

SEROTONIN / 5- HT



Sreehari .y
Assistant professor
Dept of pharmacology
G.Pulla reddy college of pharmacy

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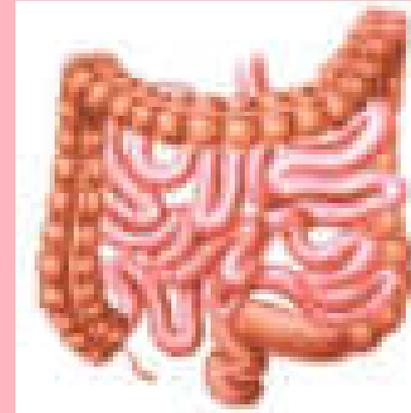
- Introduction
- Distribution of serotonin
- Synthesis , storage and release
- Receptors
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Introduction

- 5-hydroxytryptamine (5-HT) is a **monoamine neurotransmitter**.
- Biochemically derived from tryptophan
- serotonin is primarily found in the **gastrointestinal tract** (GI tract), **blood platelets**, and the **central nervous system** (CNS) of animals, including humans.
- It is popularly thought to be a contributor to feelings of well-being and happiness

Distribution of serotonin

- About 90 % of body's content of 5-HT is localized in the intestine
- In platelets and brain
- Also found in wasp and scorpion sting
- Widely distributed in invertebrates and



Cont.....

- Plants – banana ,
- tomatoes ,
- pear ,
- pineapple ,
- stinging nettle and
- cowhage



