepressant drug – Phenothiazine - LSD - Ketotifen
HISTAMINE

**Physiology:**
1) Biological Diamine
2) Present with heparin in Mast cells & Basophiles
3) Synthesis:
   \[ \text{Histidine amino acid} \xrightarrow{\text{Decarboxylase}} \text{Histamine} \]

**Kinetic:**
- Not absorbed orally
- not pass B.B.B

**Fate:**
1) **Methylation:** [the major pathway]
   \[ \text{Hist.} \xrightarrow{\text{Imidazole N-methyl}} \text{Methyl hist.} \]
   - urine
   - Major part: Methyl Indol Acetic Acid (M.I.A.A)
   - MAO

2) **Oxidation:**
   \[ \text{Hist} \xrightarrow{\text{Histaminase}} \text{Indol acetic acid (IAA)} \xrightarrow{} \text{urine} \]

3) **Acetylation:** In intestinal flora [not human cells]
4) **Histaminopexy:** = Binding to plasma protein

**Storage:** Stored with heparin in mast cells & Basophiles.

**Mechanism of action:**
Through stimulation of 4 types of H – receptors:
- \( \text{H}_1 \rightarrow \text{G}_q \rightarrow \) in smooth m. [spasmogenic] & endothelium
- \( \text{H}_2 \rightarrow \text{G}_s \rightarrow \) cardiac stim. & \( \uparrow \) gastric acidity
- \( \text{H}_3 \rightarrow \text{G}_i \rightarrow \) presynaptic & C.N.S
- \( \text{H}_4 \rightarrow \text{G}_i \rightarrow \) Esinophils – Basophils – Mast cells

**Action of Histamine**
1) **C.V.S**
   - Heart \( \rightarrow \) stimulation \( [\text{H}_2] \)
   - Bl.V. \( \rightarrow \) V.D [ \( \text{H}_1 \) mainly + \( \text{H}_2 \)] through release of (NO) from endothelium
     \( \rightarrow \) \( \uparrow \) Capillary permeability through shrinking of endothelial cells \( \rightarrow \) oedema
   - Bl. Pr \( \rightarrow \) Hypotension
   - N.B: if histamine is injected intradermally
     - Local redness (capillary V.D)
     - Triple response
       - flare (arterial V.D)
       - Wheal (edema)

2) **Stimulation of sensory nerve** \( \rightarrow \) Pain & Itching
3) **Stimulation adrenal medulla** \( \rightarrow \) \( \uparrow \) release of adrenaline
4) **Stimulation gastric acidity**
5) **Spasmogenic:** on: G.I.T, Urinary tract & Bronchi
**Uses of histamine:** (NOT USED CLINICALLY)

1) Desensitization
2) Test for paroxysmal pheochromocytoma
3) Test for gastric acidity to diagnose achlorhydria
   - Histamine alone
   - Histamine + H₁ blocker [Augmented histamine test]
   - Betazole → selective H₂ agonist
   - Pentagastrin → gastrin receptor agonist

**N.B: Histamine releasers:**
Atropine – Morphine – Curare – Trimethaphan – Heparin

**N.B: Histamine antagonists:**
1. H₁ receptor blockers = Anti histaminics
2. H₂ receptor blockers e.g: Cimitidine
3. Physiological antagonism: Adrenaline
4. ↓histamine release: - Corticosteroids
   - Mast cell stabilizers
5. Desensitization

---

**Antihistaminics [H₁ – Blockers]**

**Classification:**

<table>
<thead>
<tr>
<th>Anti histaminics</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Sedating (1ˢᵗ generation):</td>
<td></td>
</tr>
<tr>
<td>Antazoline------------------------</td>
<td>Anti arrhythmic</td>
</tr>
<tr>
<td>Promathazine----------------------</td>
<td>Marked sedation &amp; hypnosis</td>
</tr>
<tr>
<td>Chlopheniramine-------------------</td>
<td>Common cold preparation</td>
</tr>
<tr>
<td>Clemastine [ Tavegyl]------------</td>
<td>Long duration</td>
</tr>
<tr>
<td>Cyproheptadine--------------------</td>
<td>↑ appetite</td>
</tr>
<tr>
<td>Cyclizine-------------------------</td>
<td>Anti emetic - Teratogenic</td>
</tr>
<tr>
<td>Meclizine-------------------------</td>
<td>Anti emetic - Teratogenic</td>
</tr>
<tr>
<td>Dimenhydrinate--------------------</td>
<td>Anti motion sickness</td>
</tr>
<tr>
<td>Diphenhydramine-------------------</td>
<td>Anti motion sickness – anti- Parkinson</td>
</tr>
<tr>
<td>Doxylamine------------------------</td>
<td>Marked sedation &amp; hypnosis</td>
</tr>
<tr>
<td>Mepyramine------------------------</td>
<td>Experimental</td>
</tr>
</tbody>
</table>

