DRUGS ACTING ON - CVS. :-)

1) Anti-hypertensive Agents.-

As Blood flows through the arteries, it exerts pressure on the inner lining of artery wall, it is called B.P.

HTN is defined as persistant elevation of B.P.

1) DIURETICS - It removes excess Na^{+} & water from the body.

MOA -

Diuretics
↓
acts on kidney
↓
↑ urine volume
↓
Thus, decreases Extracellular fluid vol., plasma vol.
↓
↓ in Peripheral Resistance.
↓
Normalize B.P.

i) Thiazide diuretics - Eg - Hydrochlorothiazide

2) Loop diuretics - Eg - furosemide, torsemide

3) Aldosterone antagonist (K+ sparing). - Eg - Spironolactone

Adr - Hyperkalemia, Hyperuricemia,

2) Ca^{+2} channel Blocker -

Eg - Verapamil, Diltiazem, Amlodipine, Nefedipine

They mainly produce 3 effects → 1) Anti-anginal
2) Anti-arrhythmic &
3) Anti-HTN.

MOA - CCB

↓

Blocks L type Ca^{+2} channels. (L type mediate the entry of extracellular Ca^{+2} into smooth muscles)

↓

↓ Ca^{+2} entry in myocytes of S.M.

↓

causes relxn. of myocytes of S.M,

causes Vasodiln & ↓ B.P.

Adr - Verapamil is kl to cause constipation, Headache, ankle swelling.

3) Drugs Acting on RAAS :-

RAAS. Renin-Angiotensin-Aldosterone System.

Is one of the most IMP systems regulates B.P.

1) Renin Inhibitors :- Juxtaglomerular cells release

↓

Renin

Angiotensinogen ⟶ AI.

↑ X

R.I.

Eg - Aliskiren

2) ACE i - they inhibits the conversion of AI to AII, which is a vasoconstrictor.

MOA

AI

ACE ↓ ⟵ ACEi

AII

(Also, ACEi elevates Bradykinin level, which is a Vasodilator.)

Eg - Ramipril, Enalpril, Lisinopril, Captopril

Pharmacological Action -

1) Anti-HTN effect - They're effective in lowering B.P.
- They are useful in treating HTN in elderly patients & also with patients with Heart failure.

2) Cardioprotective effect - In patients with CCF, ACEi have shown a good effect.
They reduce symptoms of fatigue & dyspnea.
& with long term therapy they has prevented an ↑ in heart size (Hypertrophy).

3) Recently, ACEi has shown a benefical effect on Renal insufficiency & diabetic nephropathy.

Use - HTN, CCF, Diabetic nephropathy, Renal insufficiency

Adr - The most common S.E. is dry cough, & Hyperkalemia, Hypotension

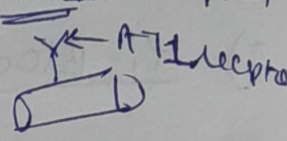
Pharmokinetics - Absorbed orally,
Except for lisinopril, most ACEi are metabolized by liver.
Excreted from kidney by glomerular filtration.
Lisinopril, Enal & capto have longer
Plasma t1/2 - 10-13 hrs.

3) Angiotensin Receptor Blockers (ARB) –

AI
↓ACE
AII. ← It also causes release of Aldosterone from Adrenal cortex

AII produces its action by acting on AT1 receptor

AII, ↑P.R. & constricts vessels.
thus, ↑es B.P.



MOA – AII produces its cardiovascular action by acting on AT1 receptor

↓

ARB Blocks AT1 receptors.

↓

causes → vascular smooth muscle relax^n,
↑ Na+ & water excretion.

↓

↓in P.R.

eg– Telmisartan, Losartan, Valsartan.

→ Taken orally. t1/2 – 2hrs.

Adr. – Hypotns. is most likely to occur in patient where B.P. is highly dependent on AII,
Hyperkalemia may also occur.

4) β-Blockers — They block β_1 receptor on heart. & thus ↓ ~~to~~ C.O. & thereby ↓ B.P.
- They also prevent the release of Noradr.
Eg - Atenolol, Metoprol, Bisoprolol

5) α_1-Blocker - Block α_1 receptor on Smooth muscle
↓
which decreases Vascular Resistence.
Eg - Prazosin.