Synthesis

Tryptophan

hydroxylase

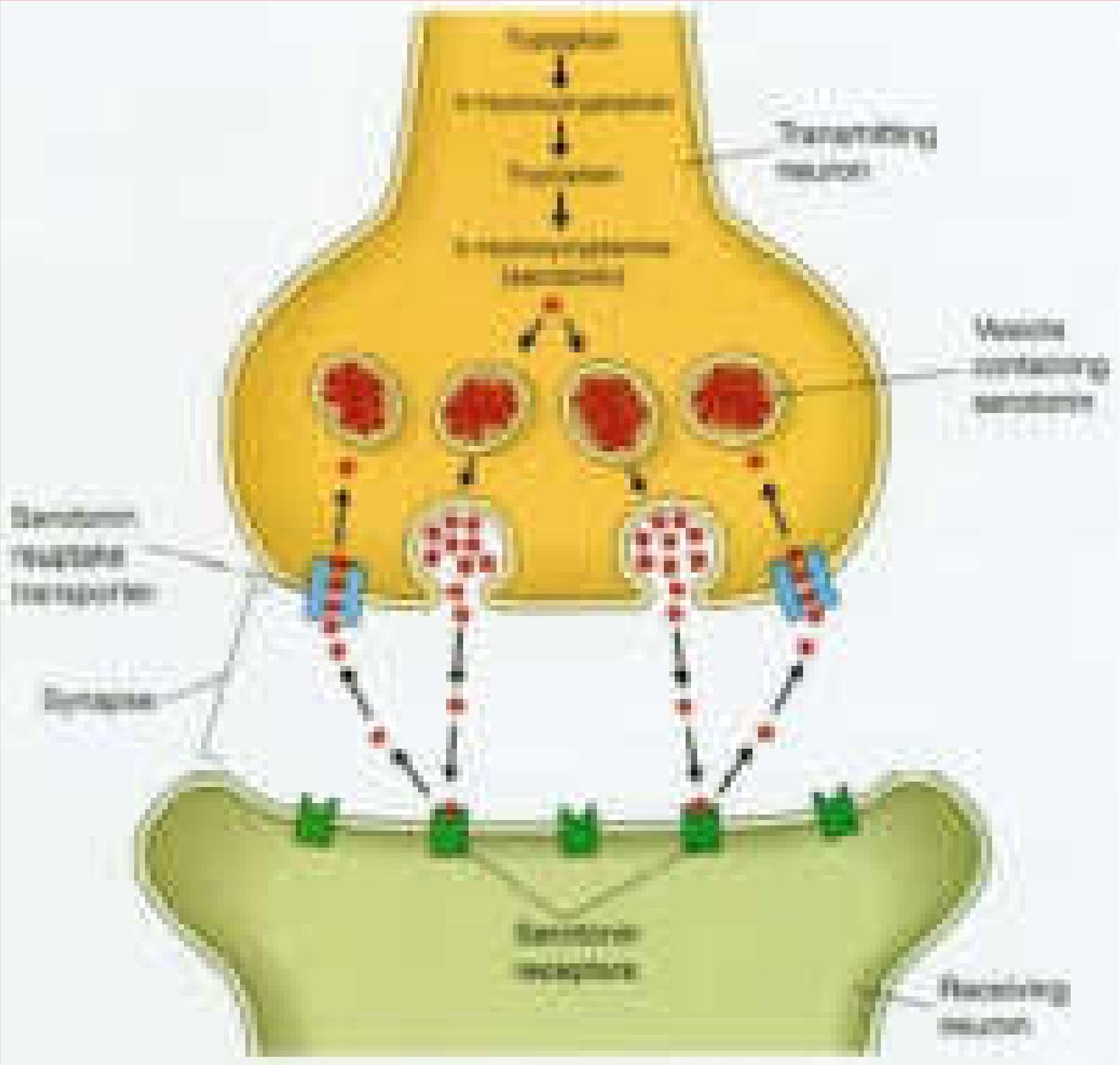
5- HYDROXY TRYPTOPHAN

decarboxylase

5- HYDROXY TRYPTAMINE

MAO

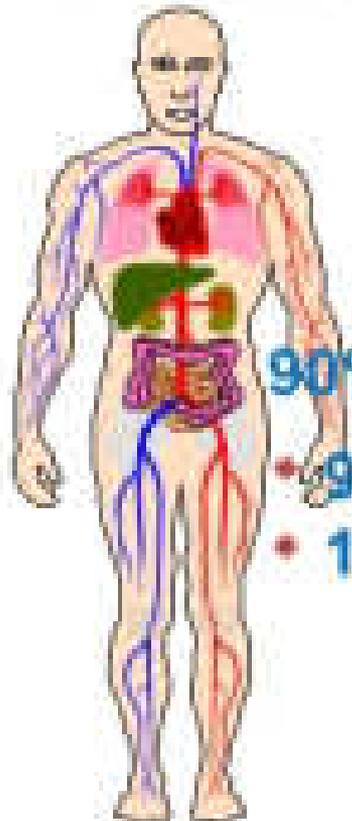
5-HYDROXY INDOLE ACETIC ACID



Storage

Physiologic Distribution of Serotonin (5-Hydroxytryptamine (5-HT))

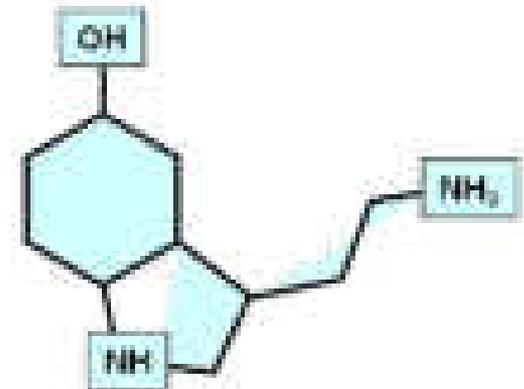
10% CNS



90% GI tract

• 90% ECs

• 10% Neurons



5-Hydroxytryptamine

Receptors

Drugs acting on 5-HT receptors

receptor	location	function	agonist	antagonist
5-HT ₁	CNS, vascular smooth muscle	Neuronal inhibition, sleep, behavior, feeding, anxiety	Buspirone(PA), triptans	Ergotamine(P A), methiothepin
5-HT ₂	CNS, PNS, smooth muscle, platelets	Neuronal excitation, smooth muscle contraction, platelet aggregation	LSD	Ketanserin, ciproheptadine, pizotifen, ketotifen

Cont....

