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UNIT - [3]nd

CHAPTER - 1st

AUTOCOIDS

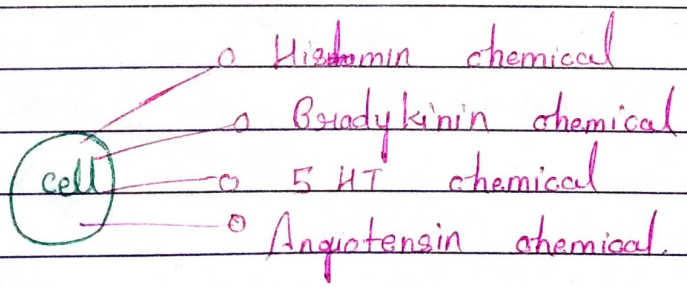
- Autacoids derived from 2 words -

Auto + Coids

↓ ↓

Self Chemical Release

- Those chemical cell in our body which release the chemical protein to the particular area of the ~~area~~ body. they are called Autacoids.
- They are movable in nature. they goes particular part of the body where it needs and they release their chemicals.



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HISTAMINE

- Histamin itself a autocoids which is release in both animal and plant body.
- The name of histamine is derived from 2 words- Hista + amine. hista means tissue and amine means amine group containing compound.

Histamine

Hist → Tissue

Amine → Amine containing groups

- Because our body and plant body produces maximum amount of chemical which contain amine group so its name was Histamine.
- The Histamine was 1st discovered. and explained by scientist Windaus and Vogt in 1907.
- The Histamine chemical was 1st isolated from the lungs and liver tissue of the animal.
- It helps in tissue injury, inflammation, Allergic reaction, Hypersensitivity reaction.

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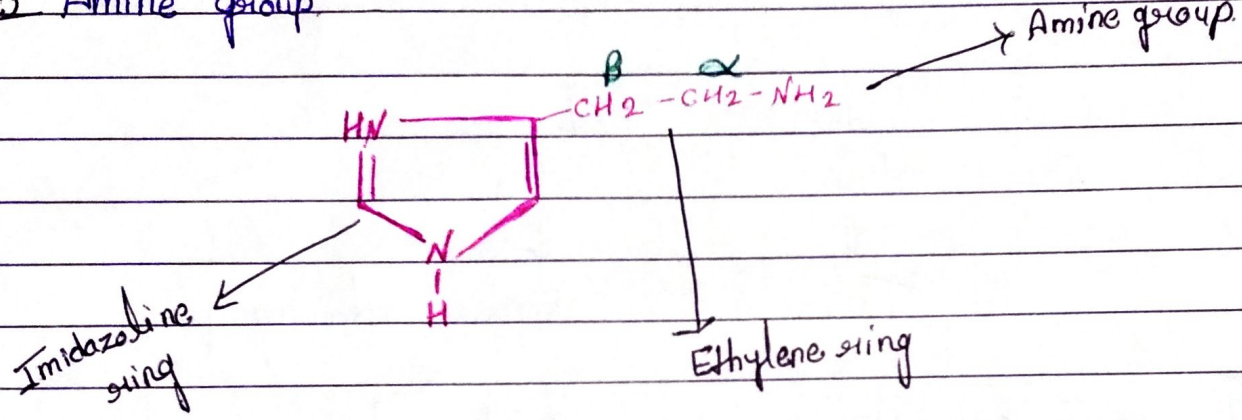
Chemistry of Histamine -

- Histamine is aminous in nature it contains amine group.
- Basically it composed of three part -

(A) Imidazoline heterocyclic ring.
(B) Ethylene ring.
(C) Amine group.



Various Physiological Process -

- Histamine causes Tissue injury.
- It is also cause Inflammation, allergic reaction, hypersensitive reaction.

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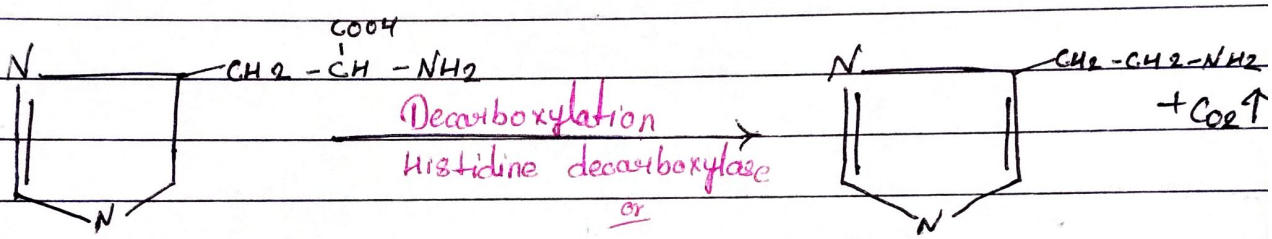
Biosynthesis, storage, Catabolism and release of Histamine

Biosynthesis - The main precursor for formation of histamine in our body the histamine amino acid.

- When histamine amino acid undergoes decarboxylation process with the help of enzyme histidine decarboxylase then after release in CO_2, histamine is convert into the Histamine.



Histamine
Histidine

Histamine

Storage - The Histamine is already present in all over part of the body. but it is basicaly found in lungs and liver and GIT.

- Most of the histamine are present inside the mast cell and basophills cell because these of both cell help in the hyper sensitivity reaction / Allergic reaction.

Catabolism - Catabolism is a process of inactivating of drug molecule.

When histamine undgoes certain reaction in our body then it is catabolise into diffrent - diffrent form and then there effect is reduce.

Catabolism process the actual structure of histamine is change by certain chemical reaction such as by methylation. diff-diff

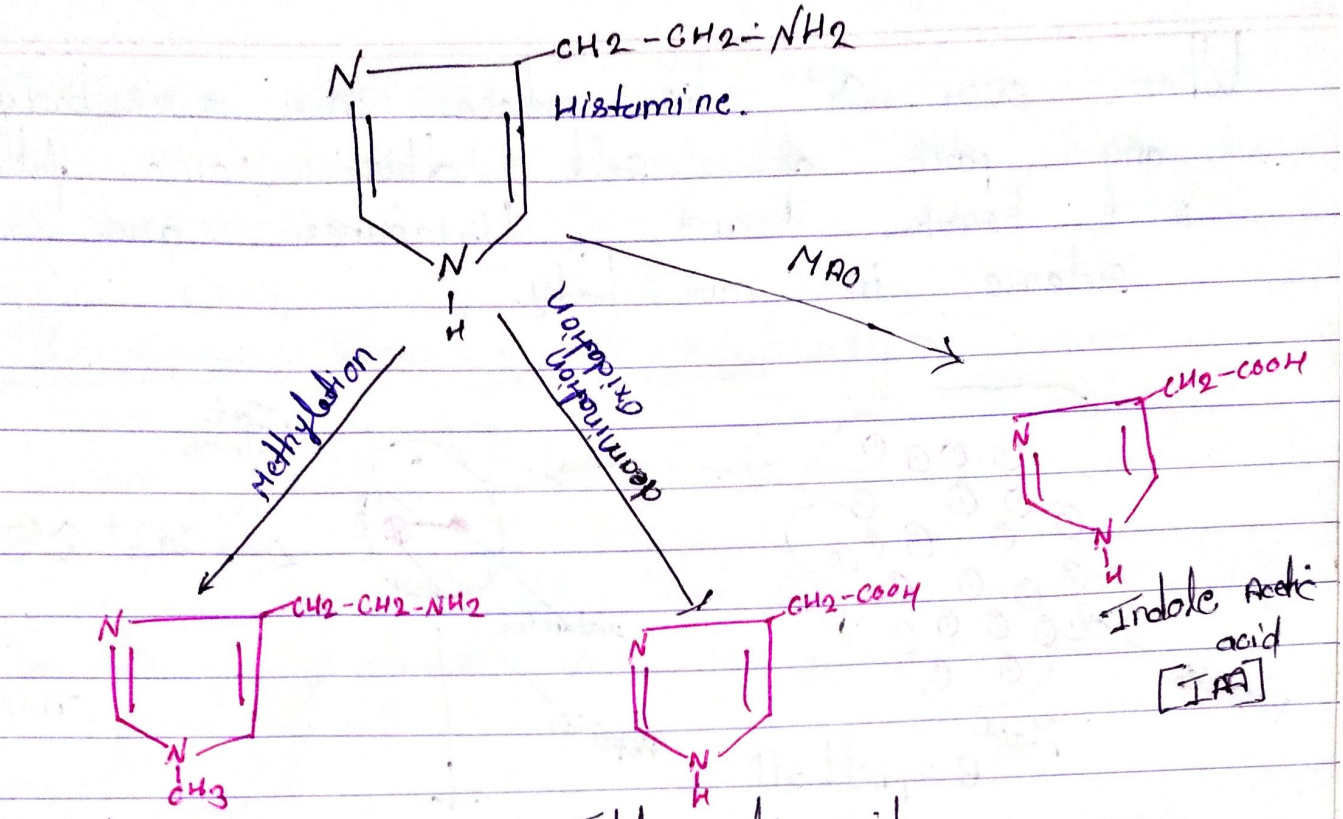
It is convert into the by N-methyl Histamine.

By determination oxydation it is convert into the IAA [Imidazole/ Indole Acetic acid]

After the reaction with enzyme MAO (Mona amino oxidase) it convert into the Indole acetic acid.

By these process it is always takes place in our body.

And by these chemical reactions Histamine actual structure catabolize into inactivated form so it couldnot affect our body.