6) Vasodilators — These are the medication that dilate Blood Vessels.
Eg - ~~Hydralazine~~ Hydralazine, sodium nitroprusside.
- Hydralazine is more selective for arterials.
whereas,
Na. nitroprusside - affects both arteries & veins.
- Sodium nitroprusside is used in Hypertensive Emergency.
- they release nitric oxide
↓
which cause rapid Vasodilation thus lowers B.P.

2) Anti- Arrhythmic Agents :-

~~It is~~ Arrhythmia is an irregular heart rhythm.

H.R < 60 - Bradycardia ; HR > 100 - Tachycardia

Classn

1) Class I - Na+ channel Blockers.

IA - Prolong Repolarisation - eg - Quinidine, Procainamide.

IB - Shorten Repolarisation - Phenytoin, Lidocaine

IC - Little effect on Repn - Propafenone

2) Class 2 - β-Blockers - Eg - Propranolol, Metoprolol

3) Class-3 - K+ channel Blockers - Amiodarone

4) Class 4 - Ca^{+2} channel Blockers - Verapamil, diltiazem

AMIODARONE

- Belongs to class - III group MOA

Amiodarone

↓ Blocks

K^+ channel (K^+ channel causes repolarisation of heart)

↓

↑ in duration of Action potential & Refractory period of cardiac muscle cells.

↓

Cardiac Muscle cells excitability is reduced

↓

Prevents Abnormal Heart rhythm.

Cological Action -

1) Heart - It works directly on heart tissue & ↑ the duration of refractory period.

↓

which treats abnormal heart rhythm.

2) B.P. - It causes hypotension.

3) Thyroid - Amiodarone contains 37% of Iodine which is structurally similar to Thyroxine.

↓

So, It may cause hypo or Hyperthyroidism.

4) Liver - Repetitive amiodarone adm. can cause liver damage.

Kinetics - Adm. - orally.
t1/2 - 29 days
met. - By liver
Ext - by urine.

use - used to treat tachycardia.
- Used to treat & prevent abnormal heart rhyt

Adr. - It can cause thyroid dysfunction
- Blue-grey skin discoloration
- liver damage.
- Hypotension

→ ANTI-ANGINAL DRUGS.

A.P. is a chest pain & discomfort caused due to reduced blood flow to the heart.

Anti-Anginal Drugs

1) Nitrates (causes VENOdilation)
   - short acting - Glyceryl trinitrate, Isosorbide dinitrate (sublingual)
   - long acting - Isosorbide dinitrate (oral), ISO mononitrate.

2) β-Blockers - Propranolol, Metoprolol, Atenolol

3) CCB - Verapamil, diltiazem, Amlodipine

4) K^+ channel opener - Nicorandil

5) Others - Trimetazidine, Oxyphedrine, Dipyridamole

MOA -

Nitrates → ~~release~~ Nitrate ~~ions~~ → converted → Nitrites

Nitrites → NO (nitric oxide) → activates → Guanylyl cyclase → GTP → cGMP

cGMP → activates → Cyclic GMP protein kinase → activates → Phosphorylates MLCK (myosin light chain kinase)

Phosphorylation inhibits MLCK → less Myosin-Actin action → Relaxation of smooth muscles

Also phosphorylates circuit pump → ↓ Ca^{+2}

Adv. of nitrates - Hypotn., Headache, arrhythmia, anaemia

Kinetics GTN → Sublingual is completely absorbed
& onset of action - 1-2 min.
IDN - is given orally.

DRUGS USED FOR HYPERLIPIDEMIAS.

1) HMG-CoA reductase inhibitors (statins) - Eg - Lovastatin, Simvastatin, Atorvastatin, Rosuvastatin.

