Chapter 12 | 5-Hydroxytryptamine, its Antagonists and Drug Therapy of Migraine

5-HYDROXYTRYPTAMINE (5-HT, Serotonin)

Serotonin was the name given to the vasoconstrictor substance which appeared in the serum when blood clotted and *Enteramine* to the smooth muscle contracting substance present in enterochromaffin cells of gut mucosa. In the early 1950s both were shown to be *5-hydroxytryptamine* (5-HT). About 90% of body's content of 5-HT is localized in the enterochromaffin cells of stomach and intestines; most of the rest is in platelets and brain. It is also found in wasp and scorpion sting, and is widely distributed in invertebrates and plants (banana, pear, pineapple, tomato, stinging nettle, cowhage).

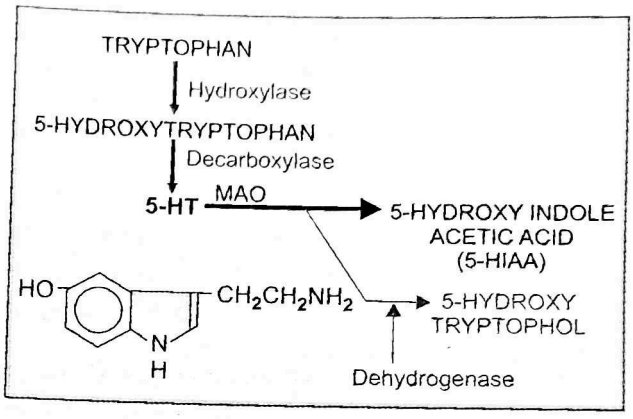

Fig. 12.1: Synthesis and degradation of 5-hydroxytryptamine (5-HT)

SYNTHESIS, STORAGE AND DESTRUCTION

5-HT is β-aminoethyl-5-hydroxyindole. It is synthesized from the amino acid tryptophan and degraded primarily by MAO and to a small extent by a dehydrogenase (Fig. 12.1).

There is close parallelism between CAs and 5-HT. The decarboxylase is non-specific, acts on DOPA as well as 5-hydroxytryptophan (5-HTP) to produce DA and 5-HT respectively. Like NA, 5-HT is actively taken up by an amine pump *serotonin transporter (SERT)*, a Na^+ dependent carrier, which operates at the membrane of platelets (therefore, 5-HT does not circulate in free form in plasma) and serotonergic nerve endings. This pump is inhibited by selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs). Platelets do not synthesize 5-HT but acquire it by uptake during passage through intestinal blood vessels. Again like CAs, 5-HT is stored within storage vesicles, and its uptake at the vesicular membrane by *vesicular monoamine transporter (VMAT-2)* is inhibited by reserpine, which causes depletion of CAs as well as 5-HT. The degrading enzyme MAO is also common for both. The isoenzyme MAO-A preferentially metabolizes 5-HT.

SEROTONERGIC (5-HT) RECEPTORS

Gaddum and Picarelli (1957) classified 5-HT receptors into musculotropic (D type) and neurotropic (M type) on the basis of their blockade by *D*ibenzyline (phenoxybenzamine) and *M*orphine. The classical 5-HT antagonists methysergide and cyproheptadine blocked D

type receptors. Subsequently 5-HT receptors were differentiated by their high or low affinity for [^{3}H] 5-HT in radioligand binding studies. The present system of classifying 5-HT receptors is based on molecular characterization and cloning of the receptor cDNAs. Some subtypes of 5-HT receptors have specific tissue distribution, but certain tissues express more than one subtype.

Four families of 5-HT receptors (5-HT_1, 5-HT_2, 5-HT_3, 5-HT_{4-7}) comprising of 14 receptor subtypes have so far been recognized. However, only some of these have been functionally correlated. Selective agonists/antagonists have been defined only for these subtypes. Knowledge of subtypes of 5-HT receptors has assumed importance because some newly developed therapeutically useful drugs can only be described in terms of 5-HT receptor subtype selective agonists or antagonists.

All 5-HT receptors (except 5-HT_3) are G protein coupled receptors which function through decreasing (5-HT_1) or increasing (5-HT_4, 5-HT_6, 5-HT_7) cAMP production, or by generating IP_3/DAG (5-HT_2) as second messengers. The 5-HT_3 is a ligand gated cation (Na^+,K^+) channel which on activation elicits fast depolarization.

5-HT_1 Receptors Six subtypes (5-$HT_{1A, B, D, E, F, P}$) have been identified. The 5-HT_{1C} receptor is now designated 5HT_{2C}. All subtypes of 5-HT_1 receptor couple with Gi/Go protein and inhibit adenylyl cyclase; 5-HT_{1A} in addition activates K^+ channels (resulting in hyperpolarization) and inhibits Ca^{2+} channels. These receptors function primarily as autoreceptors in brain—inhibit firing of 5-HT neurones or release of 5-HT from nerve endings.

The most important location of 5-HT_{1A} receptor is somato-dendritic synapses in raphe nuclei of brainstem; their activation serves to reduce firing of raphe neurones. Hippocampus is another important site. The antianxiety drug *buspirone* acts as a partial agonist of 5-HT_{1A} receptor. The 5-HT_{1D} receptor has been shown to regulate dopaminergic tone in substantia nigra–basal ganglia, and 5-$HT_{1D/1B}$ (the same receptor is 5-HT_{1B} in rat) to cause constriction of cranial blood vessels. The antimigraine drug *sumatriptan* is a selective 5-$HT_{1D/1B}$ agonist. Other functions subserved by 5-HT_{1D} receptors are inhibition of 5-HT release from forebrain serotonergic neurones, NA release from sympathetic nerve endings and that of inflammatory neuropeptides from nerve endings in cranial blood vessels.