| 2) Non sedating (2ⁿᵈ generation):|                                                  |
| Terfenadine (obsolete)            |                                                   |
| Fexofenadine (active metabolite   |                                                   |
| of Terfenadine)                   |                                                   |
| Astemizole                        |                                                   |
| Azelastine (intranasaly)          |                                                   |
| Mequitazine                       |                                                   |
| Loratadine & Desloratadine       |                                                   |
| Cetrizine                         |                                                   |

* Not pass B.B.B
* No C.N.S effect
* No atropine like
* Long duration
**Autacoids**

**Ebastine**

**Kinetic:**
- Absorbed orally (NB: Azelastine is given intranasaly)
- Pass B.B.B except non-sedating
- Pass placental barrier [e.g: meclizine & cyclizine → Teratogenic]
- Metabolized in liver
- Excreted in urine & milk → affect suckling baby

**Actions:**

1) **Anti histamine:** - Block completely → spasmogenic effect  
   - ↑ capillary permeability  
   - itching  
   - Block partially → V.D – Hypotension  
   - No effect on → Heart – Gastric acidity

2) **Anti serotonin**

3) **Anti a.ch** [Atropine – like]

4) **Na⁺-channel block** → local anesthetic effect  
   → quinidine like effect

5) **C.N.S:** [Except non-sedating]
   - Sedation & Drowsiness [may cause stimulation in children]  
   - Anti emetic & Anti motion sickness  
   - Anti parkinsonism

**Uses:**

1- Allergy, allergic rhinitis & Anaphylactic shock  
2- Parkinsonism  
3- Common cold (sedating antihistaminics)  
4- Cardiac arrhythmia (Antazoline)  
5- Motion sickness  
6- Emesis (vomiting)

**Side effects:**

1) Drowsiness & sedation [except non sedating]  
2) Dry mouth

3) Allergy  
4) Anorexia, nausea, vomiting

5) Fatal Arrhythmia with Terfenadine (obsolete)  
6) Teratogenic [Cyclizine & Miclizine]


**Autacoids**

**H₂ – Blockers**

Cimetidine – Ranitidine – Famotidine – Nizatidine

1. Cimetidine

**Pharmacokinetics:**
- Well absorbed orally & parenterally
- 1/3 metabolized in liver
- Passes B.B.B & Placenta
- 2/3 excreted in urine & milk

**Pharmacodynamics:**
1. Competitive block of H₂ receptors.
   a. ↓ HCL secretion stimulated by: Histamine – Gastrin – A.ch – Stress
   b. ↓ Effect of Histamine on heart
2. ↓ Pepsin secretion
3. ↓ Secretion of Interensic Factor

**Uses:**
1) Peptic ulcer: - 800 mg at bed time or 400 mg twice orally for 6-8 ws, then, 400 mg at bed time for 6 months
2) nonulcer dyspepsia
3) Gastroesophageal reflux disease [GERD]
4) Upper G.I.T bleeding & stress related gastritis
5) Zollinger Ellison syndrome

**Side effects of Cimeditine:**
1) Recurrence if stopped suddenly
2) G.I.T disturbances & diarrhea
3) Hypersensitivity & skin rash
4) ↓ Hepatic blood flow (non-specific enzymatic inhibition)
5) Hepatitis like (↑ serum transaminases)
6) H.M.E Inhibitor ↘↓ metabolism of Warfarin – Theophyllin – Diazepam – Phenyoitn
7) ♂  ➔ Gynecomastia – infertility (↑ estrogen level - ↓ binding of testosterone to its receptor)
8) ♀  ➔ Galactorrhea – infertility (↑ prolactin level)
9) Eldery  ➔ mental confusion & hallucination
10) Blood dyscrasias
11) Muscle pain

2- Ranitidine [Zantac]
- Like cimeditine but – Stronger [10 times] – Longer – Not pass B.B.B
- Side effects: 1-5 only [Not HME Inhibitor]
- Dose: 300 mg at bed time or 150 mg twice orally