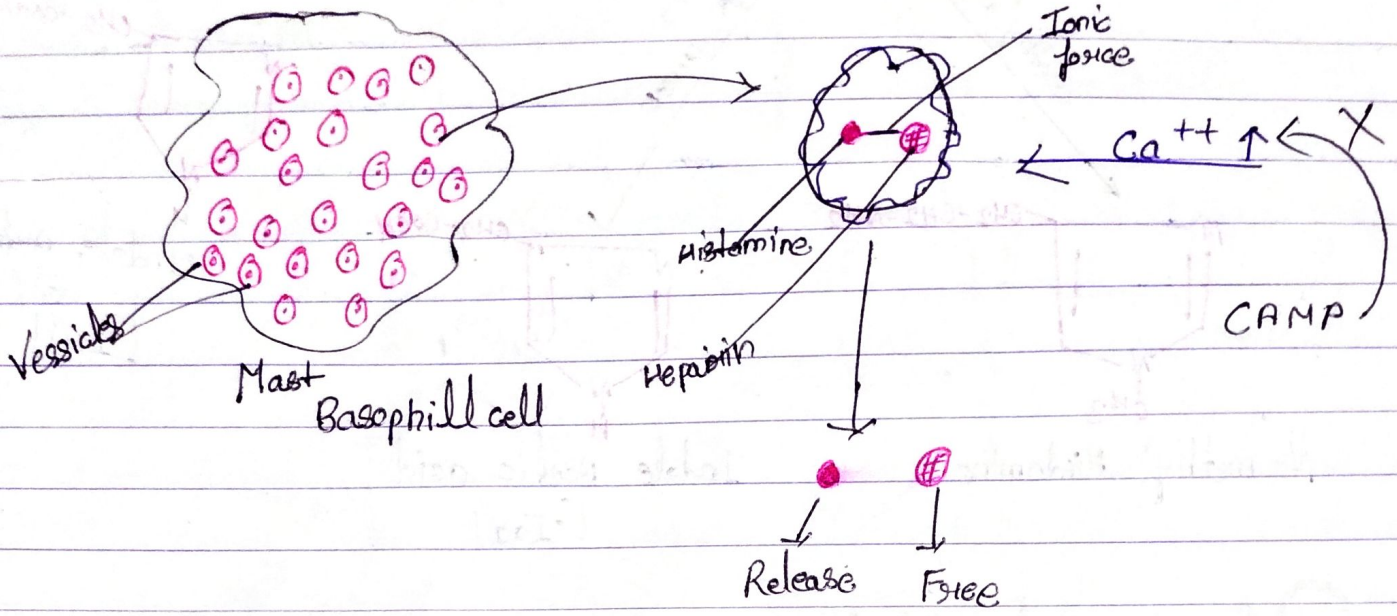
Release of Histomine -

Basicaly in normal conditions the histamine cells, the histamine are stored in the mast cells and basophill cells inside the vessicles.

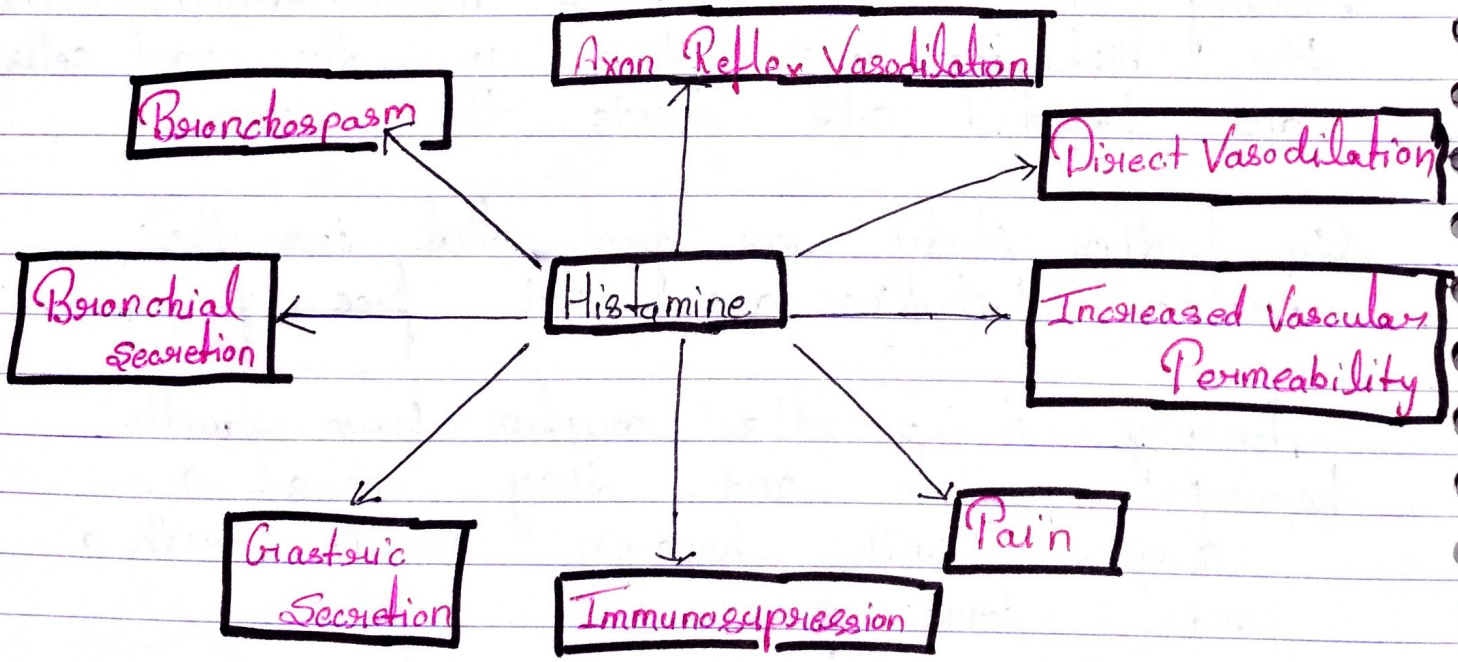
On further study we found that in the vessicles histamine are not free form.

Actually it is the complex form with hepairin protein and they make a complex with heparin protein with a weak ionic force.

When ever Ca^{++} is release in our body in any part of cell this ionic force is break and histamines are release in our body.



Physiological Role of Histamine



[1] **Pain -** Histamine activates the Nicotin and Prostaglandin molecule and which causes the pain in our body.

[2] **Increased Vasular Permeability -** During the inflamatory mechanism process. Histamine increase the vascular permeability.
So the WBC, Basofill, Neutrophil can easily migrate towards the infected site and causes the inflamation.

[3] **Direct Vasodilation -** When Histamine is release in our blood then it causes the vasodilation due to increase in the lumen size of the blood vessels the blood preswre is reduce.

[4] **Axon Reflex Vasodilation -** By the release of histamine the reflect action of axon is vasodilated so the nerve conduction is reduce.

[5] **Bronchospasm -** When Histamine is release into the bronchi muscle then it causes the bronchospasm which may leads to the Asthma.

[6] **Bronchial Secretion** - When Histamine is release and bind with the bronchi muscle, then bronchial secretion is increase and the amount of cough is increase in our bronchi muscle. Respiratory track which may cause cough and cold.

[7] **Gastric Secretion** - Due to histamine the Hcl is release from gastric acid which may cause acidity or gastric ulcer.

[8] **Immunosuppression** - The more release of Histamin it may cause Immunosuppression.

Histamine Receptor

It is a type of GPCR receptor
It has four subunits like -

1. H_1
2. H_2
3. H_3
4. H_4

Receptor	Location	Functions
H_1	Brain, GIT, CVS Lymphocyte.	Causes vasodilation, Bronchoconstriction,

			Muscle activation, pain and itching due to insect stings.
2.	H_2	Myocardial cell Perietal cell	Regulate gastric acid secretion.
3.	H_3	CNS. Gastric mucosa	Reduce Neurotransmitter release - acetylcholine, histamine, norepinephrine, serotonine.
	H_4	Spleen, Thymus. T cell, bone marrow colon	Unknown physiological role.

V.V. most

Classification of Antihistaminic Agents

Antihistaminic drugs are classified into 3 category-

[1] Drug that Inhibit histamine release.
[2] Block action of Released Histamine
[3] Drug having dual action.

[1] Drug that Inhibit histamine release-

Drug- Khellin
Cromolyn Sodium.

2] Block action of Released Histamine -

[A] H_1 Antagonist - 1st generation -

- Aminoalkyl ethers derivative
- Ethylene di amines derivative
- Propyl amine derrivative
- Phenothiazine derivates
- Piperazine derivates.

2nd generation drug -

- Terfenadine
- Fexofenadine
- Cetizine or Cetrizine.

3rd generation drug -

- Acrivastine
- Loratidine

[B] H_2 Antagonist -

- Cimetidine
- Famotidine
- Ranitidine
- Nizatidine.

[C] H3 Antagonist -

- Thioperamide.

[D] H4 Antagonist -

Doxepine
chlorpromazine.

[3] Drug having dual Action -

- Azehistine
- Olopatidine

[4] Mast cell stablizer -

- Zafirlukast
- Montelucast

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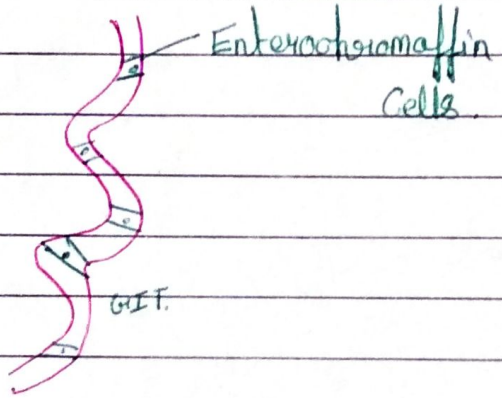
5HT - SEROTONIN

Introduction - 5HT - Serotonin is a autacoids which is release the different part of the body.