The peripheral 5-HT_{1P} receptors expressed on neurones of enteric nervous system mediate their slow depolarization.

5-HT_2 Receptors There are 3 subtypes of 5-HT_2 receptor; all are coupled to Gq protein→activate phospholipase C and function through generation of IP_3/DAG. 5-HT_{2A} receptor also inhibits K^+ channels resulting is slow depolarization of neurones. α-methyl 5-HT is a selective agonist for all 3 subtypes.

5-HT_{2A} is the most widely expressed postjunctional 5-HT receptor (designated earlier as D type) located on vascular and visceral smooth muscle, platelets and cerebral neurones especially prefrontal cortex. It mediates most of the direct actions of 5-HT like vasoconstriction, intestinal, uterine and bronchial muscle contraction, platelet aggregation and activation of cerebral neurones. *Ketanserin* is a 5-HT_2 antagonist more selective for 5-HT_{2A}.

Contraction of rat gastric fundus is mediated by 5-HT_{2B} receptor.

5-HT_{2C} receptor is located on vascular endothelium—elicits vasodilatation through EDRF release. Choroid plexus expresses large number of 5-HT_{2C} receptors which may regulate CSF formation.

5-HT_3 Receptor This is the neuronal 5-HT receptor which rapidly depolarizes nerve endings by opening the cation channel located within it and corresponds to the original M type receptor. It mediates the indirect and reflex effects of 5-HT at:

(i) Somatic and autonomic nerve endings mediating pain, itch, coronary chemoreflex (bradycardia, fall in BP due to withdrawal of sympathetic tone, respiratory stimulation or apnoea elicited by stimulation of receptors in the coronary bed), and other visceral reflexes.

(ii) Nerve endings in myenteric plexus eliciting augmentation of peristalsis, emetic reflex.

(iii) Area postrema and nucleus tractus solitarious in brainstem inducing nausea, vomiting.

Ondansetron is a selective 5-HT_3 antagonist which inhibits vomiting by blocking these receptors in the brainstem as well as in gut wall. 2-Methyl 5-HT is a selective 5-HT_3 agonist.

5-HT_{4-7} Receptors The 5-HT_4 receptor couples to Gs protein, activates adenylyl cyclase and has been demonstrated in the mucosa, plexuses and smooth muscle of the gut where it is probably involved in augmenting intestinal secretion and peristalsis. It is also located in brain, especially hippocampus and the colliculi where it causes slow depolarization by decreasing K^+ conductance.

Cisapride and *renzapride* are selective 5-HT_4 agonists.

The recently cloned 5-HT_5, 5-HT_6 and 5-HT_7 receptors are closely related to the 5-HT_4 receptor. These are mainly located in specific brain areas, but their functional role is not known. An interesting finding is that *clozapine* (atypical antipsychotic) has high affinity for 5-HT_6 and 5-HT_7 receptors in addition to being a 5-$HT_{2A/2C}$ antagonist.

Salient features of important 5-HT receptor subtypes

5-HT$_1$: Autoreceptors; inhibit serotonergic neural activity in brain.
5-HT$_{1A}$—present in raphe nuclei and hippocampus; buspirone (antianxiety) may act through these receptors.
5-HT$_{1D/1B}$—Constricts cranial blood vessels and inhibits release of inflammatory neuropeptides in them; sumatriptan (antimigraine) acts through these receptors.

5-HT$_{2A}$: Previously D type receptor; most important postjunctional receptor mediating direct actions of 5-HT like vascular and visceral smooth muscle contraction, platelet aggregation, neuronal activation in brain; ketanserin blocks these receptors.

5-HT$_3$: Previously M type receptor; depolarizes neurones by gating cation channels; elicits reflex effects of 5-HT—emesis, gut peristalsis, bradycardia, transient hypotension, apnoea, pain, itch; ondansetron (antiemetic) acts by blocking these receptors.

5-HT$_4$: Mediate intestinal secretion, augmentation of peristalsis. Renzapride (prokinetic) is a selective 5-HT$_4$ agonist.

ACTIONS

5-HT is a potent depolarizer of nerve endings. It thus exerts direct as well as reflex and indirect effects. Tachyphylaxis is common with repeated doses of 5-HT. The overall effects therefore are often variable.

1. CVS Arteries are constricted (by direct action on vascular smooth muscle) as well as dilated (through EDRF release) by 5-HT, depending on the vascular bed and the basal tone. In addition, 5-HT releases Adr from adrenal medulla, affects ganglionic transmission and evokes cardiovascular reflexes. The net effect is complex. Larger arteries and veins are characteristically constricted. In the microcirculation 5-HT dilates arterioles and constricts venules: capillary pressure rises and fluid escapes. The direct action to increase capillary permeability is feeble.

Isolated heart is stimulated by 5-HT: both directly and by release of NA from nerve endings. In intact animals, bradycardia is mostly seen due to activation of coronary chemoreflex (Bezold Jarisch reflex) through action on vagal afferent nerve endings in the coronary bed, evoking bradycardia, hypotension and apnoea. BP: a triphasic response is classically seen on i.v. injection of 5-HT in animals.

- Early sharp fall in BP—due to coronary chemoreflex.
- Brief rise in BP—due to vasoconstriction and increased cardiac output.
- Prolonged fall in BP—due to arteriolar dilatation and extravasation of fluid.

However, 5-HT is not involved in the physiological regulation of BP.