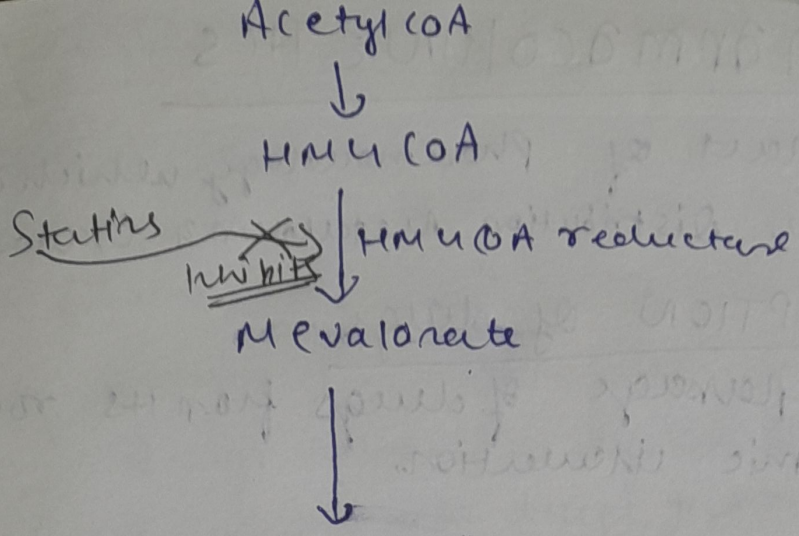
2) Bile acid ~~Binding Agents~~ Sequestrants - Colestipol, cholestyramine

3) Fibrates (Lipoprotein - lipase activators) - fenofibrate, ~~Benzofibrate~~ Bezafibrate, clofibrate

4) Lipolysis & TG. synthesis inhibitors - Nicotinic acid

5) Sterol Abs. inhibitor - Ezetimibe

MOA –



Adr – Statins are metabolized by liver, so they may elevate liver enzymes & may ↑ risk of liver toxicity

☠ – They are also associated with Myopathy & destn of skeletal muscle cells.
- Renal failure, Abd. pain

Kinetics –
Rosuvastatin t1/2 – 19 hrs.
- Excreated by liver.
- Taken P/O.

ANAESTHETICS

Anaesthetics are the drugs used to produce reversible loss of consciousness.

- There are 2 types :-

1) GENERAL - which produce loss of consciousness throughout the body.

2) LOCAL - which numbs only targeted area of the body.

GENERAL ANAESTHESIA

Stages of Anaesthesia :-

1) Stage of ANALGESIA :- It is accompained by loss of pain sensation

- Patient remain conscious, but pain is lost.
- Minor surgical operations can be performed at 1st stage.

2) Stage of Delirium or Excitement :-

- It is the stage of excitement, Muscle tone ↑
- pupils may dilate.
- H.R, B.P may Rise, Vomitting can also occurs.
- Pre-anesthetics are given to lower down these symptoms.

3) Surgical Anaesthesia -

It is characterised by recurrence of normal Respiration, H.R, B.P, & relaxn of smooth muscles.

It is further divided into 4 Planes :-

→ PLANE-1 - It is an intermediate stage characterized by gradual ↓ in reflexes, movements of eyeball & normal pupil size. reacts to light.

→ PLANE- 2 - It is an Ideal phase to perform surgery.
- Loss of Corneal & Laryngeal reflexes.
(Corneal Ref- Is an involuntary blinking of eyelids.
laryngeal Ref - such as - cough, expiration. (Laryngx & pharynx))

→ PLANE-3 - Most ideal phase for surgery.
- Pupil starts dilating., & doesn't respond to light.
- Light Reflex is lost.

→ PLANE-4 - characterized by dilation of pupil,
Respiration becoming thoracic,
fall in B.P., Intercostal paralysis.
this plane is usually avoided.

4) Medullary Paralysis - stage of Respiratory Paralysis. Medullary centres are progressively depressed.
↓
Resulting in Irregular breathing & low B.P. &
& may cause cessation of Breathing.
- pupils are dilated & light reflex is lost.
- If this stage is not properly controlled & quickly reversed, then, death can occur.