5-HT ₃	PNS, CNS	Neuronal excitation (nociceptive, autonomic neurons, emesis, anxiety)	— 2 methyl 5 HT	Ondansetron, granisetron, palonosetron
5-HT ₄	PNS (GIT), CNS	Neuronal excitation, GI motility	Metoclopramide, cisapride	
5-HT ₅	PNS, CNS	Modulation of behavior?	—	—
5-HT ₆	CNS, Leukocytes	Learning and memory??	clozapine	—
5-HT ₇	CNS, GIT, Blood vessels	Thermoregulation?	LSD	

5-HT Receptors

Receptor	5-HT ₁	5-HT ₂	5-HT ₃	5-HT ₄	5-HT ₅	5-HT ₆	5-HT ₇
Subtype	5-HT _{1A} 5-HT _{1B} 5-HT _{1D} 5-HT _{1E} 5-HT _{1F}	5-HT _{2A} 5-HT _{2B} 5-HT _{2C}	5-HT _{3A} 5-HT _{3B}			5-HT _{5A} 5-HT _{5B}	
Major signaling pathway	cAMP ↓	IP3 ↑	ion channel	cAMP ↑	cAMP ↓	cAMP ↑	cAMP ↑

Pharmacological action

1. CVS :

- ✓ arteries – constricted (by direct action)
- ✓ dilated (through EDRF release)

Isolated Heart - stimulated

In intact animals : bradycardia is seen

Triphasic response :

1. early sharp fall in BP
2. Brief rise in BP
3. Prolonged fall in BP

2.visceral smooth muscles :

- ✓ potent stimulator of GIT – by direct action as well as through enteric plexuses
- ✓ peristalsis is ↑ and diarrhoea can occur
- ✓ constricts bronchi

3. Glands :

5-HT inhibits gastric secretion

↑mucous production

has ulcer protective activity

other glands – not significant effect

4. Nerve endings and adrenal medulla :

tingling and pricking sensation as well as pain

nausea and vomiting

5. respiration :

stimulation of respiration and

hyperventilation

large doses – cause transient apnoea

6. platelets :

causes – weak aggregation

does not induce the release reaction

7. CNS :

Injection I.V., = **does not cross BBB**

Direct injection – produces

- ✓ sleepiness ,
- ✓ changes in body temperature ,
- ✓ hunger and
- ✓ a variety of behavioural effects

Pathophysiological roles

1. Neurotransmitter :

- ✓ Sleep
- ✓ Temperature regulation
- ✓ Thought
- ✓ Cognitive function
- ✓ Behaviour and mood
- ✓ Appetite
- ✓ Vomiting and
- ✓ Pain perception



Hmmmmmm...



2. precursor of melatonin

regulate biological clock and maintain circadian rhythm

3. Neuroendocrine function

hypothalamic neurons are probably regulated by serotonergic mechanism

4. Nausea and vomiting

especially that evoked by cytotoxic drugs or radiotherapy is mediated

5. Migraine

vasoconstrictor phase

and to participate in neurogenic inflammation of the affected blood vessels



Cont..

6. Haemostasis

platelet aggregation and clot formation

7. Raynaud's phenomenon

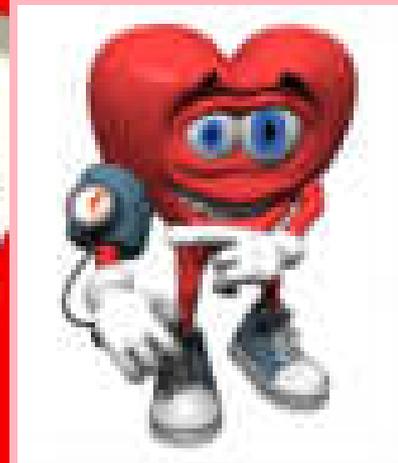
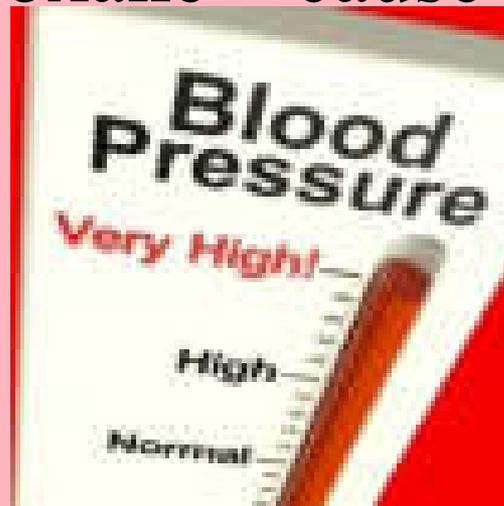
triggers acute vasospastic episodes of larger arteries