5-HT receptor function in the gut

5-HT$_{2A}$: intestinal smooth muscle—contraction.
5-HT$_3$: fast depolarization of enteric plexus neurones; release of 5-HT from enterochromaffin cells.
5-HT$_4$: lower esophageal sphincter—contraction; enteric plexus—ACh release—enhanced peristalsis; intestinal mucosa—secretion.
5-HT$_{IP}$: slow depolarization of enteric plexus neurones.

2. Visceral smooth muscles 5-HT is a potent stimulator of g.i.t., both by direct action as well as through enteric plexuses. Several subtypes of 5-HT receptors are present in the gut (*See* box). Peristalsis is increased and diarrhoea can occur (also due to increased secretion).

5-HT constricts bronchi, but is less potent than histamine. Action on other smooth muscles in man are feeble and inconsistent.

3. Glands 5-HT inhibits gastric secretion (both acid and pepsin), but increases mucus production. It thus has ulcer protective property. Effect on other glandular secretions is not significant.

4. Nerve endings and adrenal medulla Afferent nerve endings are activated by 5-HT

causing tingling and pricking sensation, as well as pain. Depolarization of visceral afferents elicits respiratory and cardiovascular reflexes, nausea and vomiting. 5-HT is less potent than histamine in releasing CAs from adrenal medulla.

5. Respiration A brief stimulation of respiration (mostly reflex from bronchial afferents) and hyperventilation are the usual response, but large doses injected i.v. can cause transient apnoea through coronary chemoreflex.

6. Platelets By acting on 5-HT_{2A} receptors 5-HT causes changes in shape of platelets, but is a weak aggregator. However, it does not induce the release reaction.

7. CNS Injected i.v., 5-HT does not produce central effects because of poor entry across blood-brain barrier. However, it serves as a transmitter, primarily inhibitory. Direct injection in the brain produces sleepiness, changes in body temperature, hunger and a variety of behavioural effects.

PATHOPHYSIOLOGICAL ROLES

1. *Neurotransmitter* 5-HT is an established neurotransmitter in the brain. The brain 5-HT has a fast turnover rate. Cells containing 5-HT are present in the raphe nuclei of brainstem, substantia nigra and few other sites. They send axons rostrally (to limbic system, cortex and neostriatum) as well as caudally to spinal cord. 5-HT appears to be involved in sleep, temperature regulation, thought, cognitive function, behaviour and mood, appetite, vomiting and pain perception. Some serotonergic neurones are present in intestines also.

Experimental evidence from pharmacological manipulation of 5-HT metabolism, genetic models (like knock out mice), as well as therapeutic effect of selective serotonin reuptake inhibitors (SSRIs) and TCAs, etc. strongly suggest a role of 5-HT in the pathogenesis of anxiety, depression, aggression and other behavioural disorders in humans.

2. *Precursor of melatonin* 5-HT is the precursor of melatonin in pineal gland. It is believed to regulate the biological clock and maintain circadian rhythm.

3. *Neuroendocrine function* The hypothalamic neurones that control release of anterior pituitary hormones are probably regulated by serotonergic mechanism.

4. *Nausea and vomiting* Especially that evoked by cytotoxic drugs or radiotherapy is mediated by release of 5-HT and its action on 5-HT_3 receptors in the gut, area postrema and nucleus tractus solitarious.

5. *Migraine* 5-HT is said to initiate the vasoconstrictor phase of migraine and to participate in neurogenic inflammation of the affected blood vessels. Methysergide (5-HT antagonist) is an effective prophylactic and sumatriptan (5-$HT_{1D/1B}$ agonist) can control an attack. However, the role of 5-HT in this condition is not precisely known.

6. *Haemostasis* Platelets release 5-HT during aggregation at the site of injury to blood vessel. Acting in concert with collagen and other mediators, this 5-HT accelerates platelet aggregation and clot formation. Thus, it serves to amplify the response. Its contractile action appears to promote retraction of the injured vessel. Both the above actions contribute to haemostasis.

7. *Raynaud's phenomenon* Release of 5-HT from platelets may trigger acute vasospastic episodes of larger arteries involved in Raynaud's phenomena. Ketanserin has prophylactic value.

8. *Variant angina* Along with thromboxane A_2, 5-HT released from platelets has been implicated in causing coronary spasm and variant angina. However, the inefficacy of anti 5-HT drugs in this condition points to the involvement of other mediators.

9. *Hypertension* Increased responsiveness to 5-HT, as well as its reduced uptake and clearance by platelets has been demonstrated in hypertensive patients. Ketanserin has antihypertensive property. 5-HT has been held responsible for preeclamptic rise in BP.

10. *Intestinal motility* Enterochromaffin cells and 5-HT containing neurones may regulate peristalsis and local reflexes in the gut. This

system appears to be activated by intestinal distension and vagal efferent activity.

11. *Carcinoid syndrome* The carcinoid tumours produce massive quantities of 5-HT. Bowel hypermotility and bronchoconstriction are features of carcinoid which appear to be due to 5-HT, but flushing and hypotension are probably caused by other mediators. Pellagra in carcinoid may occur due to diversion of tryptophan for synthesizing 5-HT.

Use Due to widespread and variable actions, 5-HT has no therapeutic use.

DRUGS AFFECTING 5-HT SYSTEM

1. *5-HT precursor* Tryptophan increases brain 5-HT and produces behavioural effects because tryptophan hydroxylase in brain is not saturated by the amount of tryptophan available physiologically.

2. *Synthesis inhibitor* p-Chlorophenylalanine (PCPA) selectively inhibits tryptophan hydroxylase (rate limiting step) and reduces 5-HT level in tissues. It is not used clinically due to high toxicity.