Class

1) Inhalational → a) Liquids - Ether, chloroform, Enflurane, Isoflurane, Desflurane

→ b) Gas - Nitrous oxide, Ethylene

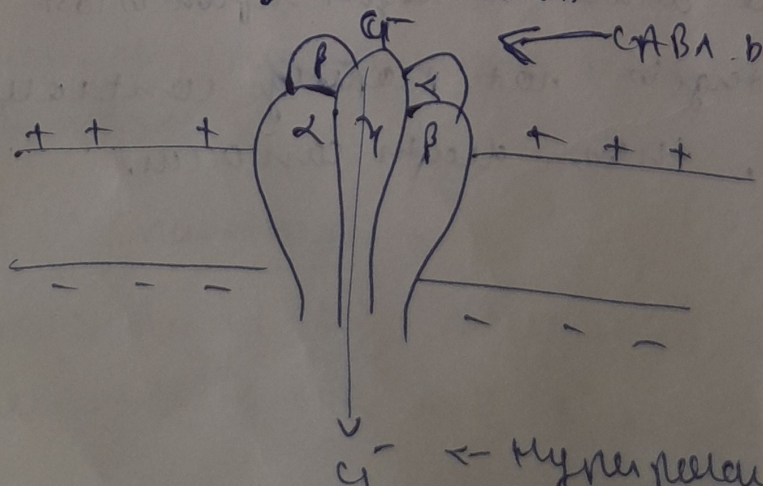
2) Intravenous → 1) fast acting: Thiopentone, Methohexitone, Propofol

slow acting - Diazepam, Lorazepam, Ketamine

MOA:- These drugs produce diff. action by acting on diff. positions on Brain

Main Site of Action - Ligand-gated ion channels (GABA - Receptor - Cl^- ion channel)

GABA is an inhibitory neurotransmitter present mainly in Brain.



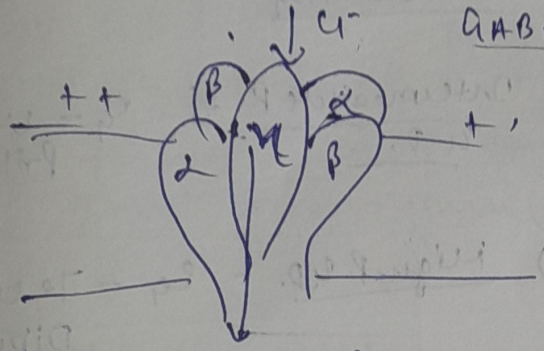
General Anesthetic ↑ the affinity of GABA towards GABAA receptors.

↓

Hyperpolarisation

↓

Inhibition of Response towards stimuli



→ General Anaesthetics ↑ the affinity of GABA towards GABAA receptors

↓

↑ in frequency of GABA-gated Cl⁻ channel opening

↓

Influx of Cl⁻

↓

Hyperpolarisation

↓

Inhibition of Response towards stimuli

* Pharmacological Action -

1) CNS - Besides Anaesthesia & amnesia, GA. ↓ the metabolic rate of the brain.
→ chloroform causes hepatotoxicity.

2) CVS - they ↓ H.R & B.P. thus it cause cardiac depression.

3) R.S. - Anaesthetics also alter Resp. volumes. & thus ↓ the Resp. rate.

LOCAL ANAESTHETIC

- Are medications used to ~~block~~ Reversibly block the pain sensation in a specific part of the body.

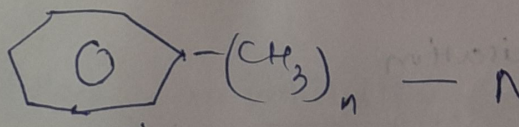
Class

1) Injectable → a) low potency, short duration → Eg - Procaine
   - b) Intermediate P' & D. → Eg - Prilocaine
   - c) High P. & D. - Eg - Tetracaine, Dibucaine

2) Surface anaesthetic - Eg - Cocaine, Lidocaine, Benzocaine

→ Characteristics of local anaesthetics :-

1) All L.A. contain a lipophilic Aromatic residue connected with Hydrophilic amino grp with may be Ester, amide, ketone or ether.



Lipophilic — Hydrophilic

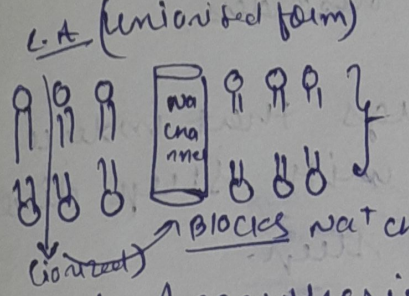
2) Lipophilic activity is essential for migration of drug into neurons.
while, Hydrophilic is water solubility is essential to get the drug to the site of action from the site of application.