3- Famotidine
- Like Ranitidine but strong [10 times]
- Dose: 40 mg at bed time or 20 mg twice orally

4- Nizatidine
- Like Ranitidine but not metabolized [100% oral bioavailability]
**KININS**

They are polypeptides: Bradykinin (9 a.a) & kallidin (10 a.a)

N.B:  
1- Kininase II is the angiotensin converting enzyme (A.C.E)  
2- ACE inhibitors [Captopril] $\downarrow$ metabolism of kinins $\Uparrow$ Bradykinin $\Rightarrow$ V.D  
3- Aspirin & Aprotinin [Trasylol] $\Rightarrow$ kallikrein .enz.$\Rightarrow$ $\downarrow$ synthesis of kinins

**Actions of kinins**

1) **C.V.S**
   - Heart $\Rightarrow$ stimulation  
   - B.V. $\Rightarrow$ Powerful art V.D (*10 times* more powerful than histamine)  
   - Venous V.C  
   - $\uparrow$ Capillary permeability  
   - B.Pr $\Rightarrow$ Hypotension

2) **Spasmogenic** on smooth m. $\Rightarrow$ Bronchoconstriction

3) **Stimulate sensory nerve** $\Rightarrow$ pain & mediator in inflammation

**PURINES**

**Types & receptors:**

1- **Nucleoside (Adenosine):** acting on P$_1$ receptors (Subdivided into A$_1$, A$_2$ & A$_3$)  
2- **Nucleotides (ATP & ADP):** acting on P$_2$ receptors

**Actions:**

1- **Adenosine:**
   - **CVS:** - Cardiac depression , $\downarrow$ A-V conduction  
     - **VD & hypotension, except** in Kidney, it produces VC
   - **Respiration:** bronchoconstriction (A$_1$)
   - **Platelets:** $\downarrow$ platelet aggregation
   - **CNS:** Presynaptic inhibition

2- **ADP:** $\uparrow$ platelet aggregation

3- **ATP:**  
   - Fast transmitter in CNS & Ganglia  
   - Cotransmitter in both adrenergic & cholinergic neurons  
   - Intracellular controlling K$^+$ channels
**Autacoids**

- Converted to ADP & Adenosine

**ANGIOTENSINS**

- **Angiotensinogen**
- **Renin**
- **Angiotensin I** [Inactive]
- **A.C.E**
- **Bradykinin**
- **Angiotensin II** [Very active]
- **Angiotensin III** [Less active]
- **Angiotensinase**
- **Inactive peptides**

**N.B:**

**Angiotensin II receptors:**
- AT₁ & AT₂
- AT₁ ⇒ G_q coupled receptor & it is present in Blood vessels.

**Rennin- angiotensin antagonists**

1) **Renin release inhibitors:**
   - 1- α₂ agonists
   - 2- β₁ blockers
   - 3- labetalol

2) **Renin inhibitors:** (bind to renin molecule, inhibiting its action)
   - Enalkiren & Remikiren (Not used clinically) – **Aliskiren** (used orally)

3) **A.C.E inhibitors:**
   - Captopril – Enalapril – Lisinopril – fosinopril ….

4) **Angiotensin II receptor blockers:**
   - Saralasin ⇒ partial agonist – used only l.V infusion
   - Losartan – Valsartan – Candesartan - Telmesartan ⇒ pure antagonist at
     AT₁ – used orally in hypertension

**ENDOTHELIN**

- Potent V.C peptide produced by endothelium acting on 2 types of G-protein coupled receptors ⇒ ETₐ & ETₐ. Its physiological role is not yet clear
- **Bosentan** is a dual ETₐ and ETₐ receptor antagonist that is approved for treating
Pulmonary arterial hypertension

**EICOSANOIDS**

- They include: *Prostaglandins (PGs)** & *Leukotrienes (LTs)*
- They are synthesized from arachidonic acid
- Arachidonic acid is produced by *Phospholipase A₂* & *Phospholipase C*