3. *Uptake inhibitor* Tricyclic antidepressants inhibit 5-HT uptake along with that of NA. The selective serotonin reuptake inhibitors (SSRI) like fluoxetine, sertraline, etc. inhibit only 5-HT reuptake and have antidepressant-antianxiety property.

4. *Storage inhibitor* Reserpine blocks 5-HT (as well as NA) uptake into storage vesicles by inhibiting VMAT-2, and causes depletion of all monoamines. Fenfluramine selectively releases 5-HT by promoting its reverse transport at serotonergic nerve endings in the brain, followed by its prolonged depletion. It has anorectic property.

5. *Degradation inhibitor* Nonselective MAO inhibitor (tranylcypromine) and selective MAO-A inhibitor (clorgyline) increase 5-HT content by preventing its degradation.

6. *Neuronal degeneration* 5, 6 dihydroxytryptamine selectively destroys 5-HT neurones.

7. *5-HT receptor agonists* A diverse range of compounds producing a variety of actions have been found to activate one or more subtypes of 5-HT receptors. Notable among these are:

(i) *D-Lysergic acid diethyl amide (LSD)*—Synthesized as an ergot derivative, LSD was found to be an extremely potent hallucinogen. It is a nonselective 5-HT agonist—activates many subtypes of 5-HT receptors including 5-HT_{1A} on raphe cell bodies, 5-$HT_{2A/2C}$ (probably responsible for the hallucinogenic effect) and 5-HT_{5-7} in specific brain areas. However, LSD inhibits 5-HT_{2A} receptors in the ileum. A number of other hallucinogens also interact with brain 5-HT receptors.

(ii) *Azapirones* like buspirone, gepirone and ipsapirone are a novel class of antianxiety drugs which do not produce sedation. They act as partial agonists of 5-HT_{1A} receptors in the brain.

(iii) *Sumatriptan* and other triptans are selective 5-$HT_{1D/1B}$ agonists. They constrict cerebral blood vessels and have emerged as the most effective treatment of acute migraine attacks.

(iv) *Cisapride* This prokinetic drug, which increases gastrointestinal motility, is a selective 5-HT_4 agonist. Renzapride is still more selective for 5-HT_4 receptors.

8. *5-HT receptor antagonists* A variety of drugs block serotonergic receptors; many are nonselective, but some newer ones are highly subtype selective.

5-HT ANTAGONISTS

The ability to antagonize at least some actions of 5-HT is found in many classes of drugs, e.g. ergot derivatives (ergotamine, LSD, 2-bromo LSD, methysergide), adrenergic α blockers (phenoxybenzamine), antihistaminics (cyproheptadine, cinnarizine), chlorpromazine, morphine, etc., but these are nonselective and interact with receptors for other signal molecules as well. Many are partial agonists or antagonize certain actions of 5-HT but mimic others. The salient features of drugs which have been used clinically as 5-HT antagonists and some newer selective antagonists are described below:

1. Cyproheptadine It primarily blocks 5-HT_{2A} receptors and has additional H_1 antihistaminic, anticholinergic and sedative properties (*see* Ch. 11). Like other antihistaminics, it has been used in allergies and is a good antipruritic, but the anti 5-HT action has no role in these conditions. It increases appetite and has been used in children as well as in poor eaters to promote weight gain. The H_1 antihistaminic action and an action on growth hormone secretion has been suggested to account for this property.

The anti 5-HT activity of cyproheptadine has been utilized in controlling intestinal manifestations of carcinoid and postgastrectomy dumping syndromes, as well as in antagonizing priapism/orgasmic delay caused by 5-HT uptake inhibitors like fluoxetine and trazodone.

Side effects drowsiness, dry mouth, confusion, ataxia, weight gain.

2. **Methysergide** It is chemically related to ergot alkaloids; antagonizes action of 5-HT on vascular and visceral smooth muscles, without producing other ergot like effects. It does not interact with α adrenergic or dopamine receptors. Methysergide is a potent 5-$HT_{2A/2C}$ antagonist with some tissue specific agonistic actions as well. Introduced briefly for migraine prophylaxis, carcinoid and postgastrectomy dumping syndrome, it went into disuse because it caused abdominal, pulmonary and endocardial fibrosis.

3. **Ketanserin** It has selective 5-HT_2 receptor blocking property with negligible action on 5-HT_1, 5-HT_3 and 5 HT_4 receptors and no partial agonistic activity. 5-HT induced vasoconstriction, platelet aggregation and contraction of airway smooth muscle are antagonized. Weak H_1 and dopaminergic blocking activities are also present.

Ketanserin has significant α_1 adrenergic blocking activity and was introduced as antihypertensive, but did not gain popularity.

Ritanserin is a relatively more 5-HT_{2A} selective congener of ketanserin.

4. **Clozapine** In addition to being a weak dopaminergic antagonist, this atypical antipsychotic is a 5-$HT_{2A/2C}$ blocker (*see* Ch. 32). Clozapine may also exert inverse agonist activity at cerebral 5-$HT_{2A/2C}$ receptors which may account for its efficacy in resistant cases of schizophrenia.

5. **Risperidone** This atypical antipsychotic is a combined 5-HT_{2A} + dopamine D2 antagonist, similar to clozapine. Like the latter, it especially ameliorates negative symptoms of schizophrenia, but produces extrapyramidal side effects.

Other atypical antipsychotics like *olanzapine* and *quetiapine* are also combined 5-HT and DA antagonists, but interact with other neurotransmitter receptors as well.

6. **Ondansetron** It is the prototypical selective 5-HT_3 antagonist that has shown remarkable efficacy in controlling nausea and vomiting following administration of highly emetic anticancer drugs and radiotherapy. The 5-HT_3 antagonists are described in Ch. 48.