3) The action of L.A. is pH dependent.

4) Vasoconstrictor are mixed with L.A. to ↑ duration of action.

5) Duration of action of L.A. ∝ to time during which it comes in contact with Nervous tissue.

MOA:-



Local Anaesthesia (unionised form)

↓

Block the voltage gated Na^+ channel

↓

No entry of Na^+ into cell.

↓

No depolarization

↓

No generation of Action potential

↓

No impulse generation to CNS.

↓

Numbness ~~not~~ specific site/local.

↓

local ~~Anaesthesia~~ Anaesthesia

Adv - - continuing numbness,
- headaches, Bradycardia
- Dizziness, Edema at site of inj.

Uses - It is used to prevent pain during medical procedures.
- Used to numb sp. part of body.
Eg- when tooth removal surgery takes place, local anaesthesia is given to patient.
- Lidocaine is widely used L.A.

SEDATIVES & HYPNOTICS

- Sedatives or tranquillisers that produces a calming effect. It is used to treat anxiety, sleep disorders, tension, panic disorders.

- Hypnotics are the drugs that induce or prolong the sleep in patient with sleep disorder (insomia) & improves quality of sleep.

SEDATIVE	HYPNOTICS
- A drug that reduces excitement, calms the patient (w/o inducing sleep).	- A drug which induce sleep
- Sedatives in therapeutic doses are anxiolytic agents.	- They are used for maintenance of sleep.
- Most sedative at high doses produce hypnosis	Hypnotics in high dose produce general Anaesthesia
- Longer duration of action	- Shorter duration of action
- Site of action - Limbic system	- Site - Midbrain & ascending RAS

Class

1) Benzodiazepines

(1) Hypnotics - Diazepam, Nitrazepam

(2) Anti Anxiety - Diazepam, Lorazepam, Oxazepam

(3) Anti-convulsant - Diazepam, Lorazepam, Clonazepam

(2) Barbiturates → (1) Long acting - Phenobarbitone

(2) Short acting - Pentobarbitone

(3) Ultra short acting - Thiopentone, Methohexitone

(3) Non-Benzodiazepines - Zopiclone, Eszopiclone

1) Benzodiazepine

MOA - Benz. Binds to its receptor site

↓

This ↑es the affinity of GABA for GABA binding site

↓

↑ in frequency of channel opening

↓

↑ influx of Cl^-

↓

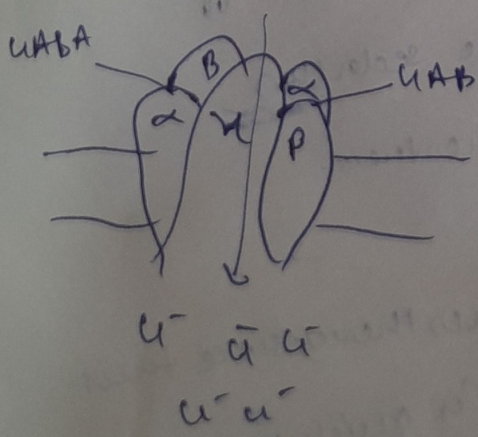
Hyperpolarisation

↓

No Initiation of Action potential

↓

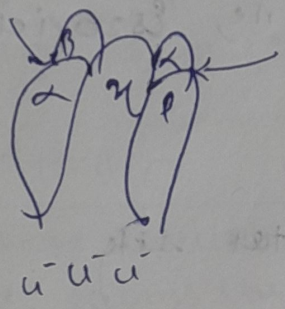
thus decreases anxiety & causes calmness.



Use - Anxiety, Insomia, Treat of epilepsy & seizures, for muscle relaxⁿ, as a pre-anesthetic medication

Adv - Main S-E is drowsiness, confusion, dizziness, decreased alertness & concentration.

2) Barbiturates



Barbiturates binds to α or β subunits of GABAA receptor

↓

Enhances the affinity of GABA for GABAA receptor.