8. Variant angina

along with thromboxane – cause coronary spasm and variant angina

9. Hypertension

rise in BP



10. Intestinal motility

may regulate peristalsis

11. Carcinoid syndrome

produces massive quantities of 5-HT

bowel hypermotility and

bronchoconstriction

DRUGS AFFECTING 5-HT SYSTEM

- **5-HT PRECURSORS:**

- Tryptophan increase brain 5-HT & produce behavioral effects.

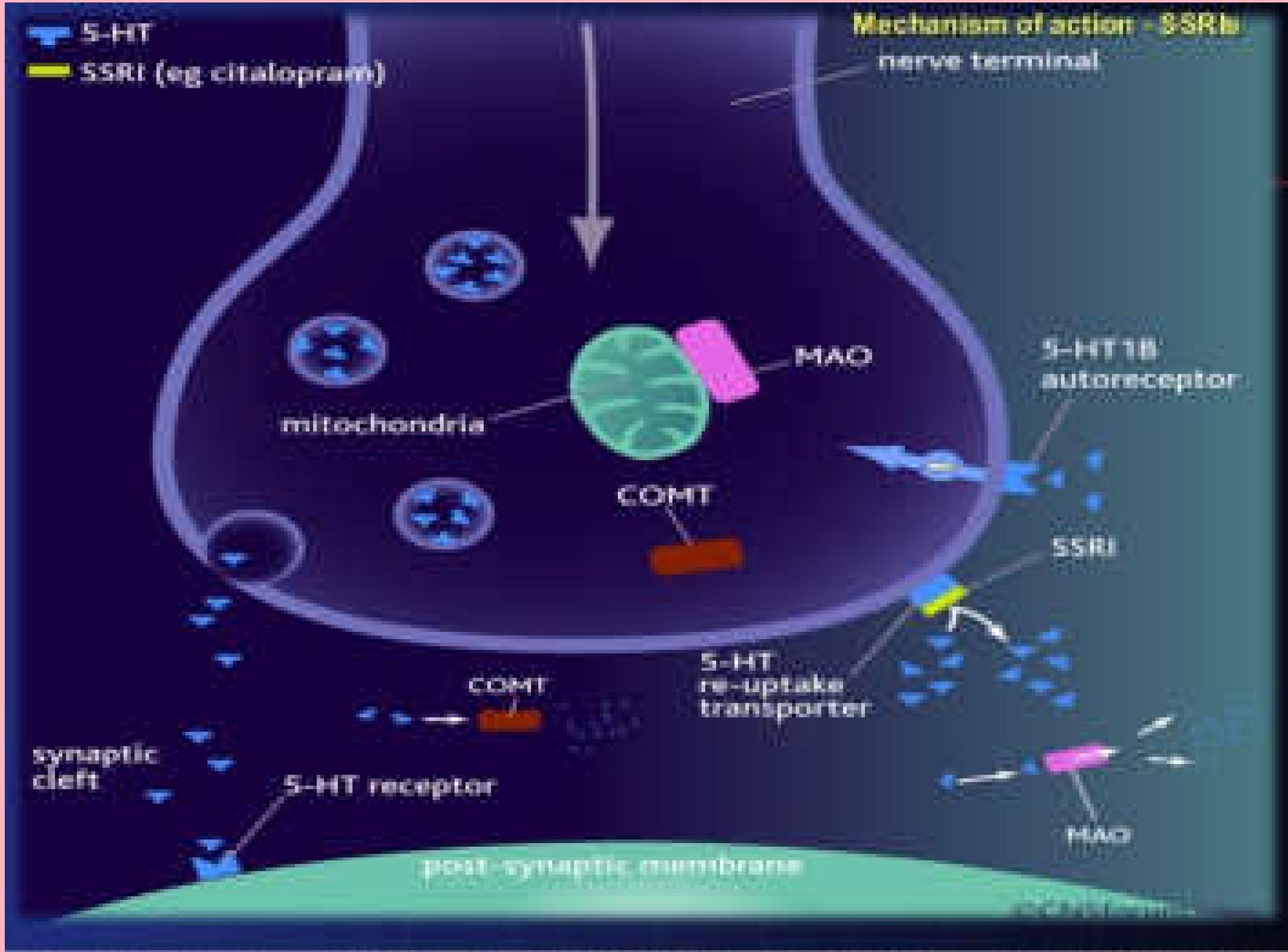
- **SYNTHESIS INHIBITORS**

- p-Chlorophenylalanin selectively inhibit tryptophan hydroxylase & reduce 5-HT level in tissue .

- **UPTAKE INHIBITORS**

- Tricyclic antidepressants inhibit 5-HT uptake along with NA .Some like fluoxetine ,sertraline are selective serotonin reuptake inhibitors.

Like Fluoxetine and sertraline





- **STORAGE INHIBITORS**

Reserpine block 5-HT uptake into storage granules & cause depletion of all cell monoamines .

- **DEGRADATION INHIBITORS**

Non-selective MAO inhibitors (tranylcypromine) & selective MAO -A inhibitors (chorgyline) increase 5-HT content by preventing its degradation.

- **NEURONAL DEGENERATION**

5,6 Dihydroxytryptamine selectively destroys 5-HT neurons .

5-HT RECEPTOR AGONISTS

1. D-Lysergic acid diethyl amide(LSD)

- Non selective 5-HT agonist
- Activates subtypes of 5-HT receptors including 5-HT_{1A}, 5HT_{2A/2C} ,5HT₅₋₇ .
- Antagonize 5HT_{2A} receptor in ileum .

AZAPIRONES

- Like buspirone ,gepirone act as partial agonist of 5HT_{1A} Receptor in brain.

8 HYDROXYDIPROPYLAMINO TETRALINE

- Selective 5HT_{1A} agonist
- Used as experimental tool



- **SUMATRIPTAN AND OTHER TRIPTAN**

- Selective 5HT_{1B/1D} agonists,