ERGOT ALKALOIDS

Ergot is a fungus *Claviceps purpurea* which grows on rye, millet and some other grains. The grain is replaced by a purple, hard, curved body called 'sclerotium'. Epidemics of ergot poisoning (ergotism), due to consumption of contaminated grains, have been recorded from the beginning of history. It still occurs in epidemic and sporadic forms. Painful dry gangrene of hands and feet which become black (as if burnt) occurs due to vasospastic ischemia. Miscarriages occur in women and cattle.

Some suffer hallucinations and a convulsive type is also described.

Ergot had been used by midwives to quicken labour since the middle ages. This use received medical sanction in the 19th century, but its dangers were recognized by the beginning of the 20th century and then it was advocated only after delivery. Dale and Barger (1906 onwards) isolated the ergot alkaloids and studied their pharmacology. Ergometrine was isolated in 1935.

Ergot contains a host of pharmacologically active substances—alkaloids, LSD, histamine, ACh, tyramine and other amines, sterols, etc.

Natural ergot alkaloids

These are tetracyclic indole containing compounds which may be considered as derivatives of *lysergic acid*. They are divided into—

(a) *Amine alkaloid* Ergometrine (Ergonovine): which is oxytocic.

(b) *Amino acid alkaloids* Ergotamine, Ergotoxine (mixture of ergocristine + ergocornine + ergocryptine): they are vasoconstrictor and α adrenergic blocker/partial agonist.

Semisynthetic derivatives

(a) Dihydroergotamine (DHE), Dihydroergotoxine (Codergocrine): are antiadrenergic, cerebroactive.

(b) 2-Bromo-α-ergocryptine (Bromocriptine): is a dopaminergic D2 agonist (*see* Ch. 17).

(c) Methysergide: it is mainly anti 5-HT.

The ergot alkaloid related compounds have diverse pharmacological properties. They act as agonists, partial agonists and antagonists on certain subtypes of α adrenergic, serotonergic and dopaminergic receptors in a tissue specific manner.

Actions

Ergotamine It acts as a partial agonist and antagonist at α adrenergic and all subtypes of 5-HT_1 and 5-HT_2 receptors, but does not interact with 5-HT_3 or dopamine receptors. Sustained vasoconstriction (because of very slow dissociation from the receptors), visceral smooth muscle contraction, vasomotor centre depression are produced, and the action of NA and 5-HT on smooth muscles is antagonized. However, the overall effect of oral/rectal doses of ergotamine on BP is insignificant. It is a potent emetic (through CTZ and vomiting centre) and moderately potent oxytocic. At high doses CNS stimulation and paresthesias may be experienced. On chronic exposure (ergot poisoning) vasoconstriction is accompanied by damage to capillary endothelium resulting in thrombosis, vascular stasis and gangrene.

Dihydroergotamine (DHE) Hydrogenation of ergotamine reduces serotonergic and α-adrenergic agonistic actions, but enhances α-receptor blocking property. Consequently DHE is a less potent vasoconstrictor; primarily constricts capacitance vessels and causes less intimal damage. It is a weaker emetic and oxytocic, but has some antidopaminergic action as well.

Dihydroergotoxine (Codergocrine) This hydrogenated mixture of ergotoxine group of alkaloids is a more potent α blocker and a very weak vasoconstrictor. In the brain, a variety of partial agonistic/antagonistic actions on 5-HT receptors, as well as metabolic and vascular effects are produced. In addition, ACh release in cerebral cortex may be enhanced. Dihydroergotoxine has been advocated for treatment of dementia (*see* Ch. 35).

Bromocriptine The 2-bromo derivative of ergocryptine is a relatively selective dopamine D2 agonist with prominent action on pituitary lactotropes (inhibits prolactin release), in striatum (antiparkinsonian) and in CTZ (emetic). The emetic action is weaker than that of ergotamine. In certain brain areas weak antidopaminergic action has also been shown. It has very weak anti 5-HT or α blocking actions and is not an oxytocic.

Ergometrine (Ergonovine) This amine ergot alkaloid has very weak agonistic and practically no antagonistic action on α adrenergic receptors: vasoconstriction is not significant. Partial agonistic action on 5-HT_2 receptors is most probably responsible for its powerful uterotonic effect. It is a moderately potent 5-HT_2 antagonist in g.i. smooth muscle and a weak dopaminergic agonist on the pituitary lactotropes as well as CTZ; emetic potential is low. The most prominent action of ergometrine is contraction of myometrium, because of which it is used exclusively in obstetrics (*see* Ch. 23).

Pharmacokinetics Oral bioavailability of amino acid ergot alkaloids and their hydrogenated derivatives is poor (< 1%) due to slow and incomplete absorption as well as high firstpass metabolism. Bioavailability is higher after sublingual and rectal administration, but still often erratic. They are metabolized in liver and excreted primarily in bile. Ergotamine is sequestrated in tissues—produces longer lasting actions compared to its plasma t½ of 2 hours. Ergot alkaloids effectively cross blood-brain barrier.

Adverse effects Nausea, vomiting, abdominal pain, muscle cramps, weakness, paresthesias, coronary and other vascular spasm, chest pain (due to coronary vasoconstriction) are the frequent side effects. These drugs are contraindicated in presence of sepsis, ischaemic heart disease, peripheral vascular disease, hypertension, pregnancy, liver and kidney disease.

Preparations and dose

Ergotamine: For migraine 1–3 mg oral/sublingual, repeat as required (max 6 mg in a day); rarely 0.25–0.5 mg i.m. or s.c.; ERGOTAMINE 1 mg tab, 0.5 mg/ml inj.