↓

But, unlike BNZ, they Increase the Ion channel opening duration

↓

Cl^- influx

↓

Hyperpolarisation

↓

Reduce anxiety & causes calm effect

Long acting Barbi → Orally → Produce sedation

→ IV → Anaesthesia.

Short & intermediate → Produces anaesthesia since their onset of action is quicker.

They cause CNS depression & Respiratory depression

↓ B.P.

2) Non-Benzodiazepine

They are structurally diff. from BZD.

↓

They bind to α1 subunit of $GABA_A$-receptor

↓

Cl^- Channel opening

↓

Cl^- influx

↓

Hyperpolarization.

↓

They leads to Sleepiness but NOT Anti-anxiety effect

AUTACOIDS

- Autacoids are those Naturally occurring substances that Produce wide range of pharmacological actions in small amts. & Produce local action.
They are also termed as 'Local Hormones'

- Amine Autacoids
  - Eg - Histamine, 5-Hydroxytryptamine (serotonin)
- Lipid derived
  - Prostaglandins
  - Platelet activating factors, leukotrienes
- Peptide
  - Kinin
  - Bradykinin
  - Angiotensin

Auto:- self ; acos - Healing ;

1) HISTAMINE

- Histamine in body tissues is found in Mast cells.

∴ Histamine is a BASE, & it binds to acid groups. like - carboxyl, thiol & phosphate.

- Any base stronger than histamine, displaces Histamine from binding.

Histamine is synthesized from A.A., Histidine

↓ decarboxylation by L-Histamine decarboxylase

Histamine.

→ There are 4 types of Hist. receptors

- H_1, H_2, H_3, H_4

Histamine

6) Nerve endings - causes pain & itching sensation

* Pharmacological Action :-

1) Smooth Muscles - S.M. are stimulated by Histamine
- It causes Contn of bronchial muscles, which can cause Asthma. & also also causes - Airway Mucosal Oedema.

2) Gastric Acid Secretion - It ↑ the G.A. secretion
- Formation of HCl is ↑. & repeated injections of histamine produces ulceration on gastric mucosa.

3) CVS - Histamine causes ↑ in force of contn & H.R. It also causes dil^n of Arteries which may cause fall in B.P.

4) Triple response in skin - Local application of hist. on skin produces - "Triple response".
↓
flush, flare & wheal.

5) ~~CNS - Histamine X cross B.B.B. ⇒ No effect.~~ via I.V.

5) CNS - Histamine is involved in various actions mediated through CNS.
Histamine acts on brain via 3 receptors - H_1, H_2 & H_3
- It is a mediator of wakefulness. & its activity is necessary to maintain wakefulness & alertness.
- Histamine can also cause Headache with intense pain.

(6) ↑↑

H_1 - Present almost the whole body, Eg. in Smooth muscle.

H_2 - Gastric cells, CNS, heart & uterus.

H_3 - @ CNS

H_4 - @ Immune cells.

Uses – It is used for diagnosis of Gastric acid secretion, leprosy & Pheochromocytoma.

- Triple response induced by histamine is absent in patient suffering from leprosy.
- Histamine is also used in treating Tinnitus (ringing of ears)

Anti-Histamines

H1 Receptors Blockers

1st Generation
(~~Cause~~ Crosses BBB)
(cause sedation)
Eg - Brompheniramine,
Chlorpheniramine,
Clemastine,
Doxylamine,
Hydroxyzine,
Diphenhydramine

2nd Generation
Eg - Cetirizine,
Levocetirizine,
Loratadine,
Fexofenadine,
Desloratadine

→ Pharmacological Action.

1) CNS - They cause CNS depression & Produce sedation & sleepiness. may also cause dizziness & disturbance of coordinate

2) ~~General Action~~

2) General Action – (Anti-H, due capacity of occupying other receptors).

→ Blockage of cholinergic receptor → causes Urine Retention.

→ Blockage of Serotonin receptor → ↑ in appetite

→ Blockage of central Histamine & Ach receptors → produces Antiemetic & Anti Nausea effect.

→ They block histamine induced action like - vasodil^n, hypotension, allergy, bronchoconst^n, triple response, headache.