- Most effective in treatment of acute migraine attack

- **CISAPRIDE**

- Prokinetic drug
- increase g.i.t motility
- Selective 5HT₄ agonist.

- **M-Chlorophenylpiperazine**

- Active metabolite of antidepressant drug TRAZODONE.
- found to be agonist of 5HT_{1B} 5HT_{2A/2C} Receptor in brain.

5-HT RECEPTOR ANTAGONISTS

- Cyproheptadine
- Methysergide
- Ketanserin
- Clozapine
- Risperidone
- Ondansetron

CYPROHEPTADINE

- Block 5HT_{2A} receptor
- Utilized in controlling intestinal manifestations of carcinoid & postgastrectomy dumping syndrome
- Antagonize priapism caused by 5HT uptake inhibitor like fluoxetine.
- Side effects: drowsiness, dry mouth, ataxia confusion.

METHYSERGIDE

- Antagonize action of 5HT on smooth muscles including that of blood vessels
- Potent 5HT_{2A/2C} ANTAGONIST & Non selectively act on 5HT₁ receptors .
- Used for migraine prophylaxis

KETANSERIN

- Selective 5HT₂ receptor blocking property with action on 5HT₁, 5HT₃ & 5HT₄ receptors .
- 5HT induced vasoconstriction ,platelets aggregation & contraction of airway smooth muscles are antagonized but not contraction of guinea pig ileum or rat stomach .

CLOZAPINE

- 5HT_{2A/2C} blocker
- Inverse agonist activity at cerebral 5HT_{2A/2C} Receptors
- Efficacy in resistant cases of schizophrenia

RISPERIDONE

- 5HT_{2A} antagonist
- Ameliorates negative symptoms of schizophrenia
- Produce extrapyramidal side effects on slightly higher doses

ONDANSETRON

- Selectively 5HT₃ Antagonist
- Remarkable efficacy in controlling nausea & vomiting following administration of highly emetic anticancer drugs & radiotherapy .