Dihydroergotamine: For migraine 2–6 mg oral (max 10 mg/day), 0.5–1 mg i.m., s.c. repeat hourly (max 3 mg); DIHYDERGOT, DHE 1 mg tab, MIGRANIL 1 mg/ml inj.

Dihydroergotoxine (codergocrine) For dementia 1–1.5 mg oral or sublingual, 0.15–0.6 mg i.m., HYDERGINE 1.5 mg tab, CERELOID 1 mg tab.

DRUG THERAPY OF MIGRAINE

Migraine is a mysterious disorder characterized by pulsating headache, usually restricted to one side, which comes in attacks lasting 4–48 hours and is often associated with nausea, vomiting, sensitivity to light and sound, flashes of light, vertigo, loose motions and other symptoms. Two major types are—*migraine with aura* (classical migraine) in which headache is preceded by visual or other neurological symptoms, and *migraine without aura* (common migraine). Pulsatile dilatation of certain large cranial vessels is the immediate cause of pain. The pathogenic mechanisms are not well understood.

The *Vascular theory* holds that initial vasoconstriction or shunting of blood through carotid arterio-venous anastomoses produces cerebral ischaemia and starts the attack. The *Neurogenic theory* considers it to be a spreading depression of cortical electrical activity followed by vascular phenomena. Some triggering event appears to produce neurogenic inflammation of the affected blood vessel wall which is amplified by retrograde transmission in the afferent nerves and release of mediators like 5-HT, neurokinin, substance P, calcitonin gene related peptide (CGRP), nitric oxide, etc. Perivascular edema occurs due to leakage of plasma from the inflamed cranial vessels, and pain nerve endings in the dura are activated by stretching.

Changes in blood/urinary levels of 5-HT and its metabolites during migraine attack, its precipitation by 5-HT releasers and efficacy of drugs having actions in the serotonergic system to prevent/abort/terminate migraine attacks suggests a pivotal role of 5-HT in this disorder.

Drug therapy of migraine has to be individualized: severity and frequency of attacks and response of individual patients to drugs used earlier determine the choice. The strategy mostly adopted is summarized in the box.

Drug therapy of migraine

Severity		*Drug therapy*
Mild	:	Simple analgesics/NSAIDs or their combinations (± antiemetic)
Moderate	:	NSAIDs combinations/a triptan/ ergot alkaloids (+ antiemetic)
Severe	:	a Triptan/ergot alkaloids (+ antiemetic)

+ Prophylaxis
- Propranolol/other β blockers
- Amitriptyline/other tricyclic antidepressants
- Flunarizine/other Ca^{2+} channel blockers
- Valproate/topiramate

Mild migraine Cases having fewer than one attack per month of throbbing but tolerable headache lasting upto 8 hours which does not incapacitate the individual, may be classified as mild migraine.

(i) *Simple analgesics* like paracetamol (0.5–1 g) or aspirin (300–600 mg) taken at the first indication of an attack and repeated 4–6 hourly abort and suppress most mild attacks.

(ii) *Nonsteroidal antiinflammatory drugs (NSAIDs) and their combinations* Drugs like ibuprofen (400–800 mg 8 hourly), naproxen (500 mg followed by 250 mg 8 hourly), diclofenac (50 mg 8 hourly), mephenamic acid (500 mg 8 hourly), indomethacin (50 mg 6–8 hourly) either alone or combined with paracetamol/codeine/diazepam or another sedative/diphenhydramine or another antihistaminic/caffeine are found more satisfactory by some patients. Dispersible or effervescent formulations of the analgesic should be preferred, because gastric stasis attending migraine attack may hamper absorption from the regular tablet. Analgesics are more effective in migraine without aura, but certain patients of migraine with aura also prefer them over specific antimigraine drugs (triptans/ergot alkaloids). Analgesics are taken only till the attack passes off. Excessive use of analgesic may itself cause headache. Taken in the prodromal stage they can also abort an attack, but long-term treatment on a regular schedule to ward off migraine attacks is not advised.

(iii) *Antiemetics* Gastric stasis occurs during migraine which delays absorption of oral drugs. Metoclopramide (10 mg oral/i.m.) is frequently used. It relieves nausea, vomiting and gastric stasis. When the patient has already vomited, it is better to give the antiemetic by injection. Domperidone (10–20 mg oral) and prochlorperazine (10–25 mg oral/i.m.) are also effective. Diphenhydramine or promethazine exert sedative as well as antiemetic action.

Moderate migraine Migraine may be labelled as moderate when the throbbing headache is more intense, lasts for 6–24 hours, nausea/vomiting and other features are more prominent and the patient is functionally impaired. One or more attacks occur per month.

Simple analgesics are usually not effective, but stronger NSAIDs or their combinations mentioned above are beneficial in many cases. The remaining are treated with a specific antimigraine drug, i.e. a triptan or an ergot preparation. Antiemetics are almost regularly needed. Prophylactic therapy is advised only when attacks are more frequent than 2–3 per month.

Severe migraine These patients suffer 2–3 or more attacks per month of severe throbbing headache lasting 12–48 hours, often accompanied by vertigo, vomiting and other symptoms; the subject is grossly incapacitated during the attack.

Analgesics/NSAIDs and their combinations usually do not afford adequate relief—specific antimigraine drugs have to be prescribed along with antiemetics. Combination of a longer acting analgesic like naproxen with a triptan may be more suitable for patients who have prolonged migraine attacks and suffer recurrences when treated with a triptan alone. Prophylactic regimens lasting 6 months or more are recommended.