3) Local Anaesthetic – Anti-Hist. also produces ⊕ action.

→ Pharmacokinetic - Absorbed orally, Metabolised by liver, Excreted in urine.

Ther. uses - → As Sedative & hypnotics

~~help to get~~ → helps to get relief from snoring, insomnia

→ helps to get relief from allergic reactions

→ Blocks the action produced by Histamine

↓

such as → vasodil^n, hypotension, Bronchoconst^n, allergy, headache, Anaphylaxis

Adr – Sedation, drowsiness, euphoria ⊕ are common, G.I. muscle incoordination, tremors, Nausea,

H_2 - Receptor Antagonist

MOA - Histamine H_2 receptors cause ↑ in cAMP
↓
Stimulates $H^+ K^+$ ATPase
↓
Release hastric acid

MOA → H_2 - blockers
↓
Block H_2 receptors
↓
↓ cAMP form^n
↓
Reduce Acid sec^n
↓
Treat ulcers

Eg - famotidine,
Ranitidine,
Cimetidine,
Nizatidine

5- Hydroxytryptamine (5-HT)

Also known as → Serotonin

- 90% of the total Serotonin is found in Intestinal wall.
- It is also found in brain Platelets, Mast cells etc.
- Vegetables like - Tomatoes, bananas also contain Serotonin.

→ Pharmacological Action :-

1) GIT - Stimulates peristalsis,
↑ mucus prodn & ↓ acid prodn. & Pepsin
- They ↑ Gastric motility & contn
↓
causes Diarrhea.

~~2) CNS - when injected, X cross BBB - no effect.~~

3) It promotes Platelet aggregation. & controls bleeding.

4) Smooth muscles of stomach & bronchioles are constricted by 5-HT.

5) Triphasic Response on B.P. →
1) Initial rise in arterial B.P.
2) Short period of fall effect
3) Prolong fall in B.P due to vasodiln

6) Heart - Direct Inotropic & Chronotropic effect.

2) CNS - via Inj, · X cross BBB → No effect

But, the serotonin present in Brain regulates :-
mood, sleep, temp. of body, behaviours, appetite.
~~Appetite~~
↓
when directly injected to brain causes
↓
sleepiness, change in body temp. & appetite.

Serotonin Receptor Antagonist

Eg) 1) **Cyproheptadin** - 1° action - $5HT_2$ receptors.

also antagonizes H_1 receptors.

Effective in - skin allergies, cold, urticaria, carcinoid syndrome

Side E. - wt. gain, drowsiness, ↑ growth in children.

⇒ It ↑ the appetite.

2) **Ketanserin** - It is a 5-HT_2 receptor antagonist.

- Antagonizes 5-HT induced activity

↓

like - vasoconst^n, platelet aggregation

3) **Ondansetron** - They are 5-HT_3 Antagonist

- controls - Nausea & vomitting.
- can be given P/O or I.V..

4) **Sarpogrelate** - It is a $5HT_{2A}$ receptor antagonist

- It has an Antiplatelet action.
- It also reduces ~~to~~ smooth muscles relax^n. & causes vasodil^n.

↓

All these properties makes Sarpogrelate cardioprotective & makes in useful in CAD.

Serotonin Receptor Agonist

1) **BUSPIRONE** — It is a **5HT$_{1A}$** partial agonist. It is used to treat anxiety & controls our mood.
S.E - dizziness, N., Vom., headache.

2) **SUMATRIPTAN** - It is a **5HT$_{1B}$ & 5HT$_{1D}$** agonist they are effective in treatment of **Migraine** & **headache**.

3) **Renzapride** - It is a **5HT$_4$** agonist.
- Helps in treatment of constipation & Irritable Bowel Syndrome (IBS).

5HT Receptors

	Agonist	Antagonist
1) 5-HT$_{1A}$	Buspirone	Spiperone
2) 5-HT$_{1B/1D}$	Sumatriptan	Ergotamine
3) 5-HT$_2$	α-m-5HT	Ketanserine, cyproheptadine
4) 5-HT$_3$	2-m-5HT	Ondansetron
5) 5-HT$_4$	Renzapride	cisapride