<table>
<thead>
<tr>
<th>Prostaglandins [PGs]</th>
<th>Leukotriens [LTs] A,B,C,D</th>
</tr>
</thead>
<tbody>
<tr>
<td>- PGs → CNS → Fever</td>
<td>(SRSA) → LTC₄ &amp; LTD₄</td>
</tr>
<tr>
<td></td>
<td>- Bronchial asthma</td>
</tr>
<tr>
<td></td>
<td>- Inflammation</td>
</tr>
<tr>
<td></td>
<td>Periphery → Inflammation</td>
</tr>
<tr>
<td></td>
<td>→ Inflammation through potentiation</td>
</tr>
<tr>
<td></td>
<td>Of bradykinin &amp; histamine</td>
</tr>
<tr>
<td></td>
<td>→ ↓ gastric acidity</td>
</tr>
<tr>
<td></td>
<td>→ Maintain patency of ductus arteriosus</td>
</tr>
</tbody>
</table>

- PGE₂ → Broncho *Dilatation*  - PGF₂ → Broncho *Constriction*
  - V.D
  - Oxytocic
  - ↑ Rennin release
- Prostacyclin [PGIs] → V.D  - Thromboxane A₂ [TxA₂] → V.C
  - ↓ Platelet aggregation
  - ↑ Platelet aggregation

**Actions of PGs & LTs:** see figure

---

**NB:** *Cyclo-oxygenase enz. (COX) is 3 types:*
- COX-1: Constitutive → ↓ gastric acidity & Renal VD
- COX-2: Inducible by inflammation
- COX-3: present in the CNS & not periphery

---

**NB:** *Arachidonic acid may undergo metabolism to produce PAF* which is important inflammatory mediator & produce broncho-constriction

* The Greek name for 20 is eicosa, hence the term eicosanoid
**Prostaglandins**: as they originate from prostatic gland. According to their structure, they have been advocated letters: A, B, C, D, E, F, & I and according to the number of double bonds, they have been subscripted 1 or 2. The Greek subscript as a in \( \text{PGi}_2 \) refers to the orientation of the hydroxyl group.

### Uses of PGs:

1. **Peripheral vascular disease (P.V.D) & Pulmonary arterial hypertension (PAH)**
   - \( \text{PGi}_2 \) [Epoprostenol]

2. **Peptic ulcer**
   - \( \text{PGE}_1 \) [Misoprostol]

3. **Bronchial asthma**
   - \( \text{PGE}_2 \)

4. **Induction** of therapeutic abortion
   - \( \text{PGE}_2 \) [Dinoprostone] & \( \text{PGF}_{2\alpha} \) [Carboprost]

5. **Induction** of erection in male & maintain patency of ductus arteriosus
   - \( \text{PGE}_1 \) [Alprostadil]

6. **Glaucoma**
   - \( \text{PGF}_{2\alpha} \) [Latanoprost]

### Uses of PGs synthesis inhibitors (NSAIDs):

1. **Analgesic & antipyretic**

2. **Anti-inflammatory**

3. **Dysmenorrheal** (as it is associated with ↑ level of PGs)

4. **Premature labor**

5. **Indomethacin** is used to induce closure if patent ductus arteriosus

### Inhibition of Eicosanoid synthesis:

1. **Cortisol** → ↓ Phospholipase A\(_2\)

2. **NSAID** [As Aspirin & Indomethacin] → ↓ COX, so, all arachidonic a. pass into the LOX pathway → ↑ LTs → bronchospasm

3. **Aspirin S.D & Dazoxipen** → ↓ selectively platelet thromboxan

4. **Fish oil** → Abnormal PG & TXA\(_2\)

5. **Anti-Leukotriene drugs**:
   - **Zileuton**: inhibit 5-LOX enz.
   - **Zafirlukast & Montelukast**: block Leukotriene receptors

They are used as bronchodilators in treatment of bronchial asthma.

**N.B:** Sulphasalazine which ↓L TB\(_4\) synthesis is used in ttt of ulcerative colitis

---

**Natriuretic Peptides**

- **Types:** 3 types: Atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) & C-type natriuretic peptide

- **Actions:** natriuretic, diuretic & vasodilator effect

- **Nesiritide:** it is a (BNP) used IV infusion in ttt of acute heart failure

---

**Other autacoids**

1. **Vaso-active intestinal polypeptide** [V.I.P] :
   - Broncho dilation - smooth m. relaxation - ↑ Rennin

2. **Substance P**:
   - Pain transmitter in CNS - V.D on artery But spasmogenic on veins.

3. **Neurotensin**:
   - ↑ anterior Pituitary Hormone release
   - CSF administration → hypothermia & analgesia
   - VD & ↓ gastric motility & secretion

4. **Interleukins**:
   - produced by leukocytes
   - activate B & T lymphocytes, fibroblasts of endothelial cells
- have role in rheumatoid disease