SPECIFIC ANTIMIGRAINE DRUGS

Ergotamine It is the most effective ergot alkaloid for migraine. Given early in attack, lower doses generally suffice, and relief is often dramatic. However, when pain has become severe—larger doses are needed and control may be achieved only after few hours. Oral/sublingual route is preferred, 1 mg is given at half hour intervals till relief is obtained or a total of 6 mg is given. Parenteral administration, though rapid in action is more hazardous.

Ergotamine acts by constricting the dilated cranial vessels and/or by specific constriction of carotid A-V shunt channels. Ergotamine and DHE have also been shown to reduce neurogenic inflammation and leakage of plasma in duramater that occurs due to retrograde stimulation of perivascular afferent nerves. These actions appear to be mediated through partial agonism at 5-$HT_{1D/1B}$ receptors in and around cranial vessels.

Dihydroergotamine (DHE) It is nearly as effective as ergotamine and preferred for parenteral administration because injected DHE is less hazardous.

Current status Because of erratic oral absorption, frequent side effects, especially nausea, vomiting, muscle cramps and availability of triptans, ergot preparations are rarely used now, except for considerations of cost or when triptans fail. Ergot alkaloids have no prophylactic value: regular use is not justified, which may itself produce a dull background headache and an attack may be precipitated on discontinuation. *Caffeine* 100 mg taken with ergotamine enhances its absorption from oral and rectal routes and adds to the cranial vasoconstricting action. Many combination preparations are available.

MIGRIL: Ergotamine 2 mg, caffeine 100 mg, cyclizine 50 mg tab.

VASOGRAIN: Ergotamine 1 mg, caffeine 100 mg, paracetamol 250 mg, prochlorperazine 2.5 mg tab.

Selective 5-$HT_{1D/1B}$ agonists (Triptans)

This novel class of antimigraine drugs selectively activate 5-$HT_{1D/1B}$ receptors, and are called 'triptans'. Currently, they are the first line drugs for patients who fail to respond to analgesics. Ergot alkaloids are now required only in few cases. Because these drugs have been designed to act on the same subtype of 5-HT receptor, pharmacodynamic differences among them are minor, but there are significant pharmacokinetic differences. All others triptans have higher oral bioavailability than the prototype drug sumatriptan. Fewer headache recurrences in an attack are reported with naratriptan and frovatriptan due to their longer t½, but they may be slower in affording initial pain relief.

Sumatriptan It is the first selective 5-$HT_{1D/1B}$ receptor agonist; activates other subtypes of 5-HT_1 receptors only at very high concentrations, and does not interact with 5-HT_2, 5-HT_3, 5-HT_{4-7}, α or β adrenergic, dopaminergic, cholinergic or GABA receptors. Administered at the onset of an attack of migraine, sumatriptan is as effective and better tolerated than ergotamine. About 3/4 patients obtain complete/significant relief

within 2–3 hours. However, recurrence of headache within 24 hr has been noted in 20–40% patients, probably due to short t½ of sumatriptan. A distinct advantage is that it tends to suppress nausea and vomiting of migraine, while ergotamine accentuates these symptoms.

The antimigraine activity of sumatriptan has been ascribed to 5-$HT_{1D/1B}$ receptor mediated constriction of dilated cranial blood vessels, especially the arterio-venous shunts in the carotid artery, which express 5-$HT_{1D/1B}$ receptors. Dilatation of these shunt vessels during migraine attack is believed to divert blood flow away from brain parenchyma. Consistent with the fact that 5-$HT_{1D/1B}$ receptors are presynaptic autoreceptors, sumatriptan can reduce 5-HT release at these blood vessels. Alternatively or in addition, it may inhibit inflammatory neuropeptide release around the affected vessels as well as extravasation of plasma proteins across dural vessels. Like ergotamine, the triptans have been found to suppress neurogenic inflammation of cranial vessels. The use of sumatriptan (or other triptans) should be restricted to treatment of acute attacks of moderate to severe migraine not responding to analgesics or their combinations.

Pharmacokinetics: Sumatriptan is absorbed rapidly and completely after s.c. injection. Oral bioavailability averages only 15%. Absorption is faster after intranasal spray, but bioavailability remains almost the same. It is the only triptan available for nasal and parenteral administration as well. Sumatriptan is rapidly metabolized by MAO-A isoenzyme and metabolites are excreted in urine; elimination t½ is ~2 hours.

Side effects of sumatriptan are usually mild. Tightness in head and chest, feeling of heat and other paresthesias in limbs, dizziness, weakness are short lasting, but dose related side effects. These are more common after s.c. injection, which is painful. Slight rise in BP occurs, but has little clinical relevance, because sumatriptan is not a drug for regular use. Bradycardia, coronary vasospasm and risk of myocardial infarction are the serious, but infrequent adverse effects. Few sudden deaths have been ascribed to sumatriptan. Seizures and hypersensitivity reactions are rare.

Contraindications: Ischaemic heart disease, hypertension, epilepsy, hepatic or renal impairment and pregnancy are the contraindications. Patients should be cautioned not to drive.

Sumatriptan and ergotamine should not be administered within 24 hours of each other. Interaction with 5-HT reuptake inhibitors, MAO inhibitors and lithium has been reported.

Dose: 50–100 mg oral at the onset of migraine attack, may be repeated once within 24 hours if required. Those not responding to the first dose should not be given the second dose. It is the only triptan available for parenteral use; 6 mg s.c. may be given to patients who cannot take the drug orally or in whom the pain develops very rapidly. After injection, it acts in 10–20 min and is more consistently effective. Alternatively, for rapid action and in patients who vomit out the oral tablet, 25 mg nasal spray can be used. It may be repeated once after 2 hours. A bitter taste may be felt after the nasal spray.