- The serotonin is maximum amount of present in the Enterochromaffin cells of the GIT.
- They are basically store and release maximum amount in the body.



- The serotonin is also present small amount in platlets and hypothalus of CNS and into the bone marrow.

It was 1st prepared in 1951. by Vittorio Erspamer scientist.

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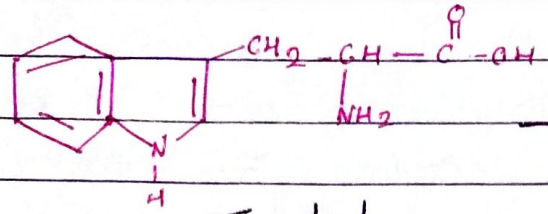
Biosynthesis -

Biosynthesis of serotonin, the precursor amino acid is Tryptophan.

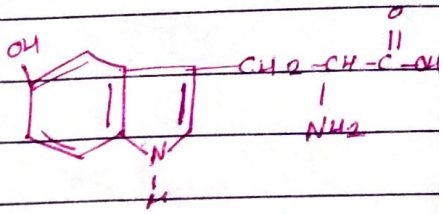
It is biosynthesis in 2 steps -



Tryptophan

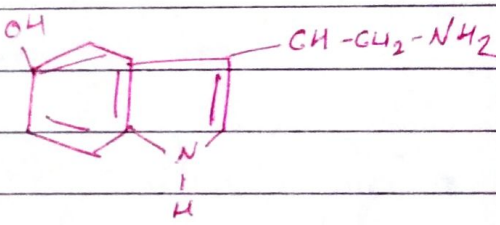
Step-1

Tryptophan Hydroxylase



5 - Hydroxy Tryptophan

Step-2 5 Hydroxy Tryptophan Decarboxylase



Serotonin 5 hydroxy Tryptophan.

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Step-1 In the 1st step amino acid tryptophan with the help of enzyme Tryptophan Hydroxylase is converted into the 5-hydroxy tryptophan structure.

Step-2 In this step with the help of enzyme 5 hydroxy decarboxylase, the tryptophan is converted into the Serotonin.

Imp.

Note - Biosynthesis of serotonin is donot occur in platlets because the enzyme 5 hydroxy T. decarboxylase is absent in platlets.

Storage - After the formation ~~5 hydroxy Tryptophan~~ serotonin they are packed into the vessicles, and after packing vessicles they mooved and store into the Enterochromaffin cell of GIP, platlets, Bone marrow and CNS region.

Release - Serotonin is influence by cholinergic and adrenergic nervous system.

- They release in the form of lipotenous chemical from the GIP, platlets and CNS.
- They are mostly release in hypothalmus region of the brain.

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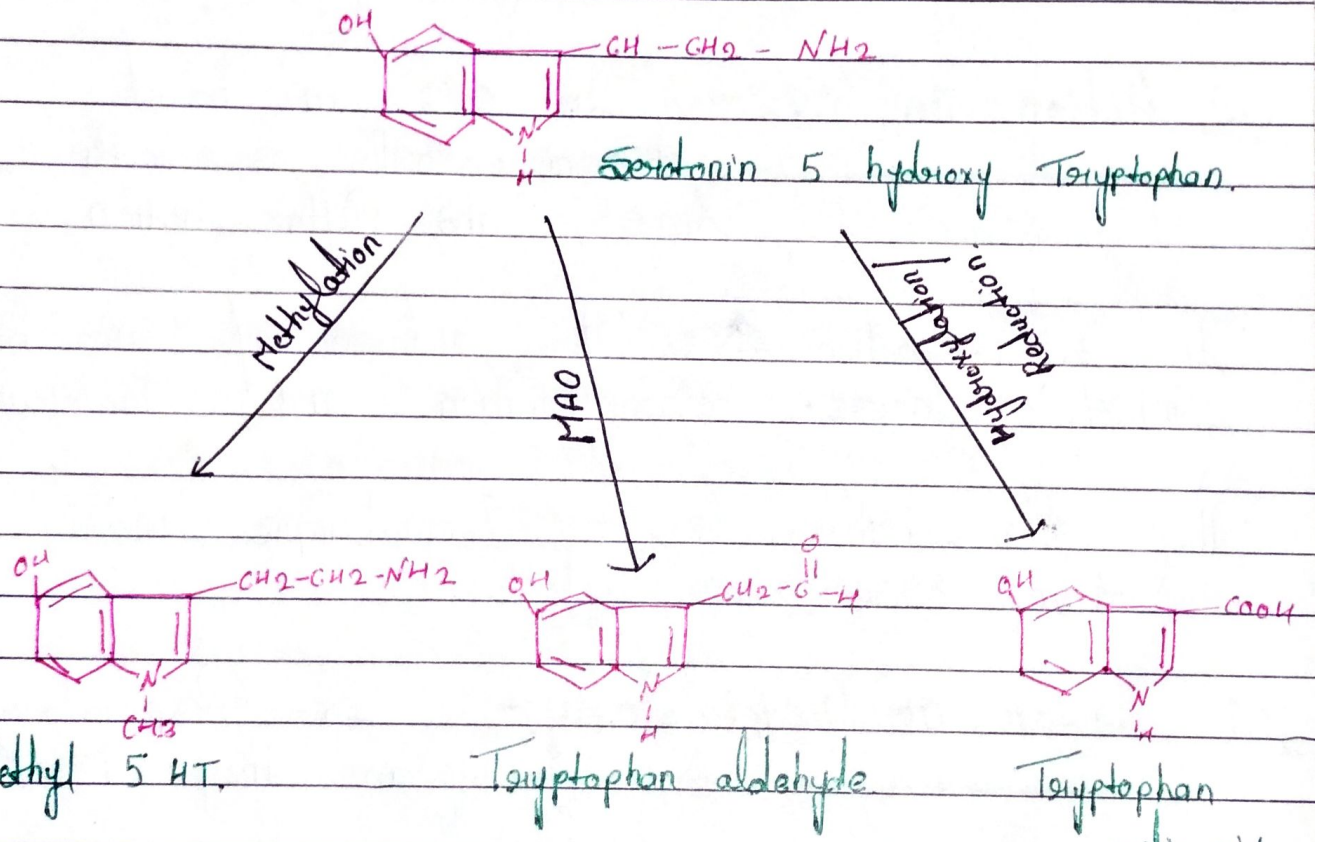
- They are also release in the pineal gland. so they are also work in harmone secretion.

Metabolism – Metabolism is a important step for deactivation of structure of serotonin to avoid the side effect of the drug.

- They canbe perform by following methods - By methylation, By MAO, By hydroxylation or dehydroxylation/ Reduction.



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Pharmacology of Serotonin

[1] Action on CNS - In CNS serotonin is release as a neurotransmitter so it is canbe study under the serotoninergic nervous system.

Basically it causes the depression because they inbibit the release of other neurotransmitter.

They can creat other kinds of problems in sleep, thought, Mood, Behaviour and mental illness.

[2] Action On CVS - In CVS in heart serotonin woorks as both direct and Reflex action.

In reflex action ↑es the release of noradrenaline which cause vasoconstriction and Tachycardia.

They also behave as +ve ionotropic and +ve chronotropic effect.

[3] Action on Respiratory - In Respiratory system they ↑es the respiratory volume they also act on

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the bronchial smooth muscle and after vaso-constriction they cause Asthmatic problem.

[4] Action on GIT - In GIT they basicaly ~~relax~~ Tes the Peristaltic movement.

But long term release they can cause the peptic ulcer.

[5] Action on Exocrine gland - They alter the reflex action and decrease the secretory actions of Hcl release / Gastric release Lacrimal release ,e tc.

[6] Action on Endocrine Gland - They can influence the release of some harmones like ACTH, FSH, LH, PL (Prolactin harmone), GH.

Serotonin Receptor

1. 5HT - 1
2. 5HT - 2
3. 5HT - 3

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[1] **5 HT - 1** – 5 HT - 1 receptor is present centraly and peripheraly, basicaly it present in the brain, les the release of neurotransmitters

[2] **5HT - 2** – They are present in smoth muscle and platlets.

[3] **5H - 3** – These receptor are present in ion channels, basicaly PNS, For example, Nicotinic receptor, GABA receptor, Glycine receptor.

Drugs –

5 HT Receptor Agonists

1. Buspirone - 5HT 1A used in anxiety
2. Sumatriptan - 5HT 1 B/D used in migraine.
3. Cisapride, Mosapride – 5HT4 used in GERD
4. Dexfenfluramine – Non selective 5HT2 agonist (BANNED)
5. Lorcaserin – 5HT2C used in obesity.

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5 HT Receptor Antagonists

Cyproheptadine - $5HT_{2A}$

Methysergide - $5HT_{2A/2C}$

Ketanserin - $5HT_{2A/2C}$

Clozapine - $5HT_{2A/2C}$ [D_2 to lesser extent]

Risperidone - $5HT_{2A}$ + D_2 Antagonist

Ondansetron - $5HT_3$ antagonist

[A] Cyproheptadine -

- 5HT $_{2A}$ receptor blocking property
- Famous for Teasing Apetite.
- H_1 antihistaminic, anticholinergic & sedative

Uses- Allergies, Appetite stimulant, Serotonin syndrome, Carcinoid syndrome, priapism.

Adverse effect. Dryness of mouth
Weight gain
Drowsiness.

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[B] Methysergide -

- Potent 5HT 2A-2C antagonist, non emetic non oxytocic.
- Used in migraine prophylaxis, carcinoid, post gastrectomy dumping.
- Most serious side effect - Retro-peritoneal Fibrosis.

[C] Ketanserin -

Selective 5HT2 receptor blocking property.

Effective antihypertensive drug.

Adverse effect - Dizziness, tiredness, nausea, & dry mouth.

Additional H_1, α_1 dopamergic Blocking.

[D] Ritanserin -

More selective 5HT2A receptor blocker, reduces TXA2.

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- **Ondansetron, dolasteron, granisteron-**

  - 5HT$_3$ receptor antagonists used as antiemetic

- **Antipsychotics (5HT$_2$ antagonists)**

  Clozapine.
  ~~Risper~~ Risperidone.

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CHAPTER - 2nd

Prostaglinds & Leukatrienes

- In 1930, 2 scientist Goldbatt & Evan saw a chemical of lipid nature is present in human seminal plasma.
- In 1964 the scientist Berg strom see that the these lipid chemical release from the prostate gland.
- So on the basis of prostate gland these named it prostate gland.
- In human body about 25 diffrent type of prostaglandin is released and store.

Chemical Significant -

[1] Stimulating & Relaving uterine smoth muscle.

[2] Bronchi constriction.

[3] Ires / Inhibit gastric acid secretion.

[4] Medeating inflammatory Respance.

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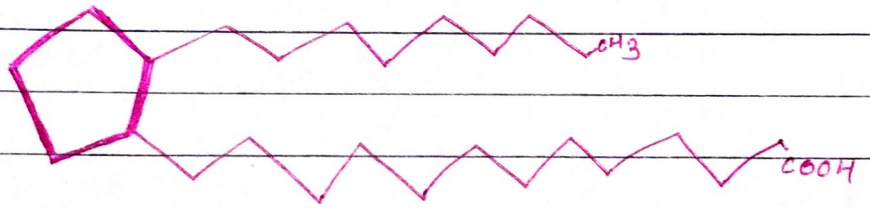
[5] Promoting Na^+ Excretion.

[6] Increasing Pain.

Chemistry of Prostaglandin -

The precursor molecule for the prostaglandin is Prostanoic acid.

In the structure of prostanoic acid a cyclopentane ring is present and, 8 carbon chain is present in first chain, and in 2nd chain 12 carbon chain is present., and in the end of 2nd carbon chain oic acid is present.



Biosynthesis -

When any tissue/ chemical injury occurs in cell. then the cell membrane contain phospholipid and after the ester hydrolysis the Phospholipid is convert into Arachidonic acid.

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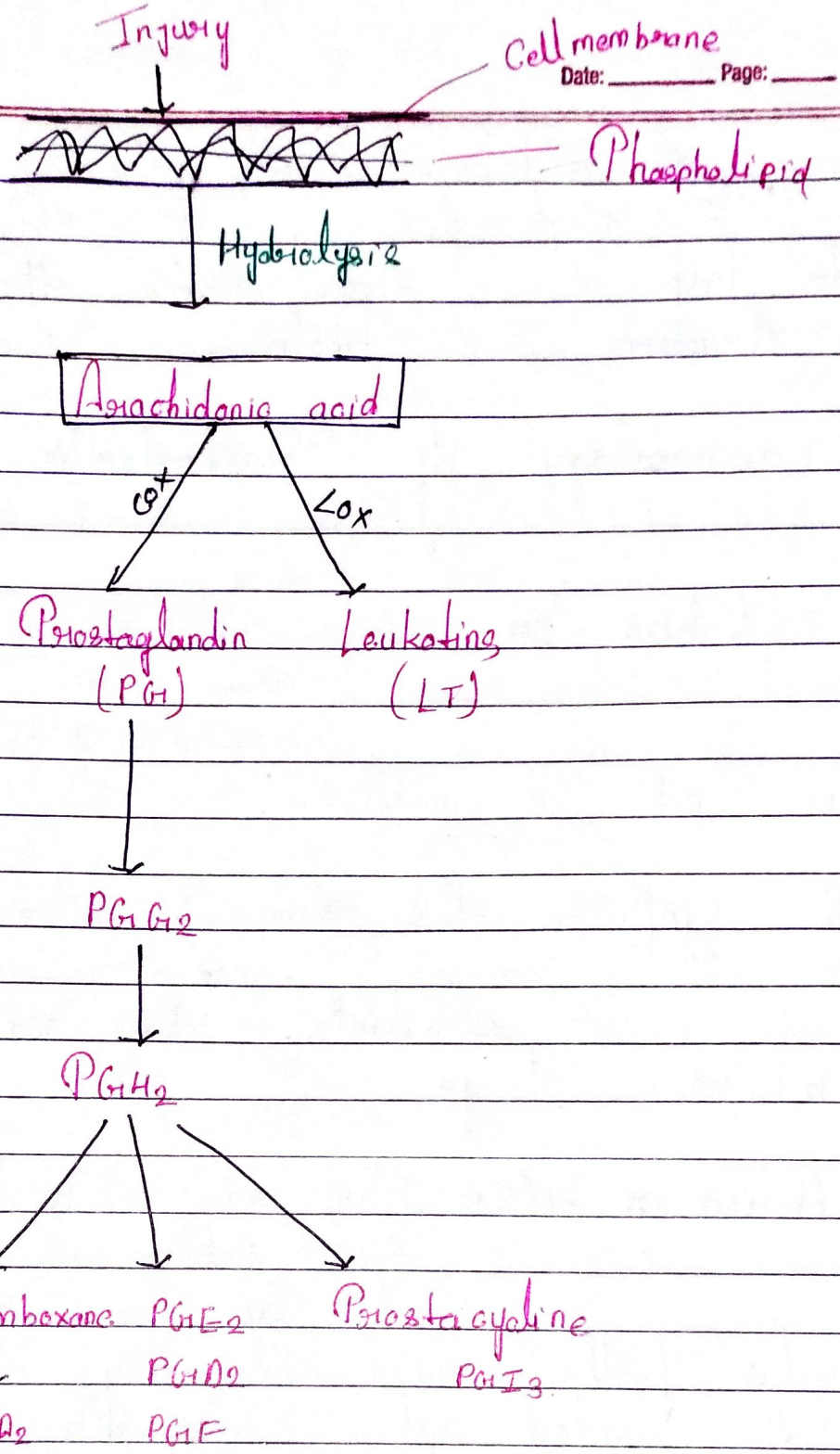
Arachidonic acid is precursor of the prostaglandin and Leukotins with the help of enzyme cyclo oxiginase (Cox), arachidonic acid is convert into the prostaglandin and with the help of enzyme lipoxygenase (Lox), arachidonic acid is convert into the Leukotins.

These prostaglandin are responsible for the Pain, inflammation and fever in the body.

After further enzymatic reaction Prostaglandin (PG_I) is convert into PG_IG_2, and PG_IG_2 is convert into PG_IH_2.

PG_IH_2 forms 3 types of molecule -

- Thromboxane
- PG_IE_2
- Prostacycline.



Metabolism - The metabolism of prostaglandin is perform in the different part of body. like kidney, spleen, liver, Bronchi cell, they contain the different enzymes for their metabolism.

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They are metabolised with the help of enzyme 5α dehydroxylase and Δ^{15} Reductase with the help of these enzyme. the prostaglandin structure is metabolised.

Pharmacology of Prostaglandin [PG] -

[1] Action on CNS - Prostaglandin and leukotrienes are not act as a neurotransmitter but they are act as modulator.

They influence the release of diffrent neurotransmitter and the release of neurotransmitter they produce CNS stimulants like sedation and behaviour change.

[2] Action on ANS - They are donot directly act on the Autonomic nervous system but by the use of negative feedback mechanism they can control the release of Noradrenaline and acetylcholine.

[3] Body Temperature - They can cause Pyrexia Tes the body temp. which is called fever.

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[4] Action on CVS- Basicaly 3 types of prostaglandin PGAs, PGEs, PGIs causes the vasodilation in the blood vessels, which causes tes the BP/ hypotension

[5] Action on Blood- Prostaglandins basicaly PGE2 & PGI_2 causes erythropoesis in blood which release the Erythropoety by the erythropoety release, platlet aggrigate which causes the Thrombosis and Ischemia.

[6] Action on Respiratory System- Respiratory system different prostaglandin behaves different- different action.

PGA and PGE2 causes bronchodilation of smoth muscle, while PGA2 and Thrombogen causes Vasoconstriction.

[7] Action on Pain- It can Tes the pain in different part of body. where it is synthesize.

[8] Action on Endocrine gland- It Tes the or influence the release of some hormones like ACTH (Adeno cortico tyroid Hormone) GH, PL, Gronadotrophin Insulin etc.

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Bradikinin - Plasma Kinin

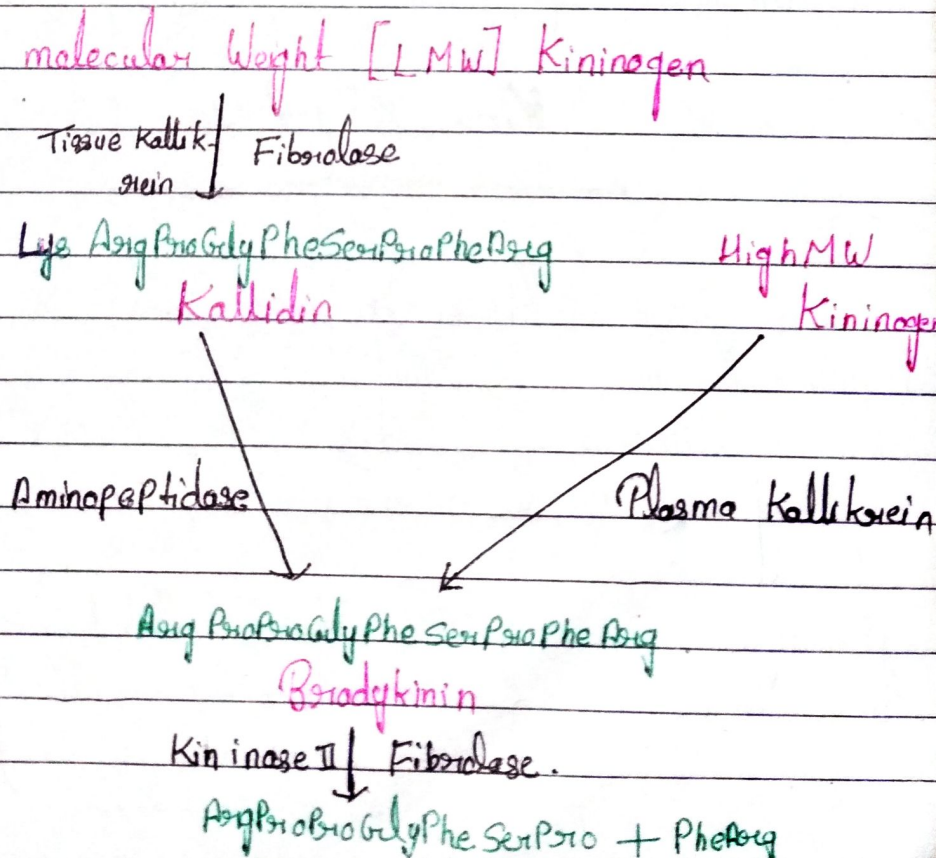
Generation and Metabolism -

Plasma kinins are polypeptide split off from a plasma globulin kininogen by the action of specific enzyme Kallikreins.

Two such important Plasma kinins are -

1. Kallidin [Decapeptide]
2. Bradykinin [Non peptide]

Generation of Bradykinin -



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Kininogens–

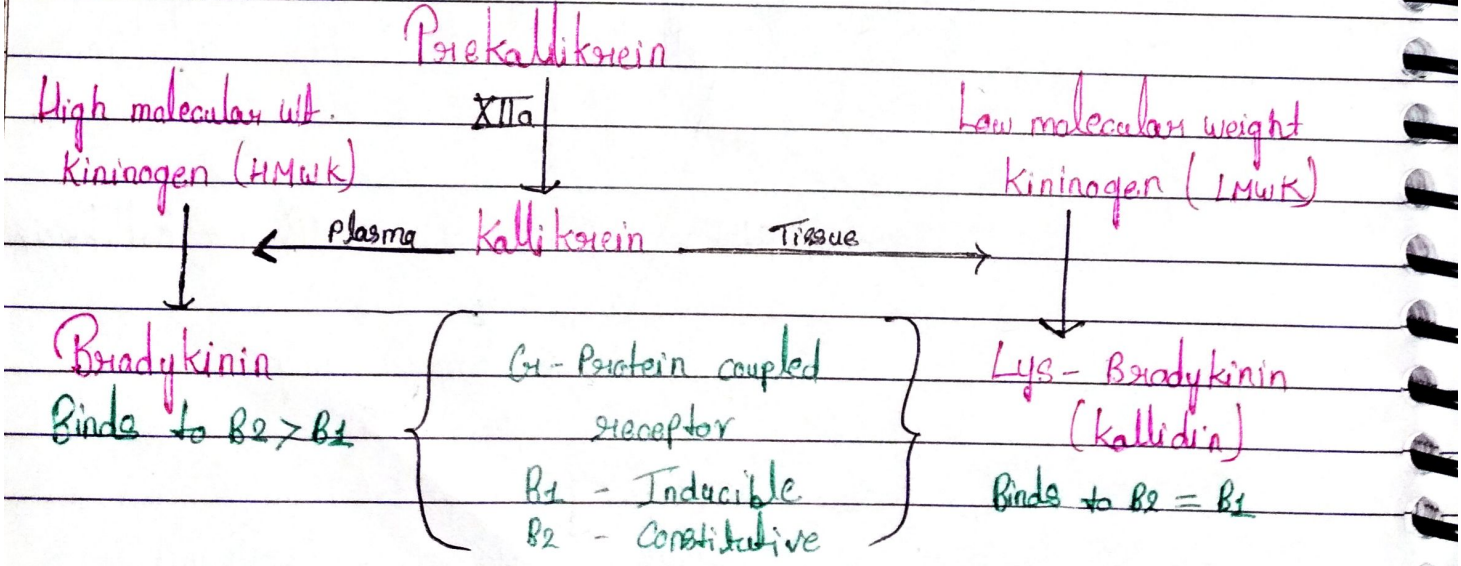
Two Kininogens are known to be present in plasma
LMW Kininogen
HMW Kininogen.

Bradykinin is generated from high molecular weight HMW kininogen by the action of Plasma kallikrein.

On the other hand, Kallidin is generated from both LMW and HMW kininogen by the action of tissue kallikrein.

Bradykinin can also be generated from kallidin on the removal of lysine residue by amino peptidase.

Kinin System



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- ↑ Vascular permeability and dilation (B_1 binding)
- ↑ Smooth muscle contraction - Bronchoconstriction (Cough) and uterine constraction
- ↑ Pain.

Kallikreins

- Kallikreins are glycoprotein enzymes produced in the liver as prekallikreins and present in plasma and in several tissue, including the kidney, pancreas, Intestine.
- Prekallikreins is activated by Hageman factor (Factor XII) which itself is activated by tissue injury and contact with surfaces having negative charge.

Ex- Collagen, basement membrane, bacterial lipopsaccharide bacterial lipopsaccharides, urate crystals.

- Kinins are also generated by trypsin, proteolytic enzyme in snake.

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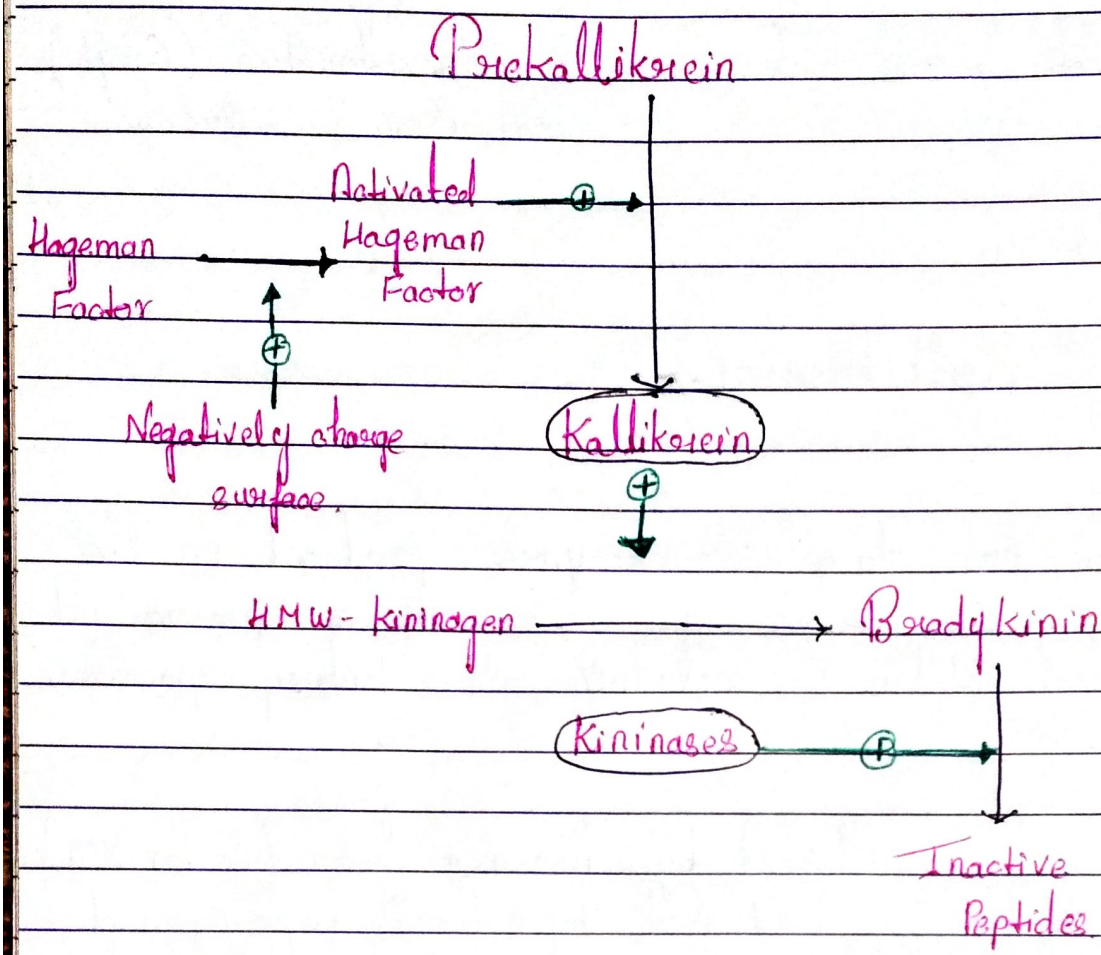
Mechanism -



Metabolism of Kinins

- Metabolised rapidly (half life < 15 seconds)
- By peptidases, commonly referred as kininases.
- Two plasma kinins are characterized -
  - Kininase I
  - Kininase II

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Kininase I- Synthesised in the liver. It releases carboxypeptidase that releases the carboxy terminal arginine residue.

Kininase II- Present in plasma and vascular endothelial cell throughout the body.

It is identical to ACE angiotensin converting enzyme.

Bradykinin Receptor

There are two types of Bradykinin receptor -

1. B1 receptor
2. B2 receptor.

B1 Receptor	B2 Receptor
• Present in low levels. It is strongly induced in inflamed or damage tissues by Cytokines like IL-1	• It is expressed in most normal tissues.
• Respond to des-Arg9bradykinin & desarg9kallidin but not to bradykinin itself.	• Selectively binds the bradykinin and kallidin and mediates the majority of actions.
• Has a role in inflammation and Hyperalgesia.	• It activates PLA2 and PLC via interaction with distinct G Protein.

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Pharmacological Actions of Kinins -

[1] Action on CVS -

- There is no direct action on heart, but reflex stimulation occurs due to fall in BP.
- Potent vasodilators than Ach and histamine.
- It release histamine and other mediators from mast cells.
- It Teses the capillary permeability and it causes the exudation and inflammation occurs.
- Larger arteries and most veins are constricted through direct action on smoth muscle.

[2] Action on Smoth muscle -

Causes marked broncoconstriction in guinea pig and asthmatic ~~probt~~ patients.

[3] Action on Neurons -

Potent pain producing agent and its action is potentiated

by the prostaglandins.

- It produces pain by stimulating nociceptive afferents in the skin and viscera.

2. Action on kidney -

It facilitate salt and water excretion by action on tubules.

Kinins ↑ses renal blood flow.

Pathophysiological Actions -

1. Mediation of Inflammation -

- Kinins produces all signs of inflammation - Redness, exudation, pain and leukocytes mobilization.
- Tissue injury can causes local kinin production which then sets in motion the above defensive and reparative process.
- Activation of B2 receptors on macrophages induces production of IL-1 and TNF alpha (Tumor necrosis factor) and other inflammatory mediatores.

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[2] Mediation of Pain- Due to directal stimulating nerve endings and by Tesing Prostaglandin production.

[3] Functional hyperemia- Hyperemia is an increased amount of blood in the vessels of an organ or tissue in the body.

Drugs affecting Kallikrein Kinin System

- Competitive antagonists of both B_1 and B_2 receptors are available for research use.
- B_1 receptor antagonist -
  - (Leu8des Arg9) Bradykinin.
  - Lys (Leu8des Arg9) Bradykinin.
- B_2 receptor antagonist -
  - Icatibant.
- The synthesis of kinins canbe inhibited with kallikrein inhibitor APROTININ
- Actions of kinins mediated by prostaglandin generation canbe blocked non specifically with inhibitors of Prostaglandin synthesis such as Aspirin.
- Inhibition of Bradykinin Metabolism by ACE inhibitors contributes to their Antihypertensive action.

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CHAPTER - 5th

Non Steroidal Anti-Inflammatory Drugs [NSAIDs]

Inflammation

Inflammation is one of the most important and most useful diffence mechanism of oath body.

It protect our body by killing the foreign particle but our own tissue are injured.

The basic symptoms of inflammation are.

[1] Swelling [Tumor]
[2] Redness [Rubor]
[3] Heat [Calor]
[4] Pain [Dolor]
[5] Loss of Funotion. [Lasa]

Inflammation involve cellular or tissue precipitant, the role of inflammation is to protect the body contain injurious agent that invades (enter) in our body.

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It is very common to have to some degrees of necrosis in the area of inflammation.

Inflammation classify on the basis of duration

[A] Pre acute Inflammation
0-4 hour

[B] Acute Inflammation
3-5 days

[C] Sub acute inflammation
Few days - 1 week

[D] Chronic inflammation.
Weak - month.

Inflammation further devide on the basis of area of body.

[A] Dermitis - Inflammation is skin.
[B] Nephritis - Inflammation in Nephron.
[C] Meningitis - Inflammation in Brain
[D] Myocites - Inflammation in muscle
[E] Pancretic - Inflammation in Pacreace
[F] Hepatitis - Inflammation in liver
[G] Conjuctivitis - Inflammation in eye.
[H] Artheritis - Inflammation in joind.
[I] Enteritis - Inflammation in Intestine.
[J] Glomerular - Inflammation in Glomerular.
Nephritis

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Antiinflammatory Drugs

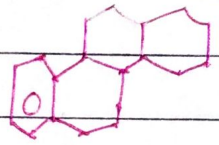
- Those chemical agents / drugs which is used to treat the inflammatory responsce in our body they are called antiinflammatory drugs.

Actually they contains analgesic and antipyretic drugs.

Classification of Antiinflammatory Drugs

[1] Steroidal Drugs
[2] Non steroidal drugs (NSAIDs)

[1] Steroidal Drugs - Those antiinflammatory drugs they contain steroidal rings in their structure they are called steroidal antinflammatory drugs.



[2] Non Steroidal Drugs - (NSAIDs)

Those antiinflammatory drugs they donot have steroidal ring in their structure they are called NSAIDs

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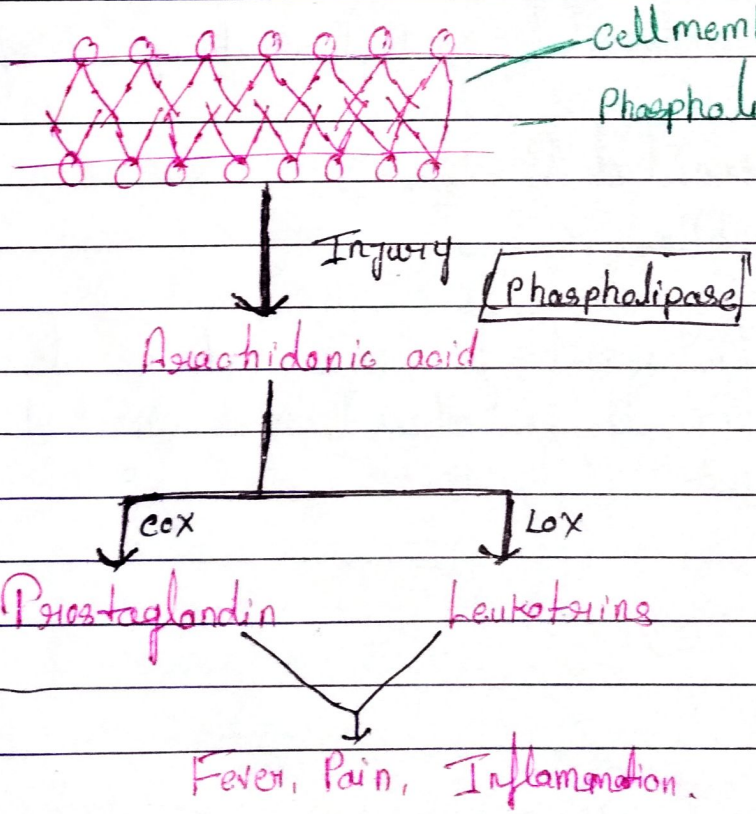
Mechanism of Inflammation-

- During the any cellular injury / autoimmune responce, when the phasphalipid of cell membrane is damaged then due to in the presence of Phasphalipase, it is convert into Arachidonic acid.
- Now Arachidonic acid will further convert into the Prostaglandin and leukotrins in the presence of enzyme cycle oxiginase (cox) and lipooxiginase (LOX).
- When the prostaglandin and leukotrins ~~neurotransmitter~~ or inflammatory mediators are generated in our body then it causes the Fever, pain and Inflammation.



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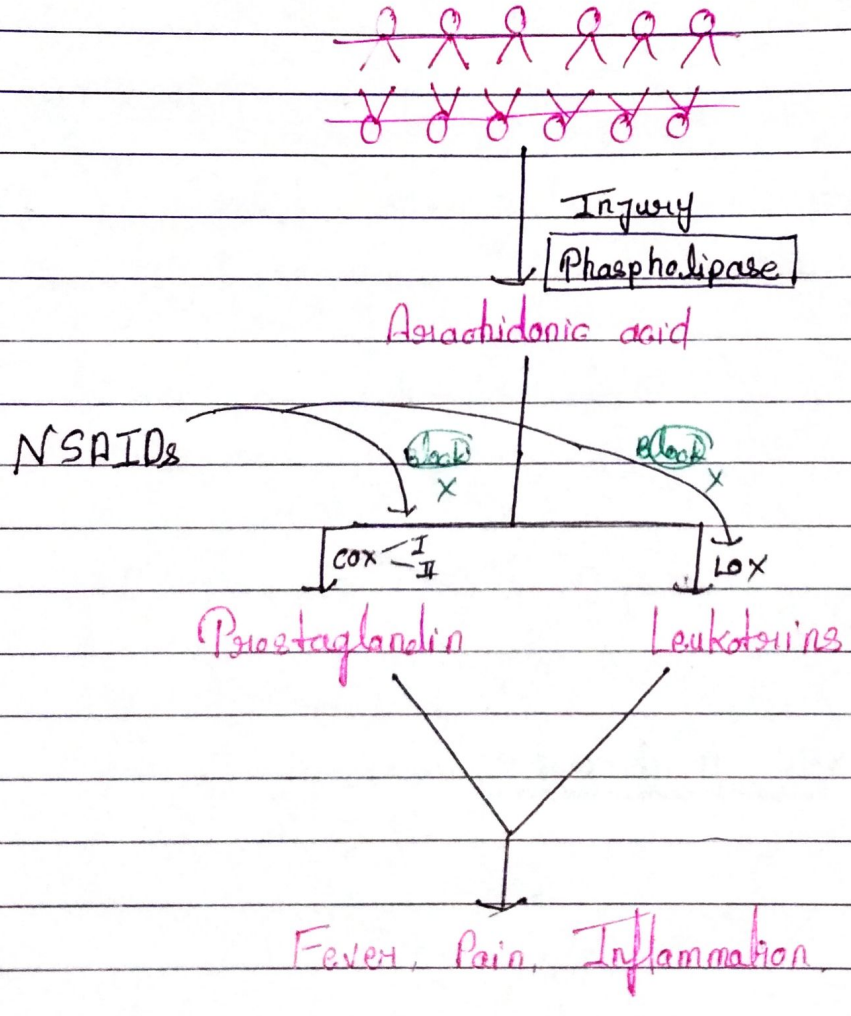
MOA of NSAIDs

- Arachidonic acid is convert into the Prostaglandin and Leukotrins in the presence of enzyme cyclo oxiginase (cox) and Lipooxiginase (Lox).
- And the basicaly drugs NSAIDs inhibit the formation of enzyme Cox and Lox so their is no production of Prostaglandins and leukotrins and it relieves from the Pain, Fever, Inflammation.



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Classification of Nonsteroidal Antiinflammatory Drugs [NSAIDs]

[A] Non selective cox inhibitors [Traditional NSAIDs] -

Ketoprofen
Aspirin
Naproxen
Ibuprofen

Mephenamic acid
Oxyphenbutazone
Nabumetone
Indomethacin.

Tenoxicam
Ketorolac
Flubiprofen
Piroxicam.

Trick - KANI MONI तूने किले फल परीले।

[B] Preferential cox-2 inhibitors -

Nimesulide
Diclofenac
Meloxicam

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Aceclofenac
Etodolac

Trick- निम्नी दी को मेल कर दो
AC एक दो लाख वाला है।

[C] Selective Cox-2 Inhibitors-

Celecoxib
Etoricoxib
Parecoxib

Trick- सीलिंग पर इटा रखा है?

[D] Analgesic - antipyretics with poor antiinflammatory action.

Paracetamol (Acetaminophen)
Metamizol (Dipyrone)
Propiphenazone.
Nefopan.

Trick- Paracetamol मे तो नका नही है? पर फिट भी बैठना है।

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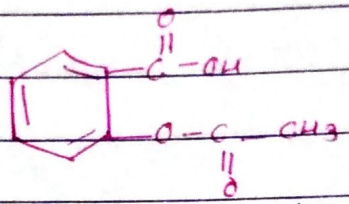
Brief Notes of NSAIDs -

[1] Aspirin



Aspirin

- Rarely used as an anti-inflammatory medication.
- But it has proved to be beneficial for CVS patient in term of its anti-platelet effects.
- Salicylic acid is a simple organic acid.

Pharmacology - Salicylates are rapidly absorbed from the stomach and upper small intestine.

- Peak plasma level within 1-2 hours.
- It is rapidly hydralyzed also (serum half life 15 min) to acetic acid and salicylate by esterases in tissue and blood.
- Alkalization of urine Teses the rate of excretion of free salicylate and its water soluble-conjugate- Salicylate posioning.

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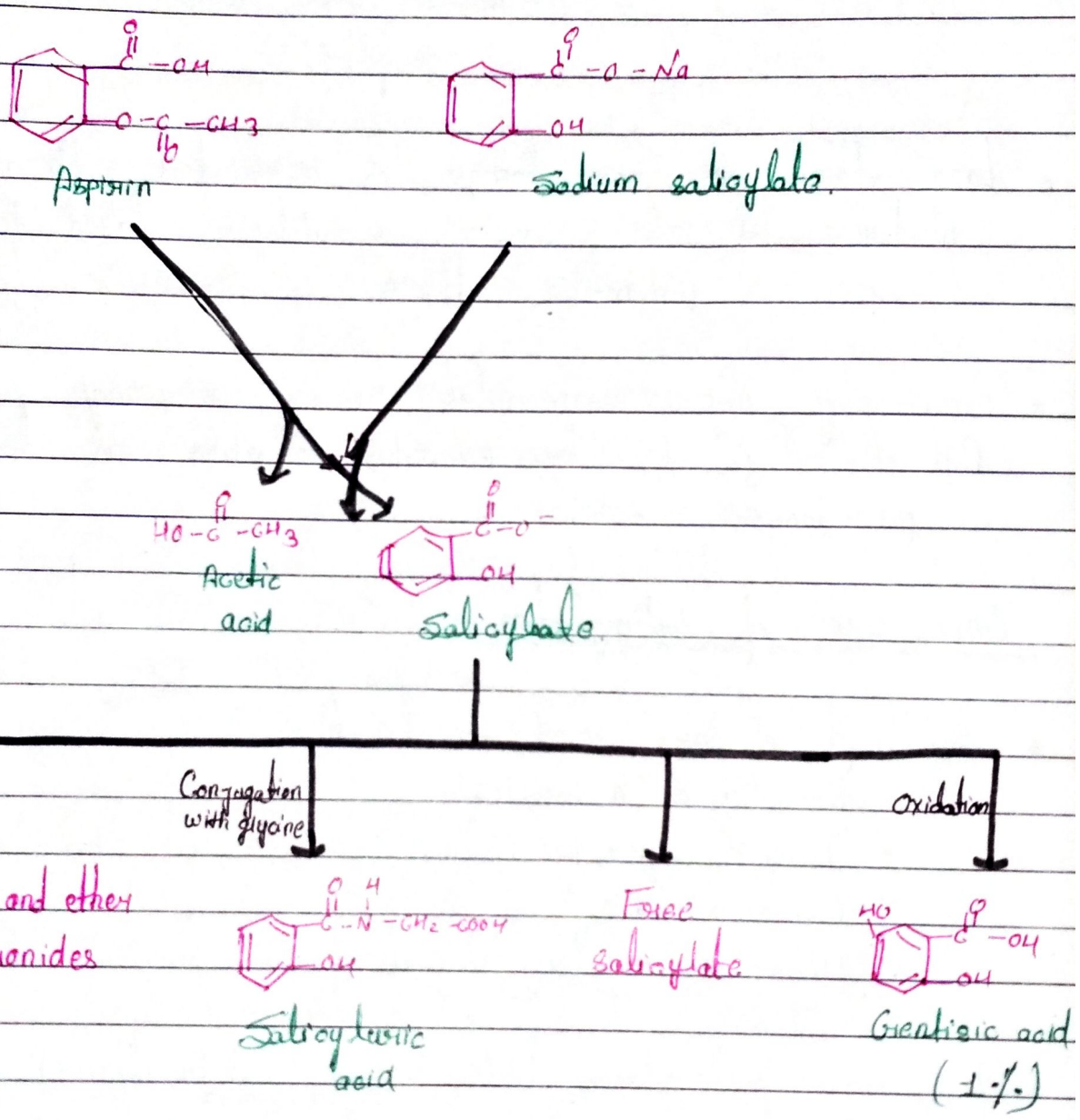
Mechanism of Action- Irreversibly inhibits platelet cox so that aspirin's anti-platlet effect lasts 8-10 days.

Metabolism of the Salicylates-



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Clinical Uses -

- Cardiovascular effect - decreases the incidence of -
  - transient ischemic attacks
  - Unstable angina
  - Coronary artery thrombosis with MI.
  - Thrombosis after coronary artery bypass grafting.

- Long term use low dosage is associated with a lower incidence of colon cancer - possibly related to its cox- inhibiting effects

- Previously not recommended during pregnancy.
  - But recently it has proved valuable in treating preeclampsia - eclampsia.

Other uses of salicylates -

- Salicylates are used to treat -
  - Rheumatoid arthritis.
  - Juvenile arthritis
  - Osteoarthritis
  - Other inflammatory disorders.

- 5 - amino salicylates (Mesalamine, Sulfasalazine)
  - Crohn's disease.

- Salicylic acid is used topically to treat -
  - Plantar warts. - Fungal infections, - Corns.

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Adverse effects -

- Adverse effects at antithrombotic doses are gastric upset and gastric duodenal ulcers.
- Hepatotoxicity, asthma, rashes, GI bleeding, and renal toxicity rarely if ever occur at antithrombotic doses.
- Contraindicates its use by patients with hemophilia.
- Teted inaidence of Reye's syndrome, characterized by -
  Vomiting
  Hepatic disturbences.
- The use of aspirin and other salicylates to control fever during viral infections in children and aldosteronts is totally contraindicated.

[B] Ibuprofen -

- Better tolerated alternative to aspirin.
- All have similar Pharmacodynamic properties, differ potenty and to some extent duration of action.
- The analgesic, antipyretic and anti-inflammatory efficacy is rated somewhat lower than high dose of aspirin.
- All inhibit PG synthesis - Naproxen being most potent.

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- Inhibition of platlet aggregation is short-lasting with ibuprofen, but longer lasting with naproxen.

Clinical Use- Available as an 'over the-counter' OTC drug 200 mg, 400 mg, 600 mg.

- Used as a simple analgesic and antipyretic.
- Effective in dysmenorrhoea.
- Ibuprofen and its congeners are widely used in rhematoid arthritis, osteoarthritis and other mucoskeletal disorder.
- Indicated in soft tissue injuries, fracture, vasectomy, tooth extraction and relieve post-partum pain.
- Effective in closing patent ductus arteriosus in preterm infants.
- Oral and intravenous routes are equally effective.
- Topical cream preparation appears to be absorbed into fascia and muscle.-
  Relieve joint pain in osteoarthritis.
- A liquid gel preparation 400 mg, provides prompt relief and good overall efficacy in postsurgical dental pain.

Adverse effect - Contraindicated in individuals with nasal polyps, angioedema and bronchospastic reactivity to aspirin.

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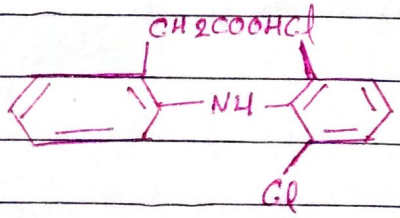
- Aseptic meningitis and fluid retention have been reported.
- Concomitant administration of ibuprofen and aspirin
  - Antagonistic effect

[3] Celecoxib

- Selective Cox-2 inhibitor - about 10-20 times more selective for COX-2 than for Cox-1.
- Associated with fewer endoscopic ulcers than most other NSAIDs.
- Probably because it is a sulfonamide, celecoxib may cause rashes.
- Does not affect platlet aggregation at usual doses.
- It interacts occasionally with warfarin
- Adverse effects are the common toxicities listed above.

[4] Diclofenac



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- Phenylacetic acid derivative that is relatively non-selective cox inhibitor.
- Its available as diclofenac sodium salt.
- Gastrointestinal ulceration may occur less frequently than with some other NSAIDs.
- Antiplatelet action is short lasting
- T 1/2 = 2 hrs.
- Good tissue penetrability.

Clinical Use - Most extensively used NSAID.

- Combination of diclofenac and omeprazole : Effect with respect to the prevention of recurrent bleeding.
- But renal adverse effect were common in high-risk patients.
- Dosage above 150 mg/d : Impair renal blood flow and glomerular filteration rate.
- Other combination include ibuprofen + diclofenac excellent pain management as OTC drug.
- 0.1% Opthalmic preparation : Prevention of postoperative ~~eff~~ ophthalmic inflammation.

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- Canbe used after intraocular lens implantation and strabismus surgery.
- Topical gel containing 3% diclofenac is effective for solar Keratoses.
- Rectal suppository form canbe considered for preemptive analgesia and postoperative nausea.
- Also available as an oral mouthwash and for intramuscular administration.
- Osteoarthritis, bursitis, ankylosing spondylitis, toothache dysmenorrhoea - quick relief of pain.

[5] Ketorolac

- Novel NSAID with potent analgesic and moderate anti-inflammatory effect.
- In post operative pain it has equivalent efficacy of morphine.
  - but it doesnot interact with opoid receptors and is free of opioid side effect.

Pharmacokinetic - Rapidly absorb after oral and I.M. administration.

- T1/2 5-7 hrs, highly plasma bound and 60% excreted unchanged.
- Metabolic pathway is glucuronidation conjugation.

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Clinical Use- Frequently used in postoperative pain menagement - Dental and acute musculoskeletal pain.

When used with an opoid, it may decrease the opoid requirement by 25 - 50 %.

Ophthalmic preparation is available for ocular inflammatory conditions.

Renal colic and pain due to bony metastasis.

Orally it is used in a dose of 10 - 20 mg.

Rated superior to aspirin, paracetamol (600 mg) and equivalent to ibuprofen (400 mg).

Continuous use for more than 5 day is not recommended - renal toxicity.

[6] Nimesulide

Newer NSAID is a relatively weak inhibitor of PG synthesis.

There is some evidence to indicate relative COX-2 selectivity.

Analgesic, antipyretic and anti-inflammatory activity hasbeen rated comparable to other NSAIDs.

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MOA-
- Reduced generation of superoxide by neutrophils,
- inhibition of PGE synthesis and TNFα release,
- free radical scavanging,
- inhibition of metalloproteinase activity in cartilage.

Pharmacokinetic-
- Almost completly absorbed orally.
- T1/2 2-5 hrs, plasma protein bound.
- Extensively metabolized and excreted mainly urine.
- Dose 100 mg BD.

Clinical Uses- Primarily for short-lasting painful inflammatory conditions.
- Sports injuries.
- Sinusities and other ear, nose, throat disorder.
- Dental surgery
- Bursitis, low backache.
- Dysmenorrhoea.
- Postoperative pain.
- Osteoarthritis and for fever.

Adverse effect- Common

GIT - Epigastralgia, heart burn, nausea, loose motion

Dermatological - Rash, pruritus

Central - Somnolence, dizziness

Hematuria is reported in few children.

Instances of fulminant hepatic failure have been associated with nimesulide.

Banned in almost all developed countries.

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But extremely useful for asthmatics and those who develop bronchospasm or intolerance to aspirin and other NSAIDs.

So it should be limited use in such person only.

V.V. Imp

[7] Paracetamol

- Acetaminophen - De-ethylated active metabolite of Phenacetin.
- Central analgesic action of paracetmol is like aspirin, that is it raises pain threshold.
- It is a poor inhibitor of PG synthesis in peripheral tissues, but more active on cox in the brain.
- Its a good and promptly acting antipyretic, but negligible anti-inflammatory action.

Pharmacology-

- Analgesic action of aspirin and paracetamol is additive.
- Well tolerated orally, but only about 1/4 th is protein bound.
- It is uniformly distributed in the body.

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- Metabolism occurs mainly by conjugation of glucuronic acid and sulfate.
- Plasma $t_{1/2}$ 2, 3 hrs, effects after an oral dose last for 3-5 hours.

Clinical Use- One of the most commonly OTC drug for analgesic - headach, migraine, musculoskeletal pain, dysmenorrhea.

- But is relatively inaffective when inflammation is prominent.
- First choice analgesic for osteoarthritis by many professional bodies.
- Drug of choice - as antipyretic, especially in children (no risk of Reye's syndrome).

Adverse effect - Safe and well tolerated.

Nausea and rashes occur occasionally and other side effects are similar to other NSAID.

Analgesic nephropathy - After years of heavy use - Personality defect.
Pathological lesions like necrosis, tubular atrophy followed by renal fibrosis.

Acute paracetamol poisoning - Especially in small children who have low hepatic glucuronide conjugating ability.

- If a large dose >150 mg/kg or >10mg in an adult - Serious toxicities
- Fatality is common >250 mg/kg.

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Day- Wednesday

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CHAPTER - 6th

GOUT

It is an inflammatory disease of joints due to imbalance of purin metabolism.

Etiology- Due to purin metabolism purin is convert into uric acid and uric acid after reaction with Sodium metal form mono sodium urate crystal [MSU]

These crystals are deposited in synovial joint due to deposition of MSU crystals. the synovial fluid is disappeare so there is problem in movement of joints.

After deposition of MSU crystals inflammation is start which completly affect the joint and this condition is called Gout.

Cause of Gout- There are basicaly 2 reasons of gout.

Due to purin metabolism deposition of purin crystals in Synovial joint.

At low temp. there is rapid change in uric acid with cause acidosis.

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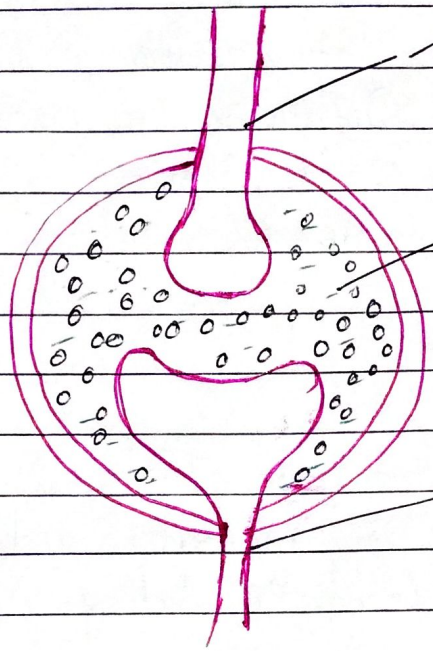
Due to acidosis and low temp. the crystals of Proteio-glycon and chondroitin sulphate is also deposited in joint.

Purin
↓ metabolism
Uric acid



Factors- Gout depends upon following factors.

[A] Life Style- Excessive intake of alcohal and protein diet.
More consumption of nonvage or meat.
High intake of protein powder or gym protein.

[B] Genetics- The gene SLC22A9/ SLC22A12 is responsible for the gout and it canbe transfer from 1 generation to another.

[C] Medical Condition- Excessive fat and obesity may cause gout.

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[D] Medication - Diuretics, Niacin, Aspirin, ACE inhibitor.

Sign & Symptoms -
- Recurrent attack
- Swelling.
- Hot tendon
- Difficulty in movement
- Joint pain.
- Redness.

Complications -

[A] Recurrent Gout — Gout in Joints.
[B] Advanced Gout — Gout in skin, and eyelids.
[C] Kidney stone. — Gout in kidney.

ANTI-GOUT DRUGS

Those drugs which Tes the excretion of uric acid from the body is called Uricoseric drugs.

Uricoseric Drugs - Those drugs which inhibits the formation of uric acid and increase the excretion of uric acid from body they are called Uricoseric drugs.

Uricoseric drugs are 2 types -
1. Colchicine drugs
2. Allopurinol

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02 Colchicine –

- It is an alkaloidal drugs which is obtained from ~~plant~~ Colchicum autominals
- It was discovered by Von stroak in 1763.
- It is not used as analgesic in other type of pain it cannot ↓ inhibit production of Prostaglandin.
- It is used as a painkiller in the case of acute gouty arthesitis
- The Mon of colchicine is decrease the tubul reabsorption of uric acid from the nephron so the level of uric acid is decrease and ammount of uric acid is ↑es in urine.
- After the phagocytosis of uric acid crystal they decrease the release of inflammatory mediators so the inflammation is reduce.

Pharmacokinetics- Its absorption are good, so it administrate by oraly and IV form. Its excrete through urine.

Adverse effect

Nausea
Vomiting
Diarrhoea
Abdominal pain
Leucopenia.

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(2) Allopurinal- The structure of allopurinal is very similar to the Hypoxanthine.

It is the non competative inhibitor for the xanthine oxidase enzyme and is inhibit the xanthine oxidase enzyme to ~~inhibit~~ Produce the uric acid.

It can also lower formation of crystals of uric acid or hyperuricaemia.

Adverse effects- Nausea
Vomiting
Diarrhoea
Gastric irritation
Headache, hypersensitivity.