MIGRATAN, 50, 100 mg tabs, SUMINAT 25, 50, 100 mg tab, 25 mg nasal spray, 6 mg/0.5 ml inj. SUMITREX 25, 50, 100 mg tab, 6 mg/0.5 ml inj.

Rizatriptan: This congener of sumatriptan is more potent, has higher oral bioavailability with slightly faster onset of action.

Dose: 5-10 mg; repeat once after 2 hr (if required).

RIZACT, RIZATAN 5, 10 mg tab.

Naratriptan, Zolmitriptan, Almotriptan, Frovatriptan and *Eletriptan* are other triptans used in some countries.

Features of some triptans are compared in the box.

PROPHYLAXIS OF MIGRAINE

Regular medication to reduce the frequency and/or severity of attacks is recommended for moderate-to-severe migraine when 2–3 or more attacks occur per month, or when attacks are disabling despite treatment, or in patients with contraindications for triptans/ergotamine. Diverse classes of drugs are used, but none is effective in all cases, and none abolishes the attacks totally. It may be prudent to discontinue pophylaxis every 6 months to check whether its continuation is needed or not. It is important to avoid the precipitating factor(s).

Comparative features of triptans

	Suma.	*Frova.*	*Riza.*	*Nara.*	*Zolmi.*
1. Oral bioavailability (%)	15	25	45	70	40
2. *Tmax** (hr)	1.5–2	2–4	1–1.5	2–3	1.5–2
3. Plasma t½ (hr)	~2	26	2–3	6	2–3
4. Oral dose					
Initial (mg)	50–100	2.5	5–10	2.5	2.5
Max. in 24 hr (mg)	200	5–7.5	20	5	10

* *Tmax*: Time to peak plasma concentration after oral dosing.

(i) *β-Adrenergic blockers* Propranolol is the most commonly used drug. It reduces frequency as well as severity of attacks in upto 70% patients. Effect is generally seen in 4 weeks and is sustained during prolonged therapy. The starting dose is 40 mg BD, which may be increased upto 160 mg BD if required. The mechanism of action is not clear; that it is due to β adrenergic blockade has been questioned. Other nonselective (timolol) and β_1 selective (metoprolol, atenolol) agents are also effective, but pindolol and others having intrinsic sympathomimetic action are not useful.

(ii) *Tricyclic antidepressants* Many tricyclic compounds, of which *amitriptyline* (25–50 mg at bed time) has been most extensively tried, reduce migraine attacks. It is effective in many patients but produces more side effects than propranolol. Whether its 5-HT (and other monoamine) uptake blocking property is causally related to the prophylactic effect is not known. The antimigraine effect is independent of antidepressant property, but this class of drugs are better suited for patients who concurrently suffer from depression.

(iii) *Calcium channel blockers* Verapamil was found to reduce migraine attacks, but was judged inferior to propranolol.

Flunarizine is a relatively weak Ca^{2+} channel blocker that inhibits Na^+ channels as well. It is claimed to be as effective as propranolol, but convincing proof is lacking. Frequency of attacks is often reduced, but effect on intensity and duration of attacks is less well documented. It is claimed to be a cerebro-selective Ca^{2+} channel blocker, which may benefit migraine by reducing intracellular Ca^{2+} overload due to brain hypoxia and other causes. Side effects are sedation, constipation, dry mouth, hypotension, flushing, weight gain and rarely extrapyramidal symptoms.

Dose: Flunarizine 10–20 mg OD, children 5 mg OD, NOMIGRAIN, FLUNARIN 5 mg, 10 mg caps/tab.

(iv) *Anticonvulsants* *Valproic acid* (400–1200 mg/day) and *gabapentin* (300–1200 mg/day) have some prophylactic effect in migraine. The newer drug *topiramate* has recently been approved for migrain prophylaxis. A 50% reduction in the number of attacks in half of the patients was noted in 2 randomized trials. Start with topiramate 25 mg OD and gradually increase to 50 mg OD or BD. Efficacy of anticonvulsants in migraine is lower than that of β blockers. They are indicated in patients refractory to other drugs or when propranolol is contraindicated.

(v) *CGRP antagonist* A fully human monoclonal antibody *Erenumab* which blocks calcitonin gene-related peptide (CGRP) receptor has been recently found to reduce number of migraine attacks when injected s.c. once a month in patients with severe migraine (*see* p. 555). It has now been approved by US-FDA.

(vi) *5-HT antagonists* The prophylactic effect of methysergide and cyproheptadine is less impressive than β blockers. They are not used now for migraine.

PROBLEM DIRECTED STUDY

12.1 A 36 years lady presents with the complaint of episodes of unilateral pulsatile headache for the past 2 years or so. During the initial episodes, the headache was mild, was relieved by paracetamol/ibuprofen tablets, and did not interfere with her daily activities. However, the severity and frequency of pain episodes has progressively increased, so that now episodes recur nearly every 1-2 weeks, especially at the beginning of her periods. Headache is preceded by lethargy, anorexia, nausea and is accompanied by blurred vision, flashes of light seen on closing the eyes, unsteadiness and frequent vomiting. The pain lasts for 12–18 hours and she is incapacitated for nearly 24 hours. The headache is not relieved now by over-the-counter analgesics or combination analgesics.

(a) What medication can be prescribed to treat the headache episodes. What instructions should be given regarding timing, dose, etc. of this medication?

(b) What specific medical history needs to be elicited, physical examination/investigation performed before prescribing the above medication?

(c) Apart from treatment of pain episodes, can this patient be put on some regular medication to prevent/minimise the